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Association of age at menarche and different causes of infertility: a retrospective study of 7634 women undergoing assisted reproductive technology

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Abstract

Background Infertility has become a world-wide public health problem. To identify women in a high-risk of infertility at an early stage when more treatments are available, early risk factors such as age at menarche (AAM) are being investigated. AAM is often used in epidemiological studies as a marker of the timing of pubertal development and the onset of the hypothalamic-pituitary-ovarian axis functions. Therefore, our study aimed to elucidate the association of AAM and different infertility causes in women undergoing assisted reproductive technology.

Methods A total of 7643 women were retrospectively included from the reproductive hospital affiliated with Shandong University between January 2017 and December 2019. Multivariate logistic regression models and restricted cubic spline (RSC) were performed to analyze the relationship between AAM and different infertility causes. Information on variables was obtained from medical records.

Results Compared with primary infertility, secondary infertility would 7.7% increase risk with each one-year increase in menarche age after adjusted odds ratio (OR) [95% confidence interval (CI)], 1.077 (1.036, 1.119). In primary infertility group, each one-year increase in menarche age corresponded with a 16.7% increase in PCOS risk OR (95% CI), 1.218 (1.138, 1.303). AAM of women with DOR were significantly decreased in primary and secondary infertility group [OR (95% CI), 0.832 (0.716, 0.965) and OR (95% CI), 0.720 (0.603, 0.859)], respectively compared with the reference group. Moreover, there is a non-linear dose–response relationship between DOR ($P < 0.001$) with AAM.

Conclusion This study demonstrates a significant impact of AAM on endocrine-related infertility in women. Further research on the relationship between the onset of menarche and the pathogenesis of infertility is warranted.

Keywords Infertility, Age at menarche, Polycystic ovary syndrome, Endometriosis, Diminished ovarian reserve

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Introduction

Infertility, defined as failure to achieve pregnancy after 12 months or longer of regular unprotected sexual intercourse [1, 2], affects 1 in 6 couples in the world [3, 4] and its incidence is gradually increasing [5, 6]. In China, the incidence of infertility in reproductive-aged women is 15.5% [7]. In 85% of infertile couples, infertility is caused by an identifiable physiological abnormality or underlying disease [1]. A variety of causes contribute to female infertility, including tubal factors, ovulatory disorders, endometriosis and unexplained conditions [1, 3]. Common causes of anovulation include polycystic ovary syndrome (PCOS), hypothalamic amenorrhea (HA), and diminished ovarian reserve (DOR) [8]. In order to identify women in a high-risk of infertility at an early stage when more treatments are available, early risk factors like age at menarche (AAM) are being investigated. Menarche is the milestone that indicates the reproductive capacity [9] and has significant health implications. AAM, which a girl begins her first menstrual period, is often used in epidemiological studies as a marker of the timing of pubertal development and the onset of the hypothalamic-pituitary-ovarian axis functions [10]. However, a significant worldwide decline in AAM has been reported, which has been widely assessed in studies [11–13]. This trend presumably reflects changes in the nutritional status and endocrine environment of children [14].

In recent decades, an increase in the incidence of infertility [15] has coincided with a long-term decline in the mean AAM [16]. Although the significant increase in the incidence of infertility is undoubtedly driven by dramatic environmental and lifestyle changes, these concurrent trends may in part reflect a biological link between the timing of puberty and the risk of infertility. The causes of infertility are diversity and its pathophysiological changes are complex, so the relationship between AAM and the risk of infertility has not been well illustrated. It has been identified that timing of menarche is related to PCOS and DOR. The patients with PCOS were significantly older at menarche and women with a DOR were younger at menarche [17]. Besides, early menarche also increased the risk of endometriosis [18–20]. However, the conclusion was still controversial with opposite findings. It was found that women with late menstruation were more likely to suffer from endometriosis comparing to women with normal menarche [21].

Restricted cubic spline (RCS) analysis models allow for deviations from linearity and allow flexibility in modeling the relationship between AAM and infertility. There are no studies analyzing the dose-response relationship between AAM and specific infertility risk at present. Therefore, we designed a retrospective study to elucidate the impact of AAM on different infertility causes and to explore the dose-response relationship between AAM and different infertility causes by RCS analysis.

Materials and methods

Study participants

The women treated by in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) were recruited between January 2017 and December 2019 from the Center for Reproductive Medicine, Cheeloo College of Medicine, Shandong University. A total of 7643 women with single factor infertility were included in this study. The following subjects were excluded from the study: (i) women with any chromosomal or genetic defect such as fragile X or Turner syndrome, (ii) women who had life-threatening major diseases such as hepatic failure, renal failure, malignant tumors, or severe cardiovascular and cerebrovascular diseases and (iii) women with missing or implausible information. All participants provided written informed consent. The study was approved by the Reproductive Medicine Ethics Committee, Hospital for Reproductive Medicine Affiliated to Shandong University.

Exposure assessment

Participants were asked to recall AAM as the exact age at first menstruation or exact calendar year of first menstruation (years; registered only in integers). We mitigated recall bias in self-reported AAM by, (i) using medical records as our data source, which are objective; (ii) using a standardized interview guide to ensure that all participants were asked the same questions to minimize bias due to differences in questioning styles; and (iii) training healthcare professionals conducting the interviews to ensure that they asked consistent and neutral questions and avoid leading questions.

Outcome assessment

The medical information on infertility diagnosis was obtained from the medical records. Primary infertility was defined as a woman who has never been diagnosed with a clinical pregnancy and meets the criteria of being classified as having infertility, while secondary infertility was defined as a women unable to establish a clinical pregnancy but who has previously been diagnosed with clinical pregnancy [22]. PCOS diagnosis was defined according to the Rotterdam criteria [23, 24]. Any two of the following three characteristics were required to be present: oligo-ovulation; clinical and/or biochemical hyperandrogenism, and ovarian polycystic morphology in ultrasound examination. Endometriosis was diagnosed by laparoscopy or ultrasound. There is no uniform agreement on the diagnostic criteria for DOR. To explore the relationship between AAM and DOR, we referred to the Bologna criteria [25, 26] and expert consensus [27] for

the diagnosis. Any two of the following three abnormal ovarian reserve test criteria are required to be present: bilateral antral follicle count (AFC) < 5, antimullerian hormone (AMH) levels < 1.1 ng/mL and follicle-stimulating hormone (FSH) > 10IU/L. Unexplained infertility was diagnosed when patients with infertility did not involve anovulation, tubal pathology, significant impairment of semen parameters and any known causes of infertility [28, 29]. Tubal factor was defined by hysterosalpingography or laparoscopy. The reference group consisted of infertile women with only tubal factor, including peritubal adhesions, tubal obstruction and hydrosalpinx. We assumed that endocrine factors did not play a prominent role in this specific cause of infertility.

Covariate assessment

Weight was divided by height squared to calculate body mass index. All participants had a routine baseline evaluation before infertile treatment, including age, BMI, educational level, reproductive history and laboratory evaluation of endocrine function parameters. Reproductive history included that whether mother had infertility, whether menstruation was irregular, whether happened dysmenorrhea and number of previous abortions. Basal endocrinological profiles were tested on days 2–3 of menstruation and AMH on random cycle days. Follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone (P), estradiol (E_2), prolactin (PRL), testosterone (T), thyroid stimulating hormone (TSH) levels were tested by chemiluminescence immunoassays (Roche Diagnostics, Germany), with intra- and inter-assay coefficients of variation of < 10%. AMH was tested using an enzyme-linked immunosorbent assay (Ansh Labs, Webster, USA).

Statistical analysis

All statistical analyses and plots were performed using SPSS 27.0 (SPSS Inc., Chicago, IL, USA) and R software 4.3.1. Shapiro-Wilk test was utilized to test the normality of continuous variables. Continuous variables in non-normality distribution were expressed as median (25th-75th percentile) and categorical variables were expressed as number (percentage %). Characteristics between two groups were compared by Wilcoxon rank-sum test for non-normally distributed continuous variables and chi-squared test or Fisher's exact test for categorical variables. Multivariate logistic regression models were performed to analyze the relationship between age at menarche and different type of infertility, adjusting for confounding factors, including age, BMI, education level, family history, whether menstruation was irregular, whether happened dysmenorrhea and different causes of infertility. Subgroup analysis adjusted for confounding factors, including age, BMI, education level, and family history explaining the relationship between AAM and different infertility causes. Effects were described as odds ratio (OR) for logistic regressions with 95% confidence intervals (CIs). RCS is a commonly used method to flexibly explore nonlinear relationships in regression models and is widely used in epidemiology and clinical trials [30]. In the presence of multicollinearity, RCS can provide more robust estimates than traditional linear models. Compared to polynomial regression models, RCS reduces the risk of overfitting by limiting the degrees of freedom of the spline and provides stable estimates when the amount of data is small [31]. Therefore, the dose–response relationship between AAM and infertility was evaluated by RCS with covariates adjusted. $P < 0.05$ was considered as statistically significant.

Results

Baseline and reproductive characteristics

The baseline and reproductive characteristics of all participants were presented in Table 1. A total of 7643 women were retrospectively recruited in this study, including 4378 patients with primary infertility and 3265 patients with secondary infertility. They all had single factor infertility including 635 patients with polycystic ovary syndrome (PCOS), 151 with endometriosis, 175 with diminished ovarian reserve (DOR), 303 with unexplained infertility, and 6379 reference women with tubal factor (Fig. 1). Among the infertile women, the difference between primary and secondary infertility was statistically significant by age, BMI, AAM, educational level, irregular menstruation, dysmenorrhea and different causes of infertility ($P < 0.001$, Table 1). The comprehensive findings of the subgroup analysis can be observed in Supplementary materials (Supplementary Tables 1 and 2) according to different causes of infertility.

As previously observed [17, 32], PCOS patients had a significantly higher BMI ($P < 0.001$, Table 2). Furthermore, compared with the reference women, women with DOR or unexplained infertility had a significantly older mean age at study entry and PCOS patients had a significantly younger mean age ($P < 0.01$, Table 2). Table 2 also showed the endocrine variables in different causes of in fertile groups. As expected, PCOS patients had a higher LH, E_2, P, T, TSH, AMH, and a lower FSH ($P < 0.001$, Table 2). FSH, E_2, and PRL was significantly increased and AMH was significantly decreased in the endometriosis group ($P < 0.01$, Table 2). DOR group had a higher FSH, LH, and a lower PRL, T, AMH than reference groups ($P < 0.01$, Table 2).

Association of AAM and infertility

The logistic regression between AAM and type of infertility was used to adjust for the effects of confounding factors such as age at study entry, BMI at study entry,

Table 1 Comparison of baseline and reproductive characteristics of the difference between primary and secondary infertile groups

	Primary infertility (*N* = 4378)	Secondary infertility (*N* = 3265)	*P* value
Age at time of study (years)	28.00 (26.00, 31.00)	34.00 (30.00, 38.00)	< 0.001***
BMI at time of study (kg/m^2)	22.56 (20.44, 25.36)	23.59 (21.48, 25.98)	< 0.001***
Age at menarche (years)	14.00 (13.00, 15.00)	14.00 (13.00, 15.00)	< 0.001***
AAM category n (%)			
≤12	658 (15.0)	351 (10.8)	< 0.001***
13	1105 (25.2)	734 (22.5)	
14	1203 (27.5)	889 (27.2)	
15	794 (18.1)	661 (20.2)	
16	439 (10.0)	397 (12.2)	
≥17	179 (4.1)	233 (7.1)	
Educational level n (%)			
Primary school and below	171 (3.9)	247 (7.6)	< 0.001***
Middle school	1402 (32.0)	1293 (39.6)	
High school or technical secondary school	949 (21.7)	724 (22.2)	
Junior college degree	905 (20.7)	423 (13.0)	
Bachelor's degree	775 (17.7)	530 (16.2)	
Master's degree and above	176 (4.0)	48 (1.5)	
Irregular menstruation n (%)			
No	3402 (77.7)	2763 (84.6)	< 0.001***
Yes	976 (22.3)	502 (15.4)	
Dysmenorrhea n (%)			
No	3751 (85.7)	2951 (90.4)	< 0.001***
Yes	627 (14.3)	314 (9.6)	
Family history (Whether mother had infertility) n (%)			
No	4304 (98.3)	3220 (98.7)	0.276
Yes	74 (1.7)	45 (1.3)	
Cause of infertility n (%)			
PCOS	486 (11.1)	149 (4.6)	< 0.001***
Endometriosis	90 (2.1)	61 (1.9)	
DOR	99 (2.3)	76 (2.3)	
Unexplained infertility	190 (4.3)	113 (3.5)	
Tubal factor	3513 (80.2)	2866 (87.8)	

Notes: *** Primary infertility group vs. Secondary infertility group, $P < 0.001$

Abbreviations: BMI, body mass index; AAM, age at menarche; PCOS, polycystic ovary syndrome; DOR, diminished ovarian reserve

educational levels, irregular menstruation, dysmenorrhea, family history and different causes of infertility and the results were presented in Table 3. We found that a significant relationship ($P < 0.001$) AAM and type of infertility. Compared with primary infertility, every year increase in AAM, there is a corresponding 7.7% risk increase in secondary infertility (OR 1.077, 95% CI 1.036–1.119, $P < 0.001$) (Table 3, Adjusted) after adjusting confounding factors. In models using categorical AAM, there appeared to be a protective effect of women with menarche both at age ≤ 12 years group (OR 0.794, 95% CI 0.661–0.955, $P = 0.014$) against secondary infertility after accounting for potential confounding factors, using menarche at age 14 years group (middle category) as a control (Table 3, Adjusted).

For different causes of infertile groups, we adjusted confounding factors including age at study entry, BMI at study entry, educational levels, family history and type of infertility. When AAM was analyzed as a continuous variable, multivariate logistic regression analysis showed that per one year increase of AAM was associated with 17.6% increased risk of PCOS (OR 1.176, 95% CI 1.109–1.247, $P < 0.001$) and 21.4% reduced risk of DOR (OR 0.786, 95% CI 0.701–0.880, $P < 0.001$) (Table 4, Adjusted). The association between AAM and PCOS was more pronounced with increasing AAM. As for using categorical AAM, the risk of PCOS was significantly higher in menarche at age 15 years group (OR 1.393, 95% CI 1.082–1.792, $P = 0.010$), at age 16 years group (OR 1.619, 95% CI 1.207–2.171, $P = 0.001$) and at age ≥ 17 years group (OR 2.346, 95% CI 1.625–3.389, $P < 0.001$) after accounting for potential confounding factors (Table 4, Adjusted). Women with menarche both at age ≤ 12 years group (OR 2.565, 95% CI 1.535–4.287, $P < 0.001$) and 13 years group (OR 3.026, 95% CI 1.940–4.720, $P < 0.001$) faced more risk of DOR (Table 4, Adjusted). There were no significant association between AAM and two infertile groups including endometriosis and unexplained infertility after accounting for potential confounding factors.

We further evaluated the dose-response relationship between AAM and infertility (type of infertility, PCOS and DOR) by RSC analysis (Fig. 2). After adjusted aforementioned potential confounding factors, the risk of DOR was significantly associated with AAM (non-linear, $P < 0.001$, Fig. 2C). There were no significant non-linear association of AAM with type of infertility ($P = 0.206$, Fig. 2A) and PCOS ($P = 0.227$, Fig. 2B). In subgroup analyses, the risk of DOR was significantly associated with AAM in 26–30 years (non-linear, $P = 0.044$), > 36 years patients (non-linear, $P = 0.002$) and normal weight/lean patients (non-linear, $P = 0.003$). The comprehensive findings of the subgroup analysis on how participant characteristics (e.g., BMI, age, and education) influenced dose-response relationship between AAM and infertility-can be observed in Supplementary Tables 3–5.

Discussion

Our results have demonstrated that a significant relationship between AAM and type of infertility. Further analysis has revealed patients with different causes of infertility do differ significantly in terms of AAM. Patients with PCOS tended to have an older AAM. However, a younger AAM was significantly associated with DOR, which is non-linearly associated with AAM. These

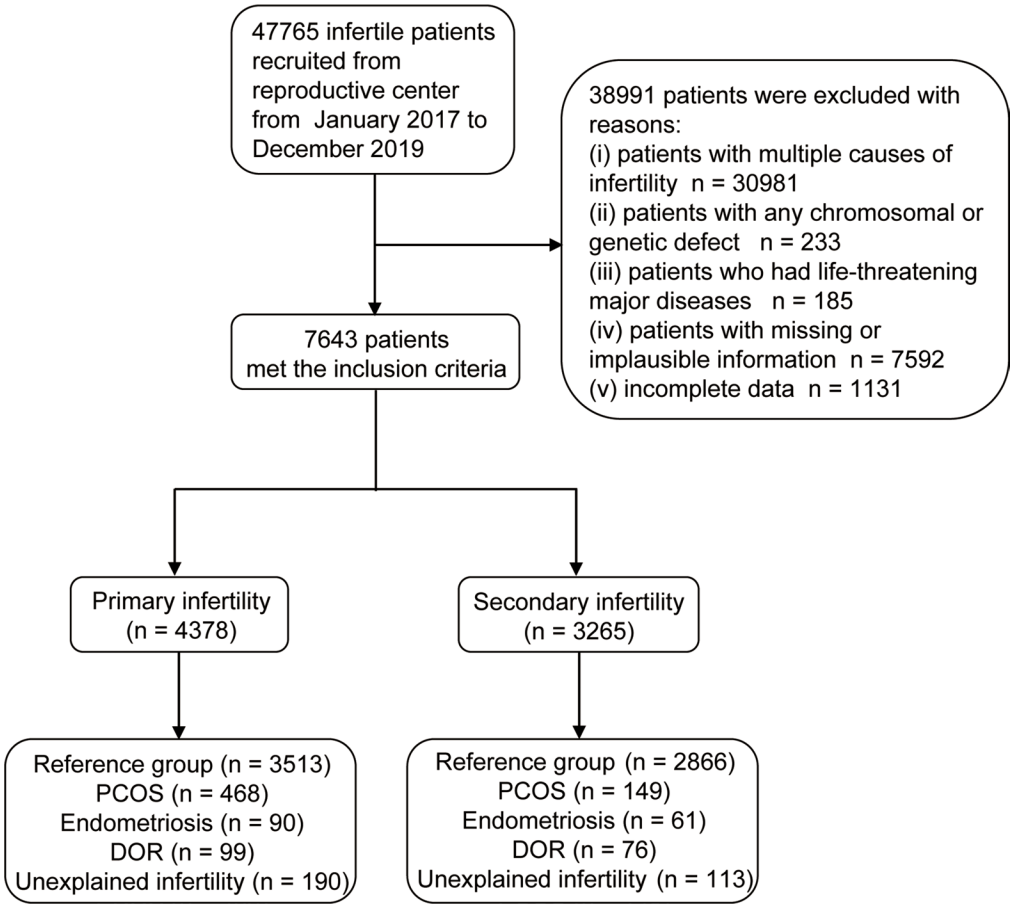

Fig. 1 Flow chart of the participants in group divisions

findings suggest that earlier or later puberty is associated with the risk of infertility.

Pulsatile gonadotropin-releasing hormone (GnRH) released by neurons of the hypothalamus causes pituitary to release LH and FSH, which in turn induces steroidogenesis in the ovary [33]. Fluctuations in estrogen and progesterone cause the first shedding of the endometrium, which is menarche. The significant association between AAM and PCOS has been previously published [17, 21], which is consistent with our findings. Later AAM affects the establishment of regular ovulatory cycles, which is associated with PCOS [21, 34]. The causality of the association between menarche timing and the pathogenesis of PCOS is unclear. Given that serum endocrine hormone levels are correlated with both AAM and PCOS, it is plausible that AMH could be causal links between them. During the early stages of follicle growth, FSH and androgens promote follicle growth and AMH is thought to hinder follicle replenishment and growth [35]. Therefore, in the pathogenesis of PCOS, AMH plays a positive role. On the other hand, PCOS is often accompanied with insulin resistance [34]. Hyperinsulinemia stimulates thecal cell proliferation, amplifies LH-mediated androgen secretion and increases the expression of LH and IGF-1 receptor [36]. However, the true nature of this relationship is difficult to determine without information about AMH during childhood, which was unavailable in our study.

In women with earlier menarche, earlier and increased exposure to dysregulated inflammatory or angiogenic mechanisms accompanied by retrograde menstruation [37] is widely discussed as causes of endometriosis [38]. Accordingly, AAM which reflects the start time of exposure to menstruation, might be expected to influence endometriosis risk [39]. Meanwhile, it increases the risk of endometriosis by extending exposure to estrogens which mediates cellular growth and differentiation in the ectopic endometrial tissue [40]. There is consistent evidence of subtle pituitary-ovarian dysfunction associated with endometriosis, which may be reflected in LH [41]. Although several studies have explored the association between the risk of endometriosis and AAM in women, these studies included different sample sizes, so there was substantial heterogeneity across previous studies. Some studies found that women with endometriosis had earlier menarche [42, 43]. However, a study reported that no

Table 2 Baseline and reproductive characteristics of the participants in different causes of infertility groups

	Reference group (*N* = 6379)	PCOS (*N* = 635)	*P* value	Endometriosis (*N* = 151)	*P* value	DOR (*N* = 175)	*P* value	Unexplained infertility (*N* = 303)	*P* value
Age at time of study (years)	30.00 (27.00, 35.00)	28.00 (26.00, 31.00)	< 0.001***	31.00 (29.00, 35.00)	0.034*	33.00 (27.00, 38.00)	0.001**	31.00 (28.00, 35.00)	0.007**
BMI at time of study (kg/m^2)	22.89 (20.81, 25.44)	24.57 (21.80, 27.71)	< 0.001***	22.48 (20.59, 24.55)	0.063	22.56 (20.31, 25.49)	0.133	22.94 (20.82, 25.46)	0.708
Age at menarche (years)	14.00 (13.00, 15.00)	14.00 (13.00, 15.00)	0.012*	14.00 (13.00, 15.00)	0.016*	13.00 (13.00, 14.00)	< 0.001***	14.00 (13.00, 15.00)	0.801
AAM category n (%)									
≤12	831 (13.0)	72 (11.3)	0.039*	30 (19.9)	0.179	34 (19.4)	< 0.001***	41 (13.5)	0.977
13	1511 (23.7)	148 (23.3)		37 (24.5)		71 (40.6)		72 (23.8)	
14	1785 (28.0)	153 (24.1)		41 (27.2)		28 (16.0)		85 (28.1)	
15	1220 (19.1)	132 (20.8)		25 (16.6)		20 (11.4)		58 (19.1)	
16	697 (10.9)	83 (13.1)		13 (8.6)		14 (8.0)		29 (9.6)	
≥ 17	335 (5.2)	46 (7.2)		5 (3.3)		8 (4.6)		18 (5.9)	
Educational level n (%)									
Primary school and below	366 (5.7)	29 (4.6)	0.022*	5 (3.3)	0.004**	5 (2.9)	0.050	13 (4.3)	0.157
Middle school	2245 (35.2)	259 (40.8)		38 (25.2)		56 (32.0)		97 (32.0)	
High school or technical secondary school	1418 (22.2)	128 (20.1)		28 (18.5)		36 (20.5)		63 (20.7)	
Junior college degree	1089 (17.1)	116 (18.2)		37 (24.5)		27 (15.4)		59 (19.4)	
Bachelor's degree	1068 (16.7)	92 (14.5)		36 (23.8)		44 (25.1)		65 (21.5)	
Master's degree and above	193 (3.0)	11 (1.7)		7 (4.6)		7 (4.0)		6 (2.0)	
Irregular menstruation n (%)									
No	5557 (87.1)	67 (10.6)	< 0.001***	142 (94.0)	0.012*	142 (81.1)	0.021*	257 (84.8)	0.246
Yes	822 (12.9)	568 (89.4)		9 (6.0)		33 (18.9)		46 (15.2)	
Dysmenorrhea n (%)									
No	5607 (87.9)	572 (90.1)	0.106	103 (68.2)	< 0.001***	159 (90.9)	0.235	261 (86.1)	0.360
Yes	772 (12.1)	63 (9.9)		48 (31.8)		16 (9.1)		42 (13.9)	
Family history (Whether mother had infertility) n (%)									
No	6281 (98.5)	627 (98.7)	0.586	149 (98.7)	0.834	171 (97.7)	0.429	296 (97.7)	0.290
Yes	98 (1.5)	8 (1.3)		2 (1.3)		4 (2.3)		7 (2.3)	
Type of infertility n (%)									
Primary infertility	3513 (55.1)	486 (76.5)	< 0.001***	90 (59.6)	0.268	99 (56.6)	0.694	190 (62.7)	0.009**
Secondary infertility	2866 (44.9)	149 (23.4)		61 (40.3)		76 (43.4)		113 (37.3)	
Number of previous abortions	0 (0, 1)	0 (0, 0)	0.012*	0 (0, 1)	0.620	0 (0, 1)	0.078	0 (0, 1)	0.599
Hormone levels									
FSH (IU/L)	6.54 (5.59, 7.76)	5.83 (5.06, 6.73)	< 0.001***	6.86 (5.92, 8.15)	0.024*	11.66 (8.58, 17.16)	< 0.001***	6.68 (5.50, 7.95)	0.379
LH (IU/L)	4.69 (3.54, 6.12)	8.02 (5.06, 11.71)	< 0.001***	4.53 (3.55, 5.62)	0.435	5.85 (3.65, 8.85)	< 0.001***	4.51 (3.44, 6.17)	0.552
E_2 (pg/mL)	33.80 (25.80, 44.30)	36.70 (28.10, 46.60)	< 0.001***	36.50 (29.20, 48.00)	0.002**	35.50 (21.10, 56.90)	0.581	35.1 (26.00, 45.70)	0.221
P (ng/mL)	0.53 (0.38, 0.70)	0.62 (0.42, 0.82)	< 0.001***	0.50 (0.39, 0.66)	0.351	0.55 (0.41, 0.69)	0.465	0.53 (0.37, 0.73)	0.782
PRL (ng/mL)	15.43 (11.40, 20.63)	15.97 (11.32, 21.08)	0.388	16.90 (12.00, 23.20)	0.008**	13.69 (9.95, 19.17)	0.002**	14.87 (10.70, 19.26)	0.068
T (ng/dL)	22.84 (16.29, 30.70)	37.27 (26.89, 47.91)	< 0.001***	22.16 (15.43, 28.74)	0.124	21.07 (14.23, 26.90)	0.001**	23.90 (15.46, 31.71)	0.733

Table 2 (continued)

	Reference group (*N* = 6379)	PCOS (*N* = 635)	*P* value	Endometriosis (*N* = 151)	*P* value	DOR (*N* = 175)	*P* value	Unexplained infertility (*N* = 303)	*P* value
TSH (μIU/mL)	2.13 (1.54, 2.90)	2.26 (1.60, 2.94)	0.024*	2.08 (1.41, 2.91)	0.281	2.23 (1.66, 3.02)	0.312	2.18 (1.49, 2.96)	0.508
AMH (ng/mL)	3.37 (1.76, 5.77)	9.41 (6.16, 13.68)	< 0.001***	2.62 (1.34, 4.70)	0.001**	0.44 (0.10, 0.88)	< 0.001***	3.14 (1.71, 5.34)	0.335

Notes: * Case group vs. Reference group, $P < 0.05$; ** Case group vs. Reference group, $P < 0.01$; *** Case group vs. Reference group, $P < 0.001$

Abbreviations: PCOS, polycystic ovary syndrome; DOR, diminished ovarian reserve; BMI, body mass index; AAM, age at menarche; FSH, follicle stimulating hormone; LH, luteinizing hormone; P, progesterone; E_2, estradiol; PRL, prolactin; T, testosterone; TSH, thyroid stimulating hormone; AMH, antimullerian hormone

Table 3 Multivariate regression models for AAM and risk of different types infertility

	Age at menarche										Per + 1 year age at menarche	
	≤ 12		13		14	15		16		≥ 17		
	OR (95%CI)	*P*	OR (95%CI)	*P*	Ref	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Type of infertility													
Rude	0.722 (0.618, 0.844)	< 0.001	0.899 (0.791, 1.021)	0.101	1.00	1.127 (0.984, 1.289)	0.083	1.224 (1.042, 1.438)	0.014	1.761 (1.423, 2.180)	< 0.001	1.148 (1.113, 1.185)	< 0.001
Adjusted	0.794 (0.661, 0.955)	0.014	0.981 (0.844, 1.140)	0.799	1.00	1.051 (0.895, 1.233)	0.544	1.134 (0.936, 1.374)	0.200	1.251 (0.967, 1.619)	0.089	1.077 (1.036, 1.119)	< 0.001

Notes: Adjusted for age at time of study, BMI at time of study, educational level, family history, irregular menstruation, dysmenorrhea and different causes of infertility

Abbreviations: AAM, age at menarche; BMI, body mass index

Table 4 Multivariate regression models for AAM and risk of different causes of infertile groups

	Age at menarche										Per + 1 year age at menarche	
	≤12		13		14	15		16		≥17		
	OR (95%CI)	*P*	OR (95%CI)	*P*	Ref	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
PCOS													
Rude	1.025 (0.766, 1.371)	0.868	1.143 (0.902, 1.447)	0.268	**1.00**	1.262 (0.989, 1.611)	0.061	1.389 (1.049, 1.840)	0.022	1.602 (1.129, 2.272)	0.008	1.083 (1.025, 1.114)	0.005
Adjusted	0.879 (0.650, 1.189)	0.404	1.086 (0.851, 1.385)	0.508	**1.00**	1.393 (1.082, 1.792)	0.010	1.619 (1.207, 2.171)	0.001	2.346 (1.625, 3.389)	< 0.001	1.176 (1.109, 1.247)	< 0.001
Endometriosis													
Rude	1.572 (0.974, 2.535)	0.064	1.066 (0.680, 1.671)	0.780	**1.00**	0.892 (0.540, 1.475)	0.656	0.812 (0.432, 1.525)	0.517	0.650 (0.255, 1.656)	0.367	0.865 (0.771, 0.971)	0.014
Adjusted	1.446 (0.891, 2.348)	0.135	1.043 (0.664, 1.638)	0.854	**1.00**	0.917 (0.554, 1.518)	0.736	0.852 (0.451, 1.608)	0.621	0.676 (0.263, 1.735)	0.416	0.889 (0.790, 1.002)	0.053
DOR													
Rude	2.608 (1.571, 4.330)	< 0.001	2.996 (1.924, 4.664)	< 0.001	**1.00**	1.045 (0.586, 1.864)	0.881	1.280 (0.670, 2.447)	0.454	1.522 (0.688, 3.369)	0.300	0.789 (0.707, 0.880)	< 0.001
Adjusted	2.565 (1.535, 4.287)	< 0.001	3.026 (1.940, 4.720)	< 0.001	**1.00**	1.031 (0.577, 1.843)	0.917	1.261 (0.657, 2.422)	0.486	1.410 (0.632, 3.146)	0.402	0.786 (0.701, 0.880)	< 0.001
Unexplained infertility													
Rude	1.036 (0.707, 1.518)	0.855	1.001 (0.726, 1.380)	0.997	**1.00**	0.998 (0.709, 1.405)	0.992	0.874 (0.568, 1.344)	0.539	1.128 (0.670, 1.901)	0.650	0.994 (0.918, 1.076)	0.877
Adjusted	0.960 (0.652, 1.414)	0.836	0.992 (0.719, 1.370)	0.963	**1.00**	1.023 (0.725, 1.441)	0.899	0.926 (0.599, 1.430)	0.728	1.183 (0.697, 2.009)	0.534	1.019 (0.938, 1.106)	0.713

Notes: Adjusted for age at time of study, BMI at time of study, educational level, family history and different types of infertility

Abbreviations: AAM, age at menarche; BMI, body mass index; PCOS, polycystic ovary syndrome; DOR, diminished ovarian reserve

significant relationship was found between the length of menstrual cycles, the AAM and the presence of endometriosis, regardless of the subgroups of subjects analyzed [44]. Our study including a large sample size suggested that AAM was not correlated with the risk of endometriosis in Chinese infertile women after adjusting potential confounding factors.

Additionally, in our study DOR tended to have an earlier AAM compared with the reference group. Although the onset of menarche cannot be attributed to a single trigger, the emergence of pulsatile GnRH secretion has been assumed essential [45]. The hypothesis that the GnRH pulsatility is feedbacked by ovarian activity and the observation of peak nongrowing follicles lost around menarche suggest a possible relationship between AAM and the female follicular pool [45, 46]. Our study has demonstrated a statistically significant association between AAM and DOR later in life. These results were consistent with some previous findings [47, 48]. The clear etiology and pathophysiology mechanisms between AAM and the follicular pool need to be further revealed. In our study, there was a significant nonlinear dose-response relationship between AAM and the occurrence of DOR, suggesting that AAM can be used as an indicator for assessing ovarian reserve function in women. The nonlinear relationship suggests that certain specific ranges of AAM may be associated with an increased risk of DOR. The nonlinear relationship emphasizes individual differences and helps to personalize medical advice and interventions for women with different menarche ages. For women with earlier AAM, special attention may need to be paid to healthy lifestyle interventions including diet, exercise and stress management, and regular ovarian function monitoring is recommended for timely detection of signs of DOR.

However, the findings of our study are still generalizable given the regional focus. The findings of our study were consistent with a previous study in Netherlands [17], which PCOS patients had an older AAM but DOR patients had a younger AAM. From a large survey among Italian secondary schoolgirls, the higher incidence of oligomenorrhea and irregular menstrual cycles among girls with older AAM, which are significant manifestations of PCOS [49]. The advantage of AAM as a screening tool is that it is easily accessible and inexpensive. However, it may not be sensitive and specific enough to be used alone to predict infertility. AAM may be more valuable as a risk factor for the development of infertility, and in combination with other risk factors (e.g., menstrual cycle regularity, history of previous pregnancies, lifestyle factors, etc.) the accuracy of infertility prediction can be improved.

The strength of our study is that all patients came from the same center with strong homogeneity. We focused on the relationship between earlier or later biological

Fig. 2 Association of AAM with different causes of infertility. (**A**. Association of AAM with type of infertility adjusted for age at time of study, BMI at time of study, educational level, family history, irregular menstruation, dysmenorrhea and different causes of infertility; **B**. Association of AAM with PCOS adjusted for age at time of study, BMI at time of study, educational level, family history and different types of infertility; **C**. Association of AAM with DOR adjusted for age at time of study, BMI at time of study, educational level, family history and different types of infertility). Abbreviations: AAM, age at menarche; BMI, body mass index; PCOS, polycystic ovary syndrome; DOR, diminished ovarian reserve

maturation and reproductive health outcomes in adulthood through their clinical and laboratory data. Despite its strengths, the current analysis does have some limitations. First, AAM, as reported by individuals, could be a source of bias. However, due to the impact of the first menstruation on a young girl's life, it is likely that recall bias will have minimal effect, particularly for women who reach menarche at an early or late age. Secondly, due to the lack of endocrine levels at the time of menarche, it is impossible to analyze the impact of this part on infertility. Thirdly, some causes of infertility, such as idiopathic hypogonadotropic hypogonadism (IHH) and luteinized unruptured follicle syndrome (LUFS), had relatively small sample sizes and were not included in the analysis. In the future, this needs to be further explored in studies with larger sample sizes.

Conclusion

In conclusion, our study indicated that early or late AAM was significantly associated with an increased risk of infertility. Early or late AAM may be a potential indicator of long-term reproductive health status and physicians should be aware of its clinical significance. All physicians should be alert to the problems associated with early or late menarche and take appropriate measures to prevent its consequences. Moreover, strategies to prevent early and late menarche and its complications may be important in their own right.

Supplementary Information

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Supplementary Material 1

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Author contributions
M.B. contributed to studying design, data analyses and writing the main manuscript text. J.J. and J.Z. performed data collection. L.C. and Z.C. conducted supervision. H.W. conducted a review of the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
The study involving human participants was reviewed and approved by the Reproductive Medicine Ethics Committee, Hospital for Reproductive Medicine Affiliated to Shandong University in accordance with the Declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study. The ethics approval number was No. 2023 (51).

Competing interests
The authors declare no competing interests.

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