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Reproductive outcome after Intra Uterine Insemination in young women stratified by serum AMH level in different protocol cycles

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Abstract

Objective: To estimate pregnancy outcomes following intrauterine insemination (IUI) in young women with low ovarian reserve compared to their age-matched controls. This is a retrospective cohort study done in a single Fertility Centre between Jan 2017 to Dec 2019. Patients who included in the study were <35 years of age undergoing at least one IUI cycle with a documented serum anti-Mullerian hormone (AMH) level, patent fallopian tubes, and total motile sperm count of >10 million at the time of intrauterine insemination. As this is a retrospective observational study none of the intervention was done.

Primary outcome measure was the presence of positive serum β hCG pregnancy test (> 20 mIU/mL) done 2 weeks after the IUI procedure. Secondary outcome included were the incidence of live birth, clinical pregnancy rate, biochemical pregnancy loss, clinical abortion and ectopic pregnancy. Cumulative pregnancy rate including up to 3 IUI cycles were calculated apart from per cycle pregnancy and compared between different protocols groups.

Results: There were total 385 patients included out of which 112 with AMH < 1.2 ng/ml and 273 with AMH > 1.2 ng/ml. When adjusting for IUI treatment strategy, number of dominant follicles at the time of intrauterine insemination (IUI) and body mass index, no difference in per cycle or cumulative pregnancy outcome was seen between the two arms. Analysis by treatment strategy also show no difference in reproductive outcome.

Conclusion: Young patients (< 35 years of age) with diminished ovarian reserve conceived as often as their age matched control after IUI and had similar per cycle and cumulative pregnancy rate whatever protocol was used.

Keywords: Anti-Mullerian Hormone (AMH), Intrauterine insemination (IUI), basal antral follicle count (AFC), In Vitro Fertilization (IVF)

Introduction

With advanced age and due to other factors ovarian aging occurs and the follicular pool diminishes which results in decline of serum AMH level progressively [1-3]. As a result, as a tool to assess the size of the remaining follicular pool or ovarian reserve serum AMH has gained popularity. Anti-Mullerian hormone (AMH) is synthesised by the granulosa cells of preantral and small antral follicles [4-7], and the number of small antral follicles is related to the size of the residual follicular pool.

Serum basal follicle stimulating hormone (FSH), estradiol (E2) and basal antral follicle count (AFC) via transvaginal ultrasound are some other tests of ovarian reserve which are widely used. None of them are superior to other either as a single test or in combination. However, as compared with serum basal FSH and E2, serum AMH is both more convenient and more reliable due to its gonadotropin independent nature and can be measured on any day of the menstrual cycle [8-10]. Additionally, serum AMH is not subject to operator discretion, unlike basal transvaginal AFC.

Majority of evidence has demonstrated that AMH levels are directly correlated with ovarian response to controlled ovarian stimulation but do not prognosticate clinical outcomes (22-88% positive predictive value and 97-100% negative predictive value) for diminished response to stimulation [11-13]. So, role of serum AMH as prognostic indicator in IVF outcomes is debatable. But some patients have shown that with low AMH number of oocytes retrieved were low along with poor quality of oocytes and embryos and diminished pregnancy rate [14-18], However, the association between serum AMH levels and reproductive outcomes after minimal or no ovarian stimulation followed by intrauterine insemination (IUI) is not very clear, as prior studies in this area have yielded contradictory results [19-26]. Additionally, limited data exist on AMH as a predictor of reproductive outcomes in young sub fertile patients (i.e., women with AMH <1.2 ng/mL). So, we hypothesized that young patients with low AMH would conceive less often than age-matched controls, but once pregnant, would have similar pregnancy outcomes.

Materials and Methods

This was a retrospective cohort study of all sub fertile couples with female patients <35 years of age undergoing IUI cycles at a single Fertility Centre between 2017 to 2019. Only stimulated cycles followed by IUI were included. The treatment plan for each IUI cycle was based on reproductive history of couple, results of the infertility evaluation, and the couple's reproductive goals. Stimulated cycles consisted of controlled ovarian stimulation with injectable gonadotropins, oral clomiphene citrate, or oral letrozole or combination of

drugs depending upon previous treatment history of ovulation induction. A serum AMH level within 3 months of the IUI cycle start date was required for inclusion of sub fertile women. In the event of more than one AMH value, the AMH value drawn closest to the IUI cycle was used.

Exclusion criteria of patients were, if hysterosalpingogram (HSG) showed one or both fallopian tubes to have moderate or significant tubal dilatation(hydrosalpinx) or lack of patency (block). Couples with post- wash total motile spermatozoa count of <10 million spermatozoa at the time of IUI were also excluded from the final analyses. Patients who were having severe endometriosis as primary causes of infertility were also excluded from the study as they might have altered endometrial receptivity, suspected tubal pathology and/or poor oocyte quality.

The majority of serum AMH samples were done using automated VIDAS AMH Assay autoanalyzer. The VIDAS AMH Assay principle combines a one-step enzyme immunoassay sandwich method with a final fluorescent detection (ELFA). For this assay, reported range from 0.01 ng/mL to 9.00 ng/mL.

On day 3 of menstrual cycle, serum estradiol and progesterone levels were obtained and baseline transvaginal ultrasounds were performed to evaluate antral follicle count (AFC) along with endometrial thickness and to exclude presence of follicular cyst. The total number of follicles measuring 2 to 9 mm in both ovaries were counted to comprise the basal AFC. Monitoring of follicular growth was started in the mid-follicular phase and performed every 1-3 days, depending on dominant follicle size. Every dominant follicle >10 mm was measured [(27)]. Ovulation trigger with human chorionic gonadotropin (hCG) was done when at least one follicle was >17 mm in diameter. IUI was then performed approximately 36-40 hours post-trigger injection. And transvaginal ultrasound at the time of IUI was done to see the evidence of ovulation which was indicated by decreased size of dominant follicle or fluid in Pouch of Douglas. Repeat IUI was done in patients showed no evidence of ovulation. Patient and partner and/or sperm donor identification were confirmed prior to the start of the IUI procedure. The washed sperm specimen was aspirated into a syringe attached to an IUI catheter. A sterile speculum examination was then performed, followed by gentle deposition of the washed sperm with media into the lower uterine segment via the catheter while avoiding fundal touch and patient was asked to lie-down for 10 minutes. Luteal phase was supported with tab dydrogesterone 10 mg twice daily and continued till 12 weeks of gestational age if pregnancy test was positive. The presence of a pregnancy was determined by serum human chorionic gonadotropin (hCG) measurement drawn approximately 14 days after the IUI procedure.

The characteristics of patients with a serum AMH level <1.2 ng/mL were determined and compared to those of patients with serum AMH >1.2ng/mL. Body mass index (BMI) was determined for each patient at the time of initiating treatment. Type and aetiology of Infertility were mentioned in the medical record upon initial patient presentation and patient's all old records were reviewed, based on them they were stratified into different groups. These groups included diminished ovarian reserve, minimal to mild endometriosis, hypothalamic amenorrhea and other ovulatory dysfunction (excluding polycystic ovarian syndrome), mild male factor infertility, recurrent pregnancy loss, sexual dysfunction (male and/or female), unexplained infertility, and uterine

(e.g., the presence of leiomyomas not indenting the uterine cavity) or cervical factor. The couple having more than one infertility diagnosis, only the primary diagnosis was considered for this study purposes.

In all treatment strategies reproductive outcome of the first IUI cycles were compared with age matched control group at a single fertility centre. Positive serum β hCG > 20 mIU/ml which was done 2 weeks after the IUI procedure was primary outcome. Biochemical pregnancy loss, clinical pregnancy rate, live birth rate, clinical abortion, ectopic pregnancy were secondary outcomes.

Subsequently, reproductive outcomes of IUI cycles as per treatment type (i.e., clomiphene citrate, letrozole, gonadotropins or combination of oral ovulogens and gonadotropins) were evaluated between both AMH groups while adjusting for body mass index (BMI), number of follicles >10 mm at the time of trigger, and total gonadotropin dose.

Finally, cumulative reproductive outcomes including up to 3 IUI cycles were calculated and compared between groups. LBR was described as the number of gestations resulting in live birth divided by the total number of IUI cycles. Biochemical pregnancy loss was defined as a positive serum β hCG value that later on underwent spontaneous decline without showing any evidence of intrauterine pregnancy on ultrasound. Clinical abortion described pregnancies in which an intrauterine gestational sac was identified on ultrasound but the pregnancy didn't progress. Ectopic pregnancies were those in which either an extrauterine gestational sac was seen on transvaginal ultrasound, or a dilation and curettage failed to obtain products of conception and the serum β hCG level declined after treatment with either methotrexate or operative laparoscopy.

Statistical Analysis

Descriptive statistics were obtained for all the parameters. For all quantitative parameters mean and standard deviation were used. Difference between percentages was studied using Chi-square test generalised to the comparison of several proportions. To describe about the data descriptive statistics frequency analysis, for categorical variables percentage analysis was used and for continuous variables the mean and S.D. was used. To find the association of significance in categorical data the Chi-Square test used. The Statistical significance was defined as a P value of <0.05 by statistical package for social science software (SPSS Version 23).

Ethical Approval

All included patients undergoing evaluation and treatment were consented at the initiation of treatment. Institution review board approval was granted for retrospective queries of the medical record in September 2021. (No./ MGMC&H/IEC/JPR/2021/542)

Results

The patients who included in the final analysis of study after application of exclusion criteria were in total 385, 112 (29.09%) with AMH < 1.2 ng/mL and 273 (70.91%) with AMH ≥ 1.2ng/mL. Characteristics of these couples with female patients < 35 years of age undergoing treatment with intrauterine insemination (IUI) were stratified by female anti Mullerian hormone (AMH) level of < 1.2 ng/ml (n=112) and ≥ 1.2 ng/ml(n=273)

Table 1: Demographic variables of couples with female patients < 35 years of age undergoing IUI treatment stratified by female AMH level

Patients' characteristics	AMH <1.2 ng/ml (N=112)	AMH≥1.2 ng/ml (N=273)	P value

AMH	0.56(±0.25)	5.2(± 5.8)	<.001
D3 FSH	8.6(± 3.9)	5.9(±0.76)	<.001
AFC baseline	10.8(± 4.2)	21.2(±12.1)	<.001
Age (years)	32.1(± 1.6)	29.5(±1.8)	NS
BMI (kg/m2)	25.1(± 4.5)	26.4(±5.9)	NS
TMSC Post wash (millions)	56.5(± 39.2)	54.3(±35.6)	NS
Max. estradiol level on day of trigger	432(±157)	563(±275)	NS
Total follicle > 10mm on day of trigger	3.2(±0.8)	3.7(±1.1)	NS
Gonadotropin used	1345±267 IU	725±135 IU	<0.001

As anticipated, the mean AMH, day 3 serum FSH, and basal AFC by transvaginal ultrasound significantly different between patients grouped by AMH <1.2 ng/mL & with AMH ≥1.2ng/mL (AMH 0.56 ng/mL vs. 5.2 ng/mL, P < .001, respectively; day 3 FSH 8.6 vs. 5.9, P < .001, respectively; AFC 10.8 vs. 21.2, P < .001, respectively). Serum AMH values and AFC were found to be strongly correlated.

No difference was observed between the different groups in the demographic characteristics of patients studied, patients with AMH <1.2 ng/mL & with AMH ≥ 1.2ng/mL in respect to mean age, BMI, post wash total motile sperm count at time of IUI, maximum estradiol level on day of trigger, and total number of follicles >10 mm present at the time of hCG injection for final oocyte maturation.

Table 2: Reproductive outcome after first IUI in young (<35 years) by serum AMH level

	AMH <1.2 ng/ml (N=112)	AMH ≥ 1.2 ng/ml (N=273)	P value
positive pregnancy test	21.43% (24/112)	24.54% (67/273)	NS
Biochemical loss	4.17% (1/24)	2.99% (2/67)	NS
Clinical pregnancy loss	8.34% (2/24)	10.45% (7/67)	NS
Ectopic pregnancy	0%	1.49% (1/67)	NS
Live birth rate	18.75% (21/112)	20.87% (57/273)	NS

Reproductive out comes were compared between the groups using logistic regression adjusting for BMI, number of follicles at time of trigger and treatment type. No statistically significant difference was identified between groups.

Table 3: Cumulative pregnancy rate & live birth rate after 3 IUI cycles

After 3 IUI cycles	AMH <1.2 ng/ml (N=112)	AMH ≥1.2 ng/ml (N=273)	P value
Cumulative pregnancy rate Positive hCG	36.6% (41/112)	37.36% (102/273)	NS
Cumulative live birth rate	28.57% (32/112)	30.40% (83/273)	NS

Reproductive outcome was compared between the groups and found no statistically significant difference

Table 4: Different aetiology of infertility by serum AMH level in young females < 35 years

	AMH <1.2 ng/ml (N=112)	AMH ≥ 1.2 ng/ml (N=273)	P value
Diminished ovarian reserve only	32.14% (36/112)	1.10% (3/273)	<0.001
Hypothalamic amenorrhea and other ovulatory dysfunction	11.60% (13/112)	32.23% (88/273)	<0.001
Male factor	22.32% (25/112)	24.18% (66/273)	>0.05
Recurrent pregnancy loss	14.28% (16/112)	16.84% (46/273)	>0.05
Sexual dysfunction (male or female)	10.71% (12/112)	13.55% (37/273)	>0.05
Uterine /cervical factor	8.93% (10/112)	12.08% (33/273)	>0.05

Infertility diagnoses were compared between groups. As anticipated, patients with AMH< 1.2 ng/mL undergoing an IUI cycle were found to have a higher incidence of diminished ovarian reserve as their primary infertility diagnosis as compared to patients with AMH ≥1.2 ng/mL (32.14% vs. 1.10%, respectively; P < .001). Alternatively, patients with AMH <1.2 ng/mL were found to have a lower incidence of ovulatory dysfunction, including hypothalamic amenorrhea (11.60% vs. 32.23%, P < .001), as compared with age-matched controls engaging in an IUI cycle.

Table 5: Reproductive outcome after first IUI in young women (< 35years) by serum AMH level in different protocols of ovulation induction in IUI cycles

	Gonadotropin cycles (N=109)		Clomiphene citrate cycles (N=76)		Letrozole cycles (N=48)		Oral ovulogens & gonadotropins (N=152)	
	AMH <1.2 (N=34)	AMH ≥1.2 (N=75)	AMH <1.2 (N=12)	AMH ≥1.2 (N=64)	AMH <1.2 (N=8)	AMH ≥1.2 (N=40)	AMH <1.2 (N=58)	AMH ≥1.2 (N=94)
Positive pregnancy test	23.53% (8/34)	26.66% (20/75)	16.67% (2/12)	21.87% (14/64)	12.50% (1/8)	20.00% (8/40)	22.41% (13/58)	26.59% (25/94)
Biochemical pregnancy loss	12.50% (1/8)	0%	0%	7.14% (1/14)	0%	0%	0%	4% (1/25)
Clinical pregnancy loss	0%	5% (1/20)	0%	7.14% (1/14)	100% (1/1)	12.50% (1/8)	7.69% (1/13)	16.00% (4/25)
Ectopic pregnancy	0%	0%	0%	0%	0%	0%	0%	4.00% (1/25)

Live birth rate	20.59% (7/34)	25.33% (19/75)	16.67% (2/12)	18.75% (12/64)	0.00%	17.50% (7/40)	20.69% (12/58)	20.21% (19/94)

There is a slight increase in the percentage of positive pregnancy test and live birth rate among participants who have an AMH Level ≥1.2 in all the protocols but the difference is not statistically significant in any protocol.

Table 6: Relationship between Pregnancy Test Result & AMH Level among different protocols of ovulation induction.

Protocol of ovulation induction	AMH Level	Pregnancy test		Positive Pregnancy Percentage	p Value
		Positive	Negative		
Gonadotropin cycles	<1.2	8	26	23.53	0.82
	≥1.2	20	55	26.67	
Clomiphene citrate cycles	<1.2	2	10	16.67	1
	≥1.2	14	50	21.88	
Letrozole cycles	<1.2	1	7	12.50	1
	≥1.2	8	32	20.00	
Oral ovulogens & gonadotropins	<1.2	13	45	22.41	0.7
	≥1.2	25	69	26.60	
Total	<1.2	24	88	21.43	0.6
	≥1.2	67	206	24.54	

There is an apparent increase in the percentage of positive pregnancy test among participants who have an AMH Level ≥1.2 in all the protocols but the difference is not statistically significant in any protocol.

Table 7: Relationship between Live birth & AMH Level among different protocols of ovulation induction.

Protocol of ovulation induction	AMH Level	Live Birth		Live Birth Percentage	p Value
		Present	Absent		
Gonadotropin cycles	<1.2	7	27	20.59	0.63
	≥1.2	19	56	25.33	
Clomiphene citrate cycles	<1.2	2	10	16.67	1
	≥1.2	12	52	18.75	
Letrozole cycles	<1.2	1	8	11.11	0.58
	≥1.2	7	33	17.50	
Oral ovulogens & gonadotropins	<1.2	11	47	18.97	0.84
	≥1.2	19	74	20.43	
Total	<1.2	21	91	18.75	0.49
	≥1.2	57	216	20.87	

There is an apparent increase in the percentage of live births among participants who have an AMH Level ≥1.2 in all the protocols but the difference is not statistically significant in any protocol.

The incidence of conception (i.e., positive serum hCG level) and LBR were marginally lower but not statistically significant for patients with AMH< 1.2 ng/mL while no difference was found with respect to other reproductive outcomes in different treatment strategies groups.

Young patients (< 35 years of age) with diminished ovarian reserve conceived as often as their age matched control after IUI and had similar per cycle and cumulative pregnancy rate whatever protocol was used.

IUI Cycle Treatment Strategies

Of patients undergoing ovarian stimulation followed by IUI, the proportions of various medications used differed between AMH groups, but the trends of most commonly and least commonly used medications were almost same between the groups; for example, the use of exogenous gonadotropins (i.e., recombinant FSH or human menopausal gonadotropin) was the most common treatment strategy (82.14%. n= 92/112, of patients with AMH <1.2 ng/mL. and 61.90%, n= 169/273, of patients with AMH≥ 1.2 ng/mL; P < .001) followed by clomiphene citrate, which was administered to 10.71% (n= 12/112) of patients with AMH <1.2 ng/mL and 23.44% (n = 64/273) of patients with AMH≥ 1.2 ng/mL (P < .001). Finally, letrozole was administered to a minority of patients in both groups (7.14%, 8/112, of patients with AMH <1.2 ng/mL and 14.65%, (n = 40/273), of patients with AMH≥ 1.2 ng/mL; P < .05).

Reproductive Outcomes of the First IUI Cycle - All Treatment Strategies

Overall, reproductive outcomes after first IUI were similar between young couples with AMH< 1.2 ng/mL undergoing their first IUI cycle as compared to those with AMH≥ 1.2 ng/mL when adjusting for BMI, number of follicles at time of hCG injection, and treatment type. Specifically, patients with AMH <1.2 ng/mL had a similar incidence of conception (as evidenced by a positive serum pregnancy test), biochemical pregnancy loss, clinical pregnancy loss, ectopic pregnancy, and live birth as compared to those with AMH≥ 1.2 ng/mL.

With respect to multiple gestations, overall, 8.33% of pregnancies were twin gestations (n = 2/24) in the AMH< 1.2 ng/mL group, whereas 4.48% of pregnancies were twin gestations (n =3/67) in the group with AMH≥ 1.2 ng/mL.

Reproductive Outcomes of the First IUI Cycle: Per Treatment Strategy

Young patients with low versus normal AMH were then compared by IUI treatment strategy type (i.e., gonadotropin/ IUI, clomiphene citrate/IUI, letrozole/IUI or oral ovulogens & gonadotropins/ IUI). The vast majority of patients in both AMH groups undergoing gonadotropin/ IUI cycles-initiated treatment with 75 IU per day. The dosage of gonadotropins was titrated to develop more than one maturing follicle (>10 mm). The total FSH/HMG dose in international units (IU) was calculated per gonadotropin/IUI cycle. The average FSH/HMG dose per cycle was significantly higher for patients with AMH <1.2 ng/mL than for those with AMH≥ 1.2 ng/mL (1345±267 IU vs.725±135 IU; P < .001). When evaluating the reproductive outcomes of gonadotropin-only cycles (n = 109) between AMH groups while adjusting for total FSH/HMG dose in addition to BMI and total number of follicles at time of trigger, the incidence of conception (i.e., positive serum hCG level) was marginally lower for patients with AMH <1.2 ng/mL. No difference was seen with respect to other reproductive outcomes, such as the incidence of biochemical loss, clinical loss, ectopic pregnancy.

No difference was identified when comparing reproductive outcomes of patients with low versus normal AMH undergoing clomiphene citrate/IUI (n=76), letrozole/IUI (n =48), or oral ovulogens & gonadotropin/IUI (n =152) treatments.

Cumulative Reproductive Outcomes

Cumulative conception rates (i.e., positive serum hCG) of these 385 patients were assessed up to three IUI cycles, which was the maximum number of cycles containing patients in both AMH groups. There was a total of 652 IUI cycles included in this analysis. No difference in cumulative conception rates (i.e., positive serum hCG) were identified when comparing patients with AMH <1.2 ng/mL to patients with AMH ≥1.2 ng/mL. Additionally, no difference in cumulative live birth rates were identified between AMH groups.

Discussion

Opposite to prediction, young patients (<35 years of age) with reduced ovarian reserve (as shown by an AMH <1.2 ng/mL) conceived as often as age-matched controls after IUI. Additionally, once pregnant, all pregnancy outcomes were similar between patients with low AMH (<1.2 ng/mL) as compared with normal AMH ≥ 1.2 ng/mL), regardless of IUI treatment type. Also, cumulative conception and live birth rates were similar between young patients with diminished ovarian reserve as compared to those without. When evaluating gonadotropin-only cycles, patients with AMH <1.2 ng/mL required higher total recombinant FSH/HMG to achieve pregnancy outcomes similar to those of patients with AMH ≥1.2 ng/mL. As such, when controlling for FSH/HMG dose, patients with AMH <1.2 ng/mL demonstrated marginally reduced conception rates but otherwise similar reproductive outcomes as compared to patients with AMH ≥ 1.2 ng/mL. These data imply that although a quantitative distinction between groups exists, a qualitative difference is not present. Furthermore, these data from IUI cycles corroborate findings from IVF cycles, indicating that young women with evidence of diminished ovarian reserve do not exhibit a qualitative diminution in outcomes as evidenced by equivalent usable blastocyst development rates per fertilized oocyte and live birth rates per embryo transferred as compared to age matched controls [19].

As a predictor of ovarian response to stimulation, AMH can probably be correlated with the likelihood of pregnancy during a stimulated cycle when oocyte quality is assumed to be excellent, as when female age is <35 years. Therefore, the intimation of a reduced follicular pool as reflected by a diminished serum AMH doesn't appear to translate into reduced per cycle fecundability or fecundity at female age <35 years because of optimization of follicular recruitment during a superovulation/IUI cycle. As such, even with a diminished follicular pool, follicular recruitment is unlikely to be exceedingly deficient in this age group. Additionally, superovulation in many of the study treatment cycles (e.g., average of three follicles >10 mm at hCG trigger) likely overcame any possible deficiency in follicular recruitment, as demonstrated by the results of the gonadotropin-only cycles.

Although generally heralded as a predictive marker for response to ovarian stimulation, prior studies have described correlations between AMH and reproductive outcomes in both natural cycles also as those using ovarian stimulation followed by IUI [27]. The bulk of these prior studies include women of all reproductive ages, with the mean female age typically greater than 35 years. Only two prior studies have evaluated the association between AMH and reproductive outcomes in

sub fertile couples with a mean female age <35 years undergoing IUI.

A Danish study published in 2010 evaluated the prognostic value of several ovarian reserve parameters, including AMH, in exogenous gonadotropin/IUI cycles of 123 couples [28]. Female patients between 25-39 years old were included. In this study the primary outcome was ovarian response, serum AMH values of patients achieving clinical pregnancy (n =23) were compared to those of patients not achieving pregnancy (n = 100). The mean AMH value of patients who achieved clinical pregnancy wasn't found to differ from that of patients who didn't (1.47 ng/mL vs. 1.48 ng/mL, P > .05).

In a latest study of 61 couples with unexplained infertility taking gonadotropin stimulation/ IUI, investigators found that there is no correlation between serum AMH and clinical pregnancy rate [26]. However, unlike the present study, both prior investigations didn't mention information regarding reproductive outcomes after IUI in young infertile women (<35 years of age) with serum AMH levels <1.2 ng/mL, as this population was not specifically evaluated.

limitations of our study relate primarily to those inherent to its retrospective nature. For example, the retrospective nature of the study limits the accuracy of infertility diagnoses assigned to each patient, as these were obtained from the medical records. However, infertility treatment history is elicited by all providers, and it is standard practice to move on to IVF if at least three failed IUIs have been performed. A limitation of the cumulative analyses includes the inability to determine elective patient drop-out prior to achieving pregnancy after any given number of IUI cycles less than three. Additionally, AMH levels were overwhelmingly performed at a single reference laboratory commonly used by the infertility practice.

The inclusion of different treatment strategies with IUI (i.e., the various stimulated cycles) may be viewed as a limitation; however, all treatment strategy and number of follicles recruited (>10 mm) at the time of hCG trigger were controlled for in logistic regression analyses of reproductive outcomes. Moreover, analyses of reproductive outcomes by AMH group were performed per treatment strategy. Additionally, individual patient history, including diagnosis and length of infertility, may have contributed to the level of superovulation desired, which may have biased pregnancy results in favour of those with more mature ovarian follicles. The disproportionate use of gonadotropins as compared to other methods of superovulation and/or ovulation induction deserves additional consideration i.e., 82.14%. n= 92/112, of patients with AMH <1.2 ng/mL. and 61.90%, n= 169/273, of patients with AMH≥ 1.2 ng/mL; P < .001). Moreover, superovulation with gonadotropins was used more frequently for patients with low AMH. Such a discrepancy is reflected in the higher multiple pregnancy rate in the low as compared to the normal AMH group (8.33% of pregnancies were twin gestations (n = 2/24) in the AMH< 1.2 ng/mL group, whereas 4.48% of pregnancies were twin gestations (n =3/67) in the group with AMH≥ 1.2 ng/mL).

Another limitation of this study is that a specific AMH threshold value for diminished ovarian reserve has not been definitively determined. In the present study, AMH of 1.2 ng/mL was chosen as a threshold value as per one of the Poseidon criteria of poor responder, above which ovarian reserve was presumed to be normal for a woman <35 years of age, and below which ovarian reserve was considered to be abnormal, or low, for this age group.

However, although it would be generally agreed that an AMH of <1.2 ng/mL for woman <35 years old is abnormally low, this threshold value is still somewhat arbitrary. Additionally, women with values just above and below this threshold value may have similar ovarian reserve and/or response to stimulation but were placed in different categories and compared to one another.

Future studies should include the prospective evaluation of this group of young women (<35 years of age) with diminished ovarian reserve. In such studies, a thorough evaluation and documentation of the rationale for each treatment strategy followed by stratifying outcomes by treatments would be required to confirm relationships. Additionally, using a combination of ovarian reserve testing parameters to distinguish those patients at risk for diminished ovarian reserve would add further accuracy to future analyses.

In conclusion, young patients who are <35 years of age, with diminished ovarian reserve (AMH <1.2 ng/mL) conceived as often as age matched controls and had pregnancy outcomes similar to those (AMH ≥1.2ng/mL) after IUI. Among gonadotropin/ IUI cycles, a relative increase in total FSH/HMG dose was needed to achieve similar reproductive outcomes in diminished ovarian reserve group. Cumulative conception and live birth rates were also similar between young patients with diminished ovarian reserve as compared to those without. These data indicate a quantitative, not qualitative distinction between groups.

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