Impact of hypocaloric dietary intervention on ovulation in obese women with PCOS

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Abstract

Polycystic ovary syndrome (PCOS) is a common cause of ovulatory dysfunction affecting women of reproductive age. Obesity and insulin resistance are thought to potentiate disruptions in antral follicle development that result in chronic anovulation, and as such, have become important therapeutic targets of dietary interventions aimed at weight loss. Caloric restriction has been shown to promote sporadic ovulation in obese women with PCOS, but improvements have occurred across a wide range of patients and little has been garnered about the factors that distinguish responders from non-responders. Further, few studies have evaluated the likelihood for modest weight loss to restore normal ovulatory cyclicity in PCOS. Consensus regarding the impact of dietary intervention on ovulation has been limited by variability in the measures used to characterize and report ovulatory status across studies. In response, this review provides an assessment of the evidence surrounding the effectiveness of hypocaloric dietary intervention to normalize ovulatory function in PCOS. The impact of physiological vs methodological factors on the evaluation of ovulatory status is discussed, and recommendations to strengthen future studies in this area are provided. Ultimately, further research is needed to understand the optimal dietary or lifestyle approaches that promote ovulation and sustained improvements in reproductive function in PCOS.


Introduction

Polycystic ovary syndrome (PCOS) is the leading cause of anovulatory infertility and has broad implications for the reproductive and metabolic health of women across the lifespan (Fauser et al. 2012). The reproductive phenotype manifests as anovulation, menstrual cycle irregularity and hyperandrogenism and reflects defects at multiple levels of the hypothalamic–pituitary–ovarian axis (Jonard & Dewailly 2004, Franks et al. 2008). The hypersecretion of luteinizing hormone by the pituitary and overproduction of androgens by the ovaries interact to impair ovarian antral follicle development (Jonard & Dewailly 2004, Franks et al. 2008). Abnormal folliculogenesis in PCOS is characterized by an accumulation of small follicles, inhibition of terminal follicular growth (called follicle ‘arrest’) and failure of the mechanisms driving morphologic selection and ovulation (Jonard & Dewailly 2004, Franks et al. 2008). Obesity is intimately linked with the pathogenesis of anovulation in PCOS (Rojas et al. 2014) (Fig. 1). Excess weight and visceral adiposity promote the development of insulin resistance and compensatory hyperinsulinemia (Diamanti-Kandarakis & Dunai 2012), which are posited to exacerbate disruptions in antral follicle development (Jonard & Dewailly 2004, Franks et al. 2008) and worsen the severity of the reproductive phenotype (Lim et al. 2013). Therefore, therapies that attenuate obesity and insulin resistance hold promise to normalize anovulation and hyperandrogenism in PCOS (Fig. 1).

Currently, dietary interventions involving caloric restriction are recommended to combat both reproductive and metabolic abnormalities in overweight and obese women with PCOS (Moran et al. 2009, 2013, Fauser et al. 2012, Legro et al. 2013). Modest reductions in energy intake (500–1000 kcal/day) and weight (5–10%) have been shown to normalize gonadotropin secretion (Bützow et al. 2000), reduce clinical and biochemical hyperandrogenism and improve insulin sensitivity in this population (Moran et al. 2009, 2011). Likewise, randomized and non-randomized trials have documented an increased frequency of spontaneous ovulation, menses and pregnancy with weight loss (Moran et al. 2009). These findings are thought to reflect a recovery of the hormonal features that underpin follicular excess and ‘arrest’ in PCOS (Moran et al. 2011) (Fig. 1). However, there are several challenges to understanding the actual effectiveness of weight loss to stimulate ovulation or restore normal ovulatory function in overweight and obese patients. Despite evidence of ovulation after dietary interventions, variability in the measures used to report endpoints across studies
has prevented systematic assessments of the impact of weight loss on reproductive outcomes (Moran et al. 2011). Further, improvements in ovulation have been noted over a wide range of women (Moran et al. 2009, Legro et al. 2013); yet, little work has been done to understand the factors that account for the variability in the ovulatory response to caloric restriction.

To that end, the purpose of this review was to assess the evidence surrounding the effectiveness of hypocaloric dietary intervention to normalize ovulatory function in PCOS. The occurrence of and factors associated with ovulation in response to modest weight loss are described. Particular consideration is given to inconsistencies in the methods used to characterize ovulatory status across studies. The impact of physiological and methodological factors on the evaluation of ovulatory potential prior to dietary intervention is also discussed.

**Literature search and selection criteria**

PubMed, CINAHL and the Cochrane Central Register of Controlled Trials were used to identify relevant studies published between January 1990 and March 2016. Bibliographies of related systematic or narrative review articles were also screened to identify additional studies. The search included a combination of keywords relevant to PCOS, dietary or lifestyle intervention, and ovulation and menstrual cyclicity. The Population, Intervention, Comparison, Outcome (PICO) framework was used to define the inclusion and exclusion criteria for studies a priori. Briefly, studies included in this review were limited to original research articles in which (1) the patient population comprised only overweight or obese women with PCOS; (2) the dietary intervention involved reductions in energy intake that were intended to promote weight loss and (3) the primary or secondary outcome of interest was ovulation. Only articles published in English were included. Overweight or obesity was defined as a BMI of 25.0–29.9 kg/m² (overweight) or ≥30 kg/m² (obesity) (Jensen et al. 2014). PCOS was defined according to the National Institutes of Health (NIH) (Zawadzki & Dunaif 1992) or Rotterdam criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004a,b). Randomized controlled trials and non-randomized intervention studies were considered. Trials that incorporated either supervised or unsupervised physical activity with caloric restriction were included. By contrast, studies with combined dietary and pharmaceutical interventions (i.e. metformin or clomiphene citrate) were excluded, unless the pharmaceutical therapy served as a comparison to changes in energy intake alone. The title and abstract of every record retrieved by this search strategy was checked to ensure that it aligned with the established inclusion criteria. Relevant articles were downloaded for full-text review. Data on general characteristics of the study, patient population, diagnosis of PCOS, inclusion and exclusion criteria, intervention design, measurement of ovulation and outcomes related to ovulatory function were extracted.

**Characteristics of the studies included for review**

The search returned 4046 records, including ones that were identified through electronic databases (n=3319) and bibliographies of other reviews (n=727). Duplicates found using multiple databases, keywords and sources were removed (n=3234). All remaining records (n=812) were evaluated in the context of the PICO framework, and 780 were excluded based on
<table>
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<th>First author</th>
<th>Population and diagnosis</th>
<th>Study design</th>
<th>Caloric restriction</th>
<th>Additional approaches</th>
<th>Weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guzick et al. (1994)</td>
<td>n = 6 Age 32 years, IBW 176% OA + HA</td>
<td>3 months RCT (diet vs waiting list)</td>
<td>2 months: 400 kcal/day 1 month: 1000–1200 kcal/day</td>
<td>Behavior modification PA goal of 2 min/day, 5 days/week</td>
<td>16.2 kg (15%) decrease in weight</td>
</tr>
<tr>
<td>Crosignani et al. (2003)</td>
<td>n = 27 Age 31 years, BMI 32.1 kg/m² OA + PCO</td>
<td>Variable ≤6 months NRS (single cohort)</td>
<td>1200 kcal/day</td>
<td>PA goal of 1–2 days/week</td>
<td>76% of subjects lost 5–10% body weight</td>
</tr>
<tr>
<td>Moran et al. (2003)</td>
<td>n = 28 Age 33 years, BMI 37.4 kg/m² OA + HA</td>
<td>4 months RCT (LP vs HP; during both caloric restriction and WMD)</td>
<td>3 months: 1400 kcal/day 1 month: WMD</td>
<td>HCLP or LC/HP diets Behavior modification Supervised PA for 60 min/week, with goal of ≥2 other days/week</td>
<td>Decrease in weight in LP (7 kg) vs HP (9 kg), NS</td>
</tr>
<tr>
<td>Moran et al. (2006, 2007a)</td>
<td>n = 33 Age 32 years, BMI 34.9 kg/m² Rotterdam; all phenotypes</td>
<td>8 months RCT (FC vs CC; WMD)</td>
<td>2 months: 2 meal replacements/day 1170 kcal/day 6 months: WMD (FC vs CC)</td>
<td>Behavior modification PA goal of 8000 steps/day</td>
<td>Cohort: 3.9 kg (4%) decrease in weight</td>
</tr>
<tr>
<td>Moran et al. (2007b)</td>
<td>n = 15 Age 32 years, BMI 35.7 kg/m² Rotterdam; all phenotypes</td>
<td>2 months NRS (PCOS vs control)</td>
<td>2 meal replacements/day</td>
<td>N/A</td>
<td>≥10% decrease in weight</td>
</tr>
<tr>
<td>Qublan et al. (2007)</td>
<td>n = 21 with OA Age 32 years, BMI 32.2 kg/m² Rotterdam; all phenotypes</td>
<td>Variable ≤6 months NRS (diet vs metformin)</td>
<td>1200–1400 kcal/day</td>
<td>N/A</td>
<td>4.8 kg/m² (15%) decrease in BMI</td>
</tr>
<tr>
<td>Palomba et al. (2008)</td>
<td>n = 20 Age 26 years, BMI 33.2 kg/m² OA + HA + PCO</td>
<td>6 months NRS (diet vs PA)</td>
<td>800 kcal/day deficit</td>
<td>LC/HP diet Behavior modification</td>
<td>Decrease in weight in R (11 kg) vs NR (2 kg), P &lt; 0.05</td>
</tr>
<tr>
<td>Thomson et al. (2008)</td>
<td>n = 53 with OA Age 29 years, BMI 36.1 kg/m² Rotterdam; all phenotypes</td>
<td>5 months RCT (DO vs DA vs DC)</td>
<td>1200–1400 kcal/day</td>
<td>LC/HP diet Behavior modification</td>
<td>Cohort: 9% decrease in weight</td>
</tr>
<tr>
<td>Thomson et al. (2009)</td>
<td>n = 52 Age 30 years, BMI 36.5 kg/m² Rotterdam; OA only</td>
<td>5 months NRS (single cohort)</td>
<td>1400 kcal/day</td>
<td>Supervised PA for 5 day/week N/A</td>
<td>Decrease in weight in R (12 kg) vs NR (6 kg), P &lt; 0.05</td>
</tr>
<tr>
<td>Palomba et al. (2010)</td>
<td>n = 32 Age 28 years, BMI 31.3 kg/m² OA + HA + PCO</td>
<td>1.5 months RCT (diet vs clomiphene)</td>
<td>1000 kcal/day deficit</td>
<td>LC/HP diet Behavior modification Supervised PA for 3 days/week</td>
<td>4 kg (5%) decrease in weight</td>
</tr>
<tr>
<td>Fux Otta et al. (2010)</td>
<td>n = 15 Age 25 years, BMI 35.6 kg/m² OA + HA</td>
<td>4 months RCT (diet vs metformin)</td>
<td>1500 kcal/day</td>
<td>Supervised PA for 40 min/day, 4 day/week</td>
<td>1.4 kg/m² (4%) decrease in BMI</td>
</tr>
<tr>
<td>Kuchenbecker et al. (2011)</td>
<td>n = 32 Age 25 years, BMI 35.6 kg/m² Rotterdam; OA only</td>
<td>6 months NRS (single cohort)</td>
<td>≥500 kcal/day deficit</td>
<td>Behavior modification Individualized PA goals</td>
<td>Decrease in weight in R (6%) vs NR (3%), P &lt; 0.05</td>
</tr>
</tbody>
</table>

(Continued)
Values for clinical characteristics and weight loss are presented as means. Sample sizes refer to the number of women with anovulatory phenotypes at baseline who completed the hypocaloric dietary intervention. Where possible, changes in weight are reported for responders (R) vs non-responders (NR) and correspond to data on ovulation presented in Table 2. 'Response' was broadly defined as any improvement in ovulatory or menstrual function. Across studies, behavior modification was defined as interactive individual or group education with a health care provider. BMI, body mass index; CC, carbohydrate counting; DA, dietary intervention with aerobic exercise; DC, dietary intervention with combined aerobic and resistance exercise; DO, dietary intervention; FC, fat counting; HA, hyperandrogenism; HC/LP, high-carbohydrate/low-protein diet; IBW, ideal body weight; LC/HP, low-carbohydrate/high-protein diet; N/A, not reported; NRS, non-randomized study; NS, not significant at \( P < 0.05 \); OA, oligo-amenorrhea; PA, physical activity; PCO, polycystic ovaries; RCT, randomized controlled trial; WMD, weight maintenance diet.

### Table 1

<table>
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<tr>
<th>First author</th>
<th>Population and diagnosis</th>
<th>Study design</th>
<th>Additional approaches</th>
<th>Caloric restriction</th>
<th>Weight loss</th>
<th>Study design</th>
<th>Additional approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ladenson et al. (2011)</td>
<td>n = 16, Age 29 years, BMI 38.3 kg/m²</td>
<td>6 months, RCT (diet vs placebo)</td>
<td>HC/LP diet, supervised and unsupervised PA</td>
<td>500 kcal/day deficit</td>
<td>Decrease in weight in diet (6%) vs placebo (5%), NS</td>
<td>Variable follow-up period, WMD</td>
<td></td>
</tr>
<tr>
<td>Nybacka et al. (2011, 2013)</td>
<td>n = 43, Age 31 years, BMI 36.1 kg/m²</td>
<td>4 months, RCT (diet vs PA vs diet/PA)</td>
<td>HC/LP diet, behavior modification</td>
<td>600 kcal/day deficit</td>
<td>Decrease in weight in diet (6%) vs PA (3%) vs diet/PA (5%), NS</td>
<td>Variable follow-up period, WMD</td>
<td></td>
</tr>
<tr>
<td>Pasquali et al. (2011)</td>
<td>n = 23, Age 31 years, BMI 34.8 kg/m²</td>
<td>RCT vs diet/placebo, PA</td>
<td>HC/LP diet, individualized PA goals</td>
<td>Variable follow-up period</td>
<td>Decrease in weight in diet (6%) vs PA (3%) vs diet/PA (5%), NS</td>
<td>Variable follow-up period, WMD</td>
<td></td>
</tr>
</tbody>
</table>

Improvements in ovulation were defined in one of two ways across studies: (1) the occurrence of one or two ('sporadic') ovulations or (2) the resumption of regular ('monthly') ovulatory cycles. Data were reported as the proportion of women with either ovulatory response or as the number of ovulatory menstrual cycles detected during the dietary intervention. Overall, most of the results on improved ovulatory function were presented as the number of women who experienced sporadic ovulation with weight loss. Only two of the studies...
Table 2: Differences in the measurement of ovulation and ovulatory response to hypocaloric dietary intervention across studies in overweight or obese women with PCOS.

<table>
<thead>
<tr>
<th>First author</th>
<th>Measurement of ovulation</th>
<th>Evaluation of baseline ovulatory function</th>
<th>Length of caloric restriction</th>
<th>Proportion of subjects with evidence of ovulation during intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Marker</td>
<td>Frequency</td>
<td>Marker (duration)</td>
<td>Sporadic ovulation</td>
</tr>
<tr>
<td>Guzick et al. (1994)</td>
<td>Serum P4</td>
<td>Weekly, 8 weeks post-diet</td>
<td>Biochemical (2 months)b</td>
<td>3 months</td>
</tr>
<tr>
<td>Crosignani et al. (2003)</td>
<td>Serum P4</td>
<td>After self-report of regular menses</td>
<td>Not completed</td>
<td>N/A</td>
</tr>
<tr>
<td>Moran et al. (2003)</td>
<td>Urinary PDG</td>
<td>Twice weekly</td>
<td>Menses diary (6 months)</td>
<td>3 months</td>
</tr>
<tr>
<td>Hoeger et al. (2004)</td>
<td>Urinary P4</td>
<td>Weekly</td>
<td>Not completed</td>
<td>N/A</td>
</tr>
<tr>
<td>van Dam et al. (2004)</td>
<td>Serum P4</td>
<td>Biweekly</td>
<td>Biochemical (once)b</td>
<td>2 months</td>
</tr>
<tr>
<td>Moran et al. (2006, 2007a)</td>
<td>Urinary PDG</td>
<td>Twice weekly</td>
<td>Menses diary (6 months)</td>
<td>2 months</td>
</tr>
<tr>
<td>Moran et al. (2007b)</td>
<td>Urinary P4</td>
<td>Twice weekly</td>
<td>Not completed</td>
<td>N/A</td>
</tr>
<tr>
<td>Qublan et al. (2007)</td>
<td>Serum P4</td>
<td>After self-report of regular menses</td>
<td>Not completed</td>
<td>N/A</td>
</tr>
<tr>
<td>Palomba et al. (2008)</td>
<td>Plasma P4</td>
<td>After spontaneous/induced menses</td>
<td>Biochemical (1 month)</td>
<td>5 months</td>
</tr>
<tr>
<td>Thomson et al. (2008)</td>
<td>Urinary P4</td>
<td>Twice weekly</td>
<td>Biochemical (5 months)</td>
<td>5 months</td>
</tr>
<tr>
<td>Thomson et al. (2009)</td>
<td>Urinary P4</td>
<td>Twice weekly</td>
<td>Not completed</td>
<td>N/A</td>
</tr>
<tr>
<td>Palomba et al. (2010)</td>
<td>Plasma P4</td>
<td>After visualization of CL on TVUS</td>
<td>Not completed</td>
<td>N/A</td>
</tr>
<tr>
<td>Fux Otti et al. (2010)</td>
<td>Serum P4</td>
<td>Uncertain</td>
<td>Not completed</td>
<td>N/A</td>
</tr>
<tr>
<td>Kuchenbecker et al. (2011)</td>
<td>Serum P4</td>
<td>After self-report of increase in BBT</td>
<td>Not completed</td>
<td>N/A</td>
</tr>
<tr>
<td>Ladson et al. (2011b)</td>
<td>Urinary PDG</td>
<td>Daily</td>
<td>Biochemical (Once)</td>
<td>Variable (6 months)</td>
</tr>
<tr>
<td>Nybacka et al. (2011, 2013)</td>
<td>Serum P4</td>
<td>After self-report of menses</td>
<td>Not completed</td>
<td>N/A</td>
</tr>
<tr>
<td>Pasquali et al. (2011)</td>
<td>Serum P4</td>
<td>Once pre- and post-diet</td>
<td>Biochemical (1Once)</td>
<td>Variable (6 months)</td>
</tr>
</tbody>
</table>

Outcomes are reported for women with anovulatory phenotypes prior to dietary intervention.

Data were reported in an inconsistent format compared to other studies and could not be extracted; b: results of baseline assessments were reported in the article.

BBT, basal body temperature; CL, corpus luteum; N/A, not reported; P4, progesterone, PDG, pregnanediol glucuronide; TVUS, transvaginal ultrasonography.
3-glucuronide (PDG). These measurements were consistently taken during the mid-luteal phase of the menstrual cycle. Several studies also evaluated the urinary estrogens in conjunction with PDG (Moran et al. 2003) or considered pregnancy to be sufficient evidence of ovulation in lieu of serum progesterone (Crosignani et al. 2003, Kuchenbecker et al. 2011).

In both clinical practice and research, a number of techniques are used to confirm the occurrence and timing of ovulation. The gold standard method involves the direct observation of follicular growth and rupture by high-resolution transvaginal ultrasonography (Baerwald et al. 2012). If this approach is not feasible, then other indirect, but objective, methods may be employed to detect ovulation. Such methods include the measurement of pituitary or ovarian hormones in the blood, urine or saliva, and the assessment of clinical symptoms including menstrual cycle length or basal body temperature (BBT) (Campbell & Rockett 2006, Lynch et al. 2006). In line with these standards, the studies were justified in their common use of serum progesterone or urinary PDG (Table 2, Column 2); both have been validated as reliable and interchangeable markers of ovulation in women with regular menstrual cycles (Roos et al. 2015). A sustained elevation in either biochemical marker is considered sufficient evidence of luteal activity and can be detected throughout the luteal phase to the end of the cycle (Roos et al. 2015).

That being said, the frequency at which these biochemical markers were measured differed substantially across studies. Approximately half of the studies (n=8) used an intermittent sampling design irrespective of the stage of the menstrual cycle. Assessments were performed daily (Ladson et al. 2011), twice weekly (Moran et al. 2003, 2006, 2007b, Thomson et al. 2008, 2009), weekly (Hoeger et al. 2004) or biweekly (van Dam et al. 2004) to detect the ovulation during the dietary intervention (Table 2, Column 3). By contrast, six studies collected a single blood sample in the mid-luteal phase based on morphologic or clinical markers (Crosignani et al. 2003, Qublan et al. 2007, Palomba et al. 2008, 2010, Kuchenbecker et al. 2011, Nybacka et al. 2011). Of these, only one used direct methods to monitor follicle growth and determine ovulation (Palomba et al. 2010). Namely, Palomba and coworkers performed transvaginal ultrasonography at baseline, every four days until visualization of a dominant follicle and then daily to follicular collapse. Ovulation was subsequently confirmed with plasma progesterone levels (Palomba et al. 2010). The other five studies relied on participant self-report of recent spontaneous menses (Palomba et al. 2008, Nybacka et al. 2011), resumption of regular menses (Crosignani et al. 2003, Qublan et al. 2007) or increase in BBT (Kuchenbecker et al. 2011) (Table 2, Column 3). When one of these events occurred, the investigators scheduled a blood draw for serum progesterone based on an estimation of time to the next luteal phase (Crosignani et al. 2003, Qublan et al. 2007, Palomba et al. 2008, Kuchenbecker et al. 2011, Nybacka et al. 2011). Finally, of the remaining three studies, one did not provide adequate information with which to judge the frequency of measurements (Fux Otta et al. 2010) and two did not assess ovulation until after the intervention had ended (Guzick et al. 1994, Pasquali et al. 2011) (Table 2, Column 3).

It is probable that the studies with intermittent sampling designs were better positioned to capture ovulatory status than the studies that relied on a single biochemical measurement or self-reported clinical data. The occurrence of ovulation is best ascertained with an intermittent sampling design that allows for hormone data to be collected either daily, every-other-day, twice weekly or weekly (O’Connor et al. 2006). If one of these approaches is not feasible, a single measurement of serum progesterone or urinary PDG in the mid-luteal phase can also be effective to determine whether ovulation has occurred (Leiva et al. 2015). However, the reliability of a single measurement to detect ovulation during long or unpredictable menstrual cycles, capture peak progesterone concentrations or judge luteal phase sufficiency is uncertain. Similar to biochemical methods, prospective menstrual diaries and BBT records have been shown to provide reliable estimates of menstrual regularity (Creinin et al. 2004) and the presence of ovulation in healthy women (Campbell & Rockett 2006, Lynch et al. 2006). Yet, variability in consecutive cycle lengths is common (Creinin et al. 2004) and ovulation is not an inevitable event during spontaneous menstrual cycles (Prior et al. 2015). Infertile patients also demonstrate abnormal fluctuations in BBT during ovulatory cycles, leading to errors in the interpretation of temperature charts and prediction of ovulation (Lenton et al. 1977). Given these challenges with self-reported clinical data, the choice to schedule blood draws during the predicted luteal phase of the next menstrual cycle implies that the first ovulation was never biochemically confirmed (Crosignani et al. 2003, Qublan et al. 2007, Palomba et al. 2008, Kuchenbecker et al. 2011, Nybacka et al. 2011). Such approaches may have resulted in a poor estimation of the number of ovulatory cycles, and consequently, a reduced likelihood to accurately report the ovulatory response to weight loss.

There was also marked variability in the methods used to define biochemical evidence of ovulation across studies. In the interventions that assessed serum progesterone (Table 2, Column 2), ovulatory thresholds were always reported and ranged from ≥4 ng/mL (13 nmol/L) (Fux Otta et al. 2010) to ≥10 ng/mL (32 nmol/L) (Qublan et al. 2007, Palomba et al. 2008, 2010). It was difficult to discern whether these thresholds were internally validated or reflected the limits of detection of the various assays used. Two of the studies implemented a commercial radioimmunoassay
(van Dam et al. 2004, Qublan et al. 2007), but the others did not describe the methods employed to measure serum progesterone. By contrast, normative values for PDG were not provided by any of the studies that used the marker, and the increase in mid-luteal excretion was qualitatively assessed (Moran et al. 2003, 2006, 2007b, Hoeger et al. 2004, Thomson et al. 2008, 2009, Nybacka et al. 2011).

Accordingly, the interpretation of ovulatory status may have been limited by the use of inappropriate thresholds for progesterone and PDG to confirm ovulation. In general, a serum progesterone concentration of 3.9 ng/mL (12.5 nmol/L) or higher is thought to be presumptive evidence of an ovulatory cycle using commonly available commercial assays (Wathen et al. 1984, Leiva et al. 2015). However, all the studies identified thresholds for progesterone that were above this concentration (Guzick et al. 1994, Crosignani et al. 2003, van Dam et al. 2004, Qublan et al. 2007, Palomba et al. 2008, 2010, Fux Otta et al. 2010, Kuchenbecker et al. 2011, Pasquali et al. 2011). This is interesting, considering that the studies that relied on the highest thresholds (≥32 nmol/L) were also the ones to report the smallest proportion of responders to the dietary intervention (Qublan et al. 2007, Palomba et al. 2008, 2010) (Table 2, Column 6). In addition, there is emerging evidence to suggest that luteal phase dynamics of progesterone are altered in obesity (Rochester et al. 2009) and PCOS (Joseph-Horne et al. 2002). Lower urinary excretion and a delayed ovulatory rise in PDG have been noted in obese women with regular menstrual cycles (Rochester et al. 2009), and lower luteal concentrations of progesterone have been documented in women with ovulatory PCOS compared to healthy controls (Joseph-Horne et al. 2002). These findings have implications for the detection of spontaneous ovulation in obese anovulatory patients and suggest that alternative thresholds may be needed to fully capture ovulatory status in PCOS.

**Heterogeneity in the clinical presentation of PCOS**

The dichotomization of the ovulatory response to hypocaloric dietary intervention likely reflects the heterogeneous nature of PCOS. PCOS exists on a spectrum, and the diagnosis encompasses a broad range of severity of reproductive and metabolic abnormalities (Diamanti-Kandarakis & Dunaf 2012, Fauser et al. 2012). Such differences may impart a variable potential between patients for weight loss to stimulate ovulation. To that end, there is utility in identifying the endocrine or metabolic characteristics that distinguish responders from non-responders prior to dietary intervention. None of the studies evaluated baseline clinical predictors of improvements in reproductive function (Moran et al. 2003, 2007a, van Dam et al. 2004, Thomson et al. 2008, 2009, Kuchenbecker et al. 2011, Nybacka et al. 2011, Pasquali et al. 2011).

Response was defined in one of two ways across studies: (1) evidence of sporadic ovulation or (2) improved menstrual cyclicity after dietary intervention. None of the studies assessed predictors of the transition to normal ovulatory function. Improvements in menstrual cyclicity were broadly characterized as a decrease in menstrual cycle irregularity, shift from irregular to regular menstrual cycles or shift from anovulatory to ovulatory cycles (Moran et al. 2003, 2007a, Thomson et al. 2008, 2009, Nybacka et al. 2011, 2013). Increased cycle regularity was not necessarily accompanied by improvements in ovulation and a shift from anovulatory to ovulatory cycles appeared to reflect evidence of sporadic, rather than regular, ovulation (Moran et al. 2003, 2007a, Thomson et al. 2009). In addition, one study evaluated women with partial or complete recovery from PCOS and identified baseline features associated with the collective normalization of hirsutism, ovulation and menstrual cyclicity (Pasquali et al. 2011).

As shown in Table 3, six of the nine studies identified significant clinical predictors of improved reproductive outcomes after dietary intervention (van Dam et al. 2004, Moran et al. 2007a, Thomson et al. 2009, Nybacka et al. 2011, 2013, Pasquali et al. 2011). The baseline characteristics that emerged were largely markers of androgen excess and adiposity. Overall, women with lower circulating concentrations of sex hormone-binding globulin (van Dam et al. 2004), testosterone (Nybacka et al. 2011), androstenedione (Pasquali et al. 2011) and anti-Müllerian hormone

<table>
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<th>Outcome</th>
<th>Baseline characteristic of responders*</th>
<th>Study</th>
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<tr>
<td>Sporadic ovulation</td>
<td>None</td>
<td>Kuchenbecker et al. (2011), Nybacka et al. (2013)</td>
</tr>
<tr>
<td>Regular (monthly) ovulation</td>
<td>Higher SHBG</td>
<td>van Dam et al. (2004)</td>
</tr>
<tr>
<td>Improved menstrual cyclicity</td>
<td>None</td>
<td>Moran et al. (2003), Thomson et al. (2008)</td>
</tr>
<tr>
<td></td>
<td>Lower AMH</td>
<td>Moran et al. (2007a), Thomson et al. (2009), Nybacka et al. (2013)</td>
</tr>
<tr>
<td>Recovery from PCOS</td>
<td>Lower androstenedione</td>
<td>Pasquali et al. (2011)</td>
</tr>
<tr>
<td></td>
<td>Lower waist circumference and WHR</td>
<td>Pasquali et al. (2011)</td>
</tr>
</tbody>
</table>

*vs non-responders.

AMH, anti-Müllerian hormone; SHBG, sex hormone-binding globulin; WHR, waist-to-hips ratio.
(AMH) (Moran et al. 2007a, Thomson et al. 2009, Nybacka et al. 2013) were more likely to experience sporadic ovulation and improved menstrual cyclicity during dietary intervention. Lower waist circumference and waist-to-hip ratio were also predictive of recovery from the syndrome (Pasquali et al. 2011). Taken together, these findings suggest that obese women with milder ovarian dysfunction at baseline may be more likely to experience reproductive benefit from hypocaloric dietary intervention (Table 3).

That being said, only three studies directly focused on clinical predictors of ovulation, and of these, two could not identify baseline differences between responders and non-responders (Kuchenbecker et al. 2011, Nybacka et al. 2013). Despite their associations with improved menstrual cyclicity, neither androgens nor AMH predicted ovulation after dietary intervention (Kuchenbecker et al. 2011, Nybacka et al. 2013) (Table 3). Inconsistencies in the ability to identify baseline predictors of ovulatory response may have been influenced by two important factors.

First, ‘response’ was broadly defined as an improvement in ovulation or menstrual cyclicity compared to baseline. However, very few studies assessed baseline ovulatory status in their participants (Table 2, Column 4). Among the studies that did, serum progesterone or urinary PDG were measured at a single time point (van Dam et al. 2004, Pasquali et al. 2011) or on a serial basis for up to two months prior to intervention (Guzick et al. 1994, Thomson et al. 2008, 2009). Alternatively, some participants were asked to keep menstrual diaries for one to six months (Moran et al. 2003, 2006, 2007b, Thomson et al. 2008, 2009, Fux Otta et al. 2010). Although these direct and indirect markers of ovulation were likely used as a reference for improvement, only two of the studies actually published the data that were collected (Guzick et al. 1994, van Dam et al. 2004) (Table 2, Column 4). As a result, it was difficult to confirm that the reported changes constituted an improvement compared to baseline and a missed opportunity was noted to characterize the variability in the degree of ovulatory response among women. The latter points to some uncertainty that a single baseline characteristic could predict a broad spectrum of reproductive improvements after dietary intervention.

Second, the use of different diagnostic criteria to define study populations resulted in the assessment of ovulatory response across multiple phenotypes (Table 1, Column 2). The most commonly accepted criteria for the diagnosis of PCOS (2003 Rotterdam Criteria) identify four distinct clinical phenotypes: (1) Frank (oligomenorrhea, hyperandrogenism and polycystic ovaries), (2) Non-PCO (oligomenorrhea, hyperandrogenism and normal ovaries), (3) ovulatory (regular menses, hyperandrogenism and polycystic ovaries) and (4) normoandrogenic or ‘mild’ (oligomenorrhea, normal androgen status and polycystic ovaries) (RotterdamESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004a,b). There is substantial evidence that the severest variants of the condition are Frank and Non-PCO PCOS (phenotypes that are also recognized by the 1990 NIH Criteria) (Zawadzki & Dunai 1992, Fauser et al. 2012). Women with combined oligomenorrhea and hyperandrogenism have the most profound disturbances in gonadotropin dynamics, ovarian androgen production and insulin sensitivity, independent of obesity (Carmina et al. 2005, Dewailly et al. 2006, Panidis et al. 2012). By contrast, the other phenotypes seem to represent milder variants of the condition. Women with ovulatory and normoandrogenic PCOS have endocrine disturbances that are intermediate to Frank PCOS and healthy controls (Carmina et al. 2005, Dewailly et al. 2006, Panidis et al. 2012), and the presence of metabolic abnormalities seems to depend on the degree of abdominal adiposity (Moran & Teeede 2009). Collectively, these differences suggest that variable improvements in endocrine and metabolic abnormalities may be needed to restore ovulatory cyclicity across phenotypes.

PCOS was diagnosed according to the NIH criteria in seven studies (Guzick et al. 1994, Moran et al. 2003, Hoeger et al. 2004, van Dam et al. 2004, Fux Otta et al. 2010, Ladson et al. 2011, Pasquali et al. 2011) and the Rotterdam criteria in 10 studies (Table 1, Column 2). Of the interventions that used the broader definition, three primarily recruited the Frank and Non-PCO phenotypes (Palomba et al. 2008, 2010, Nybacka et al. 2011). The inclusion of these two phenotypes implies that the majority of participants had the severest manifestations of the condition and met both the NIH and Rotterdam criteria for PCOS. The remaining studies (n = 7) evaluated ovulatory response across more heterogeneous cohorts. Of these, four enrolled participants who could be stratified into any of the recognized phenotypes, and as such, included women with evidence of regular ovulation and menstrual cycles at baseline (Moran et al. 2006, 2007b, Qublan et al. 2007, Thomson et al. 2008). In some cases, these studies presented outcome data on ovulation for the entire cohort and did not distinguish the women with histories of anovulation from those with normal ovulatory function prior to the intervention (Moran et al. 2006, 2007b) (Table 1, Column 2). The combined assessment of ovulatory status in these distinct cohorts may have masked the independent effect of dietary intervention on ovulation as improvements would have been challenging to characterize in women with existing ovulatory cyclicity. The other three studies enrolled anovulatory women irrespective of androgen status (Crosignani et al. 2003, Thomson et al. 2009, Kuchenbecker et al. 2011). Crosignani and coworkers required participants to demonstrate combined evidence of chronic anovulation or amenorrhea and polycystic ovarian morphology (Crosignani et al. 2003). The absence of inclusion criteria or data to corroborate androgen excess suggested that the cohort largely

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comprised women with the normoandrogenic phenotype (Crosignani et al. 2003). By contrast, Thomson and coworkers and Kuchenbecker and coworkers screened for hyperandrogenism and the resulting cohorts appeared to include all variants except ovulatory PCOS (Thomson et al. 2009, Kuchenbecker et al. 2011) (Table 1, Column 2). It is possible that weight loss would have differential effects on ovarian androgen production in normoandrogenic compared to hyperandrogenic phenotypes and that such differences would be difficult to capture using these definitions.

**Degree of change in salient endocrine or metabolic features afforded by the intervention**

The dichotomization of ovulatory response to weight loss may also reflect the ability of hypocaloric dietary intervention to recover the endocrine and metabolic abnormalities that impair antral follicle development. Currently, little is known about the salient features or degree of change required to improve reproductive outcomes with weight loss in PCOS.


Nevertheless, it is prudent to consider that these analyses produced inconsistent results across studies. Although the majority of authors noted greater changes among responders, a substantial portion (37–40%) were unable to identify significant differences in weight, hyperandrogenism or insulin sensitivity between groups (van Dam et al. 2004, Moran et al. 2007a, Thomson et al. 2008, 2009) (Table 4). These findings could reflect heterogeneity in the study populations (as described previously) or a larger issue surrounding the efficacy of the interventions that were used.

The primary therapeutic targets of caloric restriction are weight and adiposity (Jensen et al. 2014). In PCOS, it is likely that changes in weight and adiposity stimulate improvements in androgens and insulin, which together precede ovulation and menses (Moran et al. 2006). If sufficient weight loss is not achieved, then it follows that improvements in ovulatory function would be unlikely to occur (Fig. 1). In the studies included for review, women experienced sporadic ovulation with modest changes in weight (i.e. <16%) (Tables 1 and 2). This occurred despite the fact that most women were still classified as obese (BMI ≥30 kg/m²) at the end of the various dietary interventions (Hoeger et al. 2004, van Dam et al. 2004, Fux Otta et al. 2010, Kuchenbecker et al. 2011, Nybacka et al. 2011). A greater degree of weight loss, resulting in a healthier BMI, may be necessary to fully restore ovulatory cyclicity in obese women with PCOS. This idea is supported by preliminary evidence from studies involving bariatric surgery, wherein 100% of anovulatory patients resumed regular ovulation and menses after a 41-kg reduction in weight (Es cabar-Morreale et al. 2005). However, surgical approaches for weight loss have been associated with significant risks, including post-operative complications, nutritional deficiencies and increased likelihood for deleterious fetal outcomes during pregnancy (Moran & Norman 2012). Therefore, it is considered wisest to first advocate for dietary and lifestyle modifications in obese women with PCOS (Moran & Norman 2012). Further studies are needed to determine the optimal degree of weight loss to induce and sustain improvements in ovulatory function, so as to better tailor dietary interventions to individual needs.

**Table 4** Studies that have linked changes in clinical, endocrine and metabolic characteristics to improved reproductive outcomes after hypocaloric dietary intervention in overweight or obese women with PCOS.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies that found greater changes in responders¹</th>
<th>Number of studies that found no differences in responders²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in weight or BMI</td>
<td>5/8 (63%)</td>
<td>3/8 (37%)</td>
</tr>
<tr>
<td>Decrease in central adiposity</td>
<td>5/6 (83%)</td>
<td>1/6 (17%)</td>
</tr>
<tr>
<td>Decrease in hirsutism or hyperandrogenemia</td>
<td>3/5 (60%)</td>
<td>2/5 (40%)</td>
</tr>
<tr>
<td>Improvement in insulin sensitivity</td>
<td>5/8 (63%)</td>
<td>3/8 (37%)</td>
</tr>
<tr>
<td>Decrease in mean concentrations of gonadotropins or ovarian hormones³</td>
<td>1/4 (25%)</td>
<td>3/4 (75%)</td>
</tr>
</tbody>
</table>

¹ vs non-responders; ² includes luteinizing hormone; follicle-stimulating hormone; estradiol; progesterone; anti-Müllerian hormone.

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In addition, little is known about the time course of caloric restriction that is required to improve ovarian function in obese women with PCOS. Although serial assessments of ovulatory status were performed, the majority of studies did not report the time point(s) of the intervention at which ovulation was observed. Only three studies provided information on this outcome. From these data, it appeared unlikely for an ovarian response to occur within the first two weeks of a dietary intervention (Moran et al. 2003, van Dam et al. 2004, Palomba et al. 2010). Specifically, Moran and coworkers did not detect sporadic ovulation until weeks 4–6 or 12–13 of caloric restriction (Moran et al. 2003). The time course of these observations may be explained by evidence that endocrine and metabolic responses to caloric restriction precede ovulation (van Dam et al. 2004, Moran et al. 2006). Alterations in neuroendocrine feedback were identified in as a few as seven days on a very low-calorie diet (van Dam et al. 2004), and significant improvements in androgen excess and insulin sensitivity were documented within 2–4 weeks after the onset of dietary intervention (Moran et al. 2006). Consequently, a decrease in insulin-mediated androgen production (Barbieri et al. 1986) might be expected to stimulate sporadic selection and ovulation several weeks later (Moran et al. 2006).

Despite the occurrence of sporadic ovulation, it remains unclear whether short-term caloric restriction is sufficient to normalize ovulatory cyclicity in obese women with PCOS. It has been suggested that turnover of the antral follicles recruited under hyperandrogenic and insulin-resistant conditions precedes improvements in ovarian function (Thomson et al. 2009). Changes in the mechanisms of selection and ovulation may not manifest until a new cohort of follicles is activated from the primordial pool under an improved hormonal environment. Given that a pre-antral follicle takes approximately three months to reach its pre-ovulatory diameter (Gougeon 1986), it is possible that some of the dietary interventions were too short to realize improvements in reproductive function (Thomson et al. 2009) (Table 1). Further investigation is needed to determine the precise time course of caloric restriction that is required to normalize ovulatory cyclicity in PCOS.

It is also uncertain whether improvements in ovulatory function can be sustained after a hypocaloric dietary intervention is discontinued. In general, weight maintenance is challenging and weight re-gain is a common problem across populations (MacLean et al. 2014). This is essential to address in the context of PCOS, as any increase in weight could recover initial endocrine and metabolic disturbances and lead to the rebound of anovulation. Five studies performed follow-up assessments and attempted to capture these changes after the dietary intervention (Moran et al. 2003, 2006, Hoeger et al. 2004, Nybacka et al. 2011, Pasquali et al. 2011). Follow-up assessments were performed on a cross-sectional basis (Nybacka et al. 2011, Pasquali et al. 2011) or as part of a weight maintenance intervention that involved regular visits to the research unit (Moran et al. 2003, 2006, Hoeger et al. 2004). Ovulatory or menstrual status was largely measured at each time point (Moran et al. 2003, 2006, Hoeger et al. 2004, Nybacka et al. 2011). Yet, only two of the studies distinguished the data that were collected at the follow-up visits from those collected during the intervention, and menstrual status was the primary reproductive outcome of interest (Moran et al. 2003, Nybacka et al. 2011). Specifically, Moran and coworkers found that improvements in menstrual cyclicity were sustained for 4–6 months after caloric restriction in the majority of patients (Moran et al. 2003). In some cases, women reported regular menses for an average of two years after the end of the intervention (Nybacka et al. 2011). These outcomes occurred independent of increased energy intake (Moran et al. 2003) or weight gain (Moran et al. 2003, Nybacka et al. 2011). Further studies are needed to clarify whether and how these sustained changes in menstrual cyclicity are reflected in the ovaries.

Despite ambiguity surrounding the ideal dietary intervention, current dogma stipulates that caloric restriction is the primary facilitator of weight loss and ovulation in obese women with PCOS (Moran et al. 2009, 2013). Consequently, dietary interventions involving caloric restriction were highlighted in this review. However, it is important to acknowledge that most of the included studies prescribed caloric restriction as part of a larger multifactorial intervention (Table 1, Column 5). Emerging data suggest that tailored macronutrient composition, physical activity and/or behavior modification therapy can augment the effect of caloric restriction on ovulatory function (Harrison et al. 2011, Moran et al. 2013). Although these additional approaches were not addressed in this review, they have been described extensively by Moran and coworkers (Moran et al. 2013) and Harrison and coworkers (Harrison et al. 2011). Ultimately, well-designed, randomized controlled trials are still required to determine whether multifactorial dietary interventions can further improve reproductive outcomes in PCOS (Harrison et al. 2011, Moran et al. 2013).

Conclusion

In summary, commendable progress has been made toward understanding the impact of caloric restriction on ovulatory function in obese women with PCOS. It is clear that modest weight loss is associated with the occurrence of sporadic ovulation in a meaningful proportion of patients and that reductions in hyperandrogenism and insulin resistance likely precede any improvements in reproductive outcomes. The ovulatory response may also depend on the presence of milder reproductive
dysfunction at baseline and a greater degree of change in endocrine and metabolic features with intervention. Nevertheless, this review highlighted the variability in the ovulatory response to weight loss and found little evidence to support the effectiveness of hypocaloric dietary intervention to restore normal ovulatory function in PCOS. Because resumption of regular ovulatory cycles may not be a realistic goal for all patients, health care providers should be judicious in counseling the degree to which weight loss can be expected to improve ovulatory function in obese patients with PCOS. Future studies would benefit from efforts to improve the accuracy and consistency of measures used to determine and report ovulatory status both at baseline and during dietary intervention. The use of intermittent sampling of biochemical markers, assessment of alternative thresholds for ovulation to better judge luteal function in PCOS and distinction of ovulation from menstrual cyclicity in reporting improvements is recommended. Finally, the impact of phenotypic variation on the ovulatory response to weight loss should be addressed to fully capture the degree and duration of caloric restriction that is needed to effectively promote weight loss and ovulation in PCOS. The identification of optimal dietary and lifestyle approaches to treat anovulation will improve the health and wellbeing of obese women living with PCOS.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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References
Institute of Medicine 2005 Dietary References Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino

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Qublan H, Yammakoula E, Al-Qudah M & El-Uri F 2007 Dietetic intervention versus metformin to improve the reproductive outcome in women with polycystic ovary syndrome. Saudi Medical Journal 28 1694–1699.


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