Anti-Müllerian hormone: correlation with testosterone and oligo- or amenorrhoea in female adolescence in a population-based cohort study

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STUDY QUESTIONS: Can serum anti-Müllerian hormone (AMH) levels measured in female adolescents predict polycystic ovary syndrome (PCOS)-associated features in adolescence and early adulthood?

SUMMARY ANSWER: AMH levels associated well with PCOS-associated features (such as testosterone levels and oligoamenorrhoea) in adolescence, but was not an ideal marker to predict PCOS-associated features in early adulthood.

WHAT IS KNOWN ALREADY: Several studies have reported that there is a strong correlation between antral follicle count and serum AMH levels and that women with PCOS/PCO have significantly higher serum AMH levels than women with normal ovaries. Other studies have reported an association between AMH serum levels and hyperandrogenism in adolescence, but none has prospectively assessed AMH as a risk predictor for developing features of PCOS during adulthood.

STUDY DESIGN, SIZE, DURATION: A subset of 400 girls was selected from the prospective population-based Northern Finland Birth Cohort 1986 (n = 4567 at age 16 and n = 4503 at age 26). The population has been followed from 1986 to the present.

PARTICIPANTS/MATERIAL, SETTING, METHODS: At age 16, 400 girls (100 from each testosterone quartile: 50 with oligo- or amenorrhoea and 50 with a normal menstrual cycle) were selected at random from the cohort for AMH measurement. Metabolic parameters were also assessed at age 16 in all participants. Postal questionnaires enquired about oligo- or amenorrhoea, hirsutism, contraceptive use and reproductive health at ages 16 and 26.

MAIN RESULTS AND ROLE OF CHANCE: There was a significant correlation between AMH and testosterone at age 16 (r = 0.36, P < 0.001). AMH levels at age 16 were significantly higher among girls with oligo- or amenorrhoea compared with girls with normal menstrual cycles (35.9 pmol/l [95% CI: 33.2;38.6] versus 27.7 pmol/l [95% CI: 25.0;30.4], P < 0.001). AMH at age 16 was higher in girls who developed hirsutism at age 26 compared with the non-hirsute group (31.4 pmol/l [95% CI 27.1;36.5] versus 25.8 pmol/l [95% CI 23.3;28.6], P = 0.036). AMH at age 16 was also higher in women with PCOS at age 26 compared with the non-PCOS subjects (38.1 pmol/l [95% CI 29.1;48.4] versus 30.2 pmol/l [95% CI 27.9;32.4], P = 0.044). The sensitivity and specificity of the AMH (cut-off 22.5 pmol/l) for predicting PCOS at age 26 was 85.7 and 37.5%, respectively. The addition of testosterone did not significantly improve the accuracy of the test. There was no significant correlation between AMH levels and metabolic indices at age 16.

IMPLICATIONS, REASONS FOR CAUTION: AMH is related to oligo- or amenorrhoea in adolescence, but it is not a good marker for metabolic factors. The relatively low rate of participation in the questionnaire at age 26 may also have affected the results. AMH was measured in a...
subset of the whole cohort. AMH measurement is lacking international standardization and therefore the concentrations and cut-off points are method dependent.

WIDER IMPLICATIONS FOR THE FINDINGS: Using a high enough cut-off value of AMH to predict which adolescents are likely to develop PCOS in adulthood could help to manage the condition from an early age due to a good sensitivity. However, because of its low specificity, it is not an ideal diagnostic marker, and its routine use in clinical practice cannot, at present, be recommended.

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Key words: AMH / female adolescence / PCOS / oligo- or amenorrhoea / testosterone

Introduction
Anti-Müllerian hormone (AMH) plays a central role in sexual differentiation by inducing the regression of the Müllerian ducts in male fetuses. In females, AMH is produced in the granulosa cells of the human ovary after mid-gestation (Vigier et al., 1984; Rajpert-De Meyts et al., 1999; Kuiri-Hänninen et al., 2011). AMH is expressed in granulosa cells of growing follicles up to the antral stage, suggesting an important role in early ovarian folliculogenesis (Weenen et al., 2004; Stubbs et al., 2005). AMH is able to inhibit the initiation of primordial follicle growth (Durlinger et al., 2002) and may also decrease the sensitivity of antral follicles to follicle-stimulating hormone (FSH) (Durlinger et al., 1999, 2002; Gruijters et al., 2003). Testosterone has been shown to lower AMH expression in the mammalian ovary in vitro (Crisosto et al., 2009). In humans, however, the association between androgens and AMH remains uncertain, and its exact function in follicular recruitment and long-term effects is not well understood.

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women, producing symptoms of hyperandrogenism, oligo- or amenorrhoea and polycystic ovaries (PCO) (Franks 1995; Ehrmann 2005). Serum AMH levels and the ovarian antral follicle count (AFC) correlate closely both in healthy subjects and in women with PCOS (Pigny et al., 2003, 2006; Weenen et al., 2004). In PCOS, serum AMH correlates positively with serum concentrations of testosterone (T) and negatively with age (Piltonen et al., 2005). Furthermore, women with higher serum levels of AMH and T have longer menstrual cycles compared with those with lower levels (Kristensen et al., 2012). In line with these observations, in non-hirsute girls with oligo-amenorrhoea (OA), the levels of AMH are similar to those in the PCOS population but higher than in girls with normal cycles (Hart et al., 2010a,b; Park et al., 2010a,b). AMH has been reported to be not associated with metabolic risks in adolescence and in early adulthood (Lin et al., 2011; Anderson et al., 2013), but contradictory results have been published in adult female populations (Nardo et al., 2009; Park et al., 2010a,b; Skalba et al., 2011).

The use of the measurement of serum AMH serum levels as a diagnostic tool for PCOS has been recently under debate (Dewailly et al., 2011; Eilertsen et al., 2012; Iliodromiti et al., 2013). Women with PCOS have higher concentrations of AMH, and accordingly, AMH correlates with the AFC. Thus, AMH has been proposed to be a substitute for AFC in the diagnosis of PCOS (Pigny et al., 2006; Dewailly et al., 2011; Eilertsen et al., 2012). AMH has also been reported to correlate with other symptoms of PCOS, such as hyperandrogenism and oligoamenorrhoea (Pigny et al., 2003; Laven et al., 2004; Piltonen et al., 2005; Nardo et al., 2009; Li et al., 2011; Skalba et al., 2011). There are, however, no follow-up studies on the subject of AMH as a possible predictor of PCOS and its typical symptoms (oligo- or amenorrhoea, hirsutism and hyperandrogenism) in later life.

PCOS is also associated with increased metabolic risks in later life (Legro et al., 2002; Solomon et al., 2002; Nisenblat and Norman 2009). For clinicians to be able to prevent adverse health events in PCOS, predicting the syndrome early in life is important. We have recently reported that oligo- or amenorrhoea at the time of adolescence is associated with hyperandrogenaemia and may represent a risk factor for the development of PCOS in adulthood. Furthermore, we have also reported an association between obesity, hyperandrogenaemia and metabolic risks among 16-year-old adolescent girls (Pinola et al., 2012). We hypothesize that AMH could be used as an early marker for reproductive and metabolic future risks linked to PCOS to allow early preventive actions such as lifestyle changes.

The main aim of the present study was to elucidate the relationship between serum AMH and testosterone levels, oligo- or amenorrhoea, and metabolic and cardiovascular markers at the age of 16, and to evaluate whether AMH can be used as a marker for predicting future cycle irregularities, hirsutism and diagnosis of PCOS.

Materials and Methods

Study Population
The study population was a subset of 400 subjects, from the Northern Finland Birth Cohort 1986 (NFBC-86), selected to be assayed for serum AMH.

The prospective NFBC-86, comprised 9362 mothers and their 9479 births (9432 children born alive), who had an expected date of birth between 1 July 1985 and 30 June 1986, drawn from the northernmost part of Finland. In 2001–2002, when the children were 16 years old, the adolescents and their parents received postal questionnaires. Of the female adolescents (n = 4567) then living in Finland, either in the original catchment area or elsewhere; 80.3% answered the questionnaire and 74% underwent clinical examination (i.e. anthropometric measurements) and gave fasting blood samples. After excluding twins and triplets, pregnant girls (n = 20), oral contraceptive users and users of other forms of hormonal contraception and treatment (n = 377), and subjects with incomplete data (n = 824), 2448 singleton females remained eligible.

The selection of the study population for the measurement for serum AMH was completed among the subjects who answered both questionnaires at ages 16 and 26. The study population was split into testosterone quartiles and the final group of study subjects (100 subjects from each testosterone
AMH in female adolescence

The study population of 400 girls was constituted from four equal groups (quartiles) according to their testosterone levels. After dividing the study population into T quartiles, the correlation was performed between the four quartiles. In the whole study population and within each testosterone quartile, a correlation analysis was carried out between AMH and incidence of irregular anovulatory cycles/oligo-amenorrhea and hirsutism based on the F&G scores obtained at age 26. Further, in the whole population and in each testosterone quartile AMH was correlated with metabolic and cardiovascular risk markers (waist–hip ratio, serum fasting insulin, plasma fasting glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, hsCRP and HOMA for insulin sensitivity), adjusting for testosterone and BMI.

Statistical methods

The background characteristics of the study population are shown in the Table 1. At age 16, the BMI was significantly increased towards greater testosterone quartile (P-value for trend < 0.001). Mean levels of testosterone in testosterone quartiles were 1.05 in the first, 1.46 in the second, 1.83 in the third and 2.49 nmol/l in the fourth quartile.

AMH and testosterone

There was a significant correlation between serum AMH and T at age 16 (r = 0.36, 95% confidence interval (95% CI) 0.24–0.47, P < 0.001). After dividing the study population into T quartiles, the correlation was significant only in the highest T quartile (r = 0.33, 95% CI 0.11–0.56, P = 0.001). These results were independent of BMI, WHR and age at menarche. AMH levels increased significantly from the lowest towards the highest T quartile (P-value for trend < 0.001, Fig. 1).

AMH and oligo- or amenorrhea

At age 16, the girls who reported oligo- or amenorrhea (n = 200) had higher AMH levels compared with those reporting normal cycles (n = 200) (35.9 pmol/l (95% CI: 33.2: 38.6) versus 27.7 pmol/l (95% CI: 25.0; 30.45), P < 0.001), and adjustment for BMI, WHR or T did not change the results. Subjects with oligo- or amenorrhea had higher serum AMH levels in the second, third and fourth T quartiles compared with those with regular menstrual cycles (Fig. 2). Serum AMH levels at age 16 did not differ significantly between women with oligo- or amenorrhea and women without oligo- or amenorrhea at age 26. However, within the highest testosterone quartile, the women with oligo- or amenorrhea (n = 23) at age 26 had higher AMH levels at age 16, compared with women with normal menstrual cycles (n = 62) at age 26, after adjusting for T and BMI [45.5 pmol/l (95% CI: 36.0; 55.1) versus 36.1 pmol/l (95% CI: 30.3; 41.9), P = 0.04].

Results

The background characteristics of the study population are shown in the Table 1. At age 16, the BMI was significantly increased towards greater testosterone quartile (P-value for trend < 0.001). Mean levels of testosterone in testosterone quartiles were 1.05 in the first, 1.46 in the second, 1.83 in the third and 2.49 nmol/l in the fourth quartile.
AMH and hirsutism

After exclusion of oral contraceptive users (n = 122), women with evidence of hirsutism at age 26 (based on self-reported F&G score > 7) had significantly higher AMH levels at age 16 compared with non-hirsute counterparts (Table II). However, in the whole population, including the oral contraceptive users, at age 26 the statistically significant difference disappeared. Similarly, the difference disappeared after exclusion of all those using any hormonal contraceptives (oral contraceptive pill, minipill, hormone intrauterine device, subcutaneous implant or injection) at age 26.

AMH and PCOS

Women with PCOS at age 26 (n = 21, 5, 3% of the population) had significantly higher AMH levels at age 16 (Table II). The sensitivity and specificity of the serum concentration of AMH was evaluated at age 16 for PCOS at age 26 by using cut-off values according to the ROC-curve (Fig. 3). The sensitivity for PCOS at age 26 with a cut-off value for AMH of 22.5 pmol/l (3.15 ng/ml) was 85.7% and the specificity was 80.0%. Combination of different AMH and testosterone cut-offs did not significantly improve the accuracy of the test; the best combination was obtained with a cut-off of 22.5 pmol/l for AMH and 1.7 nmol/l for T (ROC-curve analysis, Fig. 3), resulting in a sensitivity of 57.1% and a specificity of 80.0%. An AMH cut-off of 22.5 pmol/l together with a T cut-off of 1.17 nmol/l resulted into a sensitivity of 23.8% and a specificity of 89.5%, whereas the combination with a T cut-off of 2.3 nmol/l resulted into a sensitivity of 4.8% and a specificity of 95.2%.

AMH and metabolic parameters

In the whole study population, there was a significant but weak correlation between serum AMH levels and BMI at the age of 16 (r = 0.124, P = 0.013), but the significance disappeared after adjusting for T. At age 16, there was no significant correlation between AMH levels and metabolic indices (WHR, plasma fasting glucose, serum insulin, HOMA-S, hsCRP, serum total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides) after adjusting for testosterone and BMI, except weak correlations in the lowest T quartile (WHR: r = −0.282, P = 0.005; fasting insulin: r = 0.290, P = 0.004; HOMA-S: r = −0.221, P = 0.033).

Discussion

In the present study, we evaluated the relationship between AMH and testosterone, oligo- or amenorrhea and metabolic and cardiovascular markers, and investigated the value of AMH measurement at the age of 16 in predicting oligo- or amenorrhea, hirsutism and the diagnosis of PCOS at the age of 26. The results showed that AMH levels associated significantly with T levels and oligo- or amenorrhoea and were a good indicator of oligo- or amenorrhea in adolescence. A serum AMH levels over 22.5 pmol/l despite its low specificity and therefore poor value as a diagnostic marker, could be used also to identify the girls at risk for PCOS in early adulthood, and allow early prevention by life style counselling.
We previously showed that obesity in adolescence and in adulthood, and also weight gain after adolescence, are associated with self-reported PCOS symptoms in adulthood (Laitinen et al., 2003). Thus, both our previous and present results, and the results from intervention studies treating PCOS (Moran et al., 2011; Teede et al., 2013) suggest that the prevention of obesity and encouragement of physical exercise are important among girls at risk to prevent the syndrome from developing.

Serum AMH levels at age 16 correlated significantly with T levels in adolescence and with self-reported hirsutism scores at age 26, which supports recent findings showing a weak correlation with androgens levels and F&G score (Eilertsen et al., 2012). In line with the present observations, previous studies have shown that increased AMH levels are associated with hyperandrogenism and/or oligo- or amenorrhea in adolescence (Park et al., 2010a,b) and adulthood (Laven et al., 2004; Li et al., 2011). In our study, however, the correlation with hirsutism was not significant in the whole study population, probably because of the beneficial effect of the OCs on hirsutism.

The correlation between AMH and T levels was the strongest in the highest T quartile, supporting our recent observation that serum T correlates with oligo- or amenorrhea at age 16 (Pinola et al., 2012). It is probable that the hyperandrogenic girls more often have polycystic ovaries and thereby higher serum AMH levels already in adolescence. Unfortunately, we were not able to verify this finding as ultrasound was not performed in this cohort, but previous studies have shown the association both in healthy and in women with PCOS or with PCO only (Pigny et al., 2003; Hart et al., 2010a,b).

To our knowledge, this is the first longitudinal follow-up study investigating the possible value of AMH as a marker for the development of PCOS later in early adulthood. Interestingly, the highest T quartile was the only one in which AMH at age 16 was significantly higher in women who experienced oligo- or amenorrhea at age 26 compared with women with a normal menstrual cycle. Based on the present and previous results (Pigny et al., 2003; Hart et al., 2010a,b), we suggest that the girls with irregular cycles and higher testosterone levels at age 16 have a higher antral follicle count and AMH levels and are therefore likely to fulfil the criteria for PCOS later in life. In line with this hypothesis, women with PCOS (either diagnosed or self-reported symptoms according to the questionnaire) at age 26 had higher serum AMH levels in adolescence compared with healthy women and serum AMH levels over 22.5 pmol/l could identify with a sensitivity of 85.7% the adolescent girls at risk for PCOS in early adulthood. The specificity of the test remained weak but improved substantially when using a cut-off of 42.8 pmol/l. Similarly, the results of previous studies have indicated that AMH alone may not be good enough as a single screening tool for PCOS. In the present study, however, the combination of AMH and T did not improve the accuracy of the test, in line with some (Casadei et al., 2013), but not all studies (Eilertsen et al., 2012) in which the power of AMH to diagnose PCOS increased substantially when combined with the other diagnostic criteria of PCOS. The girls with oligo- or amenorrhea at age 16 and PCOS or hirsutism alone at

Figure 1 Mean anti-Müllerian hormone (AMH) levels in different testosterone (T) quartiles. Standard deviations of the means are shown in the bars. P-value < 0.001 for trend from the lowest towards the highest T quartile.
age 26, however, had higher levels of AMH already at age 16, suggesting that the association between elevated AMH and symptoms of PCOS in adolescence persists also in early adulthood. Using a high enough cut-off value could help to distinguish most of the hyperandrogenic adolescents at risk for PCOS, but a routine use of this test in clinical practice cannot at present be recommended.

Figure 2 Mean anti-Müllerian hormone (AMH) levels, in the subjects with oligo- or amenorrhea (grey) and in the subjects with normal menstrual cycles (white), in testosterone quartiles, at age 16. Standard deviations of the means are shown in the bars. P-value for the difference between girls with oligo- or amenorrhea and girls with normal menstrual cycle in each T quartile.

Table II Anti-Müllerian hormone (AMH) concentrations at age 16 in women with hirsutism or polycystic ovary syndrome (PCOS) at age 26.

|                   | Hirsutism at age 26a (Ferriman & Gallwey score > 7)b | PCOS at age 26c |  |
|-------------------|------------------------------------------------------|-----------------|  |
|                   | Yes (n = 34)                                         | Mean AMH concentration (pmol/l)d | P-value |
|                   | 13.2 (11.8; 14.6)e                                   | 31.4 (27.1; 36.5)f | 0.036 |
|                   | No (n = 171)                                         | 25.8 (23.3; 28.6)g |       |
|                   | 4.4 (3.0; 5.9)                                       |                 |       |
|                   | Yes (n = 21)                                         | 38.2 (27.8; 48.5) | 0.044 |
|                   | No (n = 209)                                         | 30.2 (27.9; 32.5) |       |

a95% confidence interval in parentheses. 
bAccording to modified Ferriman & Gallway score (>7).
c73 subjects missing from the analysis due to the non-response to some items, 122 oral contraceptive users excluded.
dMean Ferriman & Gallway score, 95% confidence interval in parentheses.
eGeometric mean for AMH. 
f170 subjects missing from the analysis due to the non-response to some items.
We did not find any significant association between AMH and metabolic indices in the whole study population at age 16, which is in agreement with a recent report of a different European population (Anderson et al., 2013). This result indicates that AMH, despite its association with testosterone (Piltonen et al., 2005; Kristensen et al., 2012), is a poor marker of metabolic risks in adolescence. In contrast, in other studies (Nardo et al., 2009; Skalba et al., 2011), AMH associated positively with insulin, HOMA-IR and negatively with HDL, and in one study (Skalba et al., 2011) also positively with total cholesterol and LDL. These studies, however, were performed in older subjects in early adulthood or later, in an age range from 18 to 41. It may be that metabolic risks develop later in life and could not be identified in our study performed in adolescence.

An important pitfall is that AMH assays lack an agreed international standard and therefore the concentrations and cut-off points are method dependent. Importantly, however, in this study all the measurements were made simultaneously using the same AMH assay. Other limitations of this study are that we did not obtain blood samples from the subjects at the age of 26 and that AMH was measured in a subset of the whole cohort. Last, the diagnosis of PCOS at age 26 was based on a questionnaire, but we have previously demonstrated in a similar cohort at age 31 (the Northern Finland Birth Cohort 1966) that self-reported oligo- or amenorrhea and hirsutism can identify most women with the typical endocrine and metabolic profile of PCOS (Taponen et al., 2003, 2004). Moreover, women with both symptoms fulfilled the Rotterdam criteria for the definition of PCOS (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004).

**Conclusion**

Serum AMH levels associate significantly with T levels and oligo- or amenorrhea at age 16 and are a good indicator of oligo- or amenorrhea in adolescence. Using a high enough cut-off value of AMH to predict which adolescents are likely to develop PCOS in adulthood, despite its low specificity, could help to manage the condition from an early age with a good sensitivity. However, it is not an ideal diagnostic marker and its routine use in clinical practice cannot at present be recommended. Furthermore, AMH is not a good marker for cardiovascular risk factors in adolescence.

**Authors’ roles**

P.P.: study design, execution, analysis, manuscript drafting and critical discussion. L.C.M.-P.: study design, execution, manuscript drafting and critical discussion. A.B.: execution and analysis. K.P.: execution and analysis. A.R.: study design and critical discussion. M.-R.J.: study design and critical discussion. S.F.: study design, manuscript drafting and critical discussion. J.S.T.: study design, manuscript drafting and critical discussion. H.L.: study design, manuscript drafting and critical discussion.

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**Figure 3** ROC curves of testosterone and AMH for PCOS. Cut-off points with the best sensitivity and specificity used in the analyses are shown in the figure.
Conflict of interest
None declared.

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