The Relationship of Anti-Mullerian Hormone in Polycystic Ovary Syndrome Patients With Different Subgroups

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Abstract

Purpose To explore the value of anti-Mullerian hormone (AMH) in polycystic ovary syndrome (PCOS) patients for different phenotype and age, and identify the relationship between the hyperandrogenism (HA) and polycystic ovary morphology (PCOM) in Chinese cohort.

Methods A total of 2262 women (1631 with PCOS and 631 health controls) were enrolled. The serum AMH and total testosterone (TT) were analyzed, compared the AMH level of each subgroup and evaluated the value of each phenotype and age group of PCOS.

Results The level of AMH in PCOS(8.63±4.73ng/ml) was higher than that in health controls(5.57±3.31ng/ml) (P□0.01).The level of AMH in PCOM subgroup(11.19±6.4ng/ml) was significantly higher than that in HA subgroup(8.58±4.74ng/ml) (P□0.01), and both higher than that in health controls(P□0.01). AMH changes highly in PCOS compared with the health control, but as the same value in subgroups of PCOS patients under 30-year-old.

Conclusion AMH changed in different subgroups of PCOS, which was the possible reason why AMH was not a diagnostic indicator. However, AMH could differ the subgroup in clinical, AMH was strongly related with PCOM, not hyperandrogenism. AMH changed much as aged, but stable in PCOS patients under 30-year-old.

Introduction

Polycystic ovary syndrome(PCOS) is the most common endocrine disorder, it affected 8–13% women of reproductive age which is charactered by anovulation, hyperandrogenism(HA) and polycystic ovary morphology (PCOM) [1]. Since the phenotypic heterogeneity of PCOS, the phenotypes of the syndrome including hyperandrogenism and ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology, ovulatory dysfunction and polycystic ovarian morphology, hyperandrogenism, oligo-ovulation and polycystic ovarian morphology. Due to the large individual differences of PCOS women, there is not have an exact effect for clinical treatment, so how to achieve specific therapy initially, even once diagnosis, no relevant specific serological markers for subgroups currently. As a member of the transforming growth factor β family, anti-Mullerian hormone (AMH) is produced by granulosa cells of preantral and small antral ovarian follicles which can reflect the ovarian reserve and ovarian function[2], serum AMH levels in PCOS are elevated two-to three-fold and are positively correlated with PCOM and serum androgen levels[3–4], so it has potential as a marker for the diagnosis of PCOS [5]. Although there always has a number of studies or consensus of the relationship between AMH and PCOS, it still not be used as a one of diagnostic criteria unfortunately. Is it related to the presence of variability in the PCOS subgroup? To cover the possible cause, we have carried out the following studies that investigate the distribution of AMH and the data differences between subgroups among young PCOS patients in Chinese cohort, which can help to better understand the possible diagnostic and follow-up value of AMH in PCOS.

Materials And Methods

Study population

The study included 2262 women with the complains of menstrual disorders aged 16 to 29 years in the outpatients of gynecology of the First Affiliated Hospital of Chongqing Medical University from May 2018 to May 2020, then the population were divided to PCOS group of 1631 cases (1161 with HA subgroup, 470 with PCOM subgroup and 399 with HA + PCOM subgroup) and health control(HC) of 631 cases according to 2003 Rotterdam criteria [6].

The 2003 Rotterdam criteria: oligo- or anovulation is a necessary condition for diagnosis. Another one of the following two was consistent :(1) clinical or biochemical hyperandrogenemia; (2) PCOM (presence of 12 follicles measuring 2–9 mm in diameter in each ovary and/or increased ovarian volume (> 10 ml)) under ultrasound.

The exclusion criteria were: (1) Other endocrine diseases that cause ovulation disorders besides PCOS, such as hyperprolactinemia; congenital dysfunction of the adrenal cortex; thyroid disorders; Cushing syndrome and disease; tumors of the pelvic organs. (2) During pregnancy. (3) TT<0.1 ng/ml or AMH ≥ 23.5 ng/ml. (4) Over 30 years old.

Study methods

Total testosterone (TT), and anti-Mullerian hormone (AMH) were measured on days 2–4 of spontaneous menstrual cycle or any day for amenorrhoea women. Serum AMH and TT levels were measured with electrochemiluminescence method by Beckman DXI800 instrument, HA was defined as TT ≥ 0.5 ng/ml in our study.

Vaginal ultrasound was performed in the early follicle period (for the women with regular menstruation) or in the state of no dominant follicle (transabdominal ultrasound was performed if had no sexual life), measure the length, cross diameter, front and rear diameter of the ovaries and the size and number of follicles in each side of the ovary, and defined the presence of 12 follicles measuring 2–9 mm in diameter in each ovary and/or increased ovarian volume (> 10 ml) as PCOM.

Statistics Analyses

Analyses were performed with the use of SPSS 26.0 statistics software. Shapiro-Wilk tests was used to test whether fit normal distribution of our variables. Comparison of variables with a normal distribution was performed by parametric Student's t-test, continuous variables were presented as x ± SD. Parameters that did not fit normal distribution were analyzed using a median (Me) and an interquartile range and the Mann–Whitney U-test (Parameters are not fit normal distribution in our study from Shapiro-Wilk tests). P value of < 0.05 was considered as statistically significant.

Results

AMH comparison between PCOS (and subset) and HC group

The level of AMH in PCOS(8.63 ± 4.73 ng/ml) was higher than that in HC(5.57 ± 3.31 ng/ml) (P<0.01); and the AMH level of subgroup of HA, PCOM, HA + PCOM was 8.58 ± 4.74 ng/ml, 11.19 ± 6.4 ng/ml, 11.45 ± 4.97 ng/ml respectively, and were higher than that in HC(P<0.01) (Table 1).

Table 1
AMH level of different group

Group	n	AMH (ng/ml)	Z	P
HC	631	5.57 ± 3.31		
PCOS	1631	8.63 ± 4.73	14.652	<0.01
HA	1560	8.58 ± 4.74	14.264	<0.01
PCOM	470	11.19 ± 6.4	18.844	<0.01
PCOM + HA	399	11.45 ± 4.97	18.382	<0.01

The comparison between PCOS (and subgroup) and HC group. The AMH level of PCOS group and HA, PCOM, HA + PCOM subgroup were all higher than that in HC (P<0.01). AMH: anti-Mullerian hormone; HC: health controls; *PCOS*: polycystic ovary syndrome; *HA*: hyperandrogenemia; *PCOM*: polycystic ovary morphology

AMH comparison between PCOS subgroup

The level of AMH in PCOM subgroup(11.19 ± 6.4 ng/ml) was significantly higher than that in HA subgroup(8.58 ± 4.74 ng/ml) (P<0.01); The level of AMH in PCOM + HA subgroup(11.45 ± 4.97 ng/ml) was significantly higher than that in HA subgroup (P<0.01); The level of AMH in PCOM + HA subgroup(11.45 ± 4.97 ng/ml) was higher than that in PCOM subgroup, but had no statistical significance(P = 0.459)(Table 2).

Table 2
AMH level of different PCOS subgroup

Group	n	AMH (ng/ml)	Z	P
PCO	470	11.19 ± 6.4	0.741	0.459*
HA	1560	8.58 ± 4.74	10.443	<0.01#
PCO + HA	399	11.45 ± 4.97	10.359	<0.01&

*: PCO vs PCO + HA; #: HA vs PCO + HA; &: PCO vs HA. The comparison between three PCOS subgroups. The AMH level of HA + PCOM subgroup was higher than that in HA group(P<0.01) and that in PCOM group(P = 0.447). The AMH level of PCOM subgroup was higher than that in HA subgroup(P<0.01). *HA*: hyperandrogenemia; *PCOM*: polycystic ovary morphology

AMH level in different ages

The AMH level of 16 ~ 19,20 ~ 25,26 ~ 29 years old in PCOS and controls are listed in Table 3. The change of AMH level are roughly the same between PCOS and controls that all increased first and then decreased and reaching the highest level in 20–25 years old, it were 9.00 ± 4.89 ng/ml and 6.14 ± 3.31 ng/ml respectively.

Table 3
AMH level for age-stratified of PCOS and HC

Age	n		AMH (ng/ml)		P
	PCO	HC	PCO	HC	
16 ~ 19	226	103	8.84 ± 4.52	5.98 ± 3.62	<0.01
20 ~ 24	775	218	9.00 ± 4.89	6.14 ± 3.31	<0.01
24 ~ 29	630	310	8.10 ± 4.56	5.03 ± 3.11	<0.01
N	1631	631	8.63 ± 4.73	5.57 ± 3.31	

The different age group of AMH level of PCOS and HC. The change of AMH with age in PCOS is roughly the same as that in HC that reaching the highest level in 20–25 years old. *HC*: health controls; *PCOS*: polycystic ovary syndrome.

Discussion

AMH level and PCOS:

AMH is secreted by the granulosa cells of the pre-antral and small antral follicles. Several studies have shown that the level of AMH is two to three folds higher in women with PCOS than the healthy women of childbearing age, probably due to the increased follicular mass or the follicular hypersecretion [3–4].

Recent studies suggested that over expression of the AMHR2, an intrinsic dysregulation of the granulosa cells itself, may be related to excessive AMH [7–8]. And some authors also found that AMH receptors expressed in human GnRH neurons thus can directly increase GnRH-dependent LH secretion which favoring AMH production [9]. Serum AMH detection as a non-invasive mothed is not affected by menstrual cycle and non-fasting state, so it has potential as a new marker for the diagnosis of PCOS. Since AMH are not yet adequate for diagnosis of PCOS alone because of the different methods of detection, the influence of year, or the BMI, even though it's not clear now [10–12]. In this clinical analysis the variation of AMH in each subgroup may also be one of the reasons why it cannot be used as a diagnostic marker of PCOS, AMH was significantly affected by different characteristics of PCOS. When there was no PCOM, the mean value of AMH was the same as that of healthy controls with PCOM, however, no clear cutoff values for AMH concentrations just the same as total and free testosterone especially in adolescents [13], which all contribute to the lack of standardization and appropriate cut-offs for the different condition [14].

Our study showed that the women with PCOS had significantly higher AMH levels compared with controls, even women who didn't have HA or PCOM. What's more, our study also demonstrated that AMH was positively correlated with the severity of PCOS phenotype just consistent with previous studies [10]. According to the 2018 Chinese guideline of PCOS diagnosis [15], the ovulatory dysfunction added hyperandrogenism phenotype (1560 cases) was the most prevalent form in our patient cohort, the ovulatory dysfunction added PCOM phenotype (470 cases) was less, and the classic phenotype (399 cases) that having all three features of the syndrome was least but had the highest mean AMH level as we expected. Furthermore, the diagnostic value of AMH is of limited for the classic phenotype because of the presence of irregular cycles and HA are suffice to make the diagnosis [1]. In a study Involving in 392 Turkey women of PCOS, researchers found that AMH had poor to fair ability to diagnose the syndrome in OA + HA and OA + PCOM phenotypes [16], maybe not suitable for Chinese PCOS cohort. In our affected population especially the only HA (1161/1631) or PCOM (71/1631) subset, the AMH was obviously higher than controls as well, and in those two groups, AMH level can reflect independently the presence of HA and PCOM relatively, therefore there is still a certain auxiliary diagnostic value for PCOS.

The relationship between AMH and HA or PCOM

Our study indicated that the increase of AMH is the result of HA and PCO together, consistent with previous studies [17]. The serum AMH in PCOM + non-HA group was higher in that in HA + non-PCOM group(9.57 ± 4.3 ng/ml vs 7.6 ± 4.23 ng/ml) showed that the AMH and PCOM had the strongest relationship which was determined by the intrinsic secretion characteristics of AMH, such as increased basal follicles or delayed disappearance of AMH expression, while HA has the weaker relationship which was different from some previous finding, it was reported that the positive correlation between serum AMH and total testosterone [18–19], AMH levels was higher in PCOS when HA was present [20]. In our study, the AMH level of HA + non-PCOM group (1161/1631) was higher to HC (7.6 ± 4.23 ng/ml vs 5.57 ± 3.31 ng/ml), which can be considered as the effect of HA on AMH simply without considering the false negative of the ultrasound result. As we all know, androgens stimulate follicle stimulating hormone

receptor (FSHR) expression and promote follicular growth, which lead to elevated AMH production, and meanwhile elevated AMH suppress aromatase expression in granulosa cells hindering the transformation of androgen to estrogen that contribute to the increased androgen level [21]. Such an interaction of mutually reinforce each other may be the reason of the positive correlation between them and therefore contribute to the pathogenesis of PCOS.

But to the influence for final detected concentration of AMH level, the latter secretory pattern still seems to be negligible compared with the increased follicles. So given PCOM was more relative to AMH, AMH could deed be used as a more sensitive alternative biomarker for follicular number of per ovary (FNPO) in the diagnosis of PCOM [22], and to some extent, also could remedy the false negative results(including the effect of transabdominal ultrasound on follicular count in asexual women particularly in obese patients) of ultrasound examination, whereas with the advanced of ultrasound equipment conversely, the new international guidelines was re-defined the PCOM cut offs to a threshold of ≥ 20 FNPO[23] which could reduce the diagnostic rate of PCOS. Therefore, AMH seems to be more likely to replace FNPO as the symbol of PCOM because it can not only present the increasing basic follicles but also reflect the pathological state of hypersecretion of follicles to a certain extent.

AMH and age

As a biomarker of the number of ovarian antrum follicles and ovarian function, AMH is declined with increasing age [24]. Since the AMH level is descended obviously after 30 years old, the population we included was under 30 years old, so that it can be more accurately reflect the change of AMH with age in PCOS and non-PCOS cohort. Since the lack of an international standard for AMH, according to the recent international guideline, the areas under the ROC curve of AMH for the diagnosis of PCOS ranging from 0.66 to 0.994 and the threshold cut-off values ranging from 10 to 57 pmol/l [1], it was obvious that there was significant heterogeneity existing, which making confused for our clinician to reference. Our study confirmed that and calculate the mean AMH level of 16–20 years, 21–25 years, and 26–29 years group of PCOS and controls, which could provide a general reference range for PCOS effective diagnosis. What's more, a recent study found that AMH levels fall with increasing age in productive women with PCOS as well as in normal women [25], in our study also showed that the variation tendency of AMH level of different age group in PCOS and HC are similar that all increased first and then decreased and reaching the highest level in 20–25 years old. Some authors thought that AMH levels was high in adolescence and overlap considerably with non-PCOS and makes it difficult to differentiate PCOS from controls on AMH levels [26], but according to our study it seems not to be so difficult to distinguish since there is a concentration gap in each age group although more detailed age segments and larger population samples are needed.

The possible reason of AMH variation

As is known to all, the abnormal lipid profile and insulin resistant (IR) are common metabolic disorders in women with PCOS [27]. And the relationship of AMH between those metabolic factors still remain controversial through current data. A recent study demonstrated that there was a significant negative

correlation between AMH level and homeostasis model assessment of insulin resistance (HOMA-IR) or triglyceride levels and positive correlation between serum AMH and serum high-density lipoproteincholesterol (HDL-C) or serum adiponectin level, so that the AMH will be a potential cardiometabolic risk marker as well in women with PCOS [28]. Although the correlation between AMH and Body Mass Index(BMI) remain unclear, the associations of AMH in relation to metabolic syndrome were modified by BMI, hence the women who had PCOS with normal BMI did not had an increased risk of metabolic syndrome according to a latest study [29].This study is a retrospective study, and due to the mobility of outpatients and incomplete data, metabolic markers were not included in the clinical data, and the corresponding cause analysis data could not be obtained from this study, We will confirm it in subsequent experiments.

Conclusion

In summary, our preliminarily study deed confirmed the diagnostic value of AMH in PCOS, and the present of PCOM has the closer relationship with the AMH level than HA, which means the AMH level also play role in predicting clinical features even guiding treatment of PCOS, besides diagnosis. However, although the specificity and sensitivity were not high only use of AMH level as diagnosis of PCOS in young patients according to an analysis in 2016 [30], it is essential to set up different diagnostic threshold according to age or BMI, even different races and detection method which can achieve more cost-effective diagnostic value of AMH. Besides, it is also necessary to combined with glucose and lipid metabolism factors and estimate potential value of cardiometabolic risk markers in our further research.

AMH changed in different subgroups of PCOS, which was the possible reason why AMH was not a diagnostic indicator. However, AMH could differ the subgroup in clinical, AMH was strongly related with PCOM, not hyperandrogenism. AMH changed much as aged, but stable in PCOS patients under 30-year-old.

Abbreviations

AMH: anti-Mullerian hormone; HC: health controls; PCOS: polycystic ovary syndrome; HA: hyperandrogenemia; PCOM: polycystic ovary morphology; FSHR: follicle stimulating hormone receptor; FNPO: follicular number of per ovary; IR: insulin resistant; HOMA-IR: homeostasis model assessment of insulin resistance; HDL-C: high-density lipoproteincholesterol; BMI: Body Mass Index

Declarations

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Not applicable.

Author contributions

Yu Ran: project development, manuscript writing/editing; Cong Li: project development; Qiang Yi: data curation; formal analysis; Hong Qiao: data collection, data analysis; Qing Yang: data analysis; Yanli Ye: data collection; All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Scientific research ethics of 2020: number 2020-637). Because this was a retrospectively observational study with no intervention, formal ethical approval and written consent were not required.

Consent for publication

Not applicable.

Competing interests

All the authors declare no conflict of interest.

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