Emergence of ovulatory cycles with aging in women with polycystic ovary syndrome (PCOS) alters the trajectory of cardiovascular and metabolic risk factors

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STUDY QUESTION: What alters cardiovascular and metabolic risk factors with aging in women with polycystic ovary syndrome (PCOS)?

SUMMARY ANSWER: Lipid parameters, mainly low-density lipoprotein (LDL) cholesterol, increase with aging, but not in women who attain ovulatory cycles.

WHAT IS KNOWN ALREADY: Cardiovascular and metabolic parameters tend to increase with aging, but this has not been shown in a prospective longitudinal study in women with PCOS. Correlates of these changes have not been identified.

STUDY DESIGN: A prospective cohort of 118 hyperandrogenic women with PCOS who were followed from the age of 20–25 years at 5 year intervals for 20 years.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Thirty-five age-matched controls and another 35 age-matched controls in their 40s, 20 years later. Longitudinal measurements of body mass index (BMI), waist circumference, fasting serum steroids, glucose, insulin, lipids, prevalence of metabolic syndrome and ovulatory status.

MAIN RESULTS AND THE ROLE OF CHANCE: After 20 years, in the entire group, waist circumference increased as did glucose, total cholesterol (C), high-density lipoprotein-C (HDL-C), LDL-C and non-HDL-C. The prevalence of metabolic syndrome was 7% at the beginning and 6% at the end. Fifty-one women with PCOS were found to be ovulatory and 67 remained anovulatory after 20 years. Anovulatory women had higher insulin, lower QUICKI and higher total C, LDL-C, non-HDL-C and lower HDL-C. In ovulatory women there were no alterations in lipids or glucose and minor changes in insulin and QUICKI compared with controls. None of the parameters were influenced by BMI or waist circumference.

LIMITATIONS, REASONS FOR CAUTION: Inability to follow controls for 20 years. Associations observed between ovulatory function and lowered cardiovascular and metabolic risks cannot imply cause and effect.

WIDER IMPLICATIONS OF THE FINDINGS: Phenotypic variability, particularly ovulatory function, in women diagnosed to have PCOS appears to influence cardiovascular and metabolic risks. It is unclear if these data pertain to other populations and ethnicities of women.

STUDY FUNDING/COMPETING INTERESTS: Self-funded; no conflicts of interest.

Key words: PCOS / ovulation / aging / lipids / insulin
Introduction

Even young women with polycystic ovary syndrome (PCOS) are known to have increased cardiovascular risk factors (Lobo and Carmina, 2000) and a higher prevalence of metabolic syndrome (Apridonidze et al., 2005; Dokras et al., 2005; Carmina et al., 2006a). More specifically, women with PCOS may have altered glucose tolerance and dyslipidemia (Lobo and Carmina, 2000; Wild et al., 2011), as well as an increase in inflammation markers (Talbott et al., 2000; Carmina et al., 2006b).

In the normal population both abdominal obesity and insulin resistance tend to increase with aging and are associated with cardiovascular risk and metabolic syndrome (Fink et al., 1983; St-Onge and Gallagher, 2010). In PCOS, abdominal obesity increases with aging (Liang et al., 2011), as does the prevalence of metabolic syndrome (Dokras et al., 2005) whereas glucose utilization decreases (Brown et al., 2011). Yet it is not clear whether women with PCOS are at increased risk of cardiovascular events with aging (Pierpoint et al., 1999; Shaw et al., 2008; Carmina, 2009). In one study which suggested that an increased risk exists, the likelihood that post-menopausal women with a suggested diagnosis of PCOS would have a cardiovascular event correlated with their free testosterone concentration (Shaw et al., 2008).

Androgen levels, specifically testosterone, decrease with aging in PCOS and this may be correlated with improvements in the syndrome (Morán et al., 1999; Winters et al., 2000; Carmina et al., 2012). Some anovulatory women with PCOS may become ovulatory with aging (Elting et al., 2000; Carmina et al., 2012) reflecting a decreased follicular cohort. It is thus possible that lowered androgen and more normal ovarian function may attenuate the cardiovascular risk of women with PCOS.

Previously, we have provided data on 193 women with PCOS who were followed for 20 years, from their mid-20s to the mid-40s (Carmina et al., 2012). In these women, while androgens decreased with aging, serum insulin and insulin resistance did not change, and waist circumference increased. Here we report data on 118 of these women with a focus on the prevalence of the metabolic syndrome and their lipid profiles and metabolic status, and show a major correlation of these findings with the commencement of ovulatory function with aging.

Materials and Methods

Patients

Between 1985 and 1990, 118 women aged 20–25 years (mean age 21.8 ± 1 years) affected by PCOS were evaluated. The patients were referred to the Endocrine Unit of the Department of Clinical Medicine of the University of Palermo because of symptoms of hyperandrogenism and/or oligomenorrhea. These patients were part of a larger follow-up of women diagnosed with PCOS by Rotterdam criteria (Carmina et al., 2012). At the time of their evaluation, none of the patients had any treatment for at least 3 months. All women were assessed at 5 year intervals and followed for 20 years.

Clinical hyperandrogenism was defined by the presence of hirsutism. Hirsutism was assessed by Ferriman–Gallwey–Lorenzo scores and patients having scores >8 were considered as hirsute (Hatch et al., 1981). Biochemical hyperandrogenism was defined as finding elevated levels of serum androgens [total testosterone (T) and/or dehydroepiandrosterone sulfate, (DHEAS)]. Oligomenorrhea was defined as menstrual cycle interval >35 days.

In all women, the following data were assessed: age, menstrual status, scoring of clinical hyperandrogenism, body mass index (BMI), waist circumference, serum levels of T, DHEAS, 17-OH progesterone (17OH), progesterone (P), insulin, blood glucose and a lipid profile (serum total cholesterol (C), high-density lipoprotein-C (HDL-C), triglycerides (TG), low-density lipoprotein-C (LDL-C) and non-HDL-C. Insulin resistance was calculated by QUICKI (Katz et al., 2000).

Serum androgens and 17OHP were measured during the follicular phase (Days 5–8) of a spontaneous or progestin-induced menses. Serum P was measured on Days 21–24 of the menstrual cycle. Blood glucose, serum insulin and lipid profiles (total C, HDL-C and TG) were obtained in the fasting state.

Controls

At the onset of the study, 35 normal controls, aged 20–25 years, with normal body weight, normal ovulatory menses and no clinical or biochemical signs of hyperandrogenism were assessed.

Because we were unable to follow a control group of women for 20 years, we selected an age-matched group of 35 normal controls at the end of the study. These women were aged 40–45 years, with normal body weight, normal ovulatory cycles and with no clinical or biochemical signs of hyperandrogenism. These women had blood and body composition measurements obtained.

Assessment of women with PCOS over time

The women were included in a project designed to evaluate the long-term consequences of PCOS. It was anticipated that this project would have a duration of 30 years to observe age-dependent endocrine and metabolic changes of the disorder. The patients were re-evaluated every 5 years and at each re-evaluation, the same clinical, biochemical and hormonal data were re-assessed.

During this long period of time, the patients had various treatments, but were off any treatment for at least 3 months at the time of their re-evaluation. Most patients (n = 98) were treated with several oral contraceptives. The duration of this treatment varied and ranged between 6 months and 10 years. In long-term users of oral contraceptives, treatment was intermittent, depending on the clinical circumstances. Metformin and anti-androgens were also used; in most instances, the patients had also used oral contraceptives. No lipid-lowering medications were used by any women throughout the study. Most obese patients, during this long period of time, had been on various diets for variable periods of time but no patient had participated in a specific lifestyle program.

This research was carried out in accordance with the Helsinki Declaration of 1975 and the study was approved by the local Ethics Council. All subjects gave their informed consent to participate in the study.

Assays

Hormone levels were quantified by well-established methods that had been validated previously in our laboratory (Carmina et al., 1992; Carmina, 1998). All steroids were measured by specific radioimmunoassays after extraction using previously described methods. In all assays, intra- and inter-assay coefficients of variation did not exceed 6 and 15%, respectively.

Anovulation was defined as serum P of <3 ng/ml (<9.54 nmol/l). In patients with normal menses, at least two consecutive menstrual cycles were evaluated, and the finding of low-levels of serum P (<3 ng/ml) in both cycles confirmed the presence of chronic anovulation (Carmina and Lobo, 2009).
Biochemical hyperandrogenism was defined as serum T >60 ng/dl (>2.08 nmol/l) and/or serum DHEAS >3 mg/l (>7.8 nmol/l). These values of hyperandrogenism have been previously established with the same assays (Carmina, 1998). Increased serum 17OHP was defined as serum 17OHP >3 mg/l (>9.1 nmol/l). In patients with mildly increased serum 17OHP (<10 and >3 mg/l), increased 17OHP responses to ACTH administration (1 mg i.v. with blood samples at 0’, 30’ and 60’) was required to diagnose or rule out non-classical 21-hydroxylase deficiency (Carmina and Lobo, 2009).

Total C levels were measured by the cholesterol esterase method, while TG concentrations were determined enzymatically as glycerol following hydrolysis with lipase; HDL-C concentrations were measured by the cholesterol esterase method following selective precipitation of apolipoprotein-B containing lipoproteins with a polyanion solution. All plasma lipid analyses had intra- and inter-assay variations <3%. LDL-C was calculated using the Friedewald formula (Friedewald et al., 1972). Non-HDL-C was calculated as total C minus HDL-C.

Assessment of the metabolic syndrome

The presence of the metabolic syndrome was assessed by the joint American Heart Association/National Heart, Lung and Blood Institute Scientific Statement (National Cholesterol Education Program, 2002). The presence of any three of the following five risk factors allowed a diagnosis to be made: elevated waist circumference (>88 cm in women), elevated fasting TG (>150 mg/dl or on drug treatment for elevated TG), reduced HDL-C (<50 mg/dl in women or on drug treatment for reduced HDL-C), elevated blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mm Hg or on antihypertensive drug treatment) and elevated fasting glucose (≥100 mg/dl or on drug treatment for elevated glucose).

Statistical analysis

Statistical analyses were performed using Statview 5.0 (SAS Institute, USA). Univariate analyses were performed using the unpaired t-test for the numeric variables, whereas the differences in the prevalence for the nominal variables were analyzed by the χ² test. Group means were compared using analysis of variance (ANOVA) with post hoc least squares means pairwise comparisons (after log transformation of the values). Pearson product moment correlation and stepwise multivariate linear regression analysis with forward selection was used to assess correlations. All values are reported as the mean ± SD. Women with PCOS who were ovulatory throughout the observation period were included in the data presented in Table I but excluded from the analyses presented in Tables II and III. Therefore, in Tables II and III the ovulatory group includes only those women anovulatory at the outset who became ovulatory with age. Findings in the ovulatory and anovulatory groups were adjusted for changes in BMI and waist circumference by sequential stepwise analyses.

Results

Baseline data

Normal controls and women with PCOS were of a similar age (21.8 ± 2 and 21.8 ± 2 years) but women with PCOS had a higher BMI (27.5 ± 6 versus 21.5 ± 5), waist circumference (91 ± 15 versus 74 ± 6 cm), serum testosterone (90 ± 28 versus 31 ± 14 ng/dl, P < 0.01), DHEAS (3 ± 1.4 versus 1.8 ± 1 μg/ml, P < 0.01), serum insulin (14.6 ± 7 versus 9.8 ± 2 mU/ml, P < 0.01) and LDL-C (104 ± 21 versus 92 ± 25 mg/dl, P < 0.01) and significantly (P < 0.01) lower serum HDL-C (48 ± 7 versus 52 ± 5 mg/l)
and QUICKI (0.323 ± 0.018 versus 0.344 ± 0.012, P < 0.01). Blood glucose, total C, TG and non-HDL-C levels were similar in the two groups. One woman with PCOS (0.85%) had type 2 diabetes.

Only hyperandrogenic women were included among the patients diagnosed with PCOS in this study. The most common PCOS phenotype was the more severe form (chronic anovulation, hyperandrogenism and polycystic ovaries) known as Phenotype A or Classic PCOS which was found in 90 women (76% of the group.). This was followed by the ovulatory phenotype (hyperandrogenism, polycystic ovaries and normal ovulatory cycles (phenotype C or ovulatory PCOS), which occurred in 21 women (18% of the group). Seven women (6%) had chronic anovulation and hyperandrogenism but normal ovaries (phenotype B).

In women with PCOS, the prevalence of metabolic syndrome was 7% and the most common alterations were increased waist circumference and low-HDL-C levels (present in 50 and 40.7% of women with PCOS, respectively). The other components of metabolic syndrome were present in < 10% of the patients. An increase in total and/or LDL-C was observed in 20 women (16.9%).

**Changes occurring in women with PCOS over 20 years**

As reported previously (Carmina et al., 2012), androgen levels decreased significantly: after 20 years total T was 54 ± 28 ng/dl and DHEAS was 2.1 ± 1 µg/ml, P < 0.01.

Table I depicts the metabolic data of the women at 5 year intervals over the 20 years of follow-up. The mean BMI did not change with aging, while waist circumference increased (P < 0.05). Serum insulin and QUICKI remained unchanged but a mild but significant (P < 0.05) increase of blood glucose was observed. Serum C, HDL-C, LDL-C and non-HDL-C progressively increased and were significant higher after 20 years; significant changes began after 15 years (Table I). Serum TGs remain unchanged.

The prevalence of metabolic syndrome did not change and was 7% at baseline and 6% at 20 years, although the finding of an abnormal fasting glucose increased from 8 to 12%. The prevalence of low HDL-C was 40.7% at baseline and was 28.8% at 20 years. An increased LDL-C was observed in 14% of women at baseline and was 26% at 20 years (P < 0.05), while TGs were unchanged.

Type 2 diabetes developed in an additional three women and therefore its prevalence in the studied population increased to 3.4%.

Compared with controls aged 40–45 years, the entire group of women with PCOS at 20 years had a higher BMI (P < 0.01), waist circumference (P < 0.01), serum testosterone (P < 0.01), DHEAS (P < 0.05), insulin (P < 0.01) and LDL-C (P < 0.05). HDL-C and QUICKI were significantly lower (P < 0.05); glucose and circulating total C, TG and non-HDL-C were similar in the two groups (data reported in Tables I and II).

<table>
<thead>
<tr>
<th>Table II</th>
<th>Metabolic parameters in women 40–44 years, including 35 age-matched normal controls, 30 women with an initial diagnosis of PCOS who become ovulatory with aging and 67 women with an initial diagnosis of PCOS who remained anovulatory with aging.</th>
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<tbody>
<tr>
<td></td>
<td>Controls (Co)</td>
</tr>
<tr>
<td>BMI</td>
<td>23.8 ± 2</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>85 ± 5</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>88 ± 11</td>
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<tr>
<td>Insulin (µU/ml)</td>
<td>11 ± 3</td>
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<tr>
<td>QUICKI</td>
<td>0.335 ± 0.018</td>
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</tbody>
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<tr>
<th>Table III</th>
<th>Serum lipid levels in women 40–44 years, including 35 normal age-matched controls, 30 women with an initial diagnosis of PCOS who become ovulatory with aging and 67 women with an initial diagnosis of PCOS who remained anovulatory with aging.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Controls (Co)</td>
</tr>
<tr>
<td>Total C (mg/dl)</td>
<td>172 ± 25</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>55 ± 6</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>84 ± 20</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>102 ± 18</td>
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<tr>
<td>Non-HDL-C (mg/dl)</td>
<td>117 ± 20</td>
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</tbody>
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C, cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol.
Influence of changes in body weight, androgens and the menstrual pattern on lipids and insulin

No correlations were found between changes in BMI, waist circumference, serum testosterone or DHEAS and modifications in serum lipids or insulin or QUICKI.

After 20 years, 51 women were ovulatory, 30 of whom became ovulatory with aging, 8 in the time span of 35–39 years and 22 women during the time span of 40–44 years. Sixty-seven women remained anovulatory. No correlation was found between the occurrence of ovulatory cycles with age and baseline BMI, waist circumference, serum testosterone or serum insulin. No correlation was observed between the finding of ovulatory cycles and changes in BMI, waist circumference, total C, HDL-C, TG and non-HDL-C at 20 years. However, a significant negative correlation was found between the occurrence of ovulatory cycles and the percentage (−0.54, \(P < 0.01\)) or absolute (−0.57, \(P < 0.01\)) changes in LDL-C at 20 years.

The anovulatory group at 20 years had higher BMI, waist circumference, serum insulin, total C, LDL-C and non-HDL-C compared with controls, while QUICKI and HDL-C were lower (Tables II and III). No significant differences in blood glucose or in serum TGs were observed. Tables II and III depict unadjusted and adjusted (BMI and waist circumference) statistical significance levels for the ovulatory and anovulatory women compared with controls. The ovulatory group at 20 years had higher BMI, waist circumference, serum insulin (\(P < 0.05\)) and lower values of QUICKI (\(P < 0.05\)) but similar levels of blood glucose and serum lipids compared with controls.

Compared with their initial metabolic data at the age of 20–25 years, patients who became ovulatory with aging had no changes in BMI, waist circumference, glucose, insulin, QUICKI, TG, LDL-C and non-HDL-C, while total C and HDL-C increased significantly (\(P < 0.05\)). However, patients who remained anovulatory after 20 years had higher glucose, total C, HDL-C, LDL-C and non-HDL-C values, while BMI, waist circumference, insulin, QUICKI and TG did not change.

Comparing metabolic profiles after 20 years in the anovulatory and ovulatory women, anovulatory women had higher glucose (\(P < 0.05\)), total C, LDL-C and non-HDL-C (\(P < 0.01\)) (Table III) and there was a non-significant trend for higher BMI, waist circumference, insulin and lower QUICKI values (Table II). The differences in BMI and waist circumference between the anovulatory and ovulatory women had \(P\) values of 0.10 and 0.20, respectively. The differences in serum lipids between the two groups persisted after adjustment for BMI and waist circumference. However, the statistical increase in glucose in anovulatory women at 20 years was no longer significant after adjustments. Figure 1 depicts the changes in LDL-C values in the two groups of patients with an initial diagnosis of PCOS.

Influence of treatment on metabolic changes with the age

While most patients had some treatment during the 20-year follow-up, the variable duration of the therapy, the different composition of the different products, the use of different prescriptions during different periods, prevented the possibility of a specific evaluation of the effects of the various treatments on the evolution of the syndrome.

However, we evaluated the difference between patients who were treated for at least 6 months on oral contraceptives (\(n = 108\)) and patients who did not use any therapy (\(n = 10\)). No differences in the clinical and metabolic changes were observed.

Discussion

In the normal population, aging usually worsens metabolism and increases the risk for cardiovascular disease and type II diabetes. Metabolic syndrome is linked to obesity, and its prevalence increases significantly with age. It has been reported that in the US female population the prevalence of metabolic syndrome is 5.9% during the third decade and progressively rises to 14.9, 20 and 46.5% during the fourth, fifth and seventh decades (Park et al., 2003). Aging appears to increase the metabolic sensitivity to increased body weight most probably by progressively increasing visceral and ectopic fat (Ogden et al., 2006; Sepe et al., 2011). In women with PCOS, cross-sectional studies have suggested that the prevalence of metabolic syndrome also increases with age (Dokras et al., 2005); however, no changes in its prevalence with age were observed in a recent longitudinal study (Hudecova et al., 2011).

In this study we report on a group of women with PCOS, the large majority of whom had the more severe or classic phenotype, who were followed for 20 years from their 20s into their fourth decade. The larger cohort of women in this longitudinal follow-up for 20 years has already been reported (Carmina et al., 2012). Here a subset of the group was evaluated for metabolic and lipid parameters and for the prevalence of metabolic syndrome.

Interestingly, the prevalence of metabolic syndrome remained stable during the 20 years of follow-up. Women with PCOS in their 20s had a prevalence of 7%, and it was virtually the same (6%) in their 40s. In Italy, the prevalence of metabolic syndrome in the general population is 2.4% in the 20s and increases to around 5% at
the age of 40. Thus, the prevalence is still 3-fold higher in PCOS in younger women (Carmina et al., 2006a), but our data suggest that it tends to normalize with aging. Population differences are important to note, however, with HDL-C tending to rise with age, and a very low-prevalence of elevated TG in Italian women relative to US data (Essah et al., 2008). One of the limitations in this study is that we were unable to follow a control group of women longitudinally for 20 years. Indeed, there are no such studies in Italian women to our knowledge. Here we selected an age-matched group of normal women at the end of the study for comparisons.

While HDL-C improved with aging, there was a significant increase in total C, LDL-C and non-HDL-C. These changes in serum lipids are not specific to PCOS and also are observed in the general population (Schaefer et al., 1994; Gardner et al., 2000; Rouvre et al., 2011). The increased serum LDL-C levels were observed in 26% of women in their 40s having an initial diagnosis of PCOS, and coupled with a similar increase in non-HDL-C suggest an increase in CV risk with aging. The increased alterations in blood glucose and blood pressure, although not reflected in an increase in the prevalence of metabolic syndrome, also suggest an increased CV risk.

In this study, we confirmed previous findings that spontaneous ovulatory cycles occur with aging in 1/3 of anovulatory women with PCOS (Elting et al., 2000; Carmina et al., 2012). This may be due to changes in ovarian function occurring longitudinally over adult life. Here we have assessed risk factors only in those women (n = 30) who attained ovulatory function with aging as depicted in Tables II and III. It is known that among young women with PCOS, such as those assessed at baseline in this study, those who are ovulatory have less risk factors than anovulatory women (Jovanovic et al., 2010).

While changes in body weight may have a role in this process in some patients, in the majority of women, the spontaneous occurrence of ovulatory cycles with aging does not appear to be related to modifications of body weight or in fat distribution. In this study, the occurrence of ovulatory function did not correlate with BMI or waist circumference at baseline (in women in their 20s). In addition, after 20 years, there was no significant difference in BMI or waist circumference between ovulatory and anovulatory patients. We also assessed any changes in BMI against ovulatory function and did not find any correlation with the occurrence of ovulation. This is consistent with previous data (Elting et al., 2000) where in this northern European population there was no influence of BMI on the occurrence of ovulatory cycles with aging in PCOS.

However, interesting and novel data have been generated here suggesting that the occurrence of ovulatory function with aging in these women with PCOS is associated with a modification in cardiovascular risk. A negative correlation was observed between the appearance of ovulatory cycles and the increase in LDL-C. The rise is attenuated, and appears to be similar to values obtained 20 years earlier. Instead in patients who remained anovulatory, total C, LDL-C and non-HDL-C values significantly increased and remained significantly higher than that of the general population. We and others have reported that the cardiovascular and metabolic risk profiles of women with PCOS are less threatening with the ovulatory phenotype (Welt et al., 2006; Jovanovic et al., 2010; Guastella et al., 2010; Anaforoglu et al., 2011). Our present data suggest that patients who attain ovulatory cycles with aging have a different trajectory of lipid profile and glucose utilization. Nevertheless, we do not wish to imply that these observations are in any way a causation induced by attaining ovulatory status. We have merely observed a correlation, or an association, which cannot be proved at this time.

The possible mechanisms for this associated protective effect of ovulatory function is not clear at the present, but it has been suggested for some time that it is predominantly those women who have irregular cycles who exhibit insulin resistance (Robinson et al., 1993). It is plausible that the relative improvements in LDL-C and insulin action are occasioned by higher estradiol levels which are achieved during normal menstrual cycles. Estradiol has been shown to increase LDL receptors and to improve insulin action through a post-receptor mechanism (Wagner et al., 1991; Gorres et al., 2011).

This study was performed in a population that has a low prevalence of metabolic syndrome; specifically, HDL-C tends to be higher and TGs are not elevated, and there is a lower prevalence of obesity. Therefore, the data we report may not be automatically extrapolated to different populations of women with PCOS, particularly in the USA, where the prevalence of metabolic syndrome is noted to be particularly high.

Quantifying CV risk in women with PCOS has been difficult and has been a matter of controversy in the field (Wild et al., 2010). Here we suggest another variable. While the prevalence of ovulatory cycles increases in women with PCOS as they age, those women who attain ovulatory cycles have a different trajectory of CV and metabolic risk factors with aging.

Authors’ roles
E.C. and R.A.L. were involved in the design, analysis and writing of this work. A.C.M. was responsible for chart review, data tabulation and participated in the review of the paper. Each author participated actively in the preparation of this manuscript.

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Conflict of interest
None declared.

References


