The Value of Measurement of the Antimullerian Hormone in Prediction of the Success of Intracytoplasmic Sperm Injection

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Abstract: AMH has been a promising marker in various clinical setting of ART. Initially viewed as an accurate marker of ovarian reserve, AMH was subsequently found to be a reliable predictor of controlled ovarian hyperstimulation for both poor and hyper responses. The value of the AMH level in the prediction of pregnancy has been investigated in various studies, but the results have been inconsistent. A number of studies have demonstrated associations between the AMH level and oocyte quality, fertilization rate, blastocyst development, embryo quality, pregnancy outcome, and live birth rate but were not confirmed in other studies. This study was a Prospective study of 90 infertile women that assess serum Anti-Mullerian hormone as an ovarian reserve marker in prediction of success of intracytoplasmic sperm injection (ICSI) as regard clinical pregnancy the study population was consisted of three groups of participants according to age Group I with 30 cases below 30 years Group II with 30 cases between 30-40 years Group III with 30 cases above 40 years. **Results:** There is a statistically significant relation between serum AMH level and pregnancy in the age group of 30 yrs to 40 yrs. (group II). (1) The mean of AMH in the age group between 30yrs and 40 yrs. (group II|) is 2.52 ± 0.9 in patients with positive clinical pregnancy while those with negative clinical pregnancy is 1.66 ± 0.48 so it is highly significant in this age group. (2) In group 2 the best cut off point according to ROC curve to detect patients with positive clinical pregnancy regarding AMH level was found > 2.1 with sensitivity of 71.4%, specificity of 82.6% and AUC of 82.9%.

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1. Introduction

Various methods have been propsed and even currently used in the assessment of ovarian reserve in order to predict the outcome in assisted reproduction. The so called ovarian reserve markers are increasingly used to aid management and counseling of these patients complaining of infertility **(Buklmeza et al., 2004).**

These markers are hormonal agents and ultrasonographic assessment that include: antral follicle count (AFC), serum basal follicle stimulating hormone (FSH) and serum Estradiol (E2) **(Van Rooij et al., 2005).**

At the same time, effective strategies were developed to overcome the impact of ovarian aging and diminished ovarian reserve on pregnancy changes including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI).

The regimens for pituitary down-regulation are multiple and the individualization is essential and depend on assessment of ovarian reserve **(Arslan et al., 2005).**

The serum tests (FSH & E2) show many disadvantages, which include:

a) Cycle dependent serum level (fluctuations through the same cycle) **(Masheshwari et al., 2006).**

b) They are age related although age is arough estimating agent **(Masheshwari et al., 2006).**

c) Emerging of contradicting studies which claim that the present routine ovarian reserve markers (especially FSH) are unhelpful especially in absence of international fixed definition of a poor ovarian reserve, and definite strategies to face this problem **(Masheshwari et al., 2006).**

d) These serum levels are included in the loop of feedback system and so they are dependent on each other and on the influence of gonadotrophines not only the ovarian reserve **(Visser et al., 2006).**

All these disadvantages push the research work to identify a new marker which can assess ovarian reserve accurately and in the same time free of the former detailed disadvantages.

In these attempts, Anti-Mullerian hormone (AMH) appears to be the goal standard marker. AMH and also called Mullerian Inhibiting Substance (MIS) is a glycoprotein dimmer composed of two 72 KDa monomers. It belongs to the transforming growth factor –B family (TGF-B) which is involved in the regulation of tissue differentiation **(Teixeria et al., 2001).**

In males, it is secreted by sertoli cells and its role is regression of the mullerian ducts and thus the

normal development of the male reproductive system takes place **(Durlinger et al., 1999).**

In females, AMH is secreted by granulose cells, after puberty when menstrual cyclying begins. circulating AMH level decreases throughout life and becomes undetectable at menopause **(Teixeria et al., 2001).**

AMH has many potential clinical applications as it may be used in assessment of 1) ovarian reserve 2) perimenopausal transition 3) granulose cell tumors 4) precocious puberty and delayed puberty 5) intersex disorders **(Gruijters et al., 2003).**

AMH effect on the folliculogenesis is summarized by its inhibitory effect on the primordial follicle recruitment and inhibitory effect FSH-dependent follicle growth **(Wennen et al., 2004).**

The specific expression pattern of AMH on growing non selected follicles is indication for the size of the growing follicle pool while the direct measurement of the primordial follicle pool is impossible, however the numbers of primordial follicles is indirectly reflected by the number of growing follicles **(Scheffer et al., 1999).**

Hence AMH as a factor secreted by growing follicles will reflect the size of the primordial follicle pool and so the ovarian reserve **(Durlinger et al., 2002).**

Also the results of investigating AMH showed early decline in its serum level in the sequence of events associated with ovarian aging **(Van Rooij et al., 2004; Van Rooij et al., 2005).**

Aim of the Work

To evaluate serum Anti-Mullerian hormone as an ovarian reserve marker in prediction of the success of intracytoplasmic sperm injection (ICSI) as regard clinical pregnancy.

2. Patients and Methods

Study design:

- **Type of the study:** Prospective study of 90 infertile women all patients enrolled in the study after obtaining written consent.
- **Setting:** This study was carried out in Sayed Galal Hospital Infertility Clinic and Assisted Reproduction Unit at El Galaa Maternity Teaching Hospital during the period between December 2016 and October 2018.
- The study population consisted of three groups of participants according to age.

The three groups are:

Group I: 30 cases below 30 years.

Group II: 30 cases between 30-40 years.

Group III: 30 cases above 40 years.

Inclusion criteria:

The aim of Inclusion criteria is to eliminate any variables that could affect the ovarian functions.

A) Both ovaries are present

B) No previous cauterization or surgical intervention to the ovaries.

C) First cycle for assisted reproduction induction.

Exclusion criteria:

a) Patients with pelvic pathology that may alter AMH level e.g endometriosis.

b) Patients with morphologically abnormal ovaries e.g ovarian cysts.

c) Patients with major endocrinopathies e.g hyper or hypothyroidism, hyperprolactinemia, hyperandrogenism.etc.

d) Irregular menstrual cycles.

Methods:

All patients enrolled in this study subjected to:

- Full history taking including past medical, surgical history and past history of induction of ovulation e. g.: oral e. g. clomide or injection e. g (HMG) or controlled ovarian hyperstimulation and any other protocols of induction of ovulation.
- General and abdominal examination for signs of disturbed endocrinological function (e. g.: hyperandrogenism etc).
- On day 3 of spontaneous cycles all patients had basal hormonal profile for screening of ovarian reserve FSH, LH, E2, TSH, AMH and prolactin.
- Transvaginal ultrasound on day 3 of non-stimulated cycles done by transvaginal probe to measure and detect morphological changes in ovary and uterus to evaluate the number and size of early antral follicles and to calculate the mean ovarian volume.

Follicles from 2mm to 10mm in mean diameter in both ovaries will be counted.

- Ovarian hyperstimulation protocol performed according to a long GnRh agonist protocol starting from midlueteal phase by daily subcutaneous injection of triptoreline acetate (Decapeptyl 0. 01 mg daily, Ferring Pharmaceuticals, Kid, Germany), then on day 3 of the next cycle ovarian hyperstimulation was started by daily injection of HMG (Menogon 75 IU/ampule (Ferring Pharmaceutical, Kid, Germany) the starting dose of gonadotropins prescribed according to age and body built of the subjects, then the dose adjusted according to ovarian response that was assessed by TV folliculometry which was done on cycle day 7 or day 9. According to the ovarian response, day after day TV U/S was performed and at the moment where the leading follicle reach 16 mm daily TV U/S was performed till the largest follicle reach a diameter > 18 mm. HCG was administrated. On day of administration of HCG, TVU/S was performed to count all follicular > 10 mm. This protocol was approved by ART unit in El Galaa Maternity Teaching Hospital.

- 36 hours after HCG injection on the day of ovum pick up:

Laboratory Assessment of Antimullerian Hormone (AMH)

The assay was performed by the non-competitive enzyme-linked immunosorbent assay (ELISA) technique using a commercially available kit supplied by Immunotech (Marseilles, France). This assay is a sandwich type assay with two immunological steps. The first step leads to the capture of AMH by monoclonal anti-AMH antibody bound to the wells the wells of the microtitre plate. In the second step, a second monoclonal anti-AMH antibody, which is biotinylated, is added together with streptavidin-peroxidase conjugate. The biotinylated antibody binds to the solid phase antibody-antigen complex and in turn binds the conjugate. After incubation, the wells are washed and the binding of the streptavidin-peroxidase via biotin is followed by the addition of a chromogenic substrate of peroxidase. The intensity of the colour produced is measured at 450 nm and is directly proportionate to the AMH in the sample or standard. The standard curve was constructed from which the results were deduced.

Statistical Analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric. Also qualitative variables were presented as number and percentages.

The comparison between groups regarding qualitative data was done by using **Chi-square test.**

The comparison between two independent groups with quantitative data and parametric distribution were done by using **Independent t-test**

The comparison between more than two independent groups with quantitative data and parametric distribution was done by using **One Way ANOVA test**.

Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same groups.

Also **Receiver operating characteristic curve (ROC)** were used to assess the best cut off point with sensitivity, specificity, positive and negative predictive value and area under curve (AUC).

3. Results

After data collection and samples analysis, after excluding the missed patients the remaining patients were only 80 patients.

The missed patients as follow:

Out of group 1: 3 patients had their cycle cancelled due to risk of OHSS.

Out of group 2: 3 patients had their cycle cancelled one of them due to risk of OHSS and the other 2 due to missed unreported data.

Out of group 3: 4 patients had their cycle cancelled 2 of them due to no oocytes collected during VEC and the other 2 due to no fertilization.

Out of the 80 patients who had embryo transfer, 19 patients had a positive pregnancy test, while the other 61 patients had a negative pregnancy test, the pregnancy test was done after embryo transfer by 14 days.

Table (1): Comparison between the three studied groups regarding the personal and medical history

		Group I < 30 yrs	**Group II 30-40 yrs**	**Group III > 40 yrs**	**Test value**	**P-value**	**P1**	**P2**	**P3**
		No.= 30	**No.= 30**	**No.= 30**					
Age (years)	Mean ± SD	25.73 ± 2.59	35.33 ± 2.77	41.57 ± 0.77	382.677•	**0.000**	0.000	0.000	0.000
	Range	21 – 29	30 – 39	40 – 44					
BMI (kg/m^2)	Mean ± SD	34.17 ± 5.70	33.30 ± 4.47	33.70 ± 5.29	0.210•	0.811	0.519	0.727	0.765
	Range	24 – 42	25 – 42	24 – 42					
Type of infertility	1ry	27 (90.0%)	20 (66.7%)	24 (80.0%)	4.937*	0.085	0.028	0.278	0.242
	2ry	3 (10.0%)	10 (33.3%)	6 (20.0%)					
Cause of infertility	Male factor	12 (40.0%)	9 (30.0%)	4 (13.3%)	69.354*	**0.000**	0.004	0.000	0.000
	PCO	4 (13.3%)	1 (3.3%)	0 (0.0%)					
	Poor Ov. Reserve	2 (6.7%)	3 (10.0%)	24 (80.0%)					
	Tubal	4 (13.3%)	16 (53.3%)	2 (6.7%)					
	Unexplained	8 (26.7%)	1 (3.3%)	0 (0.0%)					
Duration of infertility	Mean ± SD	3.25 ± 1.51	5.97 ± 2.24	3.33 ± 1.35	23.597•	**0.000**	0.000	0.853	0.000
	Range	1 – 7	2 – 10	1 – 6					

The previous table shows that there was statistically significant difference found between the three studied groups regarding Age (years), Cause of infertility, Duration of infertility while no statistically significant difference found between the three studied groups regarding the other parameters.

Table (2): Comparison between the three studied groups regarding hormonal profile (FSH, LH, E2, AMH, prolactin, TSH)

		Group I < 30 yrs	**Group II 30-40 yrs**	**Group III > 40 yrs**	**Test value**	**P-value**	**P1**	**P2**	**P3**
		No.= 30	**No.= 30**	**No.= 30**					
FSH	Mean ± SD	6.51 ± 4.42	7.05 ± 1.61	10.23 ± 1.95	14.041•	**0.000**	0.484	0.000	0.000
	Range	4.2 – 29	4.2 – 11	7.9 – 16					
LH	Mean ± SD	5.18 ± 2.05	5.51 ± 1.34	8.03 ± 1.42	27.203•	**0.000**	0.441	0.000	0.000
	Range	3.1 – 14	3.1 – 8.2	5.3 – 11					
E2	Mean ± SD	65.76 ± 15.82	59.90 ± 11.84	48.97 ± 15.69	10.274•	**0.000**	0.123	0.000	0.005
	Range	17.8 – 88	42 – 81	17 – 81					
AMH (ng/dl)	Mean ± SD	2.71 ± 0.99	1.86 ± 0.71	0.83 ± 0.25	52.117•	**0.000**	0.000	0.000	0.000
	Range	0.1 – 5.2	0.9 – 4.5	0.1 – 1.3					
Prolactin	Mean ± SD	14.00 ± 4.75	15.81 ± 5.03	15.40 ± 5.19	1.077•	0.345	0.165	0.281	0.753
	Range	8.2 – 25	9 – 27	6 – 31					
TSH	Mean ± SD	1.22 ± 0.47	1.37 ± 0.56	1.27 ± 0.53	0.659•	0.520	0.260	0.676	0.476
	Range	0.5 – 2.2	0 – 2.2	0.5 – 2.3					

The previous table shows that there was statistically significant difference found between the three studied groups regarding FSH, LH, E2, AMH (ng/dl), while no statistically significant difference found between the three studied groups regarding the other parameters.

Table (3): Comparison between the three studied groups regarding follicle no by u/s, Follicle average size, No of Injecting HMG 75, No of stimulation days, No of picked up follicle, No of fertilized oocytes, No of ET and Clinical pregnancy

		Group I < 30 yrs	**Group II 30-40 yrs**	**Group III > 40 yrs**	**Test value**	**P-value**	**P1**	**P2**	**P3**
		No.= 30	**No.= 30**	**No.= 30**					
Follicle no by u/s	Mean ± SD	11.63 ± 5.57	10.40 ± 4.65	4.70 ± 2.41	21.047•	**0.000**	0.282	0.000	0.000
	Range	0 – 22	0 – 20	1 – 10					
Follicle average size	Mean ± SD	16.73 ± 5.72	16.83 ± 5.78	18.67 ± 0.84	1.597•	0.208	0.935	0.116	0.136
	Range	0 – 20	0 – 20	17 – 20					
No of Injecting HMG 75	Mean ± SD	41.07 ± 17.98	49.27 ± 20.17	73.97 ± 4.87	35.013•	**0.000**	0.048	0.000	0.000
	Range	0 – 78	0 – 78	65 – 84					
No of stimulation days	Mean ± SD	10.03 ± 3.52	10.27 ± 3.62	12.40 ± 0.77	5.873•	**0.004**	0.760	0.003	0.006
	Range	0 – 13	0 – 13	11 – 14					
No of picked up follicle	Mean ± SD	10.03 ± 5.24	8.83 ± 4.07	3.30 ± 2.39	23.324	**0.000**	0.257	0.000	0.000
	Range	0 – 18	0 – 16	0 – 10					
No of fertilized oocytes	Mean ± SD	7.40 ± 3.96	7.20 ± 3.27	2.17 ± 1.93	26.255•	**0.000**	0.808	0.000	0.000
	Range	0 – 13	0 – 14	0 – 8					
No of ET	Mean ± SD	2.97 ± 1.79	3.03 ± 1.40	1.23 ± 0.82	16.056•	**0.000**	0.854	0.000	0.000
	Range	0 – 5	0 – 5	0 – 4					
Clinical pregnancy	Negative	21 (70.0%)	23 (76.7%)	27 (90.0%)	3.736*	0.154	0.559	0.052	0.165
	Positive	9 (30.0%)	7 (23.3%)	3 (10.0%)					

*: Chi-square test; •: Independent t-test P1: Group I < 30 yrs VS Group II 30-40 yrs
P2: Group I < 30 yrs VS Group III > 40 yrs P3: Group II 30-40 yrs VS Group III > 40 yrs
P-value > 0.05 Non significant P-value < 0.05 Significant
P-value < 0.01 Highly significant

The previous table shows that there was statistically significant difference found between the three studied groups regarding follicle no by u/s, No of Injecting HMG 75, No of stimulation days, No of picked up follicle, No of fertilized oocytes and No of ET while no statistically significant difference found between the three studied groups regarding the other parameters.

Table (4): Comparison between negative clinical pregnancy patients and positive clinical pregnancy patients regarding the personal, medical history and hormonal profile in group I

Group I < 30 yrs		**Negative clinical pregnancy**	**Positive clinical pregnancy**	**Test value**	**P-value**	**Sig.**
		No.= 21	**No.= 9**			
Age (years)	Mean ± SD	25.57 ± 2.71	26.11 ± 2.37	-0.517•	0.609	NS
	Range	21 – 29	22 – 29			
BMI (kg/m^2)	Mean ± SD	33.55 ± 6.02	35.56 ± 4.95	-0.873•	0.391	NS
	Range	24 – 42	27 – 40			
Type of infertility	1	18 (85.7%)	9 (100.0%)	1.429*	0.232	NS
	2	3 (14.3%)	0 (0.0%)			
Cause of infertility	Male factor	6 (28.6%)	6 (66.7%)	6.786*	0.148	NS
	PCO	2 (9.5%)	2 (22.2%)			
	Poor Ov. Reserve	2 (9.5%)	0 (0.0%)			
	Tubal	4 (19.0%)	0 (0.0%)			
	Unexplained	7 (33.3%)	1 (11.1%)			
Duration of infertility	Mean ± SD	3.07 ± 1.31	3.67 ± 1.94	-0.987•	0.332	NS
	Range	1 – 6	2 – 7			
FSH	Mean ± SD	6.82 ± 5.24	5.79 ± 1.21	0.581•	0.566	NS
	Range	4.5 – 29	4.2 – 7.6			
LH	Mean ± SD	5.33 ± 2.31	4.83 ± 1.31	0.606•	0.550	NS
	Range	3.2 – 14	3.1 – 7.2			
E2	Mean ± SD	63.51 ± 17.04	71.00 ± 11.70	-1.197•	0.241	NS
	Range	17.8 – 87	58 – 88			
AMH (ng/dl)	Mean ± SD	2.68 ± 1.06	2.80 ± 0.83	-0.310•	0.759	NS
	Range	0.1 – 5.2	1.7 – 4.3			
Prolactin	Mean ± SD	13.69 ± 4.48	14.74 ± 5.53	-0.553	0.584	NS
	Range	8.2 – 25	9 – 25			
TSH	Mean ± SD	1.28 ± 0.40	1.07 ± 0.61	1.140•	0.264	NS
	Range	0.6 – 2.1	0.5 – 2.2			

*: Chi-square test; •: Independent t-test Hs: Highly significant; S: Significant; NS: Non significant; P-value < 0.01 Highly significant; P-value < 0.05 Significant; P-value > 0.05 Non significant

The previous table shows that there was no statistically significant difference regarding the studied parameters in patients with positive clinical pregnancy than those with negative clinical pregnancy.

Table (5): Comparison between negative clinical pregnancy patients and positive clinical pregnancy patients regarding Follicle no by u/s, Follicle average size, No of Injecting HMG 75, No of stimulation days, No of picked up follicle, No of fertilized oocytes, No of ET in group I

Group I < 30 yrs		**Negative clinical pregnancy**	**Positive clinical pregnancy**	**Test value**	**P-value**	**Sig.**
		No.= 21	**No.= 9**			
Follicle no by u/s	Mean ± SD	10.10 ± 5.68	15.22 ± 3.35	-2.511•	0.018	S
	Range	0 – 18	10 – 22			
Follicle average size	Mean ± SD	15.95 ± 6.70	18.56 ± 0.88	-1.149•	0.260	NS
	Range	0 – 20	18 – 20			
No of Injecting HMG 75	Mean ± SD	40.57 ± 19.97	42.22 ± 13.16	-0.227•	0.822	NS
	Range	0 – 78	30 – 72			
No of stimulation days	Mean ± SD	9.67 ± 4.13	10.89 ± 1.05	-0.868•	0.393	NS
	Range	0 – 13	9 – 12			
No of picked up follicle	Mean ± SD	8.67 ± 5.21	13.22 ± 3.93	-2.344•	0.026	S
	Range	0 – 16	5 – 18			
No of fertilized oocytes	Mean ± SD	6.43 ± 4.15	9.67 ± 2.35	-2.180•	0.038	S
	Range	0 – 13	4 – 12			
No of ET	Mean ± SD	2.38 ± 1.75	4.33 ± 1.00	-3.123•	0.004	HS
	Range	0 – 5	2 – 5			

*: Chi-square test; •: Independent t-test Hs: Highly significant; S: Significant; NS: Non significant; P-value < 0.01 Highly significant; P-value < 0.05 Significant; P-value > 0.05 Non significant

The previous table shows that there was statistically significant increase in follicle number by U/S, number of picked up follicle, number of fertilized oocytes and number of ET in patients with positive clinical pregnancy than those with negative clinical pregnancy while no statistically significant difference found between them regarding to the other parameters.

Table (6): Comparison between negative clinical pregnancy patients and positive clinical pregnancy patients regarding the personal, medical history and hormonal profile in group II

Group II 30-40 yrs		**Negative clinical pregnancy**	**Positive clinical pregnancy**	**Test value**	**P-value**	**Sig.**
		No.= 13	**No.= 7**			
Age (years)	Mean ± SD	35.48 ± 2.97	34.86 ± 2.12	0.513•	0.612	NS
	Range	30 – 39	33 – 38			
BMI (kg/m^2)	Mean ± SD	33.70 ± 4.53	32.00 ± 4.32	0.876•	0.388	NS
	Range	26 – 42	25 – 38			
Type of infertility	1	14 (60.9%)	6 (85.7%)	1.491*	0.222	NS
	2	9 (39.1%)	1 (14.3%)			
Cause of infertility	Male factor	7 (30.4%)	2 (28.6%)	4.534*	0.339	NS
	PCO	0 (0.0%)	1 (14.3%)			
	Poor Ov. Reserve	3 (13.0%)	0 (0.0%)			
	Tubal	12 (52.2%)	4 (57.1%)			
	Unexplained	1 (4.3%)	0 (0.0%)			
Duration of infertility	Mean ± SD	5.65 ± 2.01	7.00 ± 2.77	-1.421•	0.166	NS
	Range	2 – 10	3 – 10			
FSH	Mean ± SD	7.24 ± 1.74	6.40 ± 0.95	1.221•	0.232	NS
	Range	4.2 – 11	5.3 – 8.1			
LH	Mean ± SD	5.56 ± 1.42	5.36 ± 1.12	0.338•	0.738	NS
	Range	3.1 – 8.2	4.1 – 7.2			
E2	Mean ± SD	58.61 ± 10.42	64.14 ± 15.86	-1.087•	0.287	NS
	Range	42 – 73	44 – 81			
AMH (ng/dl)	Mean ± SD	1.66 ± 0.48	2.52 ± 0.94	-3.287	0.003	HS
	Range	0.9 – 2.5	1.7 – 4.5			
Prolactin	Mean ± SD	15.61 ± 5.43	16.46 ± 3.71	-0.385•	0.703	NS
	Range	9 – 27	13 – 23			
TSH	Mean ± SD	1.27 ± 0.55	1.71 ± 0.48	-1.934•	0.063	NS
	Range	0 – 2.2	0.8 – 2.1			

*: Chi-square test; •: Independent t-test Hs: Highly significant; S: Significant; NS: Non significant

The previous table shows that there was statistically significant increase in AMH in patients with positive clinical pregnancy than those with negative clinical pregnancy while no statistically significant difference found between them regarding to the other parameters.

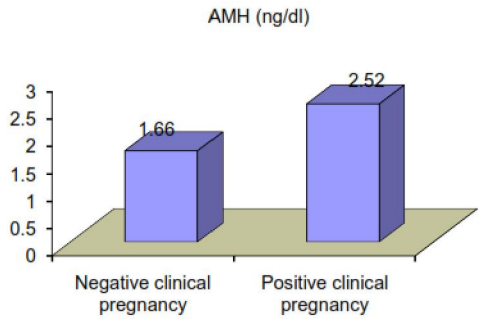


Figure (1): Comparison between negative clinical pregnancy patients and positive clinical pregnancy patients regarding AMH level in group II

Table (7): Comparison between negative clinical pregnancy patients and positive clinical pregnancy patients regarding Follicle no by u/s, Follicle average size, No of Injecting HMG 75, No of stimulation days, No of picked up follicle, No of fertilized oocytes, No of ET in group II

Group II 30-40 yrs		**Negative clinical pregnancy**	**Positive clinical pregnancy**	**Test value**	**P-value**	**Sig.**
		No.= 13	**No.= 7**			
Follicle no by u/s	Mean ± SD	9.52 ± 4.68	13.29 ± 3.40	-1.965•	0.059	NS
	Range	0 – 15	10 – 20			
Follicle average size	Mean ± SD	16.17 ± 6.47	19.00 ± 0.82	-1.139•	0.264	NS
	Range	0 – 20	18 – 20			
No of Injecting HMG 75	Mean ± SD	50.22 ± 22.95	46.14 ± 4.41	0.462•	0.648	NS
	Range	0 – 78	37 – 50			
No of stimulation days	Mean ± SD	9.96 ± 4.07	11.29 ± 0.95	-0.847•	0.404	NS
	Range	0 – 13	10 – 12			
No of picked up follicle	Mean ± SD	7.95 ± 4.08	11.71 ± 2.49	-2.291	0.030	S
	Range	0 – 13	8 – 16			
No of fertilized oocytes	Mean ± SD	6.57 ± 3.29	9.29 ± 2.36	-2.418	0.030	S
	Range	0 – 10	7 – 14			
No of ET	Mean ± SD	2.74 ± 1.36	4.00 ± 1.15	-2.221•	0.035	S
	Range	0 – 5	2 – 5			

*: Chi-square test; •: Independent t-test Hs: Highly significant; S: Significant; NS: Non significant

The previous table shows that there was statistically significant increase in number of picked up follicle, number of fertilized oocytes and number of ET in patients with positive clinical pregnancy than those with negative clinical pregnancy while no statistically significant difference found between them regarding to the other parameters.

Table (8): Comparison between negative clinical pregnancy patients and positive clinical pregnancy patients regarding the personal, medical history and hormonal profile in group III

Group III > 40 yrs		**Negative clinical pregnancy**	**Positive clinical pregnancy**	**Test value**	**P-value**	**Sig.**
		No.= 27	**No.= 3**			
Age (years)	Mean ± SD	41.56 ± 0.80	41.67 ± 0.58	-0.232•	0.818	NS
	Range	40 – 44	41 – 42			
BMI (kg/m^2)	Mean ± SD	34.00 ± 5.23	31.00 ± 6.08	0.930•	0.360	NS
	Range	25 – 42	24 – 35			
Type of infertility	1	21 (77.8%)	3 (100.0%)	0.833*	0.361	NS
	2	6 (22.2%)	0 (0.0%)			
Cause of infertility	Male factor	4 (14.8%)	0 (0.0%)	4.074*	0.130	NS
	Poor Ov. Reserve	22 (81.5%)	2 (66.7%)			
	Tubal	1 (3.7%)	1 (33.3%)			
Duration of infertility	Mean ± SD	3.37 ± 1.33	3.00 ± 1.73	0.445•	0.660	NS
	Range	1 – 6	2 – 5			
FSH	Mean ± SD	10.33 ± 2.02	9.33 ± 0.58	0.840•	0.408	NS
	Range	7.9 – 16	9 – 10			
LH	Mean ± SD	8.05 ± 1.49	7.80 ± 0.53	0.288•	0.776	NS
	Range	5.3 – 11	7.2 – 8.2			
E2	Mean ± SD	48.11 ± 15.63	56.67 ± 17.21	-0.893•	0.380	NS
	Range	17 – 81	43 – 76			
AMH (ng/dl)	Mean ± SD	0.83 ± 0.27	0.80 ± 0.00	0.213•	0.833	NS
	Range	0.1 – 1.3	0.8 – 0.8			
Prolactin	Mean ± SD	15.11 ± 5.33	18.00 ± 3.00	-0.913•	0.369	NS
	Range	6 – 31	15 – 21			
TSH	Mean ± SD	1.24 ± 0.51	1.57 ± 0.75	-1.013•	0.320	NS
	Range	0.5 – 2.1	0.8 – 2.3			

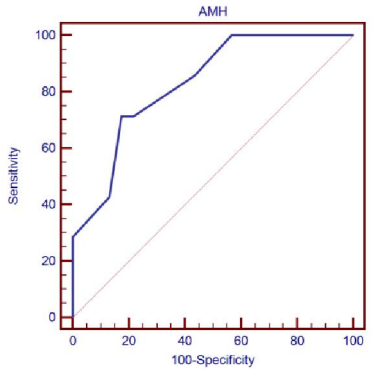
The previous table shows that there was no statistically significant difference regarding the studied parameters in patients with positive clinical pregnancy than those with negative clinical pregnancy.

Table (9): Comparison between negative clinical pregnancy patients and positive clinical pregnancy patients regarding Follicle no by u/s, Follicle average size, No of Injecting HMG 75, No of stimulation days, No of picked up follicle, No of fertilized oocytes, No of ET in group III

Group III > 40 yrs		Negative clinical pregnancy No.= 27	Positive clinical pregnancy No.= 3	Test value	P-value	Sig.
Follicle no by u/s	Mean ± SD	4.63 ± 2.50	5.33 ± 1.53	-0.474•	0.640	NS
	Range	1 – 10	4 – 7			
Follicle average size	Mean ± SD	18.67 ± 0.88	18.67 ± 0.58	0.000•	1.000	NS
	Range	17 – 20	18 – 19			
No of Injecting HMG 75	Mean ± SD	74.19 ± 4.82	72.00 ± 6.00	0.731•	0.471	NS
	Range	65 – 84	66 – 78			
No of stimulation days	Mean ± SD	12.44 ± 0.75	12.00 ± 1.00	0.947•	0.352	NS
	Range	11 – 14	11 – 13			
No of picked up follicle	Mean ± SD	3.19 ± 2.48	4.33 ± 1.15	-0.783•	0.440	NS
	Range	0 – 10	3 – 5			
No of fertilized oocytes	Mean ± SD	1.92 ± 1.66	4.33 ± 3.21	-2.176	0.038	NS
	Range	0 – 7	2 – 5			
No of ET	Mean ± SD	1.22 ± 0.85	1.33 ± 0.58	-0.220•	0.828	NS
	Range	0 – 4	1 – 2			

The previous table shows that there was statistically significant increase in number of fertilized oocytes patients with positive clinical pregnancy than those with negative clinical pregnancy while no statistically significant difference found between them regarding to the other parameters.

Negative clinical pregnancy and Positive clinical pregnancy in group II



Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>2.1	0.829	71.43	82.61	55.6	90.5

Figure (2): ROC curve between patients with negative clinical pregnancy and positive clinical pregnancy in group II regarding the level of AMH

The previous Receiver Operating Characteristic (ROC) curve shows that the best cut off point to detect patients with positive clinical pregnancy regarding AMH level was found > 2.1 with sensitivity of 71.4%, specificity of 82.6% and AUC of 82.9%.

Table (10): Correlation of AMH level with the other studied parameters in all patients

All Patient	AMH	
	r	P-value
No of picked up follicle	0.643**	0.000
No of fertilized oocytes	0.607**	0.000
Prolactin	-0.125	0.239
Age (years)	-0.809**	0.000
BMI (kg/m2)	0.014	0.897
Duration of infertility	0.026	0.806
FSH	-0.856**	0.000
LH	-0.778**	0.000
E2	0.488**	0.000
TSH	0.064	0.551
Follicle no by u/s	0.640**	0.000
Follicle average size	-0.025	0.817
No of Injecting HMG 75	-0.722**	0.000
No of stimulation days	-0.486**	0.000
No of ET	0.507**	0.000

The previous table shows that there was statistically significant positive correlation found between AMH level and number of picked up follicle, number of fertilized oocytes, E2, follicle number by U/S and number of ET and also negative correlation with age, FSH, LH, number of injecting HMG and number of stimulation days while no statistically significant correlation found between AMH level and the other studied parameters.

Table (11): Correlation of AMH level with the other studied parameters in group II

Group II 30-40 yrs	**AMH**	
	R	**P-value**
No of picked up follicle	0.617**	0.000
No of fertilized oocytes	0.630**	0.000
Prolactin	-0.060	0.752
Age (years)	-0.249	0.185
BMI (kg/m2)	-0.291	0.119
Duration of infertility	0.313	0.092
FSH	-0.588**	0.001
LH	-0.264	0.158
E2	0.014	0.940
TSH	0.387*	0.035
Follicle no by u/s	0.611**	0.000
Follicle average size	0.282	0.131
No of Injecting HMG 75	0.050	0.794
No of stimulation days	0.268	0.152
No of ET	0.471**	0.009

The previous table shows that there was statistically significant positive correlation found between AMH level and number of picked up follicle, number of fertilized oocytes, TSH, follicle number by U/S and number of ET and also negative correlation with FSH while no statistically significant correlation found between AMH level and the other studied parameters.

4. Discussion

Since its discovery, AMH has been a promising marker in various clinical setting of ART. Initially viewed as an accurate marker of ovarian reserve, AMH was subsequently found to be a reliable predictor of controlled ovarian hyperstimulation for both poor and hyper responses. In addition, one study reported AMH to be a competent surrogate marker for antral follicle count in the diagnosis of PCOS by the Rotterdam Criteria **(La Marca et al., 2010).**

The value of the AMH level in the prediction of pregnancy has been investigated in various studies, but the results have been inconsistent. A number of studies have demonstrated associations between the AMH level and oocyte quality, fertilization rate, blastocyst development, embryo quality, pregnancy outcome, and live birth rate **(Nelson et al., 2007; Majumder et al., 2010; Gleicher et al., 2010; Lehmann et al., 2014)** but were not confirmed in other studies **(Koshy et al., 2013; Riggs et al., 2011; Lie Fong et al., 2008).**

The latest systematic review and meta-analysis of the literature showed that the AMH level, independent of age, has an association with predicting live birth after ART **(La Marca et al., 2011; Iliodromiti et al., 2014)**; however, prediction of the qualitative aspects of assisted reproduction by measurement of the AMH level has not been fully reported **(Broer et al., 2014)**.

This study was a Prospective study of 90 infertile women that assess serum Anti-Mullerian hormone as an ovarian reserve marker in prediction of success of intracytoplasmic sperm injection (ICSI) as regard clinical pregnancy the study population was consisted of three groups of participants according to age Group I with 30 cases below 30 years Group II with 30 cases between 30-40 years Group III with 30 cases above 40 years.

After excluding the missed patients the remaining patients were only 80 patients.

Out of group 1 there was 3 patients had their cycle cancelled due to risk of OHSS.

Out of group 2 there was 3 patients had their cycle cancelled one of them due to risk of OHSS and the other 2 due to missed unreported data.

Out of group 3 there was 4 patients had their cycle cancelled 2 of them due to no oocytes collected during VEC and the other 2 due to no fertilization.

Out of the 80 patients who had embryo transfer, 19 patients had a positive pregnancy test, while the other 61 patients had a negative pregnancy test, the

pregnancy test was done after embryo transfer by 14 days.

There was statistically significant difference found between the three studied groups regarding Age (years), Cause of infertility, Duration of infertility, FSH, LH, E2, AMH (ng/dl), Follicle no by u/s, No of Injecting HMG 75, No of stimulation days, No of picked up follicle, No of fertilized oocytes and No of ET while no statistically significant difference found between the three studied groups regarding BMI, type of infertility, Prolactin, TSH, Follicle average size and clinical pregnancy.

As regard group 1 there was statistically significant increase in follicle number by U/S, number of picked up follicle, number of fertilized oocytes and number of ET in patients with positive clinical pregnancy than those with negative clinical pregnancy.

As regard group 2 there was statistically significant increase in AMH, number of picked up follicle, number of fertilized follicle and number of ET in patients with positive clinical pregnancy than those with negative clinical pregnancy.

The mean of AMH in group 2 is 2.52 ± 0.9 in patients with positive clinical pregnancy while those with negative clinical pregnancy is 1.66 ± 0.48 so it is highly significant in this age group.

In group 2 the best cut off point according to ROC curve to detect patients with positive clinical pregnancy regarding AMH level was found > 2.1 with sensitivity of 71.4%, specificity of 82.6% and AUC of 82.9%.

As regard group 3 there was statistically significant increase in number of fertilized oocytes patients with positive clinical pregnancy than those with negative clinical pregnancy.

So our study results indicated that there is a statistically significant relation between serum AMH level and pregnancy in the age group of 30 yrs to 40 yrs.

The association of AMH with pregnancy after assisted conception has been examined, but results were inconclusive.

Some studies have concluded that AMH is not associated with pregnancy **(Broekmans et al., 2006; van Rooij et al., 2006)** like **Wunder et al.** in which was found similar fertilization rates regardless of the AMH concentrations in serum or FF and Fanchin et al. They found that high clinical pregnancy and implantation rates correlated with FF AMH levels and concluded that FF AMH measurements could help to identify the embryos that are most likely to achieve implantation in IVF cycles.

While others have found a positive association **(Nelson et al., 2007; Honnma et al., 2013)** like Takahashi et al. who reported that the FF AMH levels of fertilized patients were 3.42 times higher than those of non-fertilized patients. However, they found no correlation between serum AMH and high-quality embryos (These results indicate that serum AMH levels did not reflect high-quality fertilization) and Silberstein et al., which included 257 patients, the authors found that AMH levels at the time of HCG administration reflect both ovarian reserve and better embryo morphology and found that AMH levels at the time of HCG administration (≥2.7 ng/ml) portended improved oocyte quality as reflected by higher implantation rates and a trend toward improved clinical pregnancy rate and Nelson et al., which investigated the value of serum AMH in the prediction of live birth and ovarian response to stimulation, it was found that plasma AMH is an accurate predictor of live birth and strongly correlated to the risk of excessive response to ovarian stimulation and the results of Selma İnat Çapkın et al., indicate that serum AMH and FF AMH concentrations are positively correlated with implantation and clinical pregnancy rates. In addition, serum AMH concentrations are associated with the number of oocytes and the number of mature oocytes retrieved.

A recent individual patient data meta-analysis in 1008 patients undergoing fertility treatment demonstrated a weak association of AMH with ongoing pregnancy **(Broer et al., 2013).**

There is a strong correlation basal AMH level and the number of retrieved oocytes **(La Marca et al., 2011; Broekmans et al., 2008).** Seifer was the first to report an association between serum AMH and ovarian response to controlled ovarian stimulation **(Seifer et al., 2002).**

Again, AMH was found to be a better marker to predict the response to gonadotropin stimulation than age, day 3 FSH, estradiol, and inhibin B. Recently, Broer performed a meta-analysis and reviewed a total of 30 studies to compare the role of AMH and AFC in predicting ovarian response. He concluded that AMH and AFC have the same accuracy level in predicting ovarian response **(Broer et al., 2011)**.

Most recently, Broer performed a review of the role of AMH in assisted reproductive technology (ART) outcome **(Broer et al., 2010)**. He reported that ovarian reserve is considered normal when 6-14 oocytes are retrieved after ART, and this resulted in optimal live birth rate. He concluded that AMH is an excellent predictor of ovarian response to controlled ovarian stimulation, but cannot predict pregnancy after ART **(Broer et al., 2010)**. Gnoth reviewed 132 oocyte retrievals and reported that an AMH cut off level 61.26 ng/ml detected poor responders (64 oocytes) with a sensitivity of 97%, and a 98 % prediction of normal response if levels were above

1.26 ng/ml, while levels <0.5 ng/ml predicted 88% of very poor responders (62 oocytes). However, AMH levels P0.5 ng/ml are not significantly correlated with clinical pregnancy rates **(Gnoth et al., 2008)**.

Studying AMH in the donor oocyte population is very useful due to their homogenous nature. Nakhuda measured AMH in 104 oocyte donors between the ages of 21-32 years **(Gary Nakhuda et al., 2009).**

In 2010, Gleicher et al. compared the concordance and discordance between FSH and AMH. He concluded that women with normal FSH and abnormal AMH will have reduced oocyte yield (women with normal FSH and normal AMH have the best oocyte yield), showing again that AMH is a better marker than FSH. Also, the same authors compared the predictive values of AMH and baseline FSH with respect to IVF outcomes and oocyte yield in 76 women. They reported that an AMH 60.5 ng/ml has a sensitivity of 87 % and specificity of 84% in predicting poor response. In contrast, FSH has sensitivity and specificity of 64.5% and 82.2 %, respectively.

Many studies indicate that measuring AMH follicular level is useful in the prediction of oocyte and embryo quality, as well as clinical pregnancy, with mixed results (Fanchin R et al., 2007). Nelson in 2007 concluded that basal AMH has a very good correlation with the number oocytes retrieved but, like basal FSH, does not seem to predict clinical pregnancy **(Nelson et al., 2007).**

Nelson et al. found that AMH was a marker of ovarian function and the relationship between AFC and serum AMH was stronger than that observed with FSH and E2, also, Nelson and colleagues found that the levels of baseline FSH were significantly higher and the baseline AMH was significantly lower in the cancelled group compared to the completed cycle group and they concluded that the plasma AMH was a better predictor of live birth and oocyte retrieved compared with FSH **(Nelson et al., 2007).**

Several studies have demonstrated that serum AMH may also possess the additional ability to predict the quality of oocytes and embryos, while others have failed to replicate such relationship **(La Marca et al., 2010)**. In a well-designed study by Wang et al., the authors revealed that both the clinical pregnancy rate per retrieval and live birth rate per embryo transfer did not differ significantly across all three AMH tertiles (≤0.29, 0.30-1.20 and ≥1.21 ng/ml) for women aged <34 years. This indicated that favorable outcomes may still be attained for the infertile patients of younger age on the basis of biologically competent oocytes, despite of the diminished ovarian reserve **(Wang et al., 2010).**

Conclusion

There is a statistically significant relation between serum AMH level and pregnancy in the age group of 30 yrs to 40 yrs. (group II) with best cut off point according to ROC curve to detect patients with positive clinical pregnancy regarding AMH level was found > 2.1 with sensitivity of 71.4%, specificity of 82.6% and AUC of 82.9%.

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