The effect of weight loss on anti-Müllerian hormone levels in overweight and obese women with polycystic ovary syndrome and reproductive impairment

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Background: Anti-Müllerian hormone (AMH) has been proposed as a clinical predictor of improvements in reproductive function following weight loss in overweight and obese women with polycystic ovary syndrome (PCOS). This study aimed to assess whether baseline and/or change in AMH levels with weight loss predict improvements in reproductive function in overweight and obese women with PCOS.

Methods: Fifty-two overweight and obese women with PCOS and reproductive impairment (age 29.8 ± 0.8 years, BMI 36.5 ± 0.7 kg/m²) followed a 20-week weight loss programme. AMH, weight, menstrual cyclicity and ovulatory function were assessed at baseline and post-intervention.

Results: Participants who responded with improvements in reproductive function (n = 26) had lower baseline AMH levels (23.5 ± 3.7 versus 32.5 ± 2.9 pmol/l; P = 0.03) and experienced greater weight loss (–11.7 ± 1.2 versus –6.4 ± 0.9 kg; P = 0.001) compared with those who did not respond (n = 26). Logistic regression analysis showed that weight loss and baseline AMH were independently related to improvements in reproductive function (P = 0.002 and P = 0.013, respectively). AMH levels did not change with weight loss in both responders and non-responders.

Conclusions: In overweight and obese women with PCOS and reproductive dysfunction, a 20-week weight loss intervention resulted in improvements in reproductive function but no change in AMH levels.

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Key words: weight loss / anti-Müllerian hormone / reproductive function / menstrual cyclicity

Introduction

Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility in women of reproductive age, affecting ~7% of this population (Norman et al., 2007). It is associated with insulin resistance, elevated androgens and reproductive problems including infertility and menstrual dysfunction (Norman et al., 2007). Although not entirely understood, the aetiology of PCOS is closely linked to obesity and abdominal adiposity that are considered to worsen the clinical presentation, particularly menstrual irregularities and hyperandrogenism (Holte et al., 1995; Barber et al., 2006; Pasquali et al., 2006). Lifestyle modification programmes focusing on weight loss have been shown to be important for improving reproductive function in obese women with PCOS (Huber-Buchholz et al., 1999; Crosignani et al., 2003; Moran et al., 2003). However, several studies have demonstrated that reproductive responsiveness to weight loss (shown by improved menstrual cyclicity or ovulation) only occurs in ~60% of previously anovulatory overweight women (Kiddy et al., 1992; Holte et al., 1995; Huber-Buchholz et al., 1999; Crosignani et al., 2003; Moran et al., 2003).
Anti-Müllerian hormone (AMH), a member of the transforming growth factor-β family, is expressed in the granulosa cells of early developing follicles in the ovary and is an inhibitor of follicular maturation and recruitment. Women with PCOS have 2- to 3-fold higher levels of AMH compared with healthy women (Cook et al., 2002; Piginy et al., 2003; LaMarca et al., 2004a, b; Laven et al., 2004; Piltonen et al., 2005; Piginy et al., 2006). AMH is secreted by small antral follicles, and elevated AMH in PCOS reflects both an increased number of these follicles due to a disturbance in the selection of the dominant follicle (Piginy et al., 2003; Laven et al., 2004; Visser et al., 2006) and an increase in production of AMH per granulosa cell, with the latter possibly related to intrinsic features of PCOS or an altered level of regulatory factors (Pellatt et al., 2007). Recently, our group has shown that pretreatment AMH levels may be a clinical predictor of reproductive responsiveness to weight loss in overweight and obese women with PCOS (Moran et al., 2007). Women who experienced menstrual improvements exhibited significantly lower baseline AMH levels compared with women who had no menstrual improvements (Moran et al., 2007). However, this study did not assess changes in AMH levels following weight loss.

Reductions in AMH levels with metformin therapy have been reported in women with PCOS (Fleming et al., 2005; Piltonen et al., 2005). Increasing serum follicle-stimulating hormone (FSH) concentrations through low-dose recombinant FSH therapy has also been associated with reduced AMH levels in anovulatory women with PCOS, which suggests inhibition of follicular function and growth, allowing the emergence of a dominant follicle (Catteau-Jonard et al., 2007). Serum AMH levels have also decreased during controlled ovarian stimulation (Fanchin et al., 2003; LaMarca et al., 2004a, b; Eldar-Geva et al., 2005), possibly involving follicular development, through the reduction in small antral follicles (Fanchin et al., 2003) or FSH-stimulated growth of larger follicles that lose their AMH expression (LaMarca et al., 2004a, b). To date, no study has examined the effects of weight loss on AMH and whether improvements in reproductive function with weight loss are associated with reductions in AMH. Therefore, the aim of this study was to confirm the findings of our earlier study and extend this work to determine whether improvements in reproductive function with weight loss in obese women with PCOS were accompanied by changes in AMH.

Materials and Methods

Participants

Fifty-two overweight and obese women with PCOS and reproductive impairment (age 29.2 ± 0.9 years and BMI 36.2 ± 0.8 kg/m²) were recruited by public advertisement and from general practitioner and specialist clinics. PCOS was diagnosed according to the current Rotterdam criteria (The Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group, 2004). Polycystic ovaries were identified by transvaginal or transabdominal ultrasound examination and clinical hyperandrogenism by elevated testosterone (>2.0 nmol/l) and/or free androgen index (FAI, >5.4). Reproductive impairment was identified by menstrual irregularity (defined as cycle length <21 or >35 days, or variation between consecutive cycles of >3 days) and/or non-ovulatory status.

Potential participants were excluded if they were using fertility treatments, metformin or oral contraceptives, were smokers, pregnant, breastfeeding or had a history of cardiovascular, liver, kidney or respiratory disease, diabetes, uncontrolled hypertension or a malignancy. Exclusion criteria also included not being weight stable (<3 kg change in 3 months) or following a weight reducing diet within 3 months prior to study commencement or the presence of any reproductive disorders unrelated to PCOS, thyroid abnormalities or non-classical adrenal hyperplasia. The protocol and potential risks and benefits of the study were explained to participants before they provided written informed consent. All experimental procedures were approved by the Human Ethics Committees of the Commonwealth Scientific and Industrial Research Organisation and the University of South Australia.

Study design

Participants were prescribed a hypocaloric dietary programme (~6000 kJ/day) for 20 weeks. Before (baseline) and after the 20-week weight loss intervention, participants attended the clinic after an overnight fast and had height (baseline only), body weight and waist circumference measured prior to the collection of a venous blood sample for the measurement of glucose, insulin, testosterone, sex hormone-binding globulin (SHBG) and AMH. Participants were advised not to consume any alcohol or participate in vigorous physical activity during the 24 h prior to these visits. During the month prior to study commencement and throughout the intervention, menses calendars were recorded to assess menstrual cyclicity and first morning spot urine samples were collected twice-weekly to assess pregnanediol-3-glucuronide (PDG) concentrations as a marker of ovulation. Following the intervention, participants were identified as responders (n = 26) and non-responders (n = 26) according to their changes in reproductive impairment. Responders were identified as having either improvement in ovulatory function (defined as a change from non-ovulatory cycles to ovulatory cycles) and/or improvements in menstrual status (defined as a change from irregular cycles to regular cycles or an improvement in consecutive intercycle variation). Non-responders had no change in menstrual cyclicity and ovulatory function status from baseline.

Clinical and biochemical measurements

Height and body weight were measured using a stadiometer (SECA, Hamburg, Germany) and electronic digital scales (Mercury, AMZ 14, Tokyo, Japan), respectively. BMI was calculated as weight (kg)/height (m²). Waist circumference was measured 2 cm above the uppermost lateral border of the iliac crest using an anthropometric tape (model W606PM, Lufkin, Houston, TX, USA). The average of three measurements was used as the measured value. Fasting plasma and serum samples were collected and stored at –80 °C for analysis following study completion. Plasma glucose was measured on a Hitachi 902 autoanalyzer (Roche Diagnostics, Indianapolis, IN, USA) using commercial enzymatic kits (Roche Diagnostics, Basel, Switzerland). Plasma insulin concentrations were determined using a commercial enzyme-linked immunosassay kit (Mercodia ELISA, ALPCO Diagnostics, Uppsala, Sweden). Insulin resistance was estimated using the homeostasis model assessment online calculator (HOMA2) (Wallace et al., 2004). SHBG was measured by coated-tube immunoassay kits using commercial kits (Diagnostic System Laboratories, Webster, TX, USA). Testosterone was measured by radioimmunoassay using commercial enzymatic kits (Diagnostic System Laboratories). FAI was calculated as testosterone/SHBG × 100. Plasma AMH was measured using an Immunotech immunoenzymatic assay (Beckman–Coulter, Marseille, France).

Spot urine samples were stored at –20 °C until analysis at completion of the study. Urinary PDG was measured according to the method of Santoro et al. (2003). Menses calendars were used to assess menstrual cyclicity and cross-referenced with PDG peaks to confirm the presence of ovulation.
Data were checked for normality prior to analysis and non-normally distributed data were transformed logarithmically (insulin, HOMA2 and FAI) or by taking the square root (AMH). Values are reported as mean ± standard error (SE). Baseline differences between groups were determined by one-way analysis of variance (ANOVA) and independent sample t-test. The effect of the intervention was determined by repeated measures ANOVA with time as the within-subject factor. Linear and logistic regressions were used to assess relationships between variables. Sensitivity and specificity were calculated using receiver operating characteristic (ROC) curve analysis in order to assess a possibility of baseline AMH concentrations to predict responsiveness of reproductive function to weight loss. Statistical analysis was performed using SPSS for Windows 14.0 (SPSS, Chicago, IL, USA) and MedCalc version 9.6 (MedCalc Software, Mariakerke, Belgium). An α-level of significance was set at P < 0.05.

**Results**

Overall at Week 20, there were significant reductions in weight (−9.0 ± 0.8 kg), waist circumference (−10.4 ± 0.9 cm), fasting insulin (−4.2 ± 0.7 mU/l), HOMA2 (−0.55 ± 0.09), testosterone (−0.38 ± 0.08 nmol/l) and FAI (−2.6 ± 0.6) and an improvement in SHBG (6.8 ± 1.4 nmol/l) (P < 0.001 for all). Of the 26 women who responded with improvements in reproductive function, 6 became ovulatory and improved in menstrual cyclicity (3 amenorrheic women regained a cycle, 2 improved cycle length variation and 1 improved cycle length). These women improved their cycle length by 28.8 ± 23.5 days. Sixteen women improved only in menstrual cyclicity, including nine now having regular cycles, five improving in cycle length (by 6.6 ± 2.1 days) and two improving cycle length variation. The remaining four women only improved in ovulation. Women who responded with improved reproductive function had greater reductions in weight and waist circumference compared with non-responders (Table I). There were no difference in changes in reproductive hormones or surrogate measures of insulin resistance with weight loss between responders and non-responders (Table I).

AMH levels did not change significantly overall for all subjects combined (pre 28.0 ± 2.4 versus post 26.3 ± 2.1 pmol/l; P = 0.34). However, changes in AMH within individuals was inversely related to baseline AMH (r = −0.50, P < 0.001), but were not associated with improvements in menstrual cycle length or variation in cycle duration. In addition, by the end of the intervention, changes in AMH did not differ between those who experienced improvements in reproductive function (responders) and those who did not (non-responders; P = 0.64; Table I). Importantly, however, the responders had lower levels of AMH at baseline compared with the non-responders (P = 0.03; Table I). ROC curve analysis indicated an upper cut-off value of 21.6 pmol/l with an area under the curve of 0.68 ± 0.07 (95% confidence interval: 0.54–0.80; P = 0.015). 65.4% sensitivity and 69.2% specificity to predict improvements in reproductive function as a result of weight loss. Logistic regression analysis revealed that baseline AMH (β = −0.52, P = 0.01) and the magnitude of weight loss achieved as a result of the intervention (β = −0.22, P = 0.002) both correlated with improvements in reproductive function. No hormonal parameters or measures of insulin resistance were significant in the regression model.

Baseline AMH levels were inversely related to the number of menstrual cycles and ovulatory cycles over the 20-week intervention (r = −0.47 and r = −0.61, respectively, P ≤ 0.001). AMH was also related to baseline levels of testosterone (r = 0.43, P = 0.002) and FAI (r = 0.33, P = 0.02) such that hyperandrogenic participants (testosterone > 2.0 nmol/l) had higher levels of baseline AMH compared with normoandrogenic participants (31.4 ± 2.7 versus 16.6 ± 3.7 pmol/l; P = 0.004). Women who were ovulating at the commencement of the study had lower baseline AMH levels compared with anovulatory participants (22.9 ± 2.9 versus 34.9 ± 3.7 pmol/l; P = 0.02). Participants who were amenorrheic had higher baseline AMH levels compared with oligo-ovulatory participants (P = 0.006; Table II). There was no difference in AMH at baseline between responders and non-responders; however, responders had lower baseline AMH levels compared with non-responders (P = 0.015), 65.4% sensitivity and 69.2% specificity to predict improvements in reproductive function as a result of weight loss.

Table I: Weight, waist circumference, insulin resistance, hormonal parameters and AMH before and following weight loss for women who responded with improved reproductive function and those who did not (non-responders).

<table>
<thead>
<tr>
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<th>Responders (n = 26)</th>
<th>Non-responders (n = 26)</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Change</td>
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<tr>
<td>Weight (kg)</td>
<td>104.2 ± 4.3</td>
<td>−11.7 ± 1.2*</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>103.9 ± 2.8</td>
<td>−12.3 ± 1.3*</td>
</tr>
<tr>
<td>Insulin (mU/l)</td>
<td>15.9 ± 1.4</td>
<td>−4.2 ± 0.7</td>
</tr>
<tr>
<td>HOMA2</td>
<td>2.05 ± 0.18</td>
<td>−0.56 ± 0.10</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>2.50 ± 0.15</td>
<td>−0.48 ± 0.11</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>31.0 ± 2.8</td>
<td>9.0 ± 2.1</td>
</tr>
<tr>
<td>FAI</td>
<td>9.38 ± 1.21</td>
<td>−3.51 ± 0.81</td>
</tr>
<tr>
<td>AMH (pmol/l)</td>
<td>23.5 ± 3.7†</td>
<td>−1.9 ± 1.6</td>
</tr>
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</table>

Values are presented as mean ± SE. HOMA2, homeostatic model assessment of insulin resistance; SHBG, sex-hormone-binding globulin; FAI, free androgen index; AMH, anti-Müllerian hormone.

*P < 0.02, significantly greater reduction in responders compared with non-responders.
†P < 0.03, significantly lower when compared with non-responders at baseline.
Weight loss and AMH in PCOS

Table II Baseline AMH and the change in AMH following weight loss for women who were amenorrhoeic, anovulatory and oligo-ovulatory

<table>
<thead>
<tr>
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<th>Baseline AMH (pmol/l)</th>
<th>Change in AMH (pmol/l)</th>
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<tbody>
<tr>
<td>Amenorrhoeic (n = 8)</td>
<td>44.0 ± 4.2</td>
<td>−3.1 ± 2.3</td>
</tr>
<tr>
<td>Anovulatory (n = 14)</td>
<td>29.7 ± 4.8</td>
<td>0.3 ± 3.2</td>
</tr>
<tr>
<td>Oligo-ovulatory (n = 30)</td>
<td>22.9 ± 2.9*</td>
<td>−2.3 ± 1.3</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SE. AMH, anti-Müllerian hormone.

*P = 0.006, significantly lower than amenorrhoeic participants.

Discussion

This is the first study to prospectively examine the effect of weight loss via caloric restriction on AMH and its relation to changes in reproductive function in overweight and obese women with PCOS and reproductive impairment. Despite considerable weight loss and improvements in reproductive function, AMH did not change significantly during the intervention. Women with higher levels of AMH at baseline experienced greater ovarian dysfunction (fewer ovulatory cycles, greater cycle irregularity and cycle length variation), and had higher levels of testosterone, suggesting that high AMH levels are associated with derangement of reproductive function. Moreover, women who demonstrated improvements in reproductive function had significantly lower AMH levels at baseline and experienced greater weight loss following the intervention compared with non-responders.

Although the effect of weight loss on AMH has not been previously studied, research investigating the effects of metformin in women with PCOS demonstrated an improvement in reproductive function that was associated with a significant decrease in AMH following 6 months of treatment (Piltonen et al., 2005). The reduction in AMH was attributed to a decrease in antral follicle number and hyperandrogenism and improvements in insulin action and menstrual pattern (Piltonen et al., 2005). Similarly, Fleming et al. (2005) reported significant reductions in AMH following metformin treatment. However, AMH reductions only occurred after 4–8 months of treatment, whereas improvements in ovulation were evident by 4 months. This indicates that improvements in reproductive function may precede any changes in AMH. It is therefore possible in the current study that despite observations of improved reproductive function, a longer period of intervention may be required for reductions in AMH to manifest. Potentially, changes in AMH may be delayed until a new cohort of antral follicles has been recruited under normalized androgen and insulin conditions, replacing the follicles recruited under elevated insulin resistance and hyperandrogenism (Fleming et al., 2005). Since ~3 months is required for the recruitment of a new antral follicle cohort once androgen and insulin conditions have normalized (Gougeon and Lefevre, 1983), it is possible that the intervention length of the current study was insufficient for the recruitment of the new follicle cohort once insulin resistance and hyperandrogenism had been normalized. Alternatively, differences in the AMH responses observed between the present and previous studies could be related to marked differences in baseline AMH (26.6 versus ~50–90 pmol/l). It is possible that the lower levels of AMH at baseline in the present study could have potentially contributed to the lack of any significant reduction in AMH, since lower levels indicate a population with less reproductive disturbances. This is supported by the observation of an inverse relationship between baseline and the change in AMH levels. Several previous studies report large ranges of AMH values between 16 and 33 pmol/l in normal and overweight non-PCOS women (Cook et al., 2002; Pigny et al., 2003; Laven et al., 2004; Piltonen et al., 2005; Pigny et al., 2006; El-Halawaty et al., 2007).

Since varying levels of AMH appear to exist between PCOS cohorts, the present results may not be applicable to all PCOS phenotypes that display higher AMH levels. Further investigation is needed to examine AMH levels after a longer intervention period in a range of PCOS phenotypes to determine whether changes in AMH occur with weight loss and whether any such changes reflect improvements in reproductive function, and to identify the time course of weight loss required for these improvements.

AMH concentrations are strongly associated with the main phenotypic features of PCOS, including oligo-ovulatory dysfunction and hyperandrogenism. Consistent with our results, amenorrhoeic women with PCOS display elevated AMH compared with oligomenorrhoeic women with PCOS, indicating an association between AMH in the pathogenesis of PCOS-related anovulation (La Marca et al., 2004a, b; Pigny et al., 2006). There is also evidence that AMH correlates with the extent of ovarian dysfunction (Jonard and Dewailly, 2004; Laven et al., 2004), with higher levels reflecting greater impairment in menstrual cyclicity, follicular development and granulosa cell function (La Marca et al., 2004a, b; Pellatt et al., 2007). In addition, previous studies have shown that AMH was positively related to testosterone (Pigny et al., 2003; Laven et al., 2004; Eldar-Geva et al., 2005; Piltonen et al., 2005; Pigny et al., 2006; Moran et al., 2007) and FAI (Laven et al., 2004; Eldar-Geva et al., 2005; Moran et al., 2007) and inversely related to SHBG (La Marca et al., 2004a, b), suggesting a possible link between AMH and hormonal profile.

AMH levels vary between PCOS women presenting with hyperandrogenism and those with normal androgen levels (both testosterone and FAI), such that the presence of hyperandrogenism is associated with higher AMH (Eldar-Geva et al., 2005; Pigny et al., 2006). An association between AMH and insulin resistance has also been suggested, but there is a lack of consistency surrounding this relationship, with the majority of studies including the current study reporting no association between baseline AMH and surrogate markers of insulin resistance (Pigny et al., 2003; Laven et al., 2004; Eldar-Geva et al., 2005; Fleming et al., 2005; Bayrak et al., 2007), one showing a positive relationship (La Marca et al., 2004a, b) and another a negative relationship (Chen et al., 2008).

The inconsistent results between studies may be influenced by the presence of differing PCOS phenotypes, with either primary ovarian dysfunction or insulin and obesity being the greater contributor to reproductive dysfunction. The relationship between AMH and both hormonal profile and insulin resistance is still unclear and additional research is required to specifically investigate potential weight loss effects on additional hormonal and insulin parameters that may influence reproductive function.
The current data and a prior study by Moran et al. (2007) suggest that higher AMH levels in women with PCOS may indicate a greater contribution of gonadotrophic or steriodogenic abnormalities and a lesser contribution of obesity and insulin resistance to menstrual dysfunction. Furthermore, AMH has been suggested as a useful clinical marker for potential reproductive responsiveness to weight loss, with a recent study reporting participants with lower AMH levels (i.e. less ovarian dysfunction) responding to weight loss with improvements in menstrual cyclicity (Moran et al., 2007). The present study confirms this finding, in which women with lower AMH levels experienced greater improvements in reproductive function. ROC curve analysis revealed a 68% change of predicting reproductive responsiveness following weight loss. In a recent study, AMH was used to predict response to clomiphene citrate in obese women with PCOS (El-Halawaty et al., 2007). A cut-off value of 16.8 pmol/l was proposed with similar ROC curve values to those seen in the current study (area under the curve 0.71, sensitivity 71% and specificity 65.7%). However, the weak prediction value of AMH observed in the current study (i.e. low area under the curve) suggests that AMH may have a limited ability to predict reproductive responsiveness to weight loss and data from the ROC curve analysis should be interpreted with some caution. It is possible that the lack of prediction strength may have been influenced by the small sample size. Additional studies are needed in larger cohort studies to further investigate any potential use of AMH to predict reproductive response to various treatments.

Previous studies have reported no differences in weight loss between reproductive responders and non-responders (Holte et al., 1995; Moran et al., 2007). Conversely, in this current study, the greater reproductive responsiveness post weight loss may be presumed to be a function of the greater weight loss achieved for responders compared with non-responders. However, we have extended this finding to explore the contribution of AMH to predict reproductive responsiveness. Due to the lack of a non-diary control group, it is difficult to be certain whether the improvements are a function of the intervention, and furthermore, without long-term prospective studies, we are unable to determine if the improvements in reproductive function translate to improved fecund ability. Logistic regression revealed that baseline AMH levels and weight loss were independent contributors to improved reproductive function. Since no other parameters measured were significant in the logistic regression model, the mechanism by which weight loss might have contributed to the improvement in reproductive function could not be determined.

In conclusion, we have shown in overweight and obese women with PCOS that a 20-week weight loss intervention resulted in improvements in reproductive function but no change in AMH levels. Additional research is needed to examine long-term effects of weight loss on AMH levels. Participants who responded with improved reproductive function had lower levels of AMH at baseline and experienced greater weight loss. Further investigation is required to identify the mechanisms by which weight loss and lower baseline AMH levels improve reproductive function in overweight and obese women with PCOS.

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