

# Anti-Müllerian hormone (AMH): a reliable biomarker of oocyte quality in IVF

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## Abstract

**Purpose** To evaluate the impact of serum AMH levels on stimulated IVF implantation and clinical pregnancy rates.

## Methods

- Design: Retrospective study with multivariate analysis.
- Setting: Clinique ovo (Montreal University affiliated Center).
- Patient(s): Six hundred and thirty seven patients undergoing a stimulated IVF protocol were included. Only non-polycystic ovary patients at their first IVF attempt were considered for the analysis.
- Intervention(s): None.
- Main outcome measures(s): Implantation and ongoing pregnancy rates.

**Result(s)** Cycle outcomes were analysed according to AMH percentiles based on the AMH normogram per patient's age of our infertile population. Multivariate analyses were done to adjust for potential confounding factors such as age, total exogenous FSH dosage and number of eggs retrieved. Compared to the reference population, a significant lower mean implantation rate (0.26 vs 0.45) was observed in patients under 35 years of age with AMH < 1 ng/ml. Women with

AMH < 25th percentile had less chances of having an embryo transferred, lower chances of having an ongoing pregnancy per started IVF cycle and a lower embryo freezing rate compared to the reference population.

**Conclusion(s)** Patients with AMH < 0.47 ng/ml should be advised before starting a stimulated IVF cycle of the poorer prognosis compared to our reference population independently of their age, total exogenous FSH dosage and number of eggs retrieved. Therefore, AMH could enable a more individualized number of embryo transfer policy based on oocyte quality.

**Keywords** AMH · Ovarian reserve · Oocyte quality · IVF

## Introduction

To obtain higher success rates in Assisted Reproductive Techniques (ART), in vitro fertilization (IVF) programs must invest into improvement of various limiting factors including oocyte quality and endometrial receptivity. Indeed, only a small percentage of oocytes collected lead to the birth of a child. While techniques have evolved to diagnose low ovarian reserve [1, 2], there have been few markers for the individual evaluation of oocyte quality. The polar body biopsy [3] or the analysis of cumulus oophorus [4] are both time consuming and cumbersome techniques rendering them difficult to be used routinely.

The AMH, discovered in 1947 by Alfred Jost, is a homodimeric glycoprotein whose gene is located on the chromosome 19p13.3. and belongs to a TGF beta family growth factor [5, 6]. Its function was initially noted as being exclusively responsible for female Mullerian duct regression [7].

Ovarian aging is characterized by a gradual decrease in both quantity and quality of the oocytes residing within the follicles. The availability of a test able to provide reliable information with respect to a woman's ovarian reserve within a given age category is of clinical importance.

**Capsule** Our results suggest that AMH is a reliable biomarker of oocyte quality. It could enable a more individualized number of embryo transfer policy based on oocyte quality.

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**Table 1** Population characteristics

AMH percentile (ng/ml)	<25th ( $\leq 0.46$ )	25–75th (0.47–1.76)	>75th ( $\geq 1.77$ )	<i>P</i> value
Number of patients, <i>n</i> (%)	136 (21.4)	334 (52.4)	167 (26.2)	
Average age, mean, (SD)	38.04 (3.4)	36.6 (3.9)	34.3 (4.4)	<0.001 <sup>a</sup>
AFC (SD)	7.0 (3.1)	12.2 (4.7)	16.5 (4.4)	<0.001 <sup>a</sup>
Baseline FSH (mIU/ml)	9.7 (4.3)	7.5 (2.0)	6.5 (1.5)	<0.001 <sup>a</sup>
Total gonadotropin used (UI)	5 190 (2 100)	4 364 (1 541)	3 003 (1 322)	<0.001 <sup>a</sup>
Infertility causes, <i>n</i> (%)				<0.001 <sup>b</sup>
Low ovarian reserve	53 (39.0)	34 (10.2)	4 (2.4)	
Tubal factor	5 (3.7)	19 (5.7)	10 (6.0)	
Male factor	21 (15.4)	116 (34.7)	74 (44.3)	
Unexplained	9 (6.6)	85 (25.5)	34 (20.4)	
Mixed	40 (29.4)	55 (16.5)	21 (12.6)	
Others	8 (5.9)	25 (7.5)	24 (14.4)	

<sup>a</sup> Kruskal Wallis<sup>b</sup> Fisher exact test

AMH is a known quantitative biomarker of the ovarian reserve [8–12]. Nevertheless, its ability to determine oocyte competence is a matter of debate [13–16].

This retrospective study was undertaken to evaluate the impact of serum AMH levels (ng/ml) on implantation and pregnancy rates of stimulated in vitro fertilization (sIVF) cycles.

## Materials and methods

### Study design

AMH levels are known to differ between races and ethnicities [17]. Hence, fertility centers could benefit from the development of age-specific AMH levels from their own population. To this end, we developed an AMH-age nomogram from 948 infertility patients investigated at OVO clinic (tertiary infertility center affiliated with the University of Montreal) between the ages of 18 to 43 years. Only the first AMH test performed in the patient was included in the nomogram. For each age

group, the AMH levels were stratified into their respective percentiles.

The present study included data from 637 patients undergoing an IVF protocol with ovarian stimulation at OVO clinic between January 2009 and December 2011. Only non-polycystic ovary patients at their first IVF attempt were considered for the analysis.

Cycle outcomes were analysed according to AMH percentiles (<25th percentile, 25–75th percentile and >75th) based on the AMH nomogram per patients' age of our infertile population.

The study was undertaken as a clinical quality control evaluation and was properly reviewed and approved by the scientific review committee (granted December 16th, 2011).

### Ovarian stimulation protocols

Different ovarian stimulation protocols were used including long GnRH agonist, GnRH antagonist and short GnRH agonist protocols. Stimulation protocol was decided according to individual patient characteristics. Gonadotropins were

**Table 2** IVF outcomes, univariate analysis

AMH percentile (ng/ml)	<25th ( $\leq 0.46$ )	25–75th 222(0.47–1.76)	>75th ( $\geq 1.77$ )	<i>P</i> value
Number of patients, <i>n</i> (%)	136 (21.4)	334 (52.4)	167 (26.2)	
Cancelled cycle, <i>n</i> (%)	18 (13.2)	9 (2.7)	1 (0.6)	<0.001 <sup>a</sup>
Mature oocytes per patient, mean (SD)	4.3 (2.7)	7.2 (4.2)	7.2 (4.2)	<0.001 <sup>a</sup>
Embryo transfers performed, <i>n</i> (%)	88 (64.7)	265 (79.3)	135 (80.8)	0.001 <sup>b</sup>
Ongoing pregnancy per started cycle (%)	12.5	23.4	30.5	0.001 <sup>b</sup>
Ongoing pregnancy per transfer (%)	19.3	29.4	37.8	0.01 <sup>b</sup>
Miscarriage (%)	26.1	19.6	20.6	0.8 <sup>b</sup>
Embryo freezing rate (%)	19.1	40.4	56.9	<0.001 <sup>b</sup>

<sup>a</sup> Fisher exact test<sup>b</sup> Chi-square

**Table 3** IVF outcomes all age combined, multivariate analysis

AMH percentile (ng/ml)	<25th (≤0.46) OR (95 % CI)	25–75th (0.47–1.76) Reference	>75th (≥1.77) OR (95 % CI)
Cancelled cycle	6.54 (2.71–15.76)	1	0.15 (0.02–1.24)
Embryo transfers performed	0.48 (0.31–0.74)	1	1.10 (0.69–1.75)
Ongoing pregnancy per started cycle	0.56 (0.31–0.99)	1	1.09 (0.70–1.69)
Miscarriage	1.25 (0.43–3.67)	1	1.30 (0.57–2.97)
Embryo freezing rate (%)	0.40 (0.24–0.65)	1	1.54 (1.04–2.28)

prescribed at the discretion of the physicians according to the ovarian reserve tests (AMH, antral follicular count AFC) and age. The dosage was then adjusted according to follicular growth until the day of hCG administration.

For the long protocol, acetate buserelin (Suprefact 1 ml/day; Sanofi-Aventis, Laval, Canada) was given after 14 to 21 days of contraceptive pills (Marvelon, Merck, Kirkland, Canada). Ovarian stimulation was started and the dose of acetate buserelin was lowered once the serum oestradiol level reached below 150 pmol/l.

In the antagonist protocol, 17 Beta-oestradiol (Estrace 4 mg/day P.O., Shire Canada, Saint Laurent, Canada) pre-treatment was given in the luteal phase of the preceding cycle of ovarian stimulation cycle. Daily subcutaneous injections of Cetorelix (Cetrotide; Serono, Mississauga, Canada) or Ganirelix (Orgalutran, Merck Canada, Kirkland, Canada) 0.25 mg were administrated once the dominant follicle reached 14 mm or the oestradiol level was above 2,000 pmol/l.

For the short protocol, similar 17 Beta-oestradiol (Estrace) pre-treatment was conducted during the luteal phase of the preceding cycle. Then, both Buserelin Acetate (0.05 ml, bid) and gonadotropins stimulation were started at menses.

When at least two follicles reached 18 mm in diameter, 5,000 IU subcutaneous injection of hCG (Ferring Canada, North York, Canada) was administrated to achieve final follicular maturation and oocyte retrieval was performed transvaginally under ultrasound guidance 36 h later.

Before June 2011, the embryos were scored according to the cumulative embryo score formulated by Steer et al. (1992)

[18]. Thereafter, the Istanbul consensus of the Alpha ESHRE meeting was implemented to evaluate embryos (2011) [19].

Luteal phase was supported with intramuscular injection of 50 mg of progesterone once daily or vaginal progesterone (Endometrin 200 mg/day, Ferring Canada, North York, Canada) until 10 weeks of gestation. Serum beta hCG was measured 14 days after oocyte retrieval.

Primary outcome included ongoing pregnancy and implantation rates. Ongoing pregnancy rate was defined by the detection of fetal heart beat through transvaginal ultrasound at 5 weeks gestation age. Implantation rate was defined by the mean of the number of intrauterine gestational sacs divided by the number of transferred embryos for each patient.

Hormone assays and antral follicle count (AFC) measurement

AMH was measured in duplicate using the enzyme amplified two-site immunoassay (ELISA) provided by Beckman Coulter (AMH Gen II ELISA, Beckman Coulter inc., Brea, CA, USA) [20]. AMH was checked between day 2 and 5 of the menstrual cycle along with other predictors of ovarian reserve such as FSH, E2 and AFC measurements, within 3 at 6 months before starting ovarian stimulation.

Serum for AMH assay was separated within 2 h from blood collection and frozen in aliquots at –20 °C. The lowest amount of AMH in a sample that can be detected with a 95 % probability is 0.08 ng/ml. The estimated minimum level that could be achieved at 20 % total imprecision is 0.16 ng/ml.

Meanwhile, a transvaginal ultrasound scan was performed by an experienced ultrasonographer to assess the AFC where

**Table 4** IVF outcomes for patients <35 years of age, multivariate analysis

AMH percentile (ng/ml)	<25th (≤0.99) OR (95 % CI)	25–75th (1.0–2.33) Reference	>75th (≥2.34) OR (95 % CI)
Cancelled cycle	–	1	–
Ongoing pregnancy per started cycle	0.46 (0.22–0.96)	1	1.31 (0.67–2.56)
Embryo freezing rate	0.41 (0.21–0.80)	1	1.37 (0.68–2.73)
Miscarriage (%)	1.5 (0.33–6.87)	1	1.56 (0.45–5.38)
Embryo transfer performed	0.92 (0.38–2.28)	1	0.70 (0.29–1.65)

**Table 5** IVF outcomes for patients between 35 and 39 years of age, multivariate analysis

Age group	35–39 years N=264		
AMH percentile (ng/dl)	<25th ( $\leq 0.50$ )	25–75th (0.51–1.59)	>75th ( $\geq 1.6$ )
Multivariate analysis	OR (IC95%)	Reference	OR (IC95%)
Cancelled cycle	3.9 (1.20–12.8)	1	–
Ongoing pregnancy per started cycle	0.51 (0.22–1.19)	1	1.46 (0.74–2.88)
Frozen embryos	0.45 (0.23–0.86)	1	1.30 (0.72–2.36)
Miscarriages (%)	7.88 (1.65–37.7)	1	1.35 (0.25–7.40)
Embryo transfer performed	0.72 (0.37–1.42)	1	2.0 (0.91–4.42)

the overall number of antral follicles sized between 2 and 9 mm were counted in both ovaries.

### Statistical analysis

Continuous variables are presented as mean and standard deviation (SD). For categorical variables, the values are presented as raw frequencies with corresponding percentages. The inter-group differences were assessed using Chi square, Fisher exact, ANOVA, and Kruskal Wallis tests where indicated. Logistic regression was used to adjust for potential confounding factors (age, total exogenous FSH dosage and number of eggs retrieved) in the multivariate analysis. Statistical analysis was performed using the STATA 10.0 software (TX: StataCorp).

### Results

The AMH normogram per patient's age of our infertility patients showed decreasing levels of both means and medians with advancing age. Wide range of AMH was shown for each age group and reference values for low (<25th percentile, <0.47 ng/ml), average (25–75th percentiles, 0.47–1.76 ng/ml) and high AMH (>75th percentiles, >1.76 ng/ml) were determined accordingly. The main characteristics of our population are shown in Table 1. Our reference population was defined

by the AMH group between 25th and 75th percentile (0.47 to 1.76 ng/ml).

The univariate analysis showed that AMH was positively correlated to AFC, number of mature oocytes, implantation rate ( $P=0.04$ ) and frozen embryos rate ( $p=0.001$ ). However, AMH was negatively correlated to baseline FSH levels, age and total dose of exogenous gonadotropins used ( $P<0.001$ ) (Table 2). The miscarriage rate didn't differ regardless of the AMH group ( $P=0.8$ ). The cancellation rate was higher in group AMH<25th percentile compared to our reference population (13.2 % vs. 2.7 %,  $P<0.001$ ) along with significantly lower embryo freezing rate (19.1 % vs. 40.4 %,  $P<0.001$ ).

Multivariate analysis (Table 3) demonstrated after adjustment for potential confounding factors that women with AMH levels <25th percentile (<0.47 ng/ml) were twice less likely to obtain an ongoing pregnancy per sIVF started cycle (OR 0.56, 95 % CI, 0.31–0.99), had a decreased embryo transfer (OR=0.48 95 % CI, 0.31–0.74) and embryo freezing rate (OR 0.40 95 % CI, 0.24–0.65) compared to the reference population ( $\geq 25$ th percentile–AMH $\leq 75$ th percentile).

Moreover, the multivariate analysis showed that women with AMH levels <25th percentile (<0.47 ng/ml) had a significant lower number of retrieved mature and immature oocytes ( $P<0.001$ ). Regarding implantation rate, the results didn't show an overall significant difference ( $P=0.38$ ) after adjustment for confounding factors.

**Table 6** IVF outcomes for patients between 40 and 43 years of age, multivariate analysis

Age group	40–43 years N=171		
AMH percentile (ng/dl)	<25th ( $\leq 0.30$ )	25–75th (0.31–1.29)	>75th ( $\geq 1.3$ )
Multivariate analysis	OR (IC95%)	Reference	OR (IC95%)
Cancelled cycle	4.5 (1.20–17.1)	1	–
Ongoing pregnancy per started cycle	0.92 (0.22–3.76)	1	0.77 (0.19–3.12)
Frozen embryos	0.18 (0.04–0.82)	1	1.18 (0.49–2.83)
Miscarriages (%)	0.32 (0.02–6.08)	1	3.04 (0.28–33.06)
Embryo transfer performed	0.30 (0.13–0.69)	1	1.12 (0.44–2.87)

However, subgroup analyses revealed that the population of women younger than 35 years with AMH levels <25th percentile (<1 ng/ml) had a significant lower mean implantation (0.26 Vs 0.45,  $P$  0.04) and ongoing pregnancy rates (23.2 % Vs 39.6 %  $P$  0.03) compared to the reference population. The multivariate analyses confirm that this young cohort patients are twice less likely to obtain an ongoing pregnancy compared to our reference population (OR 0.46 CI 0.22–0.96) after adjustment for confounding factors (Table 4). Such results weren't found in the population over 39 of age. Also, age factor became more important than amh for those patients (Tables 5 and 6).

## Discussion

Our study suggests that AMH could be a reliable biomarker of oocyte quality. Interestingly, we found that the mean implantation rate was lower for patients younger than 35 years with AMH <1 ng/ml. In addition, for patients with serum AMH <0.46 ng/ml (<25th percentile), the study showed that they sustain six times more chances of having a cycle cancellation, twice less likely to perform an embryo transfer, to obtain frozen embryos and to obtain an ongoing pregnancy independent of their age, total exogenous gonadotropins dosage and the number of eggs retrieved after a first sIVF, compared to our reference population (25–75th percentile).

AMH has demonstrated its effectiveness in many areas. It is the best hormonal marker of ovarian reserve [8–11, 16, 21]. Moreover, its stable value in the menstrual cycle allows a more objective evaluation independent of cycle day [11–13, 15, 22]. AMH is a useful tool to predict low response to controlled ovarian stimulation and conversely the risk of excessive response [21, 23]. A prior measurement of AMH could enable a more appropriate formulation of gonadotropins doses [13–15].

Other applications included diagnosing patients with polycystic ovaries syndrome with AMH higher than 4–5 ng/ml [24] and conversely low or normal AMH could be found in specific causes of primary ovarian insufficiency patients [25, 26]. Nevertheless, its ability to determine the oocyte competence is a matter of debate (2). The dogma that AMH doesn't predict pregnancy rates has often been adopted. Smeenk et al. (2007) [27] showed that basal AMH is not related to embryo quality nor to the probability of achieving a pregnancy. Nelson et al. (2007) [28] explained the close relationship between AMH and the pregnancy rate in IVF through the oocyte yield.

Recent studies concluded that AMH could be a reliable biomarker of oocyte quality [29, 30]. Hazout et al. (2004) [31] demonstrated an association between AMH level on day 3 and the number of mature oocytes, the number of embryos and clinical pregnancy rates in 109 IVF patients. Blazar et al. (2011) [32], showed in a prospective study including 190

IVF cycles that AMH is a useful predictor of cycle outcome and strongly predicts an increased number of oocytes and ongoing pregnancy ( $P$ <0.0001). In 2011, Irez et al. [33], demonstrated that AMH levels may predict the oocyte quality. Wang et al. (2010) [34] found that for women between 34 and 41 years of age, AMH concentrations was associated with greater chances of pregnancy ( $P$ <0.01).

To the best of our knowledge, this is the largest retrospective analysis investigating the relationship between serum AMH and the rate of ongoing pregnancy after first sIVF cycles. Our findings imposes a greater duty to cautiously counsel our infertility patients prior to initiating sIVF cycle and more specifically in patients with AMH <0.47 ng/ml of the poorer prognosis compared to our reference population. Accordingly, physicians would be able to provide a better counseling for their patients. AMH level could be a useful tool to adjust the number of embryo transferred for patients younger than 35 years. Therefore, elective double embryo transfer (eDET) should be evaluated for patients in this category of age with anticipated poor prognosis in a future randomized control trial.

AMH plays a major role in assisted reproductive technology. It allows not only the quantification of the ovarian reserve, but also the prediction of an eventual ovarian response to the IVF stimulation. Our results suggest that AMH is a reliable biomarker of oocyte quality. We emphasize the fact that each fertility center should develop his own normogram of AMH stratified by age in order to be able to deliver a better patient counselling. Further, we believe in a score based on clinical (patient age) biological (AMH) and sonographic (automated 3D AFC) features. These three elements are the cornerstone that could enable a more individualised patient's management based on oocyte quality.

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