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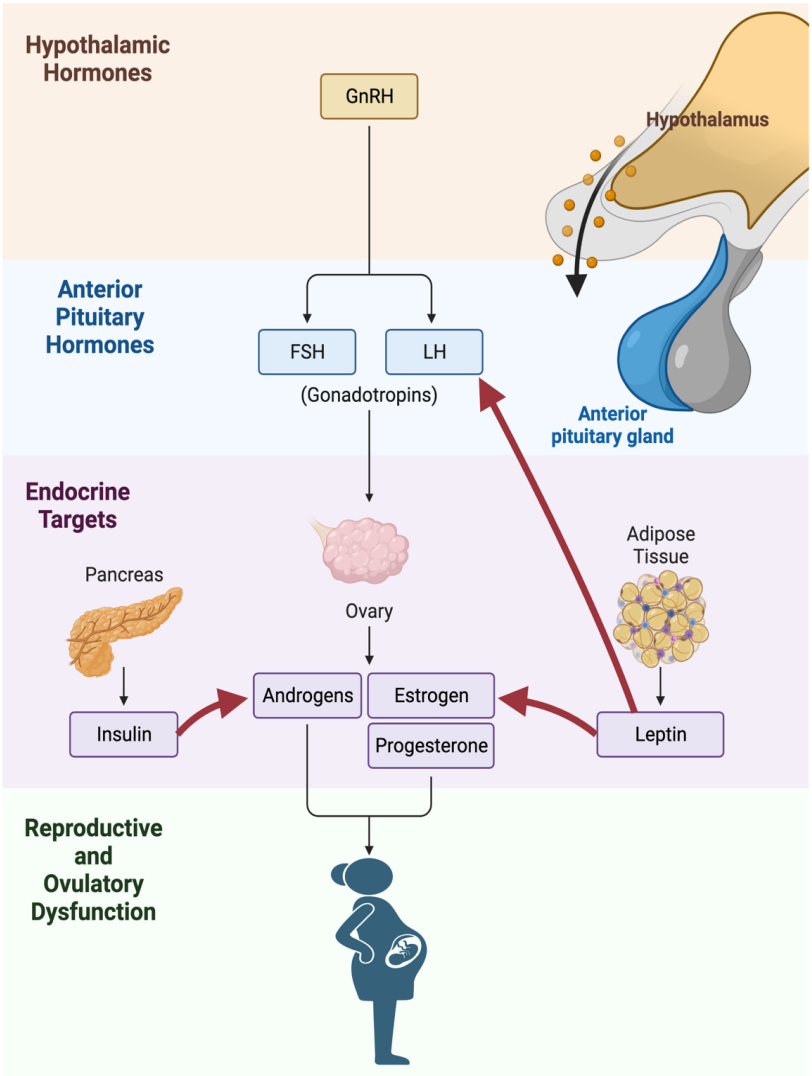
Shang Y, Zhou H, He R, Lu W. Dietary Modification for Reproductive Health in Women With Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. *Frontiers in Endocrinology (Lausanne)*. 2021;12:735954.

What We Know, Think We Know, or Are Starting to Know

Polycystic Ovarian Syndrome [PCOS] is the most common endocrine disorder in women of reproductive age, with a prevalence rate of 5-10%, although some estimates may be nearer to 20% depending on the diagnostic criteria used [1,2].



The figure above helps to piece together the complex reproductive disorder in women with PCOS. At the top, you can see that PCOS is driven by disturbances of the hypothalamic-pituitary-adrenal-ovarian [HPAO] axis [3]. In the top two layers [Hypothalamic Hormones and Anterior Pituitary Hormones], we can see a characteristic feature of PCOS: gonadotropic dysfunction, i.e., dysfunction of hormones secreted by the pituitary gland that act on maturation and function of the ovaries [3].

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Increased gonadotropin-releasing hormone [GnRH] from the hypothalamus causes hypersecretion of luteinizing hormone [LH] from the pituitary, which stimulates the production of androgens by the ovaries [3]. Inadequate production of follicle-stimulating hormone [FSH] also contributes to anovulation in PCOS [3].

If we then look at the third level [Endocrine Targets], we can see a critical relationship in PCOS between HPAO axis dysfunction and disordered insulin function [3]. In women with PCOS, insulin levels influence the production of androgens, i.e., male sex hormones, from the ovaries [4]. Insulin interacts with LH by augmenting the stimulatory effect of LH on ovarian androgen production [3,4].

As a result of this HPAO-axis and insulin dysfunction, PCOS appears to be the leading cause of infertility in women, secondary to the loss of ovulatory cycles [5,6]. This extends to risk of miscarriage, which is increased in women with PCOS whether pregnancy was achieved spontaneously, or with assistance [5].

So, can dietary interventions make a difference to reproductive outcomes in women with PCOS?

The Study

The present study was a meta-analysis of dietary interventions for reproductive outcomes in PCOS. To be included in the analysis, studies had to meet the following inclusion criteria:

- **Design**: parallel-arm [where the intervention and comparison groups run at the same time], randomised controlled trials [RCTs].
- **Population**: Women with a clear diagnosis of PCOS.
- **Intervention**: Dietary pattern interventions, i.e., not single-nutrient trials or supplement trials. Exercise and/or medications were also considered.
- **Control**: Comparison diets, fertility treatments, and/or drugs [e.g., nutrients].
- **Outcomes**:
    - **Primary**: Pregnancy rate, miscarriage rate, and ovulation rate.
    - **Secondary**: Menstrual cycle regularity, total testosterone, sex hormone-binding globulin [SHBG], and the free androgen index [FAI; calculated by dividing total testosterone with SHBG].

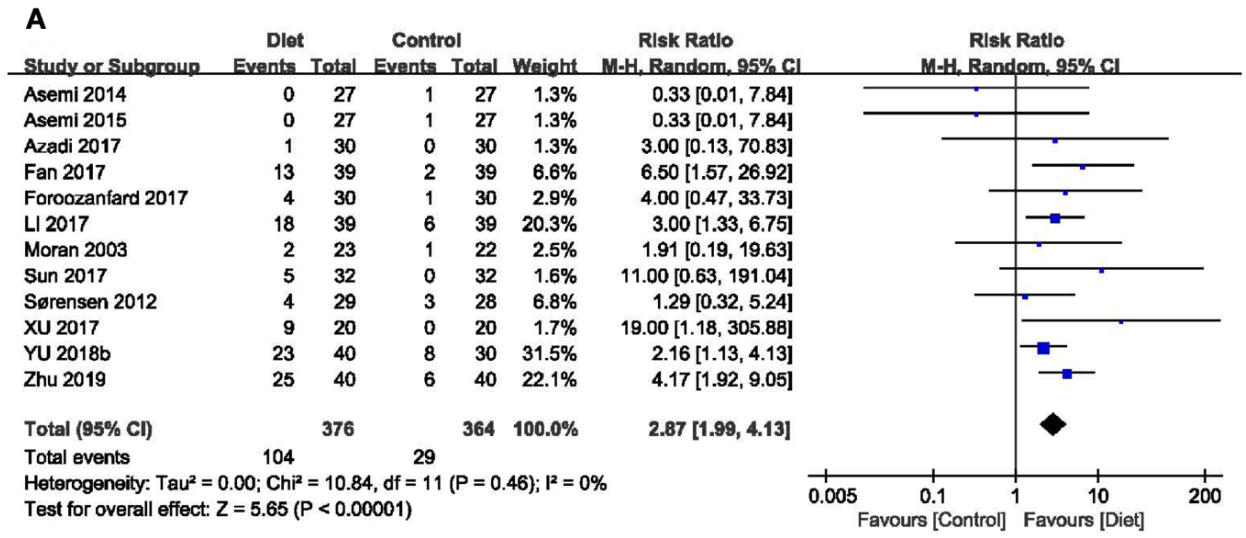
Results for binary outcomes [i.e., "yes"/"no"] including pregnancy rate and ovulatory cycles were expressed as risk ratios [RR] and 95% confidence intervals [95% CI]. Results for continuous outcomes [e.g., testosterone, FAI, etc.], were expressed as the mean difference and 95% CI.

Results: 20 RCTs were included in the overall analysis. Of these trials, seven were conducted in China, four in Iran, two each in the U.S. and Australia, and one each in the UK, Canada, Denmark, Egypt, and Mexico.

The intervention was a low-carbohydrate diet in nine studies, a low glycaemic index/glycaemic load [LGI/LGL] diet in six studies, a DASH diet in four trials, and a Mediterranean diet in one trial.

The duration of the studies on average were 3 to 6 months, with four trials lasting 8-weeks or less and one trial lasting 12-months.

- ***Pregnancy Rates*:** Based on 12 trials with 740 participants, women in the dietary intervention groups had 187% [RR 2.87, 95% CI 1.99 to 4.13] higher probability of pregnancy compared to women in the control groups. In subgroup analysis, the increase in pregnancy rate was significant for the low-carb diets, and only for studies greater than 3-months in duration.



Forest plot *from the paper for the effect of dietary interventions compared to controls on pregnancy rates; somewhat counter-intuitively, this is expressed as risk ratios, and thus >1.0 in this case is not an "increased risk of pregnancy" but an increase in favour of diet.*

- ***Ovulation Rates*:** Based on three trials with 192 participants, women in the dietary intervention groups had a 30% [RR 1.30, 95% CI 1.02 to 3.03] higher probability of ovulation compared to women in the control groups. In subgroup analysis, this improvement in ovulation rate was only observed in studies without calorie restriction, not with calorie restriction.
- ***Menstrual Function*:** Based on four trials with 205 participants, women in the dietary intervention groups had a 75% [RR 1.75, 95% CI 1.10 to 1.43] higher probability of menstrual regularity compared to women in the control groups. In subgroup analysis, this return of menstrual regularity was only significant in the one study lasting 12-months in duration.

- ***Total Testosterone, FAI, and SHBG*:** For total testosterone, nine studies with 412 participants showed that dietary interventions lowered total testosterone by 0.22nmol/L [95% CI, 0.09 to 0.34nmol/L]; subgroup analysis indicated that DASH diets, 3-6 months duration of intervention, and calorie restriction, were all associated with a significant reduction in testosterone.

  Based on seven trials with 326 participants, SHBG increased by 7.08nmol/L [95% CI, 3.41 to 10.74nmol/L] from dietary interventions; subgroup analysis indicated that calorie restriction and 3-6 months duration of intervention showed the greatest effects.

  The FAI decreased by 1.51% [95% CI, 0.29 to 2.72%], with similar subgroup analysis findings to total testosterone.

- ***Anti-Müllerian Hormone [AMH]*:** Based on three trials with 190 participants, dietary interventions reduced AMH by 2.20ng/mL [95% CI, 2.02 to 2.38ng/mL] compared to controls.

- ***Ferriman-Gallwey Score [Hirsutism]*:** The FG score, which grades hirsutism in women with PCOS, decreased by 3.91 [95% CI, 1.95 to 5.87] from dietary interventions compared to controls, based on two studies with 86 participants.

The Critical Breakdown

Pros: The study appears to be the first meta-analysis to specifically investigate reproductive outcomes from dietary interventions. The inclusion criteria were clearly stated, although not as well defined as possible [see **Cons**, below]. The investigators did conduct a number of subgroup analyses to determine factors that influenced the main outcomes. They also conducted sensitivity analyses by removing studies at high risk of bias, and this did not influence the main outcomes. The study was preregistered, including the planned subgroup analyses which were all stated in the registration.

Cons: The inclusion criteria permitted adjuvant use of medications and/or exercise, and it is not clear whether these factors were adjusted for in deriving the estimates of effect from the primary included studies. Thus, the effects of diet may not be entirely independent. Although it may seem like a decent number of trials, the sample sizes in the included studies were small, and the overall numbers of participants in several of the analyses is low; some caution is required in considering some of the effect sizes. All bar one of the low-carb diets were conducted in China, and may not necessarily generalise to other populations. While it is not technically incorrect to use risk ratios for dichotomous or binary outcomes, the language is misleading and a more neutral term like probability should have been used, e.g., “an increased probability of pregnancy rate”. They stated the miscarriage rate was reported as risk ratio, but it appears as odds ratio in the forest plot; hence why I omitted reference to this outcome, because risk and odds are not the same: this is just shoddy reporting.

Key Characteristic

Specifically analysing reproductive outcome related to diet, rather than supplements [i.e., inositol], or just hormonal markers, despite the limitations of outlined above, provides a novel insight into the potential for diet to assist with fertility-related issues that arise with PCOS.

Pharmaceutical treatment of ovulatory dysfunction in women with PCOS is effective, although the exact drug may differ relative to the bodyweight of the individual. For example, in women with PCOS and obesity, the drug clomiphene [an oestrogen-receptor agonist] appears to be the most effective for infertility, while in lean women with PCOS it appears that metformin [an insulin-sensitising agent] is more effective than clomiphene for treating infertility [7].

Supplementation with inositol also has shown to be a promising nutritional supplement intervention for infertility in PCOS [8–10]. Inositol exists in two forms; myo-inositol and d-chiro-inositol, both of which have distinct but complementary effects on PCOS; increasing insulin sensitivity and glucose tolerance, lower androgens, and menstrual cycle regularisation [9]. Myo-inositol alone has been shown to benefit reproductive function in women with PCOS [10].

However, while d-chiro-inositol alone is not beneficial, combination supplementation of myo-inositol and d-chiro-inositol administered in the physiological ratio of 40:1 may ensure better clinical results, including the reduction of insulin resistance, blood androgen levels, cardiovascular risk, and regularisation of menstrual cycle with spontaneous ovulation [8,9].

The present study adds to the research on available pharmacological and supplemental interventions for PCOS, indicating that dietary interventions, particularly those emphasising moderate carbohydrate intake [more on this point under ***Interesting Finding*** in the next section], may also be a helpful adjuvant treatment.

Interesting Finding

With the PCOS research on low-carbohydrate diets – indeed with *any* research on low-carb diets – it is important to put some definitions on "low-carb", particularly as this is often interpreted to mean "high-fat". For PCOS, this may not necessarily be optimal, however.

First, let's consider the carbohydrate levels in the primary included studies; the lowest level on average was 25-30% total carbohydrate intake. 4/7 included studies on low-carb diets had average levels of 40-50% carbohydrate. And, crucially for considering PCOS, many of these studies also emphasised low GI/GL foods, which as we covered in a previous Deepdive, lower androgen levels and insulin resistance in women with PCOS.

What about the fat content of these diets? As most of these studies were conducted in China, total fat was never higher than 30% in any study. Again, this is particularly relevant for PCOS because a prior meta-analysis suggests that the greatest improvement in androgen levels and metabolic outcomes in PCOS may be observed with diets of *both* <35% total fat *and* <45% total carbohydrate [11].

Relevance

Research indicates that women with PCOS perceive a lack of control over health-related outcomes due to their condition [12], and are more likely to express fears over their future fertility and sexual function compared to non-PCOS women with the same BMI [13]. Thus, the present study, limitations notwithstanding, has added some value to the fairly poor quality of evidence for diet and PCOS.

There were a lot of numbers thrown around in the **Results** section, above, so let' s put these outcomes in context. First, the increased probability of pregnancy appears to be an enormous effect size, but the confidence intervals are very wide and indicate a lot of variability and imprecision in the finding. Importantly, 74% of the statistical weight is derived from three studies [Li et al., 2017; Yu et al., 2018(b); Zhu et al., 2019], and each study had only ~40 participants in the intervention groups. This is not to suggest that the finding of increased probability of pregnancy is invalid, merely to temper expectations with the size of the effect noted in this study; it is primarily based on three small trials and may be overexaggerated.

What about some of the hormonal outcomes? Normal total testosterone levels in women range from 0.5 to 2.4nmol/L, so the reduction of 0.22nmol/L may be clinically meaningful depending on baseline levels. Given that normal SHBG levels for non-pregnant women is 18 to 144nmol/L, the modest increase of 7.08nmol/L may not be as relevant. However, this did occur with a decrease in the FAI of 1.5% which, with a reference range of 0.18 to 7.07%, overall indicates improvements in androgen profiles in women with PCOS from dietary interventions.

AMH is a marker of ovarian reserve and elevated levels, which are observed in women with PCOS, may arrest follicular development [14]. Estimated cut-offs for PCOS may vary from 3.5ng/mL to 7.7ng/mL, so the reduction of 2.20ng/mL shown in this study may also be clinically relevant, although the caveat is that is based on a small number of studies.

Similarly, the improvement of 3.91 in the Ferriman-Gallwey score, which scores androgen-sensitive body areas for hair growth [4 indicates extensive growth, >8 indicates hirsutism] may also be a meaningful outcome, but is based on very limited data from only 86 participants.

Application to Practice

The body of evidence for nutrition interventions in PCOS remains dominated by small trials, low statistical power, and varying consistency in effects, and the size of those effects. We are often left to caveat every finding, however, the overall body of evidence does indicate that dietary and supplemental interventions may be effective for reproductive/fertility related outcomes in PCOS.

The data on inositol was established prior to the publication of the present meta-analysis, and this is a low-hanging fruit as a supplement with minimal risk profile. Obviously, it goes without saying that pharmacological treatments are outside our scope [unless you' re a medical professional, of course!], but it is always helpful for nutrition professionals to be aware of available treatments if working with women in this area.

At this juncture, we certainly have more consistent evidence that dietary interventions improve the hormonal aspects of PCOS, in particular elevated insulin [see previous Deepdive] and androgens [see previous Deepdive]. And we understand the relationship between these risk factors and infertility in PCOS; the present study suggests that the likelihood of 'hard' outcomes such as menstrual regularity and achieved pregnancy, may also be improved with diet.

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