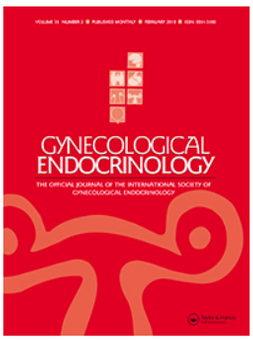

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EXTREME LOW AMH AND IVF SUCCESS

Women with extreme low AMH values could have *in vitro* fertilization success

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ABSTRACT

Circulating anti-müllerian hormone (AMH) and antral follicle count (AFC) are the best predictors of IVF outcomes. However, in extreme low AMH range especially for young patients, AMH prediction power loose its specificity to give real idea of pregnancy chance with IVF treatments and good prognosis of an extremely reduced ovarian reserve and expected poor response. Indeed, this retrospective study was conducted to evaluate IVF outcomes in patients following IVF-ICSI program with extremely low AMH levels (≤0.4 ng/ml; $n = 390$) compared to those presenting normal AMH range (1.3–2.6 ng/ml; $n = 352$) considered as control group. As expected, number of oocytes retrieved per patient, and embryological outcomes were significantly lower in the extremely low AMH levels group compared to control. Moreover, it was same trend concerning clinical outcomes but we have to note that even in extreme low AMH, patients could reach ineligible satisfying clinical pregnancy rate compared to control (17% vs 41%). For patients younger than 35 years, clinical pregnancy rate improved to 27%. Women with extreme low AMH values and especially younger ones, still have reasonable chances of achieving pregnancy, highlighting the default view of this category generally excluded from IVF program.

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Low anti-mti-mam.y hormone; IVF success; poor responders; ovarian reserve

Introduction

Anti-müllerian hormone (AMH) is an established marker of ovarian reserve [1,2] predicting ovarian response after controlled ovarian hyper-stimulation (COH) in *in vitro* fertilization (IVF) cycles [1] as a part of the gold standard for modern fertility tests. Currently, age, antral follicle count (AFC), and AMH levels are generally acknowledged as the best predictors for ovarian reserve [3]. The value of the AMH level in prediction of embryological and clinical outcomes has been investigated in various studies [1,3–5] that are controverted by others [6–8]. Though AMH level has an association with IVF outcomes prediction [2,9], its specificity still linked to age and other factors including lifestyle calling in need to establish a real consensus [10].

The poor ovarian response rate (cycle cancelation or ≤3 oocytes) is ∼10% between 30 and 35 years of age [11] or sometimes-higher reaching 24% of young women with poor response [12]. This issue enhanced the importance of personalized management strategy especially for poor responders in IVF. Indeed, they are presenting a challenge for clinicians with high risk not to achieve clinical pregnancy after IVF program with high canceled cycles' rate. Whatever, it is rare to investigate clinically in IVF these women profiles especially with an extreme low AMH limiting the study size [13].

Indeed, there is lack of clinical trials realized to evaluate the IVF outcomes of this critic category of patients with AMH under 0.5 ng/ml, evidently discriminated or rejected while they have their proper chance to achieve clinical pregnancy. For this reason, the main objective of this study was to assess IVF outcomes in women with extreme low AMH values compared firstly with control population including patients with normal AMH values, and secondly selecting younger patients under 35 years old.

Material and methods

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All patients who participated in this study signed an informed consent after being informed about the terms and issues of the study.

Patients'selection

This is a retrospective study design collecting data from January 2015 to December 2017 selecting women with extremely low AMH concentrations treated with intracytoplasmic sperm injection (ICSI) in Anfa Fertility Center. Serum AMH assays were included as a standard measure in the IVF program. A cutoff AMH value of ≤0.4 ng/ml was chosen according to Weghofer et al. [13] for the first group ($n = 390$) while the normal range of AMH considered as control ($n = 352$) was limited between 1.3 and 2.6 ng/ml [14]. AMH concentrations (ng/ml) were measured by ELISA (Elecsys AMH® assay, Cobas, Roche, Germany) prior to the start of each cycle.

All patients without exception were selected on the following inclusion-exclusion criteria: Inclusion criteria: primary infertility, endometrial thickness more than 6 mm in ovulation induction,

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Table 1. Comparison of IVF outcomes between patients with extreme low AMH and control.

	Extreme low AMH ($n = 390$)	Control-Normal AMH ($n = 352$)	p-Value
Age of patient (years)	38.05 ± 4.83	37.59 ± 5.69	.79 (ns)
AMH (ng/ml)	0.27 ± 0.12	1.8 ± 0.24	.03 (s)
AFC	4.41 ± 2.81	8.25 ± 3.39	.04 (s)
Number of retrieved oocytes per patient	2.85 ± 2.92	7.41 ± 3.94	.02 (s)
Maturation rate (%)	51%	75%	.03 (s)
Fertilization rate (%)	77%	89%	.04 (s)
Cleavage rate (%)	84%	92%	.04 (s)
Top embryo quality rate (%)	75%	78%	.47 (ns)
Total transferred embryo number	579	651	–
Number of transferred embryo per patient	1.7 ± 0.15	1.9 ± 0.12	.34 (ns)
Canceled cycle transfer rate (%)	97/390 (25%)	24/352 (7%)	.01 (s)
Clinical pregnancy rate (%) (per cycle started)	49/390 (13%)	134/352 (38%)	.01 (s)
Clinical pregnancy rate (%) (per transfer)	49/293 (17%)	134/328 (41%)	.01 (s)
Miscarriage rate (%)	4/49 (9%)	10/134 (7%)	.58 (ns)

Results are expressed as *n*, *n*(%) or mean ± standard deviation (SD). A statistic significant difference is considered when $p < .05$ (s). $p \geq .05$ is not significant (ns). Extreme low AMH was defined when its value is ≤0.4 ng/ml while normal AMH value was limited between 1.3 and 2.6 ng/ml for control group. AFC: Antral Follicle Count, AMH was measured on day 2 of the cycle and the endometrial thickness was evaluated in day of oocyte retrieval. Cleavage rate was calculated relatively to embryos at day 3 by 2 pronucleus. The miscarriage rate is expressed relative to the number of clinical pregnancies.

regular menstrual cycles, BMI <30, absence of uterine pathology and infectious negative balance. Exclusion criteria: endometriosis, uterine pathology, and patients who underwent special treatment or pretreatment, Preimplantation genetic screening.

Among the whole lot of included patients with limited age at 42 years old, we selected patients younger than 35 years old with extreme low AMH compared to control with normal AMH.

Stimulation protocol

In order to eliminate the effect of protocol and better align the sample and follicular cohort, it is preferable to use the antagonist protocol using the r-FSH (Orgalutran 0.25 and Gonal-F).

Further r-FSH administration (Gonal-F; Serono Laboratories, Saint Cloud, France) was started by daily subcutaneously injection (150–225 IU/day) for patients with normal AMH (1-1.3–2.6 ng/ml) and more (mean =300 IU/day) for patients with extreme low AMH values (≤0.4 ng/ml). The FSH dose was based on the woman's age and AMH concentration that was maintained constant for 5 days and it was adjusted according to usual parameters of follicle growth determined by serum estradiol concentrations and ultrasound monitoring. A potent, third-generation GnRH antagonist, Ganirelix (Orgalutran®, MSD Schering-Plough, France) injected subcutaneously once daily starting on day 6 of FSH administration. An intramuscular injection of 10 000 IU of human chorionic gonadotrophin (HCG, Gonadotrophines Chorioniques Ovitrelle®, Merck Serono) was performed after obtaining follicles ≥17 mm. Embryos produced by ICSI as described by Madkour et al. [15] were cultured up to day 3. Adequate embryo quality (good quality embryos; A + B) was defined based on the presence of uniformly sized and shaped blastomeres and fragmentation lower or equal to 10%. One or two good quality embryos were transferred *in utero* using a Frydman catheter (CCD Laboratories, Paris, France). Luteal phase was supported by vaginal administration of micronized progesterone 600 mg/day (Utrogestan®, Besins International, Montrouge, France) from the day of oocyte pick-up to the day of pregnancy test. If a pregnancy occurred, progesterone administration was extended up to the evidence of fetal heart activity at ultrasound.

Statistical analysis

Data are presented as mean ± standard deviation (SD) or standard number representing the total. Thus, these data are analyzed by the Student's *t*-test for comparison of mean values or chi square test for comparison of percentages using the Statistical Package, Statistical (version 6.0) to compare a significantly different populations: $p < .05$ shows the significant difference.

Results

Extreme low AMH group including 390 patients presenting AMH ≤0.4 ng/ml and control including 352 patients with normal AMH limited between 1.3 and 2.6 ng/m, were clinically comparable with non-significant difference between female age (38.05 ± 4.83 vs 37.59 ± 5.69; $p = .79$ (ns); respectively for extreme low AMH compared to control) (Table 1). Embryological outcomes including maturation, fertilization and cleavage rate were significantly lower in extreme low AMH compared to control group. However, top embryo quality rate did not show significant difference between both groups with 75% for extreme low AMH and 78% for control. Patients with extreme low AMH have higher canceled cycle transfer rate achieving 25% and lower clinical pregnancy rate of 17%. Nevertheless, miscarriage rate was comparable between both groups (9% for extreme low AMH and 7% for control) (Table 1).

The subgroup among the whole lot including just young patients under 35 years old is presented in Table 2 comparing extreme low AMH group ($n = 90$) with control ($n = 149$). The same tendencies of results were observed with non-significant difference in top embryo quality rate (78% vs 79%) and miscarriage rate (9% vs 8%) comparing extreme low AMH group with control (Table 2). Furthermore, for young patients with extreme low AMH could achieve higher clinical pregnancy 27% compared to 17% of the whole lot that includes 77% of patients with advanced maternal age under 43 years old.

Discussion

This study investigated the IVF outcomes in women with extremely low AMH concentrations, firstly compared with control including patients with normal AMH (1.3–2.6 ng/ml), and secondly selecting just young patients under 35 years old. In the past, many studies have concluded that AMH concentrations could predict pregnancy success. Nevertheless, just few large studies have shown the relationship between AMH concentrations and IVF outcomes [1,2,4,16]. A current issue for clinicians

Table 2. Comparison of IVF outcomes between young patients (under 35 years) with extreme low AMH and control.

	Extreme low AMH ($n = 90$)	Control-normal AMH ($n = 149$)	p-Value
Age of patient (years)	30.44 ± 3.28	30.59 ± 2.69	.79 (ns)
AMH (ng/ml)	0.26 ± 0.13	1.73 ± 0.34	.03 (s)
AFC	5.67 ± 3.54	8.25 ± 3.39	.04 (s)
Number of retrieved oocytes per patient	3.11 ± 2.98	9.75 ± 2.97	.02 (s)
Maturation rate (%)	54%	77%	.03 (s)
Fertilization rate (%)	86%	90%	.04 (s)
Cleavage rate (%)	88%	93%	.04 (s)
Top embryo quality rate (%)	78%	79%	.47 (ns)
Total transferred embryo number	149	278	–
Number of transferred embryo per patient	1.8 ± 0.1	1.9 ± 0.1	.75 (ns)
Canceled cycle transfer rate (%)	12/90 (13%)	8/149 (5%)	.01 (s)
Clinical pregnancy rate (%) (per cycle started)	21/90 (23%)	61/149 (41%)	.01 (s)
Clinical pregnancy rate (%) (per transfer)	21/78 (27%)	61/141 (43%)	.01 (s)
Miscarriage rate (%)	2/21 (9%)	5/61 (8%)	.83 (ns)

Results are expressed as n, n(%) or mean ± standard deviation (SD). A statistic significant difference is considered when $p < .05$ (s). $p \geq .05$ is not significant (ns). Extreme low AMH was defined when its value is ≤0.4 ng/ml while normal AMH value was limited between 1.3 and 2.6 ng/ml for control group. AFC: Antral Follicle Count, AMH was measured on day 2 of the cycle and the endometrial thickness was evaluated in day of oocyte retrieval. Cleavage rate was calculated relatively to embryos at day 3 by 2 pronucleus. The miscarriage rate is expressed relative to the number of clinical pregnancies.

is the treatment of women with extremely low AMH concentrations. In that group of patients, it can be expected poor ovarian response, which can lead to canceled cycle, consequently decreasing the probability to achieve pregnancy [2]. Instead reaching 38% of clinical pregnancy per cycle started for normal AMH, in our study, 13% of patients with extreme low AMH could become pregnant with 25% of canceled cycle transfer (Table 1). It seems clear that clinicians should communicate the probability of IVF outcomes when the woman has extremely low AMH concentrations under 0.5 ng/ml to allow both the couples and clinicians to begin either treatment or prescribe other alternatives including aromatase inhibitors treatments or estrogenic pretreatment.

Probability of success with IVF cycle largely depends on a woman's ovarian reserve and her ability to produce a large number of high-quality mature oocytes in a cycle after COH. Average serum AMH is ∼4 ng/ml in healthy young women with normal ovarian reserve [17]. However, a recent consensus reported in La Marca et al. [10] considered poor response at AMH under 1 ng/ml and high response when AMH is over 3 ng/ml. Nikmard et al. [14] considered normal AMH range at 1.3–2.6 ng/ml obtaining good ovarian response and clinical outcomes after ART.

Both La Marca et al. [2] and Nelson et al. [1] independently showed that AMH cutoff between 0.7 and 0.75 ng/ml predict poor ovarian response. Indeed, Muttukrishna et al. [17] found that women with very low AMH concentrations (0.1–0.35 ng/ml) are at very high risk for cycle cancelation calling to exclude this category from IVF. However, our study showed 25% of canceled cycle rate (Table 1), which decreased with age to 13% (Table 2) for women with extreme low AMH values tending to Revelli et al. [18] findings. The clinical pregnancy rate per transfer was favorable (low AMH group vs. normal AMH group [47% and 48%]) for women <35 years of age, including women with a low serum AMH [12] confirming our results in extreme low AMH group to pass from 17% to 27% for patients under 35 years old. Recently published, clinical outcomes for AMH under 1.3 ng/ml could obtain satisfying clinical pregnancy rate (15%) undergoing antagonist protocol compared to normal AMH (1.3–2.6 ng/ml) with 43% [14]. Compared to our findings, there is some consistence with reports from aforementioned studies [13,14,19,20]. Indeed, patients with extremely low levels of AMH can achieve reasonable treatment outcomes and should not be precluded from attempting IVF solely based on the serum AMH level. Moreover, Tocci [21] reported a case of a 34-year-old woman who had a successful delivery with AMH concentrations <0.5 ng/ml. Thus, live birth rate could be estimated around 15% [1] remaining our results with 14% for AMH under 0.5 ng/ml. Weghofer et al. [13] reported that, to manage women with AMH levels under 0.4 ng/ml reaching 6% of delivery rates per cycle with 2% deliveries per cycle for patients over 42 years of age. Moreover, this encourages clinicians to offer patients even with AMH at 0.1 ng/ml (presenting 25% in our studied population of extreme low AMH with 17% (17/98) of clinical pregnancy) their chance to undergo IVF program especially younger ones. Indeed, these results prove that endometrial receptivity in patients with extreme low AMH is not affected as it thought, but the only difference between them and those with normal AMH is the number of obtained embryos with good quality to select the best ones for embryo transfer. Nevertheless, the total quality embryo rate was not significantly affected with 75%. In the other hand, the transferred embryo number per patient is relatively same for both groups (low AMH group and control; Table 1) while almost underwent double embryo transfer. Knowing that women with extreme low AMH have just 51% of maturation rate significantly lower than control group (Table 1), it is probable to try some pretreatments as dehydroepiandrosterone (DHEA) supplementation to improve ovarian reserve [4,22].

The prognostic power of AMH to predict IVF outcomes is already approved [23,24]. However, there is presence of relativity in predictive value of AMH concentrations with risk of false-positives as previously indicated by La Marca et al. [2]. This issue calls in need to be attentive in prohibition of patients with extreme low AMH. Moreover, women with extreme low AMH must not anymore be excluded. As recently published, this category of patients could to undergo new pretreatment approach based on AMH as molecule to administrate prior to COH with starting dose of 4–8 ng/ml daily for 90 days [25]. Indeed, this innovative approach could lead to improve their chances to achieve pregnancy [25]. We have to believe that low AMH levels by themselves should not exclude a woman as a good candidate for IVF. In some cases, women with low AMH levels may have reduced oocytes quantity but still have good oocytes quality and chance to obtain clinical pregnancy.

Conclusion

Although this work presents pilot information in this field with an important population size that will help clinicians for further

investigations and therapy approaches. It could also state that women with extreme low AMH values must not anymore to be excluded while they can achieve pregnancy especially for young patients needing more time and hopeful communication.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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