Is polycystic ovary syndrome an exception for reproductive aging?

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BACKGROUND: Anti-Mullerian hormone (AMH) is increased in women with polycystic ovary syndrome (PCOS), suggesting a delay in ovarian aging. We examined AMH levels in PCOS and normo-ovulatory women in a population-based cohort over a period of 10 years and used this information to estimate their menopausal age.

METHODS: Of a subset of 1002 non-menopausal women randomly selected from the Tehran Lipid and Glucose Study, 85 cases of PCOS were diagnosed. We frequency-matched our control subjects with PCOS cases based on age and BMI. AMH levels were assessed at the time of recruitment (T1) and twice after that (T2 and T3). AMH levels were then plotted against age of the individual at the time of the measurement and the most appropriate model was selected. Menopause was calculated based on AMH levels below 0.2 ng/ml.

RESULTS: AMH levels were significantly higher in PCOS cases compared with controls at the beginning of the study (5.58 ± 3.64 versus 4.35 ± 2.90 ng/ml, P = 0.03), but the difference diminished considerably in subsequent assessments. The rate of AMH decline in PCOS cases decreased in the second compared with the first interval; however, no apparent change in the rate of decline was observed in controls. Estimated ages at menopause were 51 (95% confidence interval (CI), 34–81) and 49 (95% CI, 38–63) years in PCOS cases and controls, respectively.

CONCLUSIONS: The reproductive lifespan of PCOS women extends on average 2 years beyond that of normo-ovulatory women.

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Introduction

Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder in women of reproductive age and is characterized by disturbed folliculogenesis; notably increased progression from the primordial to the primary stage causing cycle irregularities (Wang et al., 2007). Serum anti-Mullerian hormone (AMH) concentrations are higher in PCOS women, an increase which correlates well with other clinical, endocrine and ultrasound parameters indicative of ovarian dysfunction (Pigny et al., 2003; Laven et al., 2004; La Marca et al., 2006; Pigny et al., 2006; Barton 2008; Chen et al., 2008; Kevenaar et al., 2008; Plouka et al., 2009).

The AMH, produced by growing pre-antral and early antral follicles, is the marker that best reflects the gradual decline in reproductive capacity with increasing age in normo-ovulatory women (van Rooij et al., 2002; Tehrani et al., 2009). AMH appears to regulate early follicle development directly and its absence enhances follicle-stimulating hormone (FSH)-induced follicle growth in female mice (Durlinger et al., 1999, 2002a,b). It has also been shown that AMH affects primary follicle depletion rate by inhibiting the transition from primordial follicles into primary follicles (Durlinger et al., 2002a, b; Broekmans et al., 2008), and its serum levels are strongly associated with the number of antral follicles (Kevenaar et al., 2006; Pigny et al., 2006).

Given the high levels of AMH in PCOS patients (Pigny et al., 2003; Laven et al., 2004; Piltonen et al., 2005), their steady decline over time (van Rooij et al., 2005), the strong association of AMH levels with the number of antral follicles (Ficicioglu et al., 2006; Kevenaar et al., 2006; Lambalk et al., 2009) and improvement in cycle irregularities with increase in age possibly due to a decrease in the follicle cohort size (Etling et al., 2000; Elting et al., 2003), some researchers have suggested that PCOS patients may exhibit longer reproductive lifespans (Laven et al., 2004; Piltonen et al., 2005). This hypothesis is backed up by predictions based on modeling of a cohort data by Mulders et al. (2004). We examined this hypothesis in a longitudinal study to see if the decrease in AMH serum concentration over time is any different in...
PCOS patients compared with normo-ovulatory controls, and whether this difference affects menopausal transition.

**Materials and Methods**

The study protocol was approved by the Medical Ethics Committee of the Research Institute for Endocrine Sciences, and informed consent was obtained from all participants. Our subjects were selected from participants of the Tehran Lipid and Glucose Study (TLGS; Azizi et al., 2003). TLGS is an ongoing prospective cohort initiated in 1998, in which 15 005 people aged ≥3 years were invited to participate following written consent. Information on various risk factors for non-communicable diseases, demographic variables and reproductive histories was collected during face-to-face interviews, conducted every 3 years by trained interviewers. Follow-up included a general physical examination, height and weight measurements, and blood sampling (samples were stored at −70°C for future use).

We excluded women who were already menopausal, had endocrine disorders, had histories of hysterectomy, oophorectomy or any other kind of surgery on their ovaries, or those for whom information on reproductive history was not available. Women who had been using any medication that could interfere with their hypothalamic–pituitary–gonadal axis normal function 3 months before entering the study were also excluded (Fig. 1). Information on menstrual dates and regularity, hirsutism, acne and reproductive history was collected for 1002 women via a standardized questionnaire. Hirsutism was assessed by a general practitioner using the modified Ferriman-Gallwey (mF-G) score; subjects with mF-G score >3 were reassessed by a single endocrinologist. Ovulatory dysfunction was defined using information on time intervals, cyclicity and total number of menstrual cycles per year. Subjects without hirsutism or ovulatory dysfunction by history and physical examination formed our eumenorrheic non-hirsute pool for selection of controls.

We conducted comprehensive hormonal profile testing for all of our final study participants to further identify ovulatory dysfunction or hyperandrogenemia. In women with only hirsutism, serum levels of progesterone (P4) were measured on Days 22–24 of their menstrual cycle to confirm ovulatory function, with levels <5 ng/ml indicating anovulation. Baseline blood samples were collected (after an overnight fast) between Days 3 and 7 of the spontaneous menstrual cycle or progesterone-induced menstrual bleeding. Circulating levels of FSH, luteinizing hormone (LH), prolactin (PRL), thyroid-stimulating hormone (TSH), total testosterone (T), androstenedione (A4), dehydroepiandrosterone sulfate (DHEAS), 17-hydroxy-progesterone (17-OH-P) and sex hormone-binding globulin (SHBG) were measured.

Using the National Institute of Health criteria, we defined PCOS as the presence of ovulatory dysfunction and clinical hyperandrogenism and/or hyperandrogenemia, after exclusion of other known related disorders such as hyperprolactinemia, thyroid and adrenal disorders. Ovulatory dysfunction was defined as a history of eight or fewer menstrual cycles in a year, menstrual cycles of 21 or 40 days in length, or midluteal serum P4 levels (cycle days 22–24) of <5 ng/ml in subjects with normal regular menstrual cycle (Azziz et al., 2004, 2009). The presence of hirsutism defined as mF-G score ≥8 was considered as clinical hyperandrogenism. Hyperandrogenemia was defined as T, A4 or DHEAS levels above the 95th percentile, calculated from selected healthy non-hirsute eumenorrheic women in our study population.

We frequency-matched our control subjects with PCOS cases based on age and BMI levels. To do this, we first categorized our PCOS cases into nine age and BMI groups. Subjects were then subdivided into <25, 25–30 and over 30 years old, and further into BMI <25, 25–30 and over 30 groups. Eighty-nine controls were randomly selected from all available
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**Table I Clinical and endocrine characteristics of study subjects.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>PCOS (n = 85)</th>
<th>Normo-ovulatory controls (n = 89)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), range</td>
<td>16–42</td>
<td>16–44</td>
<td>—</td>
</tr>
<tr>
<td>Age at T1</td>
<td>27.1 ± 8.4</td>
<td>27.8 ± 8.7</td>
<td>0.55</td>
</tr>
<tr>
<td>Age at T2</td>
<td>30 ± 8.6</td>
<td>31 ± 8.5</td>
<td>0.45</td>
</tr>
<tr>
<td>Age at T3</td>
<td>35 ± 8.2</td>
<td>34 ± 8.5</td>
<td>0.92</td>
</tr>
<tr>
<td>Age at menarche</td>
<td>13.2 ± 1.3</td>
<td>13.2 ± 1.2</td>
<td>0.76</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.3 ± 5.1</td>
<td>25.5 ± 4.9</td>
<td>0.26</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>83.9 ± 13.5</td>
<td>84.0 ± 12.9</td>
<td>0.87</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>102.2 ± 9.6</td>
<td>102.5 ± 9.2</td>
<td>0.85</td>
</tr>
<tr>
<td>Wrist circumference (cm)</td>
<td>15.7 ± 1.0</td>
<td>15.7 ± 1.0</td>
<td>0.69</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td>0.0 ± 1.3</td>
<td>1.5 ± 1.5</td>
<td>0.015*</td>
</tr>
<tr>
<td>% women with no pregnancies</td>
<td>27.1</td>
<td>14.6</td>
<td>0.018*</td>
</tr>
</tbody>
</table>

Intervals

<table>
<thead>
<tr>
<th>Intervals</th>
<th>PCOS</th>
<th>Normo-ovulatory controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st interval (mean, median, SD)††</td>
<td>1289, 1342, 352</td>
<td>1268, 1331, 316</td>
<td>0.78</td>
</tr>
<tr>
<td>1st interval (Range)</td>
<td>(685–1965)</td>
<td>(742–1980)</td>
<td>—</td>
</tr>
<tr>
<td>2nd interval (mean, median, SD)‡‡</td>
<td>1159, 1004, 370</td>
<td>1070, 1003, 326</td>
<td>0.32</td>
</tr>
<tr>
<td>2nd interval (range)</td>
<td>(737–1902)</td>
<td>(451–2041)</td>
<td>—</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>7.1 ± 8.8</td>
<td>6.8 ± 3.3</td>
<td>0.40</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>14.6 ± 7.6</td>
<td>8.2 ± 8.1</td>
<td>&gt;0.001*</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>1.73 ± 1.73</td>
<td>1.38 ± 0.79</td>
<td>0.01*</td>
</tr>
<tr>
<td>FAI*</td>
<td>3.9 ± 11.8</td>
<td>2.7 ± 1.6</td>
<td>0.02*</td>
</tr>
<tr>
<td>A4 (nmol/l)</td>
<td>6.98 ± 2.79</td>
<td>2.44 ± 2.68</td>
<td>&gt;0.001*</td>
</tr>
<tr>
<td>DHEAS (nmol/l)</td>
<td>441.9 ± 220.4</td>
<td>390.9 ± 187.8</td>
<td>0.59</td>
</tr>
<tr>
<td>AMH in 1st phase (ng/ml)</td>
<td>5.58 ± 3.64</td>
<td>4.35 ± 2.90</td>
<td>0.03*</td>
</tr>
<tr>
<td>AMH in 2nd phase (ng/ml)‡</td>
<td>2.77 (1.37–6.11)</td>
<td>2.72 (0.71–4.30)</td>
<td>0.16</td>
</tr>
<tr>
<td>AMH in 3rd phase (ng/ml)‡‡‡</td>
<td>2.06 (1.36–4.51)</td>
<td>1.84 (0.69–3.28)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Statistically significant.

We used Student’s t-test, where variables were normally distributed and the Mann–Whitney U-test, where assumption of normality did not hold, to compare different characteristics in PCOS cases and normo-ovulatory subjects (Table I). The Kolmogorov–Smirnov test was used to examine distribution of the variables. Mean, median, standard deviations and range are presented where appropriate. Spearman’s correlation coefficients were used to assess correlations between non-normally distributed variables.

We estimated AMH change over time by plotting the amount of change in the AMH level in two successive measurements against the time intervals between the two measurements. Linear regression lines were fitted in PCOS cases and normo-ovulatory controls for the two study intervals.

To examine AMH change by age, AMH levels were plotted against age of the individual at the time of the measurement. We explored our data by fitting a variety of linear and non-linear curves and assessed their suitability by taking into account their goodness of fit (r² values) as well as their simplicity. The generalized linear model was also tested; however, it did not provide a better fit. The linear curve was found to be the most appropriate model for our data, given its comparable r² values and ease of interpretation compared with complex non-linear models. We interpolated separate lines for PCOS cases and normo-ovulatory controls. Model assumptions were checked by examining the distribution of residuals.

The clinical and endocrine characteristics of study subjects were compared between PCOS cases and normo-ovulatory controls for the two study intervals. Linear regression lines were fitted in all samples, AMH levels were measured from stored samples obtained at the time of recruitment (T1) and twice after that (T2 and T3) at ~3-year intervals. In all samples, AMH levels were analyzed using an enzyme-immunometric assay Active MIS/AMH ELISA kit, DSL-10-14400, DSL (Diagnostic Systems Laboratories Inc.), TX, USA, according to the manufacturer’s guidelines. The limit of detection was 0.006 ng/ml and the intra- and inter-assay coefficients of variations were 5.2% and 9.1%, respectively. To keep intra-assay variability to minimum in our study, all laboratory measurements were performed simultaneously in the same laboratory by the same person.
and plotting standardized residuals against age. Ages at menopause were calculated for both study groups, with AMH levels <0.2 ng/ml being arbitrarily considered as reaching menopause, and P-values <0.05 were regarded as significant. Data were analyzed using SPSS software version 15 (SPSS Inc., Chicago, IL, USA).

Results

Of a total of 4290 women aged 16–44 years in the TLGS cohort, 1060 subjects were randomly selected in the first stage. Basic and reproductive characteristics including BMI, parity and percentage of women with regular menstrual cycle among those selected and those not selected were similar (data not presented). We finally compared 85 PCOS cases with 89 normo-ovulatory controls within the TLGS cohort (Fig. 1).

Clinical and endocrine characteristics of the PCOS cases and normo-ovulatory controls are summarized in Table I. On average, our cohort was young and had a slightly higher than normal BMI. Mean age and BMI were 27.1 ± 8.4 years and 26.3 ± 5.1 kg/m² in PCOS cases, and 27.8 ± 8.7 years and 25.5 ± 4.9 kg/m² in normo-ovulatory controls, respectively. 72.9% of PCOS and 85.4% of normo-ovulatory controls had at least one pregnancy before. All women in the control group had conceived naturally, whereas 23% of PCOS cases had received fertility treatment.

Among PCOS subjects, AMH was significantly correlated with the score of hirsutism \( r = 0.234, \) \( P = 0.04 \), number of menstrual cycles per year \( r = -0.269, \) \( P = 0.02 \), serum FSH \( r = -0.389, \) \( P = 0.05 \), serum A4 \( r = 0.255, \) \( P = 0.03 \) and free androgen index \( r = 0.233, \) \( P = 0.04 \) (data not shown).

AMH levels were significantly higher in PCOS cases (mean = 5.58 ng/ml, SD = 3.64) compared with normo-ovulatory controls (mean = 4.35 ng/ml, SD = 2.90) at the start of the follow-up (T1, \( P = 0.03 \)), but the difference disappeared in subsequent assessments at T2 and T3 (Table I).

The rate of AMH decline per year in PCOS cases decreased in the second interval \( b = 0.054 \) compared with the first interval \( b = -0.147 \) as the cohort grew older (Fig. 2, left side). No apparent change in the rate of decline per year was observed in the two time intervals among normo-ovulatory controls (Fig. 2, right side).

Figure 2 The left panel shows the scatter plot depicting the change in the AMH levels (value visit 2–value visit 1) in relation to time intervals between visit 1 and visit 2 (multiplication sign and dotted line), and the scatter plot depicting the change in AMH levels (value visit 3–value visit 2) in relation to time intervals between visit 2 and visit 3 (black diamonds and solid line) in PCOS cases. The right panel shows the scatter plot depicting the change in AMH levels (value visit 2–value visit 1) in relation to time intervals between visit 1 and visit 2 (multiplication sign and dotted line), and the scatter plot depicting the change in AMH levels (value visit 3–value visit 2) in relation to time intervals between visit 2 and visit 3 (black diamonds and solid line) in normo-ovulatory controls.
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AMH levels decreased with an increase in age in both the PCOS cases and normo-ovulatory controls. The scatter diagram suggested a linear pattern of decline for both groups (Fig. 3) and values remained relatively unchanged, at ~25% and 41% for PCOS cases and normo-ovulatory controls, respectively, when non-linear curves were fitted; the lines fitted for both groups came close together as age increased. Model residuals were normally distributed and there was no serious violation of model assumptions. Estimated ages at menopause (intersection of the lines at 0.2 ng/ml AMH value) were 51 years [95% confidence interval (CI) 34–81 years] and 49 years (95% CI 38–63 years) in PCOS cases and normo-ovulatory controls, respectively. There were 5 subjects from the normal group who reached menopause at ages 48, 46, 44, 42 and 41 while in the study (Fig. 3), and 12 more who crossed the arbitrary cut-off level of 0.2 ng/ml (of which 11 had recorded symptoms of menopausal transitions).

Discussion

We found higher AMH levels in PCOS women compared with normo-ovulatory controls matched for age and BMI. However, these levels decreased at a higher rate over time in PCOS patients, narrowing the difference. The estimated reproductive lifespan of PCOS cases was extended by 2 years on average compared with normo-ovulatory women.

AMH is secreted from granulosa cells in growing follicles (Durlinger et al., 2002a,b). It is not clear whether the increased numbers of follicles, generally present in PCOS and resulting in increased AMH production, is the first event in the cascade of events that leads to the development of PCOS (Jonard and Dewailly, 2004; Piouka et al., 2009), or whether low AMH levels in the first place is the starting point. The latter suggests a faulty AMH regulatory role in follicle development (Durlinger et al., 2002a, b; Stubbs et al., 2005; Kevenaar et al., 2008; Crisosto et al., 2009). Histological examination has demonstrated that higher serum AMH levels in PCOS women are due to an increase in the number of small antral follicles as well as greater AMH production per granulosa cell (Pellatt et al., 2007).

Serum AMH has several unique characteristics, which underline its robustness as a biological marker of the ovarian aging. Secreton exclusively in ovarian follicles (Durlinger et al., 2002a, b), it is reported to be independent of the menstrual cycle in most studies (Hehenkamp et al., 2006; Tsapelidis et al., 2007; Streuli et al., 2008; Wunder et al., 2008), with its levels remaining almost constant from one cycle to another and exhibiting a high intra-class correlation coefficient (van Rooij et al., 2002, 2005; La Marca and Volpe, 2006; Visser et al., 2006). The body of evidence for AMH as a predictor of reproductive aging is steadily growing (Lambalk et al., 2009).

We found the average age at menopause to be 49 years in normo-ovulatory women, a value which is similar to the figure reported by Mohammad et al. (2004) (49.6 years) for the general population of Iranian women in a large national survey. According to our study, on average PCOS cases reach menopause 2 years later than the normo-ovulatory women, which could be clinically important even though statistically insignificant. This was partly because of the high degree of dispersion among AMH values of study subjects, particularly in PCOS cases. It would be desirable to repeat our analysis in subgroups of PCOS cases that had similar phenotypes to minimize variability. Our main finding of relatively close reproductive lifespans in PCOS women and normal controls is in contrast with the Mulders et al. study, which, to the best of our knowledge, is the only available longitudinal study investigating this issue in PCOS women. Mulders et al. recruited cohort subjects from non-fertile women, attending a fertility clinic and fertile women responding to an advert in a local newspaper. Women in the control group were 20–35 years old, with normal body weight. This study reported that the decline in serum AMH level over time is significantly less in women with normogonadotrophic anovulation (WHO2) compared with normo-ovulatory controls, and estimated the average menopausal ages to be 74 and 42 years for the two groups, respectively. In our opinion, the average menopausal age of 74 years reported in normogonadotrophic anovulation is an overestimation, as is not been identified or reported so far by any other cross-sectional study on menopause and its related factors. Likewise, Mulders’ estimation of average age of menopause of 42 years in normo-ovulatory controls also seems to be an underestimation. General population estimates of median age of onset of menopause are between 50 and 52 years, with the range of 40–60 years (McKinlay et al., 1985; Gold et al., 2001), which is in stark contrast with the findings of Mulders et al. In addition Mulders et al.’s estimations were based on two AMH measurements in a relatively small sample of 98 WHO2 cases (median follow-up = 2.6 years) and 41 controls (median follow-up = 1.6 years), which might explain the variability in their estimates. In contrast, we measured AMH levels three times in a relatively large sample of 174 women, followed for an average of 6 years.

Our findings that AMH levels are higher in women with PCOS compared with normo-ovulatory controls, and that these serum levels decreased with an increase in age both in PCOS cases and normo-ovulatory controls. The scatter diagram suggested a linear pattern of decline for both groups (Fig. 3) and values remained relatively unchanged, at ~25% and 41% for PCOS cases and normo-ovulatory controls, respectively, when non-linear curves were fitted; the lines fitted for both groups came close together as age increased. Model residuals were normally distributed and there was no serious violation of model assumptions. Estimated ages at menopause (intersection of the lines at 0.2 ng/ml AMH value) were 51 years [95% confidence interval (CI) 34–81 years] and 49 years (95% CI 38–63 years) in PCOS cases and normo-ovulatory controls, respectively. There were 5 subjects from the normal group who reached menopause at ages 48, 46, 44, 42 and 41 while in the study (Fig. 3), and 12 more who crossed the arbitrary cut-off level of 0.2 ng/ml (of which 11 had recorded symptoms of menopausal transitions).
levels of AMH were positively correlated with the severity of the disease, are in agreement with previous studies (Jonard and Dewailly, 2004; Laven et al., 2004; Chen et al., 2008; Nardo et al., 2009; Piouka et al., 2009). However, the difference observed between AMH levels of PCOS cases and normal controls in our study is smaller than the ones previously reported. This was first because our study is population based, i.e. our PCOS cases represent a milder group of patients in the community, whereas other studies recruited symptomatic patients attending infertility clinics. Furthermore, we matched our case and control groups, based on age and BMI, eliminating any differences in AMH levels that may arise from differences in these two factors (Freeman et al., 2007; Piouka et al., 2009; Thomson et al., 2009) in our study groups.

Our model is sufficiently reliable to show that the actual ages at menopause were reasonably close to the predications for those who reached menopause, even though they represented the lower end of the spectrum in that regard (Fig. 3). A longer follow-up period is needed to include those who reached menopause later in their reproductive life. In addition, the majority of the subjects whose AMH level crossed the arbitrary level of 0.2 ng/ml had reported symptoms of menopausal transition in the form of unpredictable and irregular menstrual cycles, thereby supporting the appropriateness of the cut-off level used.

This study has a few limitations; our model is not able to accurately predict age at menopause in some of the study subjects due to the general limitation of modeling method. We were not able to measure other ovarian aging markers, including antral follicle counts, that could be a limitation of our current study. For AMH measurements, we used stored samples that had not been collected on any specific days of menstrual cycles during the second (T2) and third (T3) sampling; this we believe, however, will have minimal impact on our results, as serum AMH levels are considered to be independent of menstrual cycle (Hehenkamp et al., 2006; Tsepelidis et al., 2007; Streuli et al., 2008), and since the samples are unaffected by long-term storage (de Vet et al., 2002; Mulders et al., 2004; van Rooij et al., 2005). The use of NIH criteria rather than Rotterdam criteria (2004) may have affected our control group, since we may have lost cases of mild PCOS phenotype that could otherwise have been diagnosed using the Rotterdam criteria; these cases may have been mistakenly included in the control group, although the likelihood of this is very low since any subject with hirsutism, oligomenorrhea or hyperandrogenemia was excluded from our control pool and the likelihood of our study groups.

In conclusion, our study shows that despite higher average levels of AMH in PCOS patients, their menopausal age is slightly higher than that of the general population. Since only a few subjects actually became menopausal in our cohort, follow-up data on the exact menopausal age of the remaining cohort members could further facilitate confirmation of the ovarian aging process in PCOS subjects. The challenging concept of ovarian aging in PCOS needs further elucidation by properly designed longitudinal follow-up studies.

Authors’ roles

F.R.T. contributes in study design, execution, analysis, manuscript drafting and critical discussion. M.S.-D. contributes in study design, analysis, manuscript drafting and critical discussion. M.H. contributes in study design, laboratory testing and manuscript drafting. F.A. contributes in study design, execution and manuscript drafting.

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