

Clinical scenario:

30-year-old female patient with past medical history of obesity and irregular menstruation secondary to polycystic ovarian syndrome was previously managed with metformin. Patient ran out of metformin 6 months ago and did not take any medication since then. Her menstruation remains regular over the past 6 months, and she is wondering if that's attributed to exercise and healthy diet.

PICO Question:

Is lifestyle modification alone effective at managing symptoms of polycystic ovarian syndrome in obese women?

Question Type:

Therapy/ Prevention

Diagnosis

Etiology

Prognosis

Screening

Prevalence

Harms

PICO search terms:

P	I	C	O
Polycystic ovarian syndrome	Lifestyle modification	Metformin	Symptom relief
BMI > 30	Weight loss	Oral contraceptives	Menstruation regulation
Obese patient with PCOS	Healthy diet	Pharmacologic therapy	Fertility
	Exercise		

Search Strategy:

Database	Filter	Terms Searched	Articles Returned
PubMed	Last 10 years English Meta-Analysis Randomized Controlled Trial Systemic review	Effect of lifestyle modification in PCOS	27

	Last 5 years English Meta-Analysis Randomized Controlled Trial	Lifestyle modification alone in PCOS	10
Cochrane Library	Last 10 years English	Lifestyle modification versus metformin in PCOS	3
Google Scholar	Last 5 years English Review articles Research articles	Effect of lifestyle modification alone versus metformin in PCOS patients with obesity	38

I was looking for articles, preferably systemic review or RCT, that examine and compare the effectiveness of lifestyle modification versus metformin in managing PCOS. I narrowed down the result by relevance first; I was able to find articles that compare the effect of metformin alone and lifestyle modification alone. I also included one article that examined the effect of lifestyle change only. Even though there is no direct comparison to other therapy, it is still applicable to the search question. I further narrowed down the results by the type of design, then by the year of publication. I thought the year of publication would be less important in this case because the interventions (lifestyle modification and metformin) that are being compared have not changed significantly over the past decades.

Article 1

Citation: Wang, A., Mo, T., Li, Q., Shen, C., & Liu, M. (2019). The effectiveness of metformin, oral contraceptives, and lifestyle modification in improving the metabolism of overweight women with polycystic ovary syndrome: a network meta-analysis. <i>Endocrine</i> , 64(2), 220–232. https://doi.org/10.1007/s12020-019-01860-w
Type of Study: Meta-analysis

Abstract:

Purpose: We designed a network meta-analysis that investigated relatively different interventions that included the effects of metformin, oral contraceptives, and lifestyle modification on the metabolic parameters of patients with polycystic ovary syndrome. In addition, we searched for eligible interventions that improved the metabolism of glucose and lipids.

Methods: We searched the PubMed, EMBASE, and Cochrane Central databases from inception to May 2018. Publication types that were categorized as randomized controlled trials met our inclusion criteria. The main outcome included the homeostasis model assessment of insulin resistance, total cholesterol, low-density lipoprotein cholesterol, and total triglycerides. We performed both a pairwise meta-analysis and a network meta-analysis to evaluate the mean difference value and 95% credibility intervals, and we calculated the surface cumulative rank curve.

Results: There were a total of 12 kinds of interventions: metformin, 2 mg cyproterone acetate plus 0.05 mg ethinylestradiol (EE/CA), 0.15 mg desogestrel plus 0.03 mg ethinylestradiol (EE/DSG), and 3 mg drospirenone plus 0.03 mg ethinylestradiol (EE/DRSP), lifestyle, exercise, diet, metformin + lifestyle, metformin + diet, EE/CA + lifestyle, metformin + EE/CA, and EE/DRSP + lifestyle from the 20 eligible RCTs that were included in this study. Our meta-analysis results showed that metformin + lifestyle (MD = -2.04, 95% CrI = -3.64 to -0.41), EE/CA + lifestyle (MD = -2.23, 95% CrI = -4.11 to -0.35), and EE/DRSP + lifestyle (MD = -2.59, 95% CrI = -4.66 to -0.50) resulted in lower in the levels of total cholesterol. Women treated with metformin + lifestyle (MD = -1.82, 95% CrI = -2.88 to -0.79), EE/CA + lifestyle (MD = -2.25, 95% CrI = -3.58 to -1.08), or EE/DRSP + lifestyle (MD = -2.29, 95% CrI = -3.69 to -1.07) exhibited significantly lower low-density lipoprotein cholesterol when compared with the placebo group. There was no significant difference between any of the interventions compared with a placebo in the levels of homeostasis model assessment of insulin resistance and total triglycerides. The surface cumulative rank curve revealed that metformin + lifestyle might be the best intervention with respect to the improvement of the homeostasis model of assessment insulin resistance and EE/DRSP + lifestyle appeared to be the best intervention for the reduction of total cholesterol and low-density lipoprotein cholesterol. Moreover, the metformin + diet intervention was more effective in reducing the level of total triglycerides.

Conclusions: For overweight polycystic ovary syndrome patients, our evidence revealed that EE/CA and EE/SRSP combined with metformin or lifestyle changes can reduce the adverse effects on glucose and lipid metabolism of the use of oral contraceptive agents alone. Conventional PCOS treatments, such as metformin, EE/CA, and EE/DRSP, combined with lifestyle control can be particularly effective in improving the homeostasis model assessment of insulin resistance and lipid metabolism.

Article 2:

Citation: Kim, C.H., Chon, S.J. & Lee, S.H. Effects of lifestyle modification in polycystic ovary syndrome compared to metformin only or metformin addition: A systematic review and meta-analysis. *Sci Rep* **10**, 7802 (2020). <https://doi.org/10.1038/s41598-020-64776-w>

Type of Study: Systemic Review and Meta-analysis

Abstract:

Polycystic ovary syndrome (PCOS) is a common disease that has an effect on approximately 10% of women of childbearing age. Although there is evidence regarding the role of lifestyle factors in the development of PCOS, the exact etiology remains unclear. Additionally, metformin is used in the treatment of PCOS but its role remains unclear. We compared the effects of lifestyle modification (LSM) + metformin and metformin alone on PCOS. We performed a systematic review by searching electronic databases for publications until December 2019. The primary endpoints were clinical outcomes, such as menstrual cycles and pregnancy rates, and the secondary endpoints were anthropometric, metabolic, and androgenic parameters. The meta-analysis revealed that there was no significant difference in the improvements in the menstrual cycles between LSM and metformin alone (weighted mean difference [MD] = 1.62) and between LSM + metformin and LSM (MD = 1.20). The pregnancy rates and body mass indices were not significantly different between LSM and metformin alone (MD = 1.44 and -0.11, respectively). LSM reduced insulin resistance (MD = -0.52) and increased serum levels of sex hormone-binding globulins (MD = 8.27) compared with metformin. Therefore, we suggest recommending lifestyle modifications actively to women with PCOS if they do not have indications for metformin.

Article 3

Citation: Oberg, E., Gidlöf, S., Jakson, I., Mitsell, M., Tollet Egnell, P., & Hirschberg, A. L. (2019). Improved menstrual function in obese women with polycystic ovary syndrome after behavioural modification intervention-A randomized controlled trial. *Clinical endocrinology*, *90*(3), 468–478. <https://doi.org/10.1111/cen.13919>

Type of Study: Randomized control trial

Abstract:

Objective: Lifestyle intervention is the recommended first-line treatment for overweight women with polycystic ovary syndrome (PCOS). However, the efficacy of lifestyle change in improving reproductive function is still unclear.

Design: A randomized controlled trial (RCT) with allocation to a behavioural modification programme (intervention) or minimal intervention (control) for 4 months with a follow-up at 12 months.

Patients: Sixty-eight women, aged 18-40 years, body mass index (BMI) ≥ 27 kg/m², fulfilling all Rotterdam PCOS criteria were randomized to treatment.

Measurements: The primary outcome was improved menstrual regularity. Secondary outcomes were ovulation and pregnancy rates.

Results: At 4 months, the weight loss was significant in the intervention group (-2.1%, P = 0.002) and nonsignificant in the control group (-1.0%). A higher proportion of patients in the intervention group improved menstrual regularity compared to the control group, mean difference 35% (95% CI: 16-60), P = 0.003. There was no difference in ovulation rate between groups. Logistic regression analysis showed that intervention was the only predictor of improved menstrual function, OR 3.9 (95% CI: 1.3-11.9). At 12 months, a total of 54% of the women improved menstrual regularity compared to baseline (P = 0.000) and 43% (P = 0.000) had confirmed ovulation. 38% of the women wishing to become pregnant succeeded within 1 year of study completion.

Conclusions: This is the first RCT in overweight women with PCOS showing efficacy in improving reproductive function following behavioural modification intervention in comparison with minimal intervention. Although extensive weight loss is difficult to achieve in these women, behavioural modification intervention can help improve reproductive function.

Article 4

Citation: Domecq, J. P., Prutsky, G., Mullan, R. J., Hazem, A., Sundares, V., Elamin, M. B., Phung, O. J., Wang, A., Hoeger, K., Pasquali, R., Erwin, P., Bodde, A., Montori, V. M., & Murad, M. H. (2013). Lifestyle modification programs in polycystic ovary syndrome: systematic review and meta-analysis. *The Journal of clinical endocrinology and metabolism*, 98(12), 4655–4663. <https://doi.org/10.1210/jc.2013-2385>

Type of Study: Systemic review and Meta-analysis

Abstract:

Context: Polycystic ovary syndrome (PCOS) is a prevalent disorder that affects women of childbearing age and may be related to obesity and insulin resistance.

Objective: The purpose of this systematic review was to appraise the evidence of the impact of lifestyle modification (LSM) interventions on outcomes of women with PCOS.

Data sources: Sources included Ovid Medline, OVID Embase, OVID Cochrane Library, Web of Science, Scopus, PsycINFO, and CINAHL (up to January 2011).

Study selection: We included randomized controlled trials that enrolled woman of any age with PCOS who received LSM and compared them against women who received no intervention, minimal intervention, or metformin.

Data extraction: Two authors performed the data extraction independently.

Data synthesis: We included 9 trials enrolling 583 women with a high loss to follow-up rate, lack of blinding, and short follow-up. Compared with minimal intervention, LSM significantly reduced fasting blood glucose (weighted mean difference, -2.3 mg/dL; 95% confidence interval, -4.5 to -0.1, $I^2 = 72\%$, $P = .04$) and fasting blood insulin (weighted mean difference, -2.1 $\mu\text{U/mL}$, 95% confidence interval, -3.3 to -1.0, $I^2 = 0\%$, $P < .001$). Changes in body mass index were associated with changes in fasting blood glucose ($P < .001$). Metformin was not significantly better than LSM in improving blood glucose or insulin levels. We found no significant effect of LSM on pregnancy rate, and the effect on hirsutism was unclear.

Conclusions: The available evidence suggests that LSM reduces fasting blood glucose and insulin levels in women with PCOS. Metformin has similar effects. Translation of these short-term effects to patient-important outcomes, beyond diabetes prevention, remains uncertain.

Summary of the Evidence:

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases
Wang, A, et als	Meta-analysis (high)	Studies are identified by searching Pubmed, EMASE, and Cochrane Central for relevant literature from	homeostasis model assessment of insulin resistance, total cholesterol, low-density lipoprotein cholesterol,	<ul style="list-style-type: none"> Pairwise meta-analysis showed that metformin combined with EE/CA or lifestyle had better effects on overweight 	<ol style="list-style-type: none"> The study aimed to compare 12 interventions. Some interventions were missing due to lack of studies. The conclusions

		<p>inception to May 2018.</p> <p>Inclusion criteria include: PCOS women aged 18-49 with an average BMI of ≥ 25, RTC design, include at least one main outcome, same calculation formula for HOMA-IR, intervention time was at least 4 weeks.</p> <p>A total of 20 records were included in this meta-analysis.</p> <p>The studies were published between 2006 and 2017.</p>	<p>and total triglycerides</p>	<p>PCOS patients with respect to reducing the levels of HOMA-IR, TC, LDL-c, and TGs.</p> <ul style="list-style-type: none"> ● Metformin combined with EE/CA showed better improvement in glucose metabolism. ● NMA showed similar result as pairwise meta-analysis: metformin combined with EE/CA or lifestyle had better effect at controlling HOMA-IR, than metformin, EE/CAM or lifestyle alone. ● Lifestyle, diet, metformin plus lifestyle EE/CA plus lifestyle, and EE/DRSP plus lifestyle could be 	<p>are only applicable to overweight PCOS patients</p> <p>3) Dose of metformin, exercise volume, and diet control is not analyzed.</p>
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				<p>effective in reducing TC.</p> <ul style="list-style-type: none">● Most intervention, except exercise, could reduce LDL-c.● Combining lifestyle modification with EE/CA or EE/DRSP could reduce the adverse effects of contraceptives on lipid metabolism.● In this study, metformin plus lifestyle was the most effective in improving insulin resistance.● Metformin plus diet was more effective at reducing TG level.● EE/CA and EE/DRSP combined with lifestyle or metformin could improve insulin resistance as	
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				well as decreasing TC and LDL-c.	
Kim, C.H, et als	Systemic Review and meta-analysis	<p>13 studies were included, which include 11 RTCs, 1 clinical trial, and 1 prospective study</p> <p>The studies were published between 2000 and 2018</p> <p>4 studies from Europe, 4 studies from North America, 2 studies from South America, 2 studies from the Middle East, and 1 study from Africa</p>	<p>Clinical outcomes (primary): menstrual cycles, pregnancy rates</p> <p>Secondary outcome: anthropometric, metabolic, and androgenic parameters</p>	<ul style="list-style-type: none"> ● Clinical outcomes, such as improvement in menstruation irregularity and pregnancy outcome were not significantly different between lifestyle modification and metformin. ● Metformin alone does not improve the menstrual cycles. ● Lifestyle modification tends to increase the number of patients who experience regular menstrual cycles more than metformin alone. 	<ol style="list-style-type: none"> 1) Some of the included studies were small and have some weakness in study design. 2) Sample size of the included studies was not large enough. 3) Heterogeneity in the type of interventions made it difficult to compare and draw conclusion.

				<ul style="list-style-type: none">● The effect of lifestyle modification plus metformin in lowering BMI is not consistent. Some study showed no significant improvement in BMI while others suggest there is an improvement.● Majority of studies reported significant reduction in testosterone level with lifestyle modification plus metformin than lifestyle modification alone.● Lifestyle modification group has higher pregnancy rate than metformin but the difference is not significant.	
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				<ul style="list-style-type: none">● Drop out rates between lifestyle modification and metformin were similar. Lifestyle modification group tend to have higher number of non-compliant patients, and metformin group drop-outs were mainly due to drug side effects.● In comparison between lifestyle modification plus metformin with lifestyle modification , there was no significant difference in fasting serum glucose levels.● Lifestyle modification	
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				plus metformin significantly reduced fasting serum insulin levels.	
Oberg, E, et als	Randomized control trial	RCT conducted in Sweden. 68 women, aged 18-40 years, with a BMI of at least 27 were included.	Primary: improved menstrual regularity Secondary: ovulation and pregnancy rates	<ul style="list-style-type: none"> At 4 month follow up, there was a small but significant reduction in mean body weight in intervention group, but not in control group. But the mean weight loss is not significantly different between the groups. Only 15% of the women in the intervention group succeeded in losing more than 5% of their body weight. This result is less than expected but may be explained by the fact that 	1) Dropout rate is 16% after 4 months and 31% after 1 year.

				<p>the intervention focused on behavioral modification and did not offer specific diet or exercise instruction.</p> <ul style="list-style-type: none">● A significantly higher proportion of women in the intervention group improved their menstrual function at 4 month follow up.● No different in ovulation rate at 4 month between the groups.● At 12 month follow up, 54% of women has improved menstrual regularity and 43% has confirmed ovulation.● At 12 months, there were significant	
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				reduction in FAI, fasting insulin and HOMA in the whole cohort of women.	
Domecq, J. P, et als	Systemic review and meta-analysis	<p>9 RTCs were included. Trials were published between 1994 and 2011.</p> <p>The meta-analysis included 610 obese or overweight women, with mean age of 27.</p>	<p>Primary outcomes based on the importance rated by patients: hirsutism, fertility, amenorrhea, and acne</p> <p>Metabolic outcomes: fasting blood glucose and insulin</p>	<ul style="list-style-type: none"> ● When compare lifestyle modification with minimal intervention (placebo), lifestyle modification results in a significant but small effect on glucose and insulin blood levels. ● Effect of metformin and lifestyle modification were similar in terms of reducing fasting blood glucose, fasting blood insulin, hirsutism score, and pregnancy rate. ● There is a significant direct correlation between weight loss 	<ol style="list-style-type: none"> 1) Weakness in the quality of RTC: high rates of loss to follow-up, short trial duration, heterogeneity in interventions between different studies, small sample size. 2) None of the studies include effect of treatment on acne. 3) Conclusion only apply to overweight and obese patients.

				and improvement in metabolic parameters.	

Conclusion(s):

Article 1: The article aimed at comparing 12 different interventions. Based on the meta-analysis, they concluded that combining metformin or lifestyle change with oral contraceptive agents help reduce the glucose and lipid metabolism side effects of oral contraceptives. Pharmacologic therapy (metformin or OCP) combined with lifestyle modification are effective in improving insulin, triglyceride, and LDL-c level. Among these interventions, metformin plus dietary change is most effective at reducing triglyceride level.

Article 2: Effect of lifestyle modification and metformin on menstruation regularity and pregnancy outcomes were similar based on this systemic review. However, lifestyle modification tend to provide more benefits when compared to using metformin alone. Metformin has an additive effect on improving fasting insulin level and serum testosterone levels, but no significant benefit in lowering BMI or fasting glucose level.

Article 3: The study compared minimal intervention, where patients are only given general lifestyle recommendations, to behavioral modification, where patients are enrolled in a program that provide formal course on physical activity and dietary change. The study concluded that behavioral modification helps reduce weight, improve menstrual function and potentially improve fertility in obese women with PCOS.

Article 4: Lifestyle modification programs help decrease the fasting glucose and insulin level in obese or overweight women with PCOS. Changes of BMI were associated with fasting glucose level.

Overall conclusion based off the above studies is that lifestyle modification alone can help lower BMI, improve menstrual regularity and potentially fertility in obese women with PCOS. It's effects in alleviating symptoms and improving metabolic parameters are similar to that of metformin alone, except for lowering testosterone level. However, metformin has an additive effect on certain metabolic parameters and can more effectively improve insulin, triglyceride, LDL, and testosterone level.

Clinical Bottom Line:

I weight the level of evidence in this order: article 1 > article 2> article 4 > article 3

Article 1, Wang, A, et al: I weighted this article the highest. This is a systemic review and meta-analysis that investigated 12 different interventions, including metformin, 3 different types of oral contraceptives, lifestyle modification, and different combinations of these therapies. Even though the study is not specifically investigating the effect of lifestyle modification alone, it was included in the study and was compared to other therapies to better understand the magnitude of its effect. The article was published in 2018, and it included 20 studies published between 2006 and 2017. The inclusion criteria match with the patient in the clinical scenario and this systemic review only included RTCs, making the level of evidence higher. The author was trying to compare different combinations of interventions, and one limitation with this study was that some interventions were missing due to lack of studies. Also, this study only included patients with BMI of at least 25. Thus, the conclusion can only apply to overweight PCOS patients.

Article 2, Kim, C.H, et al: I weighted this article the 2nd. This is a systemic review and meta-analysis that included 13 studies (n=778). Of the 13 studies, 11 of them are RCTs, 1 is clinical trial, and 1 is prospective study. This article contained data from non-RCTs, making it weights less compared to first article. The article was published in 2020 and the studies included were published between 2000 and 2018, making the evidence current. The author investigated the effects of lifestyle modification alone on PCOS, and compared it to metformin alone, which is directly applicable to my PICO question. One limitation of this systemic review is that some of the studies included were small and had methodological weakness.

Article 4, Domecq, J. P, et al: I weighted this article the 3rd. This is another systemic review and meta-analysis published in 2013. The study included data from 9 RCTs (n=610). The mean age of participants was 27 years, and the average length of follow-up was 5 months. 5 RCTs enrolled obese patients and 4 RCTs enrolled overweight patients. The age and BMI of enrolled patients match with the patients in the clinical scenario. The aim of the study is applicable to the PICO question. The authors investigated the effect of lifestyle modification alone, and compared it to women who received no intervention, minimal intervention, or metformin. The RCTs included in this study was published between 1994 and 2011, leading to some variation in the diagnostic criteria of PCOS and different lifestyle modification regimens used. The limitations of this study is related to the quality of RCTs, which include high rate of loss to follow-up, short trial duration, heterogeneity and small sample size. This RCTs included in this article is less recent compared to the previous two, resulting in inconsistency in the diagnostic criteria of PCOS and lifestyle modification regimen.

Article 3, Oberg, E, et al: I weight this article the last. It was a RCT published in 2018. The study investigated the efficacy of behavioral modification program in alleviating symptoms of PCOS. The behavioral modification program consisted of a structured and formal course that focused on weight loss, physical activity, and dietary change. It is compared with controlled group, where patients received standard oral and written recommendation on lifestyle modification. I rank this article last because it only assessed the effect of lifestyle modification alone and did not compare it to any pharmacologic therapy. However, it is still applicable to the PICO question. Moreover, It's a single RCT with smaller sample size when compared to systemic

review and meta-analysis (n=68). One limitation with this study is its dropout rate (16% after 4 months and 31% after 1 year).

Magnitude of any effects

Article 1, Wang, A, et al:

The meta-analysis result showed patients treated with metformin + lifestyle had lower HOMA-IR levels than those treated with metformin (MD = 1.88, 95% CrI = 0.61 to 3.14), EE/CA (MD = 2.47, 95% CrI = 0.98 to 3.98), lifestyle (MD = 1.30, 95% CrI = 0.19 to 2.38), diet (MD = 1.55, 95% CrI = 0.26 to 2.84), and metformin + EE/CA (MD = 1.96, 95% CrI = 0.44 to 3.46). According to the triglyceride data, women treated with metformin combined with lifestyle exhibited lower TC levels than women who only modified their lifestyle (WMD = 0.43, 95% CI = 0.08 to 0.78). For LDL-c level, women who were treated with metformin combined with lifestyle showed lower LDL-c levels than women who only modified their lifestyle (WMD = 0.36, 95% CI = 0.07 to 0.65).

Article 2, Kim, C.H, et al:

Menstrual cycle: Menstrual cycles were evaluated in all studies that compared LSM with metformin alone. There was no significant difference in the improvement in the menstrual frequency between the groups ($p = 0.06$; weighted mean difference [MD] = 1.62).

Pregnancy rate: The pregnancy rate was evaluated in two studies that compared LSM with metformin alone. There was no significant difference in the pregnancy rate between the groups ($p = 0.30$, MD = 1.44).

Weight loss: There was no significant difference in the weight loss between the groups ($p = 0.73$, MD = -0.83).

Body mass index: BMI was measured in six studies that compared LSM + metformin with LSM, and four studies were included

for meta-analysis. LSM + metformin was associated with a lower BMI at study completion than LSM, whereas

there was no significant difference between the groups in our study ($p = 0.13$, MD = -1.15).

Fasting glucose: There was no significant difference in the serum fasting glucose level between the groups ($p = 0.11$, MD = 2.04).

Fasting insulin: There was no significant difference in the fasting serum insulin levels between the groups ($p = 0.11$, MD = -1.10).

Homeostatic model assessment for insulin resistance: LSM was reported to significantly reduce HOMA-IR compared with metformin alone ($p < 0.01$; MD = -0.52).

Total testosterone: Metformin alone significantly reduced the total serum testosterone level compared with LSM ($p < 0.01$; MD = 13.68).

Sex hormone-binding globulin: LSM significantly increased serum SHBG levels compared with metformin alone ($p < 0.01$; MD = 8.27).

Article 3, Oberg, E, et al:

A significantly higher proportion of patients in the intervention group improved their menstrual function at 4 months compared to the control group, 59% (n = 20/34) vs 24% (n = 8/34) with a mean difference of 35% (95% CI: 16-60), $P = 0.003$ (Figure 2B). Thirty-two percentage; (n = 11/34) of the patients in the intervention group had a regular menstrual period, compared to

21% (n = 7/34) in the control group, NS. At 12 months of follow-up, when both groups had received 4 months of intervention, a total of 54% of the patients (n = 37/68) (95% CI: 42-66) (P = 0.000) according to ITT had improved their menstrual function, and 43% (n = 29/68) (95% CI: 32-54) had a regular menstrual cycle compared to 0% at baseline (P = 0.000). The ovulation rate for the whole group at 12 months was 43% (n = 29/68) (95% CI:31-54) compared to zero at baseline (P = 0.000).

Article 4, Domecq, J. P, et al:

Compared with minimal intervention, lifestyle modification (LFM) reduced FBG (fixed effect: WMD, 2.3 mg/dL, 95% CI, - 4.5 to 0.1, P = .04, I² = 72%) and FBI (fixed effect: WMD, - 2.1 IU/mL, 95% CI, - 3.3 to - 1.0, P = .001, I² = 0%). Compared with metformin, LSM was not different in its ability to reduce FBG (fixed effect: WMD, 0.00, 95% CI - 2.4 to 2.5, P = .97, I² = 15.3%), FBI (fixed effect: WMD, 0.0, 95% CI, - 1.9 to 1.8, P = .98, I² = 0%), hirsutism score (reported in 1 RCT: WMD, - 0.8, 95% CI, - 3.5 to 1.9, P = .56), or pregnancy rate (reported in 1 RCT: OR, 1.5, 95% CI, 0.7 to 3.3, P = .35).

Clinical significance (not just statistical significance)

In patients with PCOS, their ovaries produced an abnormal amount of androgens, leading to a wide range of conditions such as menstrual irregularity and infertility. It affects approximately 10% of women of childbearing age. It is usually managed with oral contraceptives or metformin. Based on the conclusions from the 4 articles, lifestyle modification alone can provide a significant improvement in clinical outcomes, including weight loss and menstrual regulation. For example, based on the data from the included clinical trials, lifestyle modification alone improved menstruation frequency in 54% - 84% of patients, which is comparable to taking metformin alone. However, lifestyle modification requires a lot of commitment, thus can have a high rate of non-compliance. Based on the articles, multiple studies have shown better testosterone level control and improved lipid and glucose metabolism when lifestyle modification is combined with pharmacological therapy. I think patients should be educated on the important benefits of lifestyle modification. And lifestyle modification should be recommended as an adjunct therapy to pharmacological therapy.

There are variations in the type and extent of lifestyle changes in the included studies, but they were all shown to be beneficial to patients with PCOS. Most of the interventions used in the studies included both hypocaloric diet and aerobic exercise. However, making lifestyle change can be challenging. It is important to set realistic goals. Patients should start with small changes first and then gradually increase the intensity. Ideally, the patient should do 150 minutes of aerobic exercise weekly and have a daily caloric intake of 1000- 1400 kcal/day. Patients should be able to see symptom improvements in 4-6 months.

Any other considerations important in weighing this evidence to guide practice - If the evidence you retrieved was not enough to conclude an answer to the question, discuss what aspects still need to be explored and what the next studies will have to answer/provide (e.g. larger number, higher level of evidence, answer which sub-group benefits, etc)

The above 4 articles agree on the conclusion that lifestyle modification alone is effective at lowering BMI, fasting blood glucose and insulin level, and alleviating PCOS symptoms including menstrual irregularity. All 4 articles had the limitation that the sample size is not large enough, and there is some variation between lifestyle change regimen. A large-scale multicenter study with standardized lifestyle modification regimen is needed to verify its therapeutic role in PCOS patients. In addition, most of the current RCTs focused on overweight and obese patients. Further research is needed to clarify the effect of LSM in women with BMI of less than 25.