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Review Article

Delayed Age at Menarche Can be a Useful Predictive Sign of Women with Early Low Ovarian Reserve

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Abstract

Objective: Delayed age at menarche (AAM) can be a useful predictive sign of early decreased ovarian reserve hence oocytes freezing could be offered.

Design and Methods: This is a cross-sectional observational, single-centre study conducted in the department of the British-Syrian IVF and Fetal Medicine Centre, AL Rasheed Hospital, Syria the study initially included 3370 women younger than 38 years who approached fertility clinic between August 2018 and May 2022. This study comprised 3370 women who questioned in their fertility history about menarche age and their current health and lifestyle. Observations were documented and analysis.

Result: Age at menarche was late in women with low ovarian reserve. The research sample consisted of 3370 women between the ages of 20 and 38 years, the Mean ± St.D age was (31.24 ± 4.63), there were 2830 (84.0%) women as study group with AMH < 1.1, included 1730 (61.1%) with Late menarche > 14 years, and in control group 540 (16.0%) women with AMH ≤ 1.1 included 10 (1.9%) with Late menarche > 14 years, we found there is A significant relationship between low AMH and Late menarche (Chi-Square p-value: 0.00 < 0.05).

Conclusion: Delayed AAM (age at menarche) after 14 years old is associated with higher risk of low ovarian reserve at earlier age, our findings suggest an alert to investigate AMH Level at younger if there is late incidence of menarche, hence oocytes freezing could be offered or encouraged to conceive early.

***Keywords**: Menarche; Anti-Mullerian Hormone (AMH); Ovarian Reserve (OR); Age at Menarche (AAM); DFOR (Diminished Functional Ovarian Reserve)*

Introduction

Menarche is the first menstrual period in a female adolescent, with the average age of onset being 12.4 year [1]. Menarche occurs in the setting of a maturing hypothalamic-pituitary-ovarian (HPO) axis and relies on the following processes: normal hypothalamic and pituitary function, normal female reproductive anatomy, normal nutrition, and the general absence of other intervening chronic illnesses. It is a marker of normal female reproductive health and wellness. Most females recognize menarche as their body's critical declaration of fertility [2].

The median age at menarche for all US girls is 12.43 years, ten percent of all USA girls are menstruating by 11.1 year of age and 90% are menstruating by 13.75 years of age, while in the Middle East the mean age of menarche 13.05+/- 1-32 years which is greater than in north America and most EU countries [3].

It is important to present race-specific national estimates separately because there are significant differences in the ages at menarche between racial groups [4]. In females, the normal onset of puberty ranges from 8 to 13 years old, averaging age 10 years in White Americans and age 8.9 years in African-Americans. Puberty in females begins with the development of breast buds under the areola, also known as thelarche, and represents entry into Tanner Stage 2. As puberty progresses, the glandular tissue of the breast increases in size and changes in contour. In females, thelarche is followed in 1 to 1.5 years by the onset of sexual hair (pubic and axillary), known as pubarche. Menarche, the onset of menses, arrives on average at age 12.5 years, regardless of ethnicity, following thelarche on average by 2.5 years (range 0.5 to 3 years). Between Tanner Stage 2 and 3 breast development, females experience peak height velocity. African-American females have closer to 3 years between their thelarche and menarche, accounting for greater height potential [5], the physiological consequences of early or late menarche are equivocal. One study indicates that girls with late age at menarche require a longer time period before they reach ovulatory cycle than that required by girls with early age at menarche. Other studies indicate that late age at menarche is associated with a decreased time to first conception. Although data from these two studies appear contradictory, they imply that either a late age or early age at menarche might affect fecundity and fertility [6]. In addition of age at menarche (first menstrual period) which has been associated with future health [7], menarche is considered early if it occurs before or at ten years of age and late if it occurs at or later than 15 years of age [8], the precise determinants of menarche age remain to be understood, genetic influences, socioeconomic conditions, general health and well-being, nutritional status, certain types of exercise, seasonality, and family size possibly play a role [9]. Menstrual disorders are frequent and may be associated with early menarche, but not with BMI. It is important to encourage self-monitoring of the menstrual cycle to detect menstrual disorders timely and promote health and well-being [10]. It remains uncertain, however, whether age at menarche is related to age at menopause and reproductive period [11].

Some studies report the relation between menarche and early menopause, other studies report the relation between menarche and late menopause [12,13].

The variation in ovarian reserve is an important issue in our days and Anti-Müllerian hormone (AMH) is a hormonal marker help in detecting and regulation women reproductive period. Anti-Mullerian hormone (AMH) is produced by granulosa cells of small, growing follicles in the ovary. Serum AMH levels strongly correlate with the number of growing follicles, and therefore AMH has received increasing attention as a marker for ovarian reserve. Serum AMH remains the preferred ovarian reserve marker, therefore evaluate the ovarian reserve refers to a woman's fertility potential in the absence of any problems in the reproductive tract (fallopian tubes, uterus, vagina). It mainly depends on the number and quality of eggs in the ovaries and how well the ovarian follicles are responding to the hormonal signals from the brain. Age the most important factor affects ovarian reserve then the success rates of infertility treatments as well as the natural ability to get pregnant. This review summarizes recent findings and limitations in the application of serum AMH in ovarian reserve assessment [14]. Low AMH levels may suggest a shortened reproductive window [15], and this decreasing in ovarian reserve among women at an early stage of their life has become a problem and we should advise them about their reproductive life chances and ensuring that they are fully aware of factors that might influence their prospects for having a family. Unfortunately, our society encourages career development for men and women without providing, suitable flexibility and support for starting families, therefore, we seek to look for signs that predict the possibility of decreasing ovarian reserve at early age, including a delayed age of menarche. This study explains the correlation between late age at menarche ≤ 14 years old and low AMH at early age of the reproductive period.

Our study searching for predictable sign of the relationship between occurrence possibility of low ovarian reserve in early age and delayed age of menarche.

However, studying demographic patterns and trends in menarche may also be informative because earlier age at menarche has been associated with greater risk of health problems including breast cancer, obesity, diabetes, and liver disease [7,16]. In addition, early age at menarche is associated with early age at menopause [17]. Reaching menarche earlier than peers has also been associated with higher risk of depression, eating disorders, and substance abuse during adolescence [18]. Some explanations for early onset of menarche include genetics and body fat (via production of leptin), while others may be related to environmental factors that may impact reproductive hormones, such as growing up in a father-absent home, stepfather presence, and family conflict [19].

Study factors

Age at menarche

Age at menarche (in years) was based on the following question: 'At what age (years old) did you have your first menstrual period?' at young women 20 - 37 years old, in our sample age at menarche was 10 until 18 years, in our region, Middle East, 11 - 13 years considers as a normal menarche group and ≤ 14 years old as late menarche group.

AMH measurement

Serum AMH levels were measured with an enzyme immunoassay kit (YHLO, Shenzhen, China). The limit of detection (LoD) was 0.06 ng/ml, and the intra- and interassay coefficients of variation (CVs%) were ≤ 15%.

Statistical analysis

Study sample

The research sample consisted of 3370 women between the ages of 20 and 37 years with an average age of 31.24 years, they were divided into two groups:

1. **Study group**: 2830 women with low ovarian reserve by AMH < 1.1 according to Bolonga criteria.
2. **Control group**: 540 women who have higher level of AMH ≤ 1.1.

We excluded women with ovarian or uterus surgery (ovarian cyst-myomectomy-cesarean) women with endometriosis G3-4, women who have been exposed to radiotherapy or chemotherapy.

Statistical processing used

The statistical tests that fit the research data were used, which are the nominal and ordinal data, as most data were reported as numbers and ratios. Chi-square test was used to assess the correlation between AMH and late menarche. For all purposes, statistical significance was determined as $p < 0.05$. All analyses were performed using the Statistical Package for Social Sciences (SPSS-25).

Results

The research sample consisted of 3370 women, the age of women ranged between 20 and 37 years the Mean ± St.D age was (31.24 ± 4.63). The age of menarche ranged from 10 to 18 years, with Mean ± St.D age was (13.7 ± 1.80). It was found that AMH level in women ranged between 0.01 and 9 with Mean ± St.D age was (1.08 ± 1.38).

Description of study variables

	N	Min	Max	Mean	Std. Deviation
Age	3370	20	38	31.24	4.630
Menarche	3370	11	18	13.79	1.803
AMH	3370	0.01	9	1.08	1.385

Table 1

		N	%
AMH	Study Group (AMH < 1.1)	2830	84.0
	Control Group (AMH ≤ 1.1)	540	16.0
	Total	3370	100.0
Menarche	Normal	1630	48.4
	Late	1740	51.6
	Total	3370	100.0

Table 2

Normality of data

The quantitative study variables were subjected to the Kolmogorov-Smirnov normal distribution test to investigate their distribution, it was found that age, menarche age and ovarian reserve are not distributed normal because the (p-value = 0.00 < 0.05) therefore Mann-Whitney test used as alternative to T-test and Spearman's rho correlation coefficient used as a nonparametric alternative to Pearson's correlation coefficient to study the relationship between the variables and the following table shows the test results.

	Statistic	Df	P-value
Age	0.139	3369	0.000
AMH	0.342	3369	0.000
Menarche	0.154	3369	0.000

Table 3: *Normal distribution test of study variables.*

Correlation and different study

Study the differences between the groups of AMH and AAM

		N	Min	Max	Mean	Std. Deviation	Mann-Whitney P-value
AMH	Study Group	2830	0.01	1.2	0.61	0.31167	< 0.001*
	Control Group	540	0.88	9	3.5348	2.08126	
Menarche	Study Group	2830	11	18	14.1007	1.7789	< 0.001*
	Control Group	540	11	14	12.2037	0.83281	
*Significant at the 0.05 level.							

Table 4

The results of the previous table show the following: there is a significant difference between the two groups of the study (p-value = 0.00 < 0.05) in AMH and AAM that mean the AMH is significant lower in the study group and AAM is significant late in the study group.

Study the relationship between the AMH and AAM

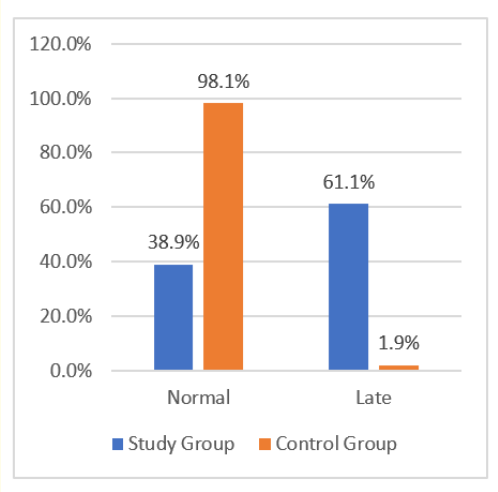
The following table of intersection shows the relationship between the AMH and AAM using the chi-square independence tests.

Studied		Group		Chi-Square P-value
		Control		
AMH	> 1.1	2830 (100.0)	0 (0.0)	< 0.001*
	≤ 1.1	0 (0.0)	540 (100.0)	
Menarche	Normal	1100 (38.9)	530 (98.1)	< 0.001*
	Late	1730 (61.1)	10 (1.9)	
*Significant at the 0.05 level.				

Table 5

The results of the previous table show the following:

- 100.0% of the women in the study group their AMH levels were smaller than 1.1 and the level of AMH in the study group are lower compared to women in the control group.
- 61.1% of women in the study group had late age of menstruation (older than 14 years), while 98.1% of women in the control group, had normal age of menstruation with (p-value = 0.00 < 0.05) so there is a real statistically significant relationship between late age of menarche and low AMH.
- The following graphs show the percentages of the categories menarche age by study groups.



Graph 1: *Percentages of the distribution of menarche groups by group.*

Study the relationship between ovarian reserve and each of (menarche, age)

In order to study the relationship between ovarian reserve and each of (menarche, age), Spearman's rho correlation coefficient will be used, the alternative to the Pearson correlation coefficient to verify the existence of a statistically significant real relationship between ovarian reserve and the variables mentioned.

Relationship between ovarian reserve and each of (menarche, age)

	AMH		
	N	**R**	**P-value**
Age	3370	-0.439*	< 0.001
Menarche	3370	-0.241*	< 0.001
*Significant at the 0.05 level.			

Table 6

The previous table shows the following:

- The relationship between age and ovarian reserve (-0.439) (p-value = 0.00 < 0.05) there is a statistically significant real correlation between the two variables, which is an average inverse relationship, and means that increasing age leads to a decrease in ovarian reserve.
- The relationship between menarche and ovarian reserve -0.241 (p-value = 0.00 < 0.05) there is a statistically significant real correlation between the two variables, which is a weak inverse relationship, which means that delayed menarche leads to a decrease in ovarian reserve.

Discussion

This cross sectional study aimed to explore whether late menarche correlate with low serum AMH In our study we found there is association between late menarche and decreased AMH level at early age, one study found there is indirect association between age at menarche and age at natural menopause, their investigation was carried out from January 2015 to May 2015 among 510 Rajbanshi women aged between 45 and 55 years residing in the district of Darjeeling, West Bengal, India. A structured schedule was used to collect data on ages at menarche and natural menopause [13]. In other large population study of 336 788 women in Norway, median age at menopause was close to 51 years, and age at menopause was almost independent of age at menarche. Accordingly, women with early menarche had, on average, a reproductive period that was several years longer than women with late menarche. In addition the duration of the reproductive period decreased by increasing age at menarche and it suggests that age at menarche is a strong indicator for the duration of women's reproductive period [12]. Some studies suggested that late age of menarche is associated with a slightly higher risk of subfecundity and infertility and Future studies using prospectively collected information on puberty as well as fecundity are needed [20] in contrast as Andrea Weghofe study about Age at menarche and diminished ovarian function it shows a significant impact of age at menarche on predictor of DFOR (Diminished Functional Ovarian Reserve) risk later in life among infertile women. The occurrence of menarche may relate to follicular pool size and/or speed of follicle recruitment, which in turn is predictive of occurrence of DFOR later in life [21]. In light of these results, we need additional studies in order to maintain and stay within the safe limits of the reproductive period.

Conclusion

In conclusion delayed AAM (age at menarche) after 14 years old is associated with higher risk of low ovarian reserve at earlier age. We do not say every woman with AAM has low AMH at earlier age than others but maybe it will be indirect marker to investigate AMH at early stage of reproductive life to provide either appropriate counseling or preservation therapy in some cases.

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