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Comparative Study of Reproductive Outcomes in Infertile Women Less Than 35 Years Having AMH < 1Ng/Ml and AMH 1-4Ng/Ml Treated with Ovulation Induction IUI and IVF ICSI

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Abstract

Background: AMH is one of the very good markers for ovarian reserve and is best used for assessing the ovarian response in ART. Its role in young infertile women to have a successful pregnancy outcome is debated. Low AMH in young infertile women creates a dilemma for choosing the treatment modalities. The study analyses low AMH (<1ng/ml) and normal AMH (1-4 ng/ml) infertile women of 35 years and less to compare the response and reproductive outcomes with ovulation induction with oral agents (OI IUI) and assisted reproduction (IVF/ICSI).

Methods: This retrospective study included 489 infertile women of less than 35 years, with regular menses having AMH less than 4ng/ml and no other infertility co-factor. These women were divided into two groups of ovulation induction with clomiphene citrate followed by intrauterine insemination (OI IUI) and assisted reproduction (IVF/ICSI). 231 women underwent OI IUI. The women of the OI IUI group were stratified into two subgroups low AMH (<1ng/ml) and normal AMH (1-4ng/ml) to compare the outcomes in these women. 258 women were treated with IVF ICSI. These women were stratified into two subgroups of low AMH (<1ng/ml) and normal AMH (1-4ng/ml) to compare their reproductive outcomes. The results were compared for clinical pregnancy rate and live birth rate.

Main Results: Pregnancy rate per patient and per cycle in women undertaken OI IUI was 25.53% and 10.34% in low AMH women and 24.45% and 11.33% in normal AMH women. Live birth rates per patient in OI IUI was 19.14% in low AMH and 20.65% in normal AMH. Pregnancy rate per patient and per oocyte retrieval cycle in women undertaken IVF/ICSI was 29.06% and 19.84% in low AMH women and 46.51% and 40.2% in normal AMH women. The clinical pregnancy rate per embryo transfer cycle was 22.72% in low AMH and 26.72% in normal AMH women. Live birth rates per patient in IVF/ICSI was 25.58% in low AMH and 37.39% in normal AMH.

Conclusion: Patients with low AMH have comparable chances of pregnancy and live birth with ovulation induction where mono-follicular growth is targeted against normal AMH counterparts. The clinical pregnancy rate and live birth rate per patient as well as per cycle were significantly low as compared to normal AMH women when women with low AMH were treated with IVF/ICSI, where multi-follicular growth is targeted. The clinical pregnancy rate per embryo transfer cycle was marginally low in the women with low AMH suggesting a reasonable chance to conceive with their own gametes.

Key words: Low AMH, Intrauterine insemination, IVF ICSI

Introduction

Anti-Müllerian hormone (AMH) denotes the stock of primordial follicles in the ovary but does not quantify the ovarian reserve in the number of oocytes. AMH is a quantitative marker of ovarian reserve.[1,2] The chances of pregnancy and live birth are dependent on various parameters, like age, BMI, smoking, cofactors of infertility in couple, and not just ovarian reserve. Unlike the age of the women, AMH has an inferior predictive accuracy of the quality of the oocytes. [3, 4] Over a while, measurement of ovarian reserve, particularly anti- Mullerian hormone, is increasingly used by infertility specialists to individualize treatment and to counsel them regarding the outcomes of fertility treatments. Declining AMH with increasing age has set a new alarm in women's life. The number of growing follicles is strongly associated with AMH hence the association between AMH and ovarian response in ART is well established.[5,6] AMH is the best predictor of the poor or excessive ovarian response [4, 7, 8, 9, 10, 11] but is not a predictor

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of pregnancy in ART[4, 12] and the general population[13]. Most of the studies consider low AMH as AMH less than 1ng/ml [14]. The debate is ongoing about AMH being the predictor for fertility potential in natural conception, fertile as well as non-fertile couples and its association with various treatment modalities. Many studies in the literature suggest low AMH is associated with low pregnancy rates in ART as compared to normal AMH women [3, 5, 14, 15, 16, 17, 18, 19, 20]. Although age is the most important determinant of reproductive outcome in ART as oocyte yield and quality is affected with advancing age. The results of ovulation induction with intrauterine insemination is the primary modality of choice all over the world in women with unexplained infertility, which is not affected by AMH levels [21].

In this study, the issue of low AMH [<1ng/ml] and its effects on treatment outcomes with oral ovulation-inducing agents followed by IUI and assisted reproduction (IVF/ICSI) as compared to normal AMH [1-4ng/ml] in young infertile women of less than thirty-five years having regular menstrual cycles has been addressed.

Materials and Methods

Study design

This study is a retrospective observational analysis of women undertaken treatment at Fertility Clinic, Mumbai between 2013 and 2017. A total of 231 women of 35 years and less undertaken 513 stimulated IUI with clomiphene citrate and 258 women with 325 oocyte retrieval and 409 embryo transfer cycles were studied.

Since the role of AMH is not well understood in sub fertile young women with regular cycles, as it is as a policy AMH was not considered to decide the line of management. All these women underwent IUI and clomiphene citrate ovarian stimulation for three to four cycles irrespective of their AMH before offering those IVF ICSI treatment option. These women considered eligible for the study: (1) women under 35yrs of age, (2) AMH <4ng/ml, (3) Regular menstrual cycles, (4) At least one patent fallopian tube, (5)Partners with Normal Semen analysis or mild oligozoospermia as per WHO criteria.

Study did not include following women: (1) premature ovarian failure, (2) women with irregular cycles, (3) women with AMH more than 4ng/ml, (4) Polycystic ovarian syndrome, (5) women with endocrine dysfunction, (6) Partners with moderate to severe oligoasthenoteratozoospermia. (7) Treatment cycles with donor gametes

Out of 489 women, 231 women underwent ovulation induction with IUI (OI IUI) for three to four cycles with oral induction agents. Out of 231, 47 women had low AMH (<1ng/ml) and 184 women had normal AMH (1-4ng/ml). Out of 489 women 258 women underwent assisted reproduction (IVF ICSI). Out of 258, 86 women had low AMH (<1ng/ml) and 172 women had normal AMH (1-4ng/ml). All models in both subgroups were adjusted for age, length of menstrual cycle, BMI and duration of infertility. All the women in four different subgroups were analyzed for the response to the treatment and treatment outcomes in OI IUI and IVF ICSI groups. Majority of women in the study had primary infertility and duration of infertility of three to four years. AMH levels were tested in these young infertile women with unexplained infertility. AMH was done by one-step immune-enzymatic ("sandwich") assay (Access AMH assay, @Beckman Coulter) in one standard laboratory. In women with AMH levels less than 1ng/ml a second test was run to confirm the results. The endocrine dysfunction like thyroid profile, prolactin in asymptomatic women were ruled out or treated and other medical evaluation was done in all subjects. Semen analysis performed in standard laboratory. Semen analysis was repeated in case of mild oligozoospermia after life style modifications and treatment to improve semen parameters for at least 3 months and then taken on program. Tubal patency was confirmed with hysterosalpingography or diagnostic laparoscopy.

Interventions

Women in OI IUI group, received clomiphene citrate 100-150mg from second day of cycle for five days. Follicular monitoring was done through transvaginal sonography. Follicular size and endometrial thickness were noted during monitoring and at the time of hCG trigger. Women underwent single or double IUI in the cycle, after 24 – 36 hours of hCG trigger at follicular rupture. Luteal support was not given routinely. Dose titration for clomiphene citrate was done in the following cycles depending on the cycle response. Semen samples used for insemination were processed within 1 hour after ejaculation. The sperm was washed by swim up technique (Earle's Balance Salt, Sigma Aldrich,). After IUI, women had bed rest for 20 min. The maximum 3 to 4 cycles of OI IUI were offered, before advising ART.

The women for IVF/ICSI were stimulated with gonadotropins, the protocol and dose used, depended on the body weight, AMH and AFC (Antral follicle count) at the beginning of stimulation cycle from second or third day of menses. In low AMH women antagonist protocol was used. In antagonist protocol stimulation with gonadotrophins (r FSH, follitropin Alfa, Merk) started from second day of period, GnRH-ant (ganirelix 0.25mg; Organon) used for down regulation from day 5-6 of the stimulation till administration of choriogonadotropin alfa (Ovitrelle 250mcg). In long protocol women were given ethinyl estradiol (0.03mg) + desogestrel (0.15mg) from 5th day of menses and downregulation was done with Triptorelin 0.1mg (Ferring) from day 21 of the menstrual cycle. The stimulation started with gonadotrophins (r FSH, follitropin Alfa, Merk) from second day of period. The cycle was monitored with follicular study and estrogen levels. The trigger was given at 2-3 leading follicles of 18mm with choriogonadotropin alfa (Ovitrelle 250mcg). Oocyte retrieval under ultrasound guidance was done at 35-36 hours later. IVF/ICSI was done as per the semen parameters. The fertilization was observed 18-20 hours after egg collection and cleavage was observed 72 hours later. Grade I–II embryos were regarded as high-quality (International morphological grading system) and used for transplantation on day 3 or day 5 in fresh cycle or artificial endometrial preparation cycle with estradiol valerate (Bayer Zydus). Luteal phase support was given with oral dydrogesterone (Abbott) and/or injectable progesterone/micronized progesterone vaginally. The outcome was tested with Beta hCG after 12 days of implantation. The clinical pregnancy was defined as the presence of intrauterine gestational sac, on ultrasound at 6 weeks amenorrhea. Live birth (LB) was defined as the live birth of a fetus.

Statistical analysis

Data were statistically described in terms of mean ± standard deviation (± SD), 95% CI, frequencies (number

of cases), and percentages when appropriate. Comparison of numerical variables between the study groups was done using the Student t test for independent samples in comparing two groups of normally distributed data and the Mann-Whitney U test for independent samples for comparing not normal data. For comparing categorical data, the chi-square ($\chi 2$) test was performed. The exact test was used instead when the expected frequency is less than 5. P values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, USA) release 22 for Microsoft Windows.

Results

The study population was stratified depending on their treatment modalities and sub grouped in low AMH and normal AMH to compare the response to the treatment and outcomes in terms of clinical pregnancy and live births.

Table 1 and table 2 Shows the comparable baseline characteristics in all the women between two groups. The baseline characteristics of weight, age, length of menstrual cycle and duration of infertility in low AMH and normal AMH women are compared.

Table 3 Shows the details of cycles in all the women. Between 2013 and 2017 the study analyzed 231 women in who underwent total of 513 Clomiphene citrate IUI cycles, each couple underwent 2.22 treatment cycles on an average. 258 women underwent 325 oocyte retrieval cycles, with average of 1.25 oocyte retrieval per patient.

Table 4 Shows the response elicited on ovulation induction in terms of number of leading follicles, size of the follicle and endometrial thickness at the time of hCG trigger. On comparison of response to stimulation to clomiphene citrated, follicular growth patterns, size of follicle rupture and endometrial thickness at the time of follicle rupture was equivalent.

Table 1: Baseline characteristics of women underwent OI IUI

Baseline characteristics	Low AMH (<1ng/ml) n=47	Normal AMH (1- 4ng/ml) n=184	P Value
Weight (kg)	62.1 (58.012,66.188)	62.6 (60.982, 64.218)	0.9526
Age (y)	31.13 (30.2723, 31.9877)	30.4 (29.952, 30.848)	0.1301
AMH (ng/ml)	0.61 (0.5385, 0.6815)	2.45(2.2766, 2.6234)	<0.01
Menstrual Cycle(d)	27.3 (26.585, 28.015)	28.74(28.5666, 28.9134)	<0.01
Type of infertility			
Primary, n (%)	31(65.95)	138(75)	
Secondary, n (%)	16(34.04)	46(25)	
Duration of infertility (y)	3.35(4.42, 2.28)	2.79(2.28, 2.31)	0.2038
Sperm Count (Million/ml)	50.5(39.836, 61.164)	51.2(6.836, 55.564)	0.8981

Values are expressed as mean (CI) or as numbers (%). Note: kg= kilograms, y= years, d = days.

Table 2: Baseline characteristics of women underwent IVF ICSI

Baseline characteristics	Low AMH (<1ng/ml) n=86	Normal AMH (1- 4ng/ml) n=172	P Value
Weight (kg)	62.13(59.49, 64.77)	62.0(60.40, 63.00)	0.9323
Age (y)	31.18(30.27, 31.73)	30.9(31.27,30.53)	0.4158
AMH (ng/ml)	0.55(0.51, 0.59)	2.28(2.400, 2.16)	<0.001
Menstrual Cycle (d)	27.3(26.76, 27.84)	30.20(31.12, 29.09)	0.0002
Type of infertility			
Primary, n (%)	86(100)	130(70.65)	
Secondary, n (%)	0(00)	54(29.34)	
Duration of infertility (y)	3.35(2.58, 4.14)	2.79(2.34, 2.96)	0.0636
Sperm Count (Million/ml)	52.55(43.85, 61.25)	51.2(46.46, 56.07)	

Values are expressed as mean (CI) or as numbers (%). Note: kg=kilograms, y=years, d=days

Table 3: Details of cycles in all women

	Ovulation induction with IUI		IVF ICSI	
	Low AMH (<1ng/ml)	Normal AMH (1-4ng/ml)	Low AMH (<1ng/ml)	Normal AMH (1-4ng/ml)
No. of women	47	184	86	172
Total OI IUI/OPU cycles	116	397	126	199
Embryo transfer cycles			110	299
Cycles/patient	2.46	2.15	1.46	1.15
Cancelled cycles	…	…	20(13.69%)	7(3.39%)

Values are expressed as mean (CI) or as numbers (%). Note: kg= kilograms, y= years, d = days.
Since sample size is less *P value* may not be applicable.

Table 4: Response elicited on ovulation induction in both groups

Parameters of OI response	Low AMH (<1ng/ml) n=47	Normal AMH (14ng/ml) n=181	P value
Size of follicle before rupture, mm	22.7±2.4	22.7±2.3	0.0636
No. of leading follicles, mm	1.84±0.77	1.9±1.11	0.7271
Endometrial thickness at the time of follicular rupture, mm	10.9±1.2	11.1±1.1	0.2794
Progesterone in luteal phase of OI	29.04±15.5	29.39±16	0.893

Values are expressed as mean ± SD.

Table 5: Time to pregnancy in both groups with ovulation induction followed by IUI

With OI	Low AMH	Normal AMH	P Value
<3 cycles	12 (100%)	42 (93.33%)	0.4572
>3 cycles	0	3 (6.66%)	0.3581*
Total Pregnancies following OI	12	45	

Values are expressed as numbers (%).
* Since sample size is less *P value* may not be applicable.

Table 6 Shows the differences in mean and confidence interval between AMH, AFC, number of oocytes retrieved, number of embryos fertilized and number of high-quality embryos in low AMH women and normal AMH women from ART group. The number of antral follicle count at the beginning of stimulation cycle, number of oocytes retrieved, embryo fertilization and high quality embryos were significantly less in low AMH group as compared with normal AMH group (*P* value 0.05).

Table 6: Parameters of women undergone IVF/ICSI

	Low AMH	Normal AMH	P value
AMH	0.55(0.04)	2.28 (0.12)	<0.0001
AFC	8.17(0.85)	12.2(1.17)	<0.0001
Oocytes retrieved	9.84(1.84)	15.6(1.4)	<0.0001
Embryos fertilized	5.76(1.18)	8.93(0.71)	0.0065
High quality embryos Grade I & II	5.22(1.08)	7.99(0.69)	<0.0001

Values are expressed in mean (confidence interval).

Table 7 Displays the reproductive outcomes in each category. The clinical pregnancy rate and live birth rate, in low AMH and normal AMH women, who underwent OI IUI, significant differences were not observed. Clinical pregnancy rate 25.53% *Vs* 24.45(*P value 0.8784*) and live birth rate 19.14% *Vs* 20.65% (*P 0.8189 value*) in low AMH and normal AMH respectively. The pregnancy per cycle was also equivalent 10.34% and 11.33% (*P value 0.8476*) in low AMH and normal AMH. Abortion rate per patient was 6.38% and 3.26% respectively. Abortion Rate is not statistically significantly high in low AMH women as opposed to normal AMH women. 258 women who

Table 7: Details of treatment outcomes in all the women

	OI IUI			IVF / ICSI		
	Low AMH (<1ng/ml)	Normal AMH (1-4ng/ml)	P value	Low AMH (<1ng/ml)	Normal AMH (1-4ng/ml)	P value
Total Women	47	184		86	172	
Total cycles	116	397		146	206	
Cancelled	…	…		20(13.69%)	7(3.39%)	0.0020*
Cycles						
Pregnancy Rate/initiated cycle	10.34%	11.33%	0.8476	17.12%	38.83%	0.004
Pregnancy Rate/OPU	..	..		19.84%	40.20%	0.0011
Pregnancy Rate/ET	..	..		22.72%	26.72%	0.4873
Pregnancy Rate/patient	12 25.53%,	45 24.45%	0.8784	25 29.06%	80 46.51%	0.0073
Live Birth Rate/patient	9 19.14%	38 20.65%	0.8189	22 25.58%	65 37.79%	0.051
Live Birth Rate/ET cycle	9 7.7%	38 9.57%	0.6927	25/110 4.4%	80/299 3.73%	0.795
Abortion Rate/patient	3 6.38%	6 3.26%	0.3248*	3 3.48%	13 7.55%	0.2019*

Values are expressed as numbers (n) and percentages (%)
* Since sample size is less P value may not be applicable.

had taken IVF/ICSI cycle in study duration after meeting the inclusion and exclusion criteria were compared for the baseline characters (table 2) of mean age, BMI, menstrual cycle length duration of infertility and semen count. A couple had taken 1.3 treatment cycles on an average In women having low AMH with IVF/ ICSI treatment significant difference was observed in clinical pregnancy rate per initiated cycle and per oocyte retrieval cycle 17.12 % and 19.84% as compared to the normal AMH women with same treatment 38.83% and 40.2% respectively with *p value of 0.004*. The live birth rate was 25.58% *Vs* 37.79% in low and normal AMH respectively. There was significant difference in the pregnancy rate per embryo transfer cycle and per patient in low AMH (22.72%, 29.06%) and normal AMH (26.72%, 46.51%) with *p value of 0.0073*. The difference in pregnancy rate per embryo transfer cycle *p value of 0.4873* and per patient was marginal with *p value of 0.0073*. As the sample size is low, interpretation about the abortion rate could be fallacious.

Discussion

The study comparatively analyses the data of young infertile women less than 35 years of age having regular menstruation with AMH less than 1ng/ml and 1-4ng/ml undergoing stimulated IUI with clomiphene citrate (OI IUI) and assisted reproduction (IVF/ICSI). The majority of women in the study had infertility duration between 2 to 5 years. The purpose of the study was to understand the management of such young infertile women. Restricted ovarian stimulation with oral ovulation induction agents like clomiphene citrate along with intrauterine insemination has shown to be equally effective in a woman with low AMH and normal AMH. Successful pregnancy and live birth are determined not only by quantity but also by quality. Age is the most important measure of oocyte quality. The study observed as low as AMH of 0.1ng/ml resulted in the successful pregnancy and live birth with the treatment of OI IUI. A low concentration of circulating AMH is not predictive of reduced fecundability in young healthy women [22]. AMH is not a single predictor of a woman's ability to conceive and no correlation is found between low AMH and ability to conceive [13]. The notion that denying infertility treatment solely based on undetectable AMH is not advisable [23].

In our analysis serum, AMH was not significantly associated with ovarian response in women undertaking OI IUI treatment with the number of leading follicles, follicular growth, endometrial thickness, and progesterone levels in the luteal phase in low AMH and normal AMH respectively. All women in our study had regular menstrual cycles indicating ovulatory cycles. The purpose of ovulation induction with clomiphene citrate was to correct the underlying subclinical dysfunction, restricting multiple follicular developments, and increase cycle fecundity. The treatment of intrauterine insemination along with ovulation induction is cost-effective and does not require stringent monitoring during the cycle. The rationale behind doing IUI is to increase the gamete density at the site of fertilization. Although there are controversies regarding the treatment of ovulation induction and IUI in women with unexplained infertility, it is the first line of treatment. The increase in the live birth rate was seen in women treated with IUI in a stimulated cycle compared with those who underwent IUI in the natural cycle. The evidence suggested that if the chance of live birth in IUI in a stimulated cycle was assumed to be 25%, the chance of live birth in IUI in a natural cycle would be between 9% and 21% [24, 25, 26].

This study analyses the results of 513 OI IUI cycles in 231 ovulatory women having low AMH (<1ng/ml) *Vs* normal AMH (1 – 4ng/ml). The clinical pregnancy rate per cycle was 10.34%% and 11.33 % in low and normal AMH women respectively. The clinical pregnancy rate per patient was 25.53% *Vs* 24.45% respectively. The live birth rate per patient was 19.14% *Vs* 20.65% in low and normal AMH women respectively.

In a study, women less than 35 years taking treatment of CC/IUI observed 7 patients (mean age 35.1 +/- 1.6) in 20 cycles with AMH levels of less than 1ng/ml, with CPR (clinical pregnancy rate) of 17.3% per cycle, 27 patients (mean age 34.6+/- 0.8) in 65 cycles with AMH levels 1-2.9ng/ml, CPR of 17.7%, 10 patients (mean age 31.7 +/- 1.3) in 20 cycles with AMH 3-4.9ng/ml with CPR of 15.4%. The study concluded that AMH levels do not predict pregnancy outcome in couples undergoing CC/IUI cycles, nor are they predictive of follicular response. Therefore, women with AMH levels <1ng/ml should still be treated with CC/IUI before IVF [18].

Ovarian response co-related with AMH levels to mild stimulation with FSH 75 IU in 62 ovulatory women. The mean age of women was 33 years and it did not show any association in ovarian response with the level of AMH [17].

The relationship was studied between AMH and OI/IUI in Clomiphene citrate 70% of the cycles and gonadotropins 30 % of the cycles. 833 OI/IUI cycles in 251 women with mean age 35.8 years (+/-4.2,26-45). Multivariate-adjusted clinical pregnancy rate (95% CI) per AMH quartile was 9.1% (4.8-16.5), 9.1% (5.5-14.5), 6.4% (3.7-10.9), and 9.8% (6.0-15.4) for AMH quartiles 1-4, respectively (*p value 0.52*). Analysis suggests that AMH may not provide additional benefit for predicting clinical pregnancy in both FSH and clomiphene citrate IUI cycle [19].

The relationship between serum AMH values and clinical pregnancy (CP) rates of unexplained infertility utilizing multiple protocols of IUI therapy has been evaluated. More aggressive protocols with IUI have a better probability of resulting in clinical pregnancy. Patients with a diagnosis of unexplained infertility and AMH greater than 2.1 were four times more likely to obtain clinical pregnancy [27]. At the same time, gonadotropins are costlier than clomiphene citrate and when strict cancellation criteria are applied to reduce multiple pregnancies, gonadotropins are not significantly effective as compared to clomiphene in sub fertile women with unexplained infertility [28].

These women treated with ovulation induction and IUI were adjusted for most of the prognostic parameters like age of the patient, duration of infertility, number of cycles, the timing of insemination, number of pre ovulatory follicles on the day of hCG. The processed total motile sperm > 5million minimum in each washed semen cycle was obtained in all cases. With similar methods of the treatment protocol, no difference was noted in the clinical pregnancy rates 25.53% (12/47) *Vs* 24.45 % (45*/84) and live birth rates19.14 % (9/47) *Vs* 20.65% (38/184)] in low AMH and normal AMH respectively. Our patients could not take treatment for a longer duration due to financial constraints and or for the need to resort to a more aggressive form of treatment like gonadotropin IUI or ART.

Currently, women are trying to conceive in their thirties than in their twenties as in the past decades. Low AMH in such women raises the uncertainties regarding the ability to conceive and apprehension about time to conceive. In dilemma about such a situation for both physician and patient, ART is offered earlier than otherwise. Young women with a short duration of infertility and low AMH need not be always addressed with financially stressful and aggressive treatment with gonadotropins or ART as the primary line of treatment. However, in young women with very low AMH and long-standing infertility management of infertility should be more aggressive [29]. One of the most important factors for successful assisted reproduction is oocyte quality. Age is the independent predictor of oocyte quality [25]. The ability of AMH to determine oocyte competence is a matter of debate [2, 30, 31, 32]. Young women with low AMH levels have better pregnancy outcomes following IVF than older women [33]. However, increasing the AMH level improves the cumulative outcomes of older women to a comparable level through a notable and superior ovarian response [34]. This study included women of 35 years and younger to compare the outcomes in low vs normal AMH.

This study analyzed 258/489 women assisted reproduction (IVF ICSI) and compared their outcomes in low AMH and normal AMH. The women with low AMH had significantly less antral follicle count, the number of oocytes retrieved, fertilization of embryos, and high-grade embryos as compared to the normal AMH levels. There was a marked difference in the cumulative as well as per cycle pregnancy rates and live birth rates between the two groups. High cycle cancellation was observed in low AMH 13.69% as compared to normal AMH (3.39%) women with IVF ICSI. The difference in the pregnancy rates per embryo transfer cycles and per patient in low AMH women (22.72%; 29.06%) and normal AMH women 26.72%; 46.51%) were significantly low but were better than pregnancy rates per initiated cycles (17.12% Vs 38.83%) and oocyte retrieval cycles (19.84% *Vs* 40.2%).

A study done by Alberto Pancheco, suggested very low AMH concentrations are not independent predictors of embryo quality and pregnancy rates. It was a retrospective cohort study involving 2971 patients undergoing 5570 IVF / ICSI cycle. The women were classified into 6 groups according to AMH value. A significant difference in pregnancy rates was observed among different age groups. In the lowest AMH group, the probability of achieving pregnancy was reasonable if the patient's age is not advanced. The probability of achieving pregnancy very much depends on age[35]. Young women with low AMH when undergo ART have a low response, less number of oocytes retrieved, less number of embryos to transfer but the possibility of producing high-quality embryo and clinical pregnancy outcome are good once eggs are retrieved[29].

In this study, the abortion rate per patient in low AMH women in the OI UI group is higher 6.38 % (3/47) than 3.26% (6/184) normal AMH women but is not of any statistical significance as the number is very small. Anti-Müllerian hormone (AMH) levels were found to be significantly lower in recurrent miscarriage patients, compared to a normal population.[36,37]. The studies done for predicting pregnancy rate with ovulation induction in low AMH women have not been scrutinized for abortion rate[17,18,19,27]. The anti-Mullerian hormone levels were found to be significantly lower in recurrent miscarriage patients, compared to the normal population[36,37]. The study was done investigated patients aged >34 years with low AMH levels displayed poorer IVF-ET outcomes, in particular, higher miscarriage rates[24].

The clinical utility of AMH is best when it is combined with age, duration of infertility, and absence of other factors towards subfertility of the couple. In young women, a single parameter of low AMH does not suggest a more complicated and costliest modality in the armamentarium

of ART has to be offered as the first line, fast- track route to conceive. The shortcoming of our study is that it is a retrospective assessment of a small number of women. AMH at a young age has been misinterpreted most of the time and further prospective trials with good sample size should back this viewpoint.

Conclusion

Counseling and management of young women with low AMH and infertility pose a significant challenge as the poor response is anticipated in assisted reproduction. Young women with diminished ovarian reserve by birth and fast depletion in ovarian reserve approaching premature ovarian failure have to be identified to choose the appropriate effective treatment. Young women of low circulating AMH perform equally well with ovulation induction and intrauterine insemination compared to their counterparts with normal AMH. Women undergoing assisted reproduction have to continue the treatment for a greater number of cycles to achieve a positive outcome. The intricacies of various aspects of low AMH levels and their interpretation has to be applied carefully while treating young infertile women. The decision to suggest a more complicated and costliest modality in the armamentarium of ART as the first line, fast- track route to conceive in young women with regular menses having low AMH without long standing infertility has to be cautious.

Unfortunately, in certain situations, women with low AMH may not be able to explore the possibilities to be treated with their gametes and are often offered oocyte donation even though they are young.

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Author's Role

Y.A.W. contributed to study conception and design, data analysis, interpretation and article drafting.

S.K.D. contributed in examination, counselling and treatment of patient, study design, data analysis, interpretation, article drafting and critical analysis. P.G. R. contributed in data acquisition and article drafting. All authors have approved the final version of the manuscript.

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