

Polycystic ovary syndrome: relation with diet and exercise - systematic review of randomized clinical trials

Síndrome dos ovários policísticos: relação com dieta e exercício - revisão sistemática de ensaios clínicos randomizados

Marina Amorim Santos¹ , Nathália Rocha Rios Mendes Machado¹ , Paulo Gabriel Barbosa de Carvalho¹ , Márcia Farias Moreira¹ , Francisco Paulo Cerqueira Mota¹ 

1. Centro Universitário UniFTC, Salvador, BA, Brazil

ABSTRACT

Introduction: Women with polycystic ovary syndrome tend to present overweight/obese and have worst results for reproduction. Knowing that the effects of weight loss have a positive factor in the prognosis of fertility, the summary of published articles about the changes of lifestyle modification has on ovulation/pregnancy is important for health professionals to reinforce the method as a first-line therapeutic strategy. **Aim:** This study aimed to describe the alterations of lifestyle modifications on ovulation/pregnancy in overweight/obese women with polycystic ovary syndrome. **Methods:** It is a systematic review of randomized clinical trials based on the Preferred Reporting Items guideline for Systematic Review and Meta-analyses (PRISMA), registered in PROSPERO under id: CRD42023421853. Publications between 2010-2021 in Portuguese or English researched in databases: Pubmed, Scielo, and Lilacs were included. The interest variables analyzed were: age, body mass index, lifestyle modification, comorbidities, and reproductive outcome (ovulation/pregnancy). **Results:** 15 studies were screened through the database, and four were manually accessed through the reference list of the selected articles. After analyzing the eligibility criteria, five studies were considered relevant and included in this review, all randomized clinical trials. **Conclusion:** The lifestyle modification treatment implementation of overweight/obese women with polycystic ovary syndrome improved ovulation rate and menstrual regularity.

Keywords: obesity; infertility; healthy lifestyle.

RESUMO

Introdução: Mulheres portadoras da Síndrome dos Ovários Policísticos apresentam maior tendência a sobrepeso/obesidade e piores resultados no desfecho reprodutivo. Sabendo que os efeitos da perda de peso possuem fator positivo no prognóstico da fertilidade, a síntese de estudos sobre a mudança no estilo de vida na ovulação é importante para que os profissionais de saúde a reforcem como estratégia terapêutica de primeira linha. **Objetivo:** O presente estudo teve como objetivo descrever as alterações que a mudança no estilo de vida tem na ovulação/gestação em mulheres com sobrepeso/obesidade portadoras de síndrome dos ovários policísticos. **Métodos:** Trata-se de uma revisão sistemática da literatura de ensaios clínicos randomizados baseada nos critérios do *Preferred Reporting Items guideline for Systematic Review and Meta-analyses* (PRISMA), com registro no PROSPERO sob id: CRD42023421853. Foram incluídas publicações entre 2010-2021, em português e inglês, presentes nas bases de dados: Pubmed, Scielo e Lilacs. As variáveis de interesse analisadas foram: idade, índice de massa corporal, mudança de estilo de vida, comorbidades e desfecho reprodutivo (ovulação/gestação). **Resultados:** Foram triados 15 estudos pela base de dados e 4 foram acessados manualmente através da lista de referências dos artigos selecionados. Após análise dos critérios de elegibilidade, 5 ensaios clínicos randomizados foram considerados relevantes e incluídos nesta revisão. **Conclusão:** A implementação da mudança do estilo de vida no tratamento de mulheres com sobrepeso/obesidade portadoras de síndrome dos ovários policísticos demonstrou resultados satisfatórios no desfecho ovulação, com melhora das taxas e regularidade menstrual.

Palavras-chave: obesidade; infertilidade; estilo de vida saudável.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects about 10% of women of reproductive age worldwide [1]. Patients with this condition have a heterogeneous disorder [2] characterized by dysfunction in the neuro-endocrine-reproductive axis, which leads to ovarian morphological alteration and high androgen production [3], which predisposes to the development of metabolic and non-metabolic systemic disorders that go far beyond infertility.

Women with PCOS who manage to become pregnant, for example, have a high rate of early miscarriage (30 to 50%) compared to the average rate in the general population, which is 15% [4]. In addition, they are at increased risk of pregnancy complications, including gestational diabetes and hypertensive disorders, which ultimately result in preterm labor and perinatal mortality [5,6].

Among the causes of infertility and gestational complications related to PCOS, it is known that pre-gestational overweight and obesity are relevant as aggravating negative factors, with a higher body mass index (BMI) being associated with a worse fertility prognosis, regardless of the mode of conception [5-7]. On the other hand, it has been shown that weight loss improves reproduction and metabolism rates [8-10]. Thus, lifestyle modification (LSM), i.e., a healthy diet and physical activity, has been recommended as a first-line strategy before any intervention for women with PCOS and reproductive desire [11-13].

Although several studies address different therapeutic options for patients with PCOS, a comparison between the already available studies that discuss the implementation of LSM as a therapeutic strategy is important for the synthesis of the most current information on its impact on ovulation/gestation. This facilitates the access of health professionals to this topic, who, in addition to detecting, preventing, and treating risk factors at an early stage in overweight/obese patients with PCOS, will be more able to instruct them about the practice of exercises daily physical exercises and food re-education.

Therefore, this study aimed to describe the changes that lifestyle modifications have on ovulation/gestation in overweight/obese patients with polycystic ovary syndrome.

Methods

This study is a systematic review of the literature based on the criteria of the Preferred Reporting Items guideline for Systematic Review and Meta-analyses (PRISMA) [14] and registered in PROSPERO under id: CRD42023421853. To this end, original articles were selected, including randomized clinical trials published between 2010 and 2021, in Portuguese and English, found registered in the following databases: Pubmed, Scielo, and Lilacs, which gathered the available evidence on the alterations that lifestyle modification has on ovulation/pregnancy in overweight/obese patients with polycystic ovary syndrome.

Studies whose intervention method was only drugs that induce ovulation, as well as studies focused exclusively on obesity and infertility, were excluded. Conference abstracts and unpublished manuscripts were considered ineligible.

Sample eligibility criteria

Women of reproductive age, aged between 18 and 40 years, with a BMI ≥ 25 kg/m², infertile due to PCOS, submitted to programs composed of exercises and/or diet, were included in the sample, and no specific definition of exercise or diet was used in the search strategy to include as many studies as possible.

Study search and selection strategy

The search strategy included the descriptors and the respective terms translated into Portuguese found in DeCS/MeSH: Polycystic Ovary Syndrome, Obesity, Ovulation, Pregnancy, Exercise and Diet, and Healthy, which were used together through Boolean operators (AND) to identify the appropriate articles.

Other articles that met the eligibility criteria were manually searched through the reference list of eligible studies.

Data summary

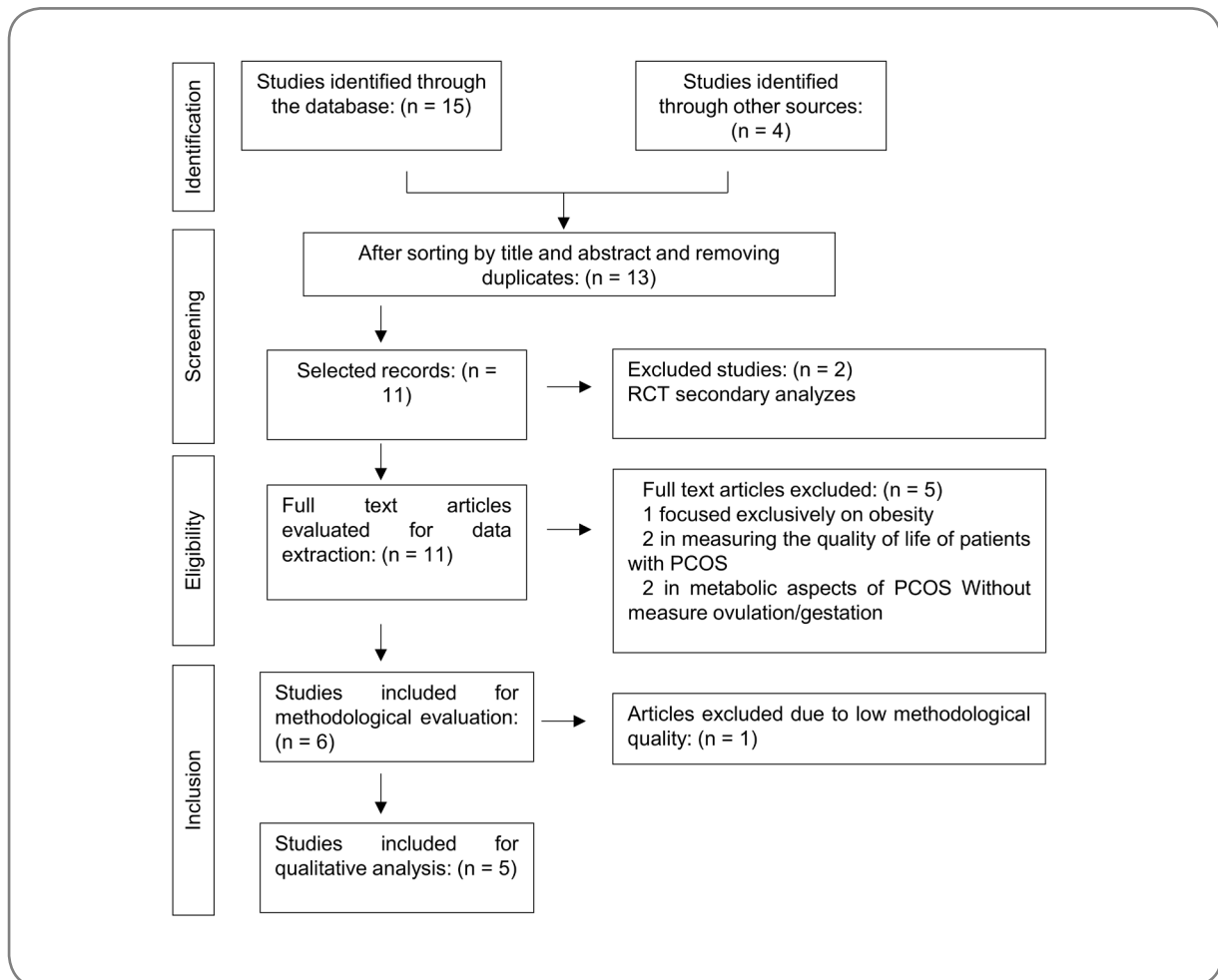
The studies were sorted by title by the authors and were analyzed by abstract to see if they met the inclusion criteria. Duplicate articles were removed manually. Those that did not meet the criteria were excluded, and the approved ones were analyzed in full for data extraction that sought information about the sample, intervention protocol (diet and/or physical exercise), and measurement of ovulation and pregnancy, including pregnancy complications. All authors participated in the stage, and disagreements about the selection and/or extraction of data were discussed among them.

Quality of evidence and risk of bias

The risk of bias in each study was ascertained using the Downs and Black Risk of Bias tool [15]. It was evaluated by all the authors. And, in case of disagreement, the finding of the majority prevailed. This tool is an accurate checklist that provides an overall score for study quality and is appropriate for evaluating randomized and non-randomized studies

Results

Nineteen studies were identified according to the proposed methodological strategy. After applying the eligibility criteria, five articles were included in this review, all randomized clinical trials. Figure 1 shows the selection of articles.



RCT = randomized controlled trial; PCOS = Polycystic Ovary Syndrome

Figure 1 - Flowchart of article selection

The samples of the selected studies ranged from 49 to 577 participants, totaling 928 individuals. The target population studied was overweight/obese infertile women with PCOS, BMI ≥ 25 kg/m², aged 18-40 years. Regarding the intervention, although all the articles used the LSM through physical activity and/or diet, the dietary and exercise strategy used differed between the studies, each one presenting particularities. This information is more detailed in Table 1.

Para avaliar a qualidade das evidências e risco de viés dos estudos incluídos na síntese qualitativa foi utilizada a escala de Downs and Black [15] (quadro 1). To assess the evidence quality and risk of bias in the studies included in the qualitative synthesis, the Downs and Black scale [15] was used (chart 1).

Table I - Qualitative synthesis of selected articles

Author, Year	Objective	Sample	Intervention protocol	Analyzed outcome	Results
Palomba et al. [16], 2010	To test the hypothesis that a 6-week intervention (structured exercise training and hypocaloric diet) increases the likelihood of ovulation after CC in overweight/obese patients with CC-resistant PCOS.	Total = 96. Women with PCOS; age: 18-35 years old; BMI = 25-34 kg/m ² .	Group 1 (n = 32): SET (3 workouts/week on an ergometric bicycle for 30 min); intensity: 60-70% VO _{2max} ; duration: 1.5 months + hypocaloric diet with 35% high protein composition and a deficit of 1000 kcal per day). Group 2 (n = 32): observation + CC (a fixed dose of 150 mg/day for 5 days). Group 3 (n = 32): SET + Diet + CC. Follow-up time: 6 weeks.	Ovulation rate monitored by serial US TV successively every 4 days and then serially daily until ovulation of the dominant follicle with mean diameter ≥ 12 mm. Ovulation was identified by the decrease in follicular dimensions and in the fluid in the cul-de-sac and confirmed by the plasma P assay (0.10 ng/ml) evaluated by US 7 days before the expected menstruation.	There was presence of menstrual bleeding at the end of the study in patients from Group 1 (12.5%), Group 2 (9.4%) and Group 3 (34.4%) and a significant increase (p = 0.008) in the rates of ovulation was observed of participants in Group 3 (p = 0.035) compared to those in Groups 1 and 2 (p = 0.020). There was also 1 pregnancy of a participant in Group C.
Nybacka et al. [17], 2011	To compare the influence of dietary management and/or physical exercise on ovarian function and metabolic variables in women with PCOS.	Total: 57. Women with PCOS; age: 18-40 years old; BMI > 27 kg/m ² .	Group 1 (n = 19): diet (total caloric intake reduced by 600 kcal/day compared to before intervention). Group 2 (n = 19): physical, aerobic and/or bodybuilding exercise, individually adjusted and supervised by a physiotherapist. Group 3 (n = 19): dietary change + physical activity. Follow-up time = 4 months.	Ovulation rate (maximum number of follicles in a plane and volume of the largest follicle and ovary) and menstrual pattern (menstrual bleeding). Both confirmed by the elevation of the serum level of progesterone in the luteal phase.	The three intervention groups improved the menstrual pattern (p < 0.05). Of the 43 participants, 69% exhibited a more regular menstrual pattern coming out of oligo/amenorrhea, and in 35% of these, ovulation was detected, with no significant difference between groups.
Legro et al. [18], 2015	To determine the relative effectiveness of pre-conception intervention on reproductive and metabolic abnormalities in overweight/obese women with PCOS.	Total = 149. Women with infertility due to PCOS; age: 18-40 years old; BMI: 27 to 42 kg/m ² .	Group 1 (n = 49): use of continuous OCC (Ethinylestradiol 200mcg/1g of Norethisterone Acetate). Group 2 (n = 50): SEM (calorie restriction + weight loss medication such as orlistat or sibutramine + increased physical activity to promote 7% weight loss). Group 3 (n = 50): combined treatment (continuous OCC + SEM). Follow-up time = 16 weeks.	Ovulation rate (monitoring of serum progesterone and ultrasound levels) and viable pregnancy rate (monitoring of serum hCG levels + US to document fetal viability). In addition, medical records of the pregnancy were reviewed to verify birth outcomes.	The ovulation rate was significantly higher (p < 0.05) in the group whose intervention was combined (67.1%) when compared to the group whose intervention was only OCC (46.1%).

Table I - Continuation

Author, Year	Objective	Sample	Intervention protocol	Analyzed outcome	Results
Mutsaerts et al. [19], 2016	To analyze the rate of vaginal delivery of a healthy full-term fetus at 24 months after the intervention.	Total = 577. Infertile women with PCOS; age: 18-39 years old; BMI: ≥ 29 kg/m ² .	Group 1 (n = 290): unsupervised exercise, 10,000 steps/day 2-3 times/week (30 min) + diet (calorie intake reduced by 600 kcal/day, with a minimum caloric intake of 1200 kcal/day) + motivational counseling), followed by standard infertility Tx. Group 2 (n = 287): standard infertility treatment (CC 50 mg/day for 5 days and gonadotropin therapy if ovulation was not induced + IVF). Follow-up time = 24 months.	Rate of vaginal deliveries of healthy fetuses 37 weeks or older.	There were no significant differences in the live birth rates of the 43.9% intervention group versus the 53.9% control group (intervention group rate ratio, 0.82; [CI] = 0.69-0.97). There was also no significant difference in the rates of pregnancy-related complications in the analyzed groups.

CC = Clomiphene Citrate; PCOS = Polycystic Ovary Syndrome; BMI = Body Mass Index; SET = Structured Exercise Training; VO_{2max} = Maximal Oxygen Ventilation; US = Ultrasonography; TV= Transvaginal; OCC = Oral Contraceptive; LSM = Lifestyle Modification; hCG = Human Chorionic Gonadotropin; Tx = treatment; IVF = In Vitro fertilization

Chart 1 – Quality of evidence according to the Downs and Black scale [15]

Author, Year	Communication	External validity	Internal validity: Bias	Confounding variable	Power	Total
	(11 points)	(3 points)	(7 points)	(6 points)	(1 point)	(28 points)
Palomba et al. [16], 2010	7	0	6	2	1	16
Nybacka et al. [17], 2011	8	0	5	3	1	17
Legro et al. [18], 2015	7	0	4	3	1	15
Mutsaerts et al. [19], 2016	8	1	5	4	1	19
Sim et al. [20], 2014	7	1	6	4	1	19
Karimzadeh et al. [21], 2012	7	0	3	2	1	13

Discussion

This review showed that the lifestyle modifications implemented in the treatment of women with PCOS significantly improved the evaluated ovulatory patterns, especially when associated with drug treatment. Soon, it was found that the ovulation rate and the regularity of menstrual cycles were higher when the intervention had LSM involved.

It appears that ovulation is influenced by obesity due to a hormonal imbalance, the main one being insulin resistance [22]. Previous studies have already proven the relationship between insulin signaling and steroidogenesis through therapeutic interventions with insulin sensitizers, which, when implemented, reduced total and free androgen concentrations and increased SHBG (sex hormone-binding globulin) [8].

Interestingly, these same changes were observed with weight loss [23] and physical activity practice, as this is effective in restoring ovulation, regardless of the decrease in BMI [24]. This happens because exercise alone can modulate inflammatory proteins with a negative effect on the insulin signal even when it does not cause weight change [25].

Thus, submitting patients with PCOS, who tend to accumulate visceral adipose tissue for reasons that are still unclear, to a routine of physical exercises and a healthy diet allows the restoration of the hormonal pattern and, consequently, the improvement of the reproductive outcome. In this regard, the studies' results reviewed here are consistent with the literature published.

As for the percentage of clinical pregnancy detected, the studies evaluated did not report relevant differences concerning the conception rate between the observed groups, except for Sim et al. [20], who demonstrated a higher pregnancy rate in the group submitted to lifestyle changes. Furthermore, in terms of gestational complications, considerable differences between the analyzed groups were also not observed in most studies, showing that, at least in these cases, LSM has little or no significant impact.

According to the existing literature, unfavorable gestational outcomes are distinguished according to the characteristics of PCOS [26] and occur independently of obesity [27]. Thus, during pregnancy, there is an increase in adverse outcomes in women with PCOS compared to women without this syndrome, with the most cited being gestational diabetes mellitus, preeclampsia, premature birth, and poor perinatal outcomes [26,27]. Similar results, however, were not found in the present study.

Regarding the limitations of this review, it is worth mentioning the non-standardization of the interventions carried out since, in an attempt to include a higher number of studies, no specific definition of LSM was used. Furthermore, the selected studies were performed with a relatively small sample of patients. It is also important to highlight that in this present study, as well as in the scientific evidence available on this subject, the mechanisms by which physical activity and diet influence the

reproductive outcome in PCOS were not fully clarified. As a result, it is necessary to continue research on this subject.

The highlight of this review is due to the most recent information regarding lifestyle changes and PCOS that were condensed in this study and the scarcity of articles focused on this topic, in addition to the selectivity of the bibliographic research carried out, including only randomized clinical trials to increase the level of scientific evidence.

Conclusion

The implementation of lifestyle modifications in the treatment of overweight/obese women with PCOS has shown satisfactory results in the ovulation outcome, with improved rates and menstrual regularity.

Academic affiliation

This article represents the course completion work of Marina Amorim Santos, Nathália Rocha Rios Mendes Machado, Paulo Gabriel Barbosa de Carvalho and Márcia Farias Moreira, supervised by Professor Francisco Paulo Cerqueira Mota at UniFTC University center, Medical School, Salvador/BA.

Potential conflict of interest

No conflicts of interest potentially relevant to this article were reported.

Financing source

There was no external funding source for this study.

Authors' contribution

Conception and design of the research: Santos MA, Machado NRR, Carvalho PGB, Moreira MF; **Data analysis and interpretation:** Santos MA, Machado NRR, Carvalho PGB e Moreira MF; **Writing of the manuscript:** Santos MA, Machado NRR, Carvalho PGB e Moreira MF; **Critical review of the manuscript for important intellectual content:** Santos MA, Machado NRR, Carvalho PGB e Moreira MF

References

1. Cooney LG, Dokras A. Beyond fertility: polycystic ovary syndrome and long-term health. *Fertil Steril*. 2018;110(5):794-809. doi: 10.1016/j.fertnstert.2018.08.021
2. Andrade VHL, Mata AMOF, Borges RS, Silva DRC, Martins LM, Ferreira PMP, et al. Current aspects of polycystic ovary syndrome: A literature review. *Rev Assoc Med Bras*. 2016;62(9):867-871. doi: 10.1590/1806-9282.62.09.867
3. Fernandes CE, Sá MFS. *Tratado de Ginecologia FEBRASGO*. 1 ed. São Paulo: Elsevier; 2018.
4. Hoffman BL, Schorge JO, Bradshaw KD, Halvorson LM, Schaffer JI. *Ginecologia de Willians*. 2ª ed. Porto Alegre: Artmed; 2014.
5. Joham AE, Palomba S, Hart R. Polycystic ovary syndrome, obesity, and pregnancy. *Semin Reprod Med*. 2016;34(2):93-101. doi: 10.1055/s-0035-1571195
6. Carneiro JS, Rosa e Silva AC. Complicações gestacionais e perinatais em mulheres com síndrome dos ovários policísticos. *Femina*. [Internet]. 2021 [citado 2022 mar 12];49(9):530-6. Disponível em: <https://www.febrasgo.org.br/media/k2/attachments/FeminaZ2021Z49Z09ZWEBZ1.pdf>
7. *Manual de ginecologia endócrina*. São Paulo: FEBRASGO; 2015 [internet]. Citado 2022 maio 12]. Disponível em: https://mediacdns3.ulife.com.br/PAT/Upload/2005426/disparadorManual_Ginecologia_Endocrina_20200827140253.pdf

8. Cena H, Chiovato L, Nappi RE. Obesity, polycystic ovary syndrome, and infertility: a new avenue for GLP-1 receptor agonists. *J Clin Endocrinol Metab.* 2020;1;105(8):e2695-709. doi: 10.1210/clinem/dgaa285
9. Azevedo JD, Costa EC, Micussi MTABC, Sá JCF. Modificações do estilo de vida na síndrome dos ovários policísticos: papel do exercício físico e importância da abordagem multidisciplinar. *Rev Bras Ginecol Obstet.* 2008;30(5):261-67. doi: 10.1590/S0100-72032008000500009
10. Doherty DA, Newnham JP, Bower C, Hart R. Implications of polycystic ovary syndrome for pregnancy and for the health of offspring. *Obstet Gynecol* 2015;125(6):1397-406. doi: 10.1097/AOG.0000000000000852
11. Campos AE, Leão MEB, Souza MA. O impacto da mudança do estilo de vida em mulheres com síndrome dos ovários policísticos. *REAS* 2022;13(2):e4354. doi: 10.25248/reas.e4354.2021
12. Colégio Brasileiro de Medicina do Estilo de Vida [Internet]. Medicina do estilo de Vida [citado 2022 maio 14]. Disponível em: <https://cbmev.org.br/medicina-do-estilo-de-vida/>
13. Guia de Atividade Física para a População Brasileira [Internet]. Ministério da Saúde [citado 2022 maio 14]. Disponível em: https://bvsms.saude.gov.br/bvs/publicacoes/guia_atividade_fisica_populacao_brasileira.pdf
14. Galvão TF, Pansani TSA, Harrad D. Principais itens para relatar revisões sistemáticas e meta-análises: A recomendação PRISMA. *Epidemiol Serv Saúde* 2015;24(2):335-42. doi: 10.5123/S1679-49742015000200017
15. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-84. doi: 10.1136/jech.52.6.377
16. Palomba S, Falbo A, Giallauria F, Russo T, Rocca M, Tolino A, Zullo F, Orio F. Six weeks of structured exercise training and hypocaloric diet increases the probability of ovulation after clomiphene citrate in overweight and obese patients with polycystic ovary syndrome: a randomized controlled trial. *Hum Reprod.* 2010;25(11):2783-91. doi: 10.1093/humrep/deq254
17. Nybacka Å, Carlström K, Ståhle A, Nyrén S, Hellström PM, Hirschberg AL. Randomized comparison of the influence of dietary management and/or physical exercise on ovarian function and metabolic parameters in overweight women with polycystic ovary syndrome. *Fertil Steril.* 2011;96(6):1508-13. doi: 10.1016/j.fertnstert.2011.09.006
18. Legro RS, Dodson WC, Kunselman AR, Stetter CM, Kris-Etherton PM, Williams NI, et al. Benefit of delayed fertility therapy with preconception weight loss over immediate therapy in obese women with PCOS. *J Clin Endocrinol Metab.* 2016;101(7):2658-66. doi: 10.1210/jc.2016-1659
19. Mutsaerts MA, van Oers AM, Groen H, Burggraaff JM, Kuchenbecker WK, Perquin DA, et al. Randomized trial of a lifestyle program in obese infertile women. *N Engl J Med.* 2016;374(20):1942-53. doi: 10.1056/NEJMoa1505297
20. Sim KA, Dezarnaulds GM, Denyer GS, Skilton MR, Caterson ID. Weight loss improves reproductive outcomes in obese women undergoing fertility treatment: a randomized controlled trial. *Clin Obes.* 2014;4(2):61-8. doi: 10.1111/cob.12048
21. Karimzadeh MA, Javedani M. An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate-metformin in patients with polycystic ovary syndrome. *Fertil Steril.* 2010;94(1):216-20. doi: 10.1016/j.fertnstert.2009.02.078
22. Hakimi O, Cameron LC. Effect of exercise on ovulation: a systematic review. *Sports Med.* 2017;47(8):1555-67. doi: 10.1007/s40279-016-0669-8
23. Kuchenbecker WKH, Groen H, van Asselt SJ, Bolster JHT, Zwerver J, Slart RHJ, et al. In women with polycystic ovary syndrome and obesity, loss of intra-abdominal fat is associated with resumption of ovulation. *Hum Reprod.* 2011;26:2505-12. doi: 10.1093/humrep/der229
24. Harrison CL, Lombard CB, Moran LJ, Teede HJ. Exercise therapy in polycystic ovary syndrome: a systematic review. *Hum Reprod Update.* 2011;17(2):171-83. doi: 10.1093/humupd/dmq045
25. Pauli JR, Cintra DE, Souza CT, Ropelle ER. Novos mecanismos pelos quais o exercício físico melhora a resistência à insulina no músculo esquelético. *Arq Bras Endocrinol Metabol.* 2009;53(4):399-408. doi: 10.1590/S0004-27302009000400003
26. McDonnell R, Hart RJ. Pregnancy-related outcomes for women with polycystic ovary syndrome. *Womens Health (Lond).* 2017;13(3):89-97. doi: 10.1177/1745505717731971
27. Rees DA, Jenkins-Jones S, Morgan CL. Contemporary reproductive outcomes for patients with polycystic ovary syndrome: a retrospective observational study. *J Clin Endocrinol Metab.* 2016;101(4):1664-72. doi: 10.1210/jc.2015-2682

