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REVIEW ARTICLE

Polycystic Ovarian Disease and Effect of Lifestyle Modification- A Systematic review of RCTs.

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ABSTRACT
PCOD is a well-known disease and is growing like a wildfire. It effects female's primary as well as secondary sexual characters. With changing lifestyle, number of incidences of PCOD isgrowing at a faster rate. This study was conducted to find out a common ground on which a relationship between PCOD and lifestyle management can be built. Data for systematic review was retrieved from various database libraries. We evaluated double blind, placebo controlled randomized trials of PCOD and studied its impact on female body. We used Scopus, CENTRAL, PubMed, Google Scholar as database libraries. Eligible studies were short listed based on inclusion and exclusion criteria, and the results were drawn. Jadad's score and MQS (Heyland methodological quality score) were used to access the quality of the studies included along with assessing the publication bias. This study concludes that PCOD can be managed with lifestyle management, but more depth study is required to assess all the type of lifestyle management and their individual impact on the disease.

Keywords: *Double-blind; Lifestyle; Metformin; Obesity; PCOD, RCTs*

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INTRODUCTION

When puberty sets on, both females and males' bodies start producing hormones necessary for reproduction. These hormones differentiate the two sexes from each other. Female hormones include progesterone, estrogen, gonadotropin releasing hormone, luteinizing hormone and follicle stimulating hormone. A small amount of androgens (male hormones) are also present in the female body.PCOS develops when the levels of androgens in the female body increases to greater extents (PCOS factsheet).Women diagnosed with PCOS may have irregular or absent menstrual periods, excessive hair on the body and face, acne, heavy periods, pelvic pain, difficulty in conceiving and dark and patchy skin. Complications related to PCOS include Sleep apnea, type 2 diabetes, heart disease, pelvic, obesity, heart disease, mood swings and endometrial cancer[1]. Inwomen of reproductive age, PCOS is the most persistent endocrine disorder[2].Division of PCOS is done in majorly five categories: type 1/insulin resistant PCOS, where the risk of developing diabetes mellitus is increased due to leptin and insulin resistance and symptoms like ovulatory interruptions, high androgen levels, acne, hirsutism and hair loss are seen; type 2/Non-insulin resistant, where women meet the criteria for PCOS, but do not show insulin resistance; Non Traditional PCOS 1, where ovulatory issues are seen with normal testosterone and insulin resistance along with obesity; Non-traditional PCOS 2 is where ovulatory issues are not seen but testosterone levels are increased with mild insulin resistance; the fifth type, known as idiopathic hirsutism, displays normal ovulatory pattern with increased testosterone and absent insulin resistance[1]. Everyone having ovarian cysts may not be diagnosed with PCOS and everyone with PCOS may not have polycystic ovaries[3]. Of the following three conditions, the presence of any two is

confirmative of the presence of PCOS: no ovulation, ovarian cysts, and high androgen levels. These cysts can be diagnosed with the help of a pelvic ultrasound[1].

PCOS is a prevalent disorder that affects about 10% of women in the reproductive ages [4] containing classic features of anovulatory fertility, hirsutism, and menstrual dysfunction [5]. Other important manifestations are insulin resistance and dislipidemia as metabolic anomalies, risk of type 2 diabetes, inflammation and cardiometabolic risk, especially when coupled with obesity [6].

About half of the women affected with PCOS are either obese or overweight, with some studies indicating greater visceral fat tissue than body mass index, matching healthy control women [7,8]. The severity of PCOS is vastly affected by obesity and it also plays an important role in the occurrence of hyperandrogenism and chronic an ovulation [9]. Numerous abnormalities of the sex steroid metabolism are associated with the increase in amounts of adipose tissues, like increase in androgen production and suppression of the reproductive hormone, binding globulin. Obese patients that have PCOS may face severe metabolic and cardiovascular risks than those without weight issues [10]. Weight gain, abdominal obesity and obesity can be thought of as predictors of development of menstrual irregularities and hirsutism in teens and adult women [11]. When the link of insulin resistance with increased cardiometabolic risk is taken into consideration, the primary goal to treat obesity and PCOS becomes its reduction [12]. It is achieved in most cases with modest weight reduction [13]. Lifestyle modification and changes in diet and physical activity are recommended for patients at high risk of diabetes to delay its onset [14], which is the most common complication of PCOS. Additionally, women that have a high body weight and PCOS are known to benefit from lifestyle management by reduction in fat mass [15], reduction in cardiovascular risk and improved ovulatory function [16] . Lifestyle management changes may improve certain effects of the phenotype of a person, but it hasn't been postulated that it helps with PCOS. However, when weight loss is sustained, either after bariatric surgery or long-term dietary intervention, it is found to have improved phenotype in most of the PCOS patients [17].Lifestyle management can also be linked to clinical improvement in PCOS. Kiddy et al., 1992, showed that weight loss in moderation carried out due to calorie restriction in the long term is linked to clinical improvement in infertility as well as menstrual function [18]. Clark et al., 1995, showed that weight loss in associated with improvement in pregnancy outcome, ovulation, endocrine function, and self-esteem in retrospective studies, as seen in overweight and infertile women [19].

The study focused on the establishment of quantitative and systematic impact of the lifestyle management changes on PCOS. It was hypothesized that these changes and the reduction of symptoms of PCOS are related in a positive manner and the complications are reduced when positive changes are brought about in a woman's lifestyle.

MATERIAL AND METHODS

Criteria of selection for the study

The studies were selected based on exclusion and inclusion criteria. A double blind, placebo controlled, and randomized trial was done, including females of any age with PCOS that received diet therapy and/or workout therapy and received metformin.

A double-blind study is one where neither the participant nor the observant knows who is receiving the treatment, which cancels out selection bias, confirmation, and observation bias[20]. RCT, an abbreviation for Randomized controlled trials is selected due to them being the corner stone for intervention in clinical research and their offering of the highest level of evidence[21]. Animal studies were excluded; along with those without placebo group, observational studies, studies concluded in under 6 weeks, conference proceedings, mechanistic research and those conducted in other languages apart from English.

Strategy for Searching

Different bibliographic databases were used via electronic searches for peer reviewed articles, including PubMed (*https://pubmed.ncbi.nlm.nih.gov/*) and Scopus® (*https://www.elsevier.com/en-in/solutions /scopus*), CENTERAL (*https://www.cochranelibrary. com/collections/doi/SC000043/full*). Google scholar lists of references (backwards search) and lists of citations of the relevant articles were also used for additional searches. CENTRAL, the Cochrane Central Register of Controlled Trials) was selected due to its vast database, while it is also the most comprehensive source for reporting of RCTs. Scopus was picked due to its largest database of scientific journals. Simultaneously, PubMed contains upwards of 30 million databases from MEDLINE and life science journals. A period of 8 days from 25th November 2021 to 2nd December 2021.

Extraction of Data

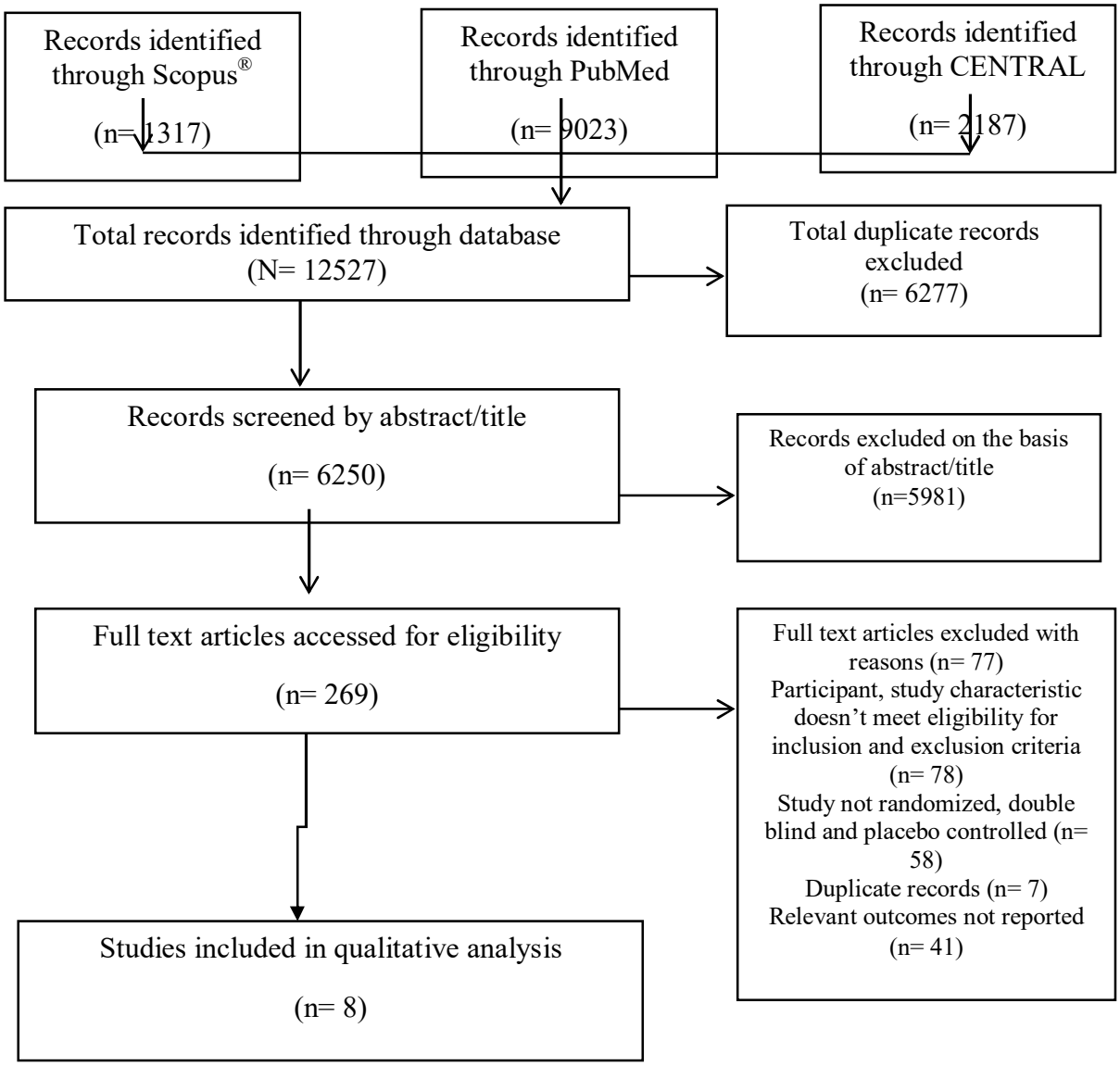
Studies were retrieved and individual screening of their title and abstract was done. Reviewal of full text articles was then carried out to check for their inclusion or exclusion from the study as per the inclusion

and exclusion criteria as stated above. Primary and secondary extraction of data was done from the selected studies. Primary data extraction focused on finding the studies investigating the effect of metformin on the outcome measure as ovulation. The secondary extraction was done to find the studies to be excluded and was single blind, devoid of the placebo group or did not fall into the definition of Randomized Controlled Trials. Data extraction selected the studies that were double blind, had placebo groups and were RCTs. These selected studies were then assessed for information such as study design, details of authors, outcomes, completer population, publication year and the effectiveness of the study. Results of interest were included in the outcomes of the study, such as menstrual cycle patterns or ovulation.

Study quality and the risks involving bias in assessment

Heyland Methodological Quality Score (MQS) and Jadad scale were the methods used for the evaluation of studies. MQS is used to quantify the methodological quality of studies based on nine criteria, namely analysis, randomization, patient selection, binding, treatment protocol, extent of follow up, baseline group compatibility, equal application of co-interventions and outcomes[22]. Scoring of the studies were done on a 14-point scale with studies being classified into the category of high quality when they scored over 8. Jadad scale was used to assess bias risk. A five-point scale, Jadad takes randomization, blinding and drop-outs into consideration. Studies that score less than 3 are moderately biased, higher than 3 are low bias and lesser than 3 are highly biased [23].

Fig 1: PRISMA flow chart of search category



RESULTS

Selection of Studies

Generation of 12,527 citations was done after the initial search (9023 from PubMed, 1317 from Scopus and 2187 from CENTRAL). 6277 were found to be duplicate, whereas 6250 abstracts remained after their removal. 5981 studies were then removed post removal of these duplicate studies. For full text reviews, 269 studies were selected, and 257 studies were then rejected based on selection eligibility criteria. The defined study selection eligibility criteria were met by 12 studies, which were included in the qualitative analysis. PRISMA search strategy-based study selection is illustrated in Figure 1.

Risk of bias

Quantification of the risk of bias is done within a study by quantification of randomization, double blinding and dropouts or withdrawals, method of randomization and method of blinding [23]. The risk of bias was high in the studies that scored below 3, moderate when the score is 3 and low when it is more than 3. The bias risk was low in 2 and moderate in 6 studies. The Jadad score are tabulated in table 1.

Study	Randomization	Double-blind	Withdrawal and drop-outs	Method of randomization	Method of blinding	Scores
Pasquali, 2000	1	1	0	1	0	3
Vanky, 2004	1	1	1	0	0	3
Hoeger, 2004	1	0	0	1	1	3
Tang, 2006	1	1	1	1	1	5
Hoeger, 2008	1	0	0	1	1	3
Karimzadeh, 2010	0	1	0	1	1	3
Ladson, 2011	1	1	1	1	1	5
Esfahanian, 2012	1	1	0	1	0	3

Table 1: Jadad Score of RCTs (n= 8)

In accordance with the MQS, the studies were each considered as high quality, if they scored over 8, except one [24]. All studies exhibited equal intervention to both control and treatment groups. The studies were randomized and double blind. The Cochrane risk of bias tool found all studies to have moderate to low bias risk. The MQS calculations are tabulated in table 2.

Study, Year	Randomization	Analysis	Blinding	Patient Selection	Treatment Protocol	Comparability of groups at baseline	Extent of follow-up	Equal application of co-interventions	Outcomes	Total
Pasquali, 2000	2	0	2	2	1	2	1	1	0	11
Vanky, 2004	2	1	2	2	2	2	2	2	2	17
Hoeger, 2004	2	2	2	2	1	2	0	1	1	13
Tang, 2006	2	2	2	2	2	2	2	1	2	17
Hoeger, 2008	2	2	1	1	1	2	0	1	1	11
Karimzadeh, 2010	0	0	0	1	1	0	0	2	1	5
Ladson, 2011	2	2	2	2	2	2	2	1	2	17
Esfahanian, 2012	2	2	1	0	0	2	1	1	0	9

Table 2: MQS of RCTs (n= 8)

Almost every study was for 6 months. Participants were obese, with BMI over 30kg/m^2 in each study. Mean BMI was >35kg/m^2 in 5 RCTs out of 8 [25,26,27,28,29].

Only two studies used dietary advice for lifestyle modification [27, 30] while combined diet and exercise were used by the remaining studies. Support and behavioral education were provided in two studies [25, 26] and access to a facility with fitness equipment in a study [28]. Every study was based on 1500 Kcal diet for each day and 1200-1400 Kcal [27], with diets being individualized by a dietician. The reduction of 500 Kcal was done in five RCTs out of the 8 selected [24, 25, 26, 28, 29].

The studies, without the exception of any, used immediate release metformin hydroxide. Dosage of metformin ranged from 1.5-2g/day. 850mg BD was used in 5 of 8 RCTs [25, 26, 27, 29, 30]. Dose

escalation was gradually applied in the five RCTs [24, 26, 28, 30, 31] for the reduction of gastrointestinal side effects of the drug. At 25% for lifestyle and metformin (71/279) or metformin alone treatment and at 29% (79/271) for lifestyle +placebo treatments, the dropout rates were calculated. The dropout rate reporting was not done for one study [24]. Exclusion was done of participants that had diabetes mellitus 2 but not glucose intolerance, before randomization for each study but one [26].

Risk of bias

No author had a conflict of interest. There was no significant difference in the baseline characteristics among intervention groups within each study for variables such as age, waist circumference, BMI, insulin, and glucose levels (fasting and post OGTT), androgen levels, lipid levels and fat distribution. The methods specified for measurement of these variables were reliable and standard.

Lifestyle ± placebo versus Lifestyle + Metformin

Markers of insulin resistance: it was assessed in three studies, where lifestyle + metformin was compared with lifestyle ± placebo [25, 27, 28]. No significant differences were observed in post OGTT insulin (Insulin AUC), insulinogenic, fasting insulin and insulin sensitivity index.

Anthropometric parameters:

Body Mass Index was measured in all said studies that compared combinations of lifestyle ± placebo with lifestyle + metformin. lifestyle + metformin was found to be linked with a lower BMI at the completion of study when compared with Lifestyle + placebo.

Glucose Intolerance:

IGT or IFG were assessed in three studies that compared lifestyle + metformin with lifestyle ± placebo [25, 26, 30].

Hoeger et al reported abnormal fasting for 2h post OGTT glucose levels in two subjects on metformin, none on lifestyle + metformin and three on lifestyle. When the study ended after 48 weeks, no subjects had IGT or IFG [25]. Another study by Hoeger et al., 2008 showed 25% of the subjects at baseline exhibiting IFG or IGT at baseline (six IGT and four IFG), with one subject having Diabetes Mellitus type 2, albeit non-noting of assignment groups was done. At the end of study, one subject on metformin showed onset IGT, while none showed such on lifestyle [26]. Gestational diabetes was reported in 8 (47%) women on lifestyle + metformin and nine (43%) pregnant women on lifestyle + Placebo by Vanky et al., 2004. Two women in lifestyle + placebo and none on lifestyle + metformin showed requirement of additional insulin for treatment [30].

Secondary Outcomes

Reproductive parameters-

There were no changes in the biochemical hyperandrogenism, ferryman-Gallwey score for hirsutism or acne at the end of the study with lifestyle + metformin, as compared to lifestyle ± placebo study. Vanky et al., 2004, noted no difference in the maternal androgen levels in women undergoing pregnancy with PCOS for lifestyle + placebo when compared to lifestyle + metformin [30].

Anthropometric parameters-

In one of the eight studies comparing lifestyle + metformin with lifestyle ± placebo [27], body composition assessed by CT, or Computed Tomography at L4-5 was provided. The total adipose tissue and visceral tissue showed no differences, WHR and waist differences at the end of study for lifestyle + metformin compared with lifestyle ± placebo.

Pregnancy rate wasn't an outcome primarily in the studies comparing lifestyle + metformin with lifestyle ± placebo. One study had it as a secondary outcome [24] with a pregnancy rate of 20% (15/75) on lifestyle + placebo and 14% (13/90) on lifestyle + metformin with no significant difference. In another study that had participants wanting pregnancy, the rates were 8.7% (6/69) on lifestyle + metformin and just 2.7% (2/74) on lifestyle + placebo with no notable difference [29]. In one study [27], two participants on lifestyle + metformin (16%) became pregnant and were excluded and two pregnancies occurred on lifestyle + placebo (18%) in a different study [25].

Metabolic parameters-

Merformin alone against lifestyle ± placebo

Three RCTs compared metformin alone against with lifestyle (± placebo) [25, 26, 31]. Six months later, key findings showed no difference in BMI, higher SHBG and lower waist circumference with lifestyle as compared to the group with metformin alone and a lower total testosterone in the group with metformin. There was no significant difference observed in insulin AUC, glucose AUC and fasting glucose between the different groups.

Discussion

For the first time in a systematic review in PCOS, it was reported that in nine studies with 837 participants being analysed, 6 months of lifestyle + metformin is associated with a lower BMI and

subcutaneous fat, with improved menstrual cyclicity as compared to lifestyle ± placebo. Studies including metformin alone, when compared with studies including lifestyle ± placebo, suggested similar effects on the BMI. Inconsistent measuring of other end points was done, and other reproductive, metabolic, or psychological outcomes did not show drastic differences across comparator groups. There was limited heterogeneity across the studies, but most studies had sample sizes limited to small and moderate to high RoB.

Significant concern regarding weight gain was reported in women with PCOS, while also exhibiting higher rates of weight gain and more proneness to obesity [32, 33, 34]. Evidence based guidelines recommend a modification of lifestyle as the first line treatment in PCOS [35], albeit compliance, engagement and sustainability remain posed as challenges. Therefore, the role of metformin in augmenting the weight management induced by lifestyle becomes highly relevant. Notable limitations have been found in the prior systematic reviews of metformin in PCOS. A trend for improved weight loss with lifestyle + metformin compared with metformin alone was reported in one review [36]. However, not all studies were in PCOS, or included lifestyle modification. Metformin alone was used in two other systematic reviews, compared with placebo or no intervention, showing no effect on BMI [37, 38]. The field here was advanced by the demonstration of addition of metformin as standard dose of 1.5-2g daily for lifestyle intervention, which resulted in0.73kg/m^2 lowering of the BMI in the six months of study, compared with lifestyle ± placebo in women having PCOS. It is also showed that metformin, when compared with lifestyle ± placebo, has similar effects on the BMI in women with PCOS.

The current results suggest metformin being the most effective in PCOS only when coupled with intervention of the lifestyle. It is consistent with the international guidelines on management of adults who have higher body weight than normal and carry co-morbidities, along with obese adults. The use of metformin in weight management is supported by data in regular populations with diabetes mellitus type 2 and in people who are prediabetic, which is a similarly affected population to those with PCOS. These groups saw lifestyle + metformin maintaining body weight and lifestyle without metformin showed significant weight gain [39]. The obese euglycemic populations showed weight management being improved upon the use of metformin [40].

CONCLUSION

in the first line therapy, a close interrelation of PCOS is seen to obesity and management of weight. Achieving and sustaining a healthy weight is a must for the management of PCOS and this requires the administration of lifestyle modification in the women that are affected. In outcomes where compliance and sustainability is limited with lifestyle modification, pharmacotherapy may be used for weight management as an adjunct for the modification of lifestyle.

This systematic review explored the addition of metformin to lifestyle against lifestyle ± placebo. It is thus reported that lifestyle + metformin apparently offers benefits pertaining to the weight loss and menstrual cyclicity. Similar effects of metformin alone were observed on BMI, as compared with lifestyle. Where pharmacotherapy is concerned with its role in weight management and comorbidities, it is suggested that metformin may have a key role in PCOS management, lifestyle and may also offerassistance in weight management and cycle regulation. However, considering the limitations brought about by the existing studies, a long term, large scale multicentre RCT that utilizes gold standard methodology containing women across BMI ranges and PCOS phenotypes, with focus on metformin along with first line therapy of lifestyle modification may be warranted to guide the use of metformin in PCOS definitively.

It is demonstrated by this systematic review that LSM programs are helpful in decreasing fasting glucose levels and insulin, while suggesting that these programs can be beneficial when administered in obese or overweight women diagnosed with PCOS. Changes with FBG were found linked to changes in BMI. For clinical benefits on PCOS to continue, it is imperative for clinicians prescribing the LSM interventions to consider the capacity of the patient to sustain exercise adherence and the diet prescribed for weight maintenance over a long period of time. There is a need of longer and larger trials at low bias risk for stronger conclusions about effects of LSM on outcomes that have a higher significance to women with PCOS and not just surrogates. Likely underestimation of the real effects of current evidence of these interventions is noted. This current systematic review, while suggesting a positive role of metformin in augmentation of lifestyle in weight management during PCOS, also acknowledges that most studies were short term and small. Therefore, a large-scale multicentre study is required in addition to lifestyle for verification of the currently observed benefits and for the clarification of the therapeutic role of metformin when added to lifestyle in PCOS, especially when used for weight management.

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