Vol 8 No 2 June 2023

BULETIN FARMATERA

E-ISSN: 2528-410X

SYSTEMATIC REVIEW

Metformin Improves Fertility in Women with Polycystic Ovary Syndrome (PCOS): A Systematic Review

Aidil Akbar

Department of Obstetrics and Gynecology, Fakultas Kedokteran, Universitas Muhammadiyah Sumatera Utara
Gedung Kampus 1 UMSU, Jl Gedung Arca No. 53 Medan 20217, Sumatera Utara

Corresponding email: aidilabr@gmail.com

Abstract: Polycystic ovary syndrome (PCOS) Causes 6-15% of female infertility, of which 80% is characterized by the occurrence of hyperinsulinemia resulting in impaired endometrial function. Metformin therapy in improving insulin sensitivity has been widely reported, but investigations are needed to determine the characteristics of metformin therapy research in PCOS cases with a literature review study approach. In the collection of systematic studies, Publish and Perish, Mendeley and Microsoft Excel applications, using the keyword metformin improves fertility in women with PCOS. From 500 articles collected, 16 articles were included in the inclusion criteria, and it was found that many studies had been conducted in several countries (Iran, India, USA, Italy, Egypt, Pakistan and Saudi Arabia involving 2295 subjects, with a dose range of 500 mg to 2000 mg, with a duration of administration of 14 days to 9 months. In this study, it was concluded that metformin intervention studies both singly and in combination clinically have been conducted in several countries where most studies show that metformin can improve clinical and laboratory improvements in PCOS patients, which can improve the fertility rate of women with PCOS.

Keywords: Female infertility, metformin, PCOS

INTRODUCTION

Polycystic ovary syndrome (PCOS) is responsible for 6-15% of infertility in women of reproductive age.[1] PCOS is an endocrine disorder, where 80% is characterized by hyperinsulinemia due to insulin resistance and central obesity in sufferers, but 40-40% can also occur in thin womenPCOS is an endocrine disorder, where 80% is characterized by hyperinsulinemia due to insulin resistance and central obesity in sufferers, but 40-40% can also occur in thin women.[2] Other manifestations include hyperandrogenemia, oligo-ovulation, cardiovascular disease disorders, and type 2 diabetes and can also be associated with the occurrence of ovarian cancer.[1,2,3]

The pathogenesis of PCOS is not yet fully understood, but the theory is that many believe that insulin resistance plays the most important role in the occurrence of various disorders in PCOS.[4] Insulin resistance affects the local secretion of insulin-like growth factor and insulin-like growth factor binding proteins in the endometrium, leading to hyperplasia and functional disorders of the endometrium.[5] Pathogenesis is associated with studies that identify various protein expressions that occur due to

E-ISSN: 2528-410X

insulin resistance that cause the growth of subcutaneous and visceral adipose tissue such as serum zinc-α2-glycoprotein (ZAG) and chemerin secreted by adipose tissue activity in insulin resistance.[6,7]

In many studies, it is reported that pharmacological treatment using insulin sensitizers can provide clinical improvements in women with PCOS.[8–10] One insulin sensitizer that is widely reported to be used is metformin.[11,12] Metformin works to increase the sensitivity of insulin receptors in muscle tissue and adipocytes.[3] Metformin, too, can not only decrease elevated parameters such as insulin, androgens, and circulating levels of free T cells, but it can also increase levels of sex *hormone-binding globulin* (SHBG) and *insulin-like growth factor-binding protein* (IGFBP).[13] Metformin can suppress liver glucose production, and increase the frequency of menstruation, ovulation, fertilization and live birth rates. This is the basis for the use of metformin in women with PCOS .[13]

Of the many studies that have been conducted, there are still few studies that investigate the benefits of metformin therapy in women with PCOS, whether this research has become an international issue, what studies have been conducted, the number of human subjects involved in the study, the dose used, how long the intervention was given and how the outcome was produced.

This systematic review study aims to investigate the benefits of metformin therapy in overcoming infertility in women with PCOS

METHODS

This *systematic review* study took 500 articles sourced from Google Scholar with the help of the Publish or Perish application with a publication period from 2019 to 2023, using the keyword "metformin improves fertility in women with PCOS". Furthermore, the results obtained, are complemented by the bibliography with the help of the Mendeley application. After the bibliographic data is complete, the article is exported to Microsoft Excel and systematically selected according to the inclusion criteria set by the researcher, which has been cited at least 10 times, the article must come from a Scopus-indexed journal with quartiles 1 and 2, the article is original reset with human subjects, and discusses metformin in women with PCOS.

RESULTS

Of the 500 articles that were successfully withdrawn, after completing the bibliographic data, a systematic review was carried out to determine the articles that fit into the inclusion criteria, this stage can be seen in the prism flow chart in Figure 1

Studies on metformin therapy in PCOS cases have been conducted in many countries such as Iran, Iran, Ecuador, China, Taiwan, Norway, Saudi Arabia, USA, Italy, and Pakistan, using RCT, RDBCT, RSBCT, Cohort, Cross Sectional Studies and Case Control studies. The number of subjects involved in this study was 2295 people with a dose range of Metformin used between 500 mg to 2000 mg per day which of course divided into one to three administrations. The range of administration ranges from 14 days to 9 months as can be seen in Table 1

E-ISSN: 2528-410X

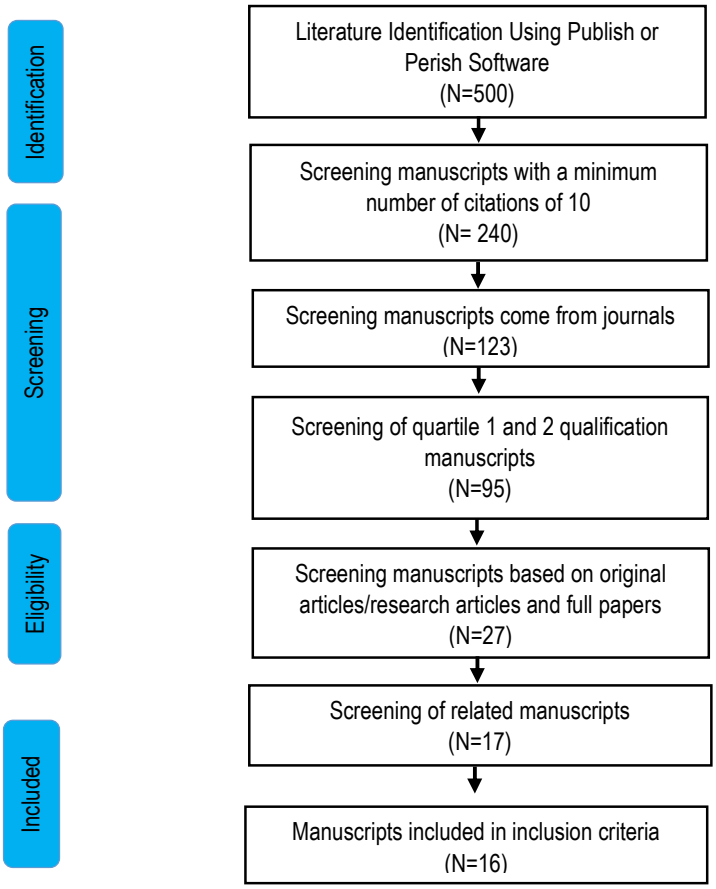

Figure 1. Prisma Flow Chart

E-ISSN: 2528-410X

Tabel 1. Articles included in the inclusion criteria on the study of the benefits of metformin therapy in women with PCOS

No	Cites	Authors	Year	Origin	Studi	N	Daily Dose	Duration	Combination	Source	Quartile	Publisher	ArticleURL
1	49	Agrawal A, et all [2]	2019	India	RCT	112	1500mg	3 months	Myo-Inositol	Gynecological Endocrinology	2	Taylor &Francis	https://www.tandfonline.com/doi/abs/10.1080/09513590.2018.1549656
2	46	Shokrpour M, et all[1]	2019	Iran	RCT	53	1500mg	12 weeks	Myo-inositol	Gynecological Endocrinology	2	Taylor &Francis	https://www.tandfonline.com/doi/abs/10.1080/09513590.2018.1540570
3	32	Abdalmageed OS, et all [14]	2019	Egypt	RDBCT	102	1000mg	12 weeks		Reproductive Sciences	2	Springer	https://link.springer.com/article/10.1177/1933719118765985
4	31	Ali DES, et all [15]	2019	Pakistan, Italy	RCT	106	1000mg	12 weeks	Pioglitazone	Hormone and Metabolic Research	2	thieme-connect.com	https://www.thieme-connect.com/products/ejournals/html/10.1055/a-1018-9606
5	30	Acosta-Torres S, et all[16]	2020	USA	Cohort	92	500-1000mg	4-5 months	Progestin	Gynecologic Oncology	1	Elsevier	https://www.sciencedirect.com/science/article/pii/S0090825820301037
6	27	Erensoy E, et all.[17]	2019	USA	Cohort	19	1500mg	90 days		Gynecological Endocrinology	2	Taylor &Francis	https://www.tandfonline.com/doi/abs/10.1080/09513590.2018.1498476
7	25	Al-Hussain F, et all.[18]	2020	Saudi Arabia	Cohort	86	1700mg	3 months		Patient Preference and Adherence	1	Taylor &Francis	https://www.tandfonline.com/doi/pdf/10.2147/PPA.S244273?needAccess=true&role=button
8	22	El Sharkwy I, et all.[4]	2019	Egypt	RDBCT	274	850mg	3 months	L-carnitine and clomiphene citrate	Gynecological Endocrinology	2	Taylor &Francis	https://www.tandfonline.com/doi/abs/10.1080/09513590.2019.1576622
9	22	Zhai J, et all [5]	2019	China	RCT	120	1500mg	14 Days		Reproductive Sciences	2	Springer	https://link.springer.com/article/10.1177/1933719118820466

E-ISSN: 2528-410X

No	Cites	Authors	Year	Origin	Studi	N	Daily Dose	Duration	Combination	Source	Quartile	Publisher	ArticleURL
10	21	Foda AA, et all.[6]	2019	Egypt	CS and CC	170	500-1500mg	3 months		Diabetes and Metabolic Syndrome: Clinical Research and Reviews	1	Elsevier	https://www.sciencedirect.com/science/article/pii/S1871402119300153
11	18	Sahu A, et all.[19]	2019	India	RCT	101	1000mg	6 months	Oral contraceptive pill (OCP) Ethinylestradiol plus 2 mg +cyproterone acetate	Journal of Gynecology Obstetrics and Human Reproduction	2	Elsevier	https://www.sciencedirect.com/science/article/pii/S2468784718303428
12	18	Zheng S, et all.[7]	2019	China	RCT	182	1000mg	12 weeks		Endocrine Journal	2	jstage.jst.go.jp	https://www.jstage.jst.go.jp/article/endocrj/66/6/66_EJ18-0153/_pdf
13	16	Pourghasem S, et all.[20]	2019	Iran	RSBCT	150	1500mg	3 months	Myo-inositol	Archives of Gynecology and Obstetrics	2	Springer	https://link.springer.com/article/10.1007/s00404-019-05064-5
14	16	Chang HH, et all. [13]	2019	Taiwan	Cohort	200	1500mg	6 months		International Journal of Molecular Sciences	1	mdpi.com	https://www.mdpi.com/1422-0067/20/7/1720/pdf
15	13	AndrÃ¦ F, et all. [21]	2020	Norway	RCT	381	2000mg	9 months		Journal of Clinical Endocrinology and Metabolism	1	academic.oup.com	https://academic.oup.com/jcem/article/105/12/3762/5899825

E-ISSN: 2528-410X

No	Cites	Authors	Year	Origin	Studi	N	Daily Dose	Duration	Combination	Source	Quartile	Publisher	ArticleURL
16	12	Tauqir S, et all [3]	2021	Pakitan	RDBCT	147	1000mg	12 weeks	Acetyl-L-Carnitine (ALC), Pioglitazone	Advances in Therapy	1	Springer	https://link.springer.com/article/10.1007/s12325-021-01789-5

BULETIN FARMATERA
E-ISSN: 2528-410X

DISCUSSION

Year of Research

The studies included in the inclusion criteria were conducted between 2019 and 2021 with details of 12 studies in 2019, 3 studies in 2020, and 1 in 2021.

Country of Origin

This study was also conducted in several countries namely India (2 studies), Iran (2 studies), Egypt (3 studies), China (2 studies), USA (2 studies), Pakistan (1 study), Saudi Arabia (1 study), Taiwan (1 study), Norway (1 study), Italy (1 study).

Types of Studies

The types of studies conducted were randomized controlled trials (RCT) 7 studies, randomized double-blind clinical trials (RDBCT) 4 studies, Cohort 4 studies, cross-sectional studies (CSS) 1 study, and a case-control study (CC) 1 study.

Amount of Sample

All studies included in the inclusion criteria looked at 2,295 research subjects, with the average number of subjects in each study being 270

Daily Dose

The daily dose of metformin used ranged from 500 mg to 2,000 mg, with the average daily dose being 1,222 mg

Duration of Administration

The duration of metformin therapy given in PCOS cases ranges from 2 weeks to 36 weeks, where the average duration of drug administration is 15 weeks.

Therapeutic Results

There was an improvement in the menstrual cycle, in this case, the length of the menstrual cycle and the day of menstrual bleeding, there was also an improvement in biochemical and hormonal parameters after 12 weeks of metformin administration, as well as an improvement in the number of births of babies born in the treatment group.[2]

Metformin therapy also showed quantitative improvements in insulin sensitivity, improved fasting blood glucose levels, serum insulin levels, serum triglycerides and homeostasis model of assessment-insulin resistance.[1,3]

In a study of overweight and obese women with PCOS who underwent in vitro fertilization (IVF) procedures and received metformin therapy, there was a decrease in the average number of retrieved oocytes.[14]

Giving metformin combined with other agents has also been shown to reduce inflammatory factors that occur in PCOS with a decrease in IL-6 and IL-8 levels that accompany the process of insulin resistance in the body of PCOS sufferers.[15]

Atypical hyperplasia/endometrial intraepithelial neoplasia (AH/EIN) and early-stage endometrioid carcinoma (EC) in PCOS cases may be reduced with metformin therapy although in studies conducted under 60% of study subjects.[16]

Combination administration of metformin with thiazolidinediones (TZDs) has been shown to improve menstrual cycles and improvements in Body Mass Index (BMI) in PCOS patients.[22]

In addition to improving insulin resistance, metformin therapy was also shown to improve mood and depressive

BULETIN FARMATERA
E-ISSN: 2528-410X

symptoms in young adult subjects and adult women suffering from PCOS.[17,18]

The combination of metformin and L-carnitine can work synergistically to significantly improve hormonal and metabolic parameters, while also improving reproductive system performance, insulin resistance and lipid profiles in women with PCOS with obesity who are resistant to clomiphene.[4]

Metformin likely increased endometrial receptivity through down-regulating miR-491-3p and miR-1910-3P expression, thereby increasing HOXA10 and ITGB3 expression in the endometrial of PCOS women.[5]

Metformin therapy results in a significant reduction in chemerin levels in cases of polycystic ovary syndrome.[6] Analysis of the characteristic k curve operation serum receiver chemerin suggests that serum chemerin levels may be beneficial for evaluating cases of polycystic ovary syndrome under various treatment methods .[6]

Treatment with an oral contraceptive pill (OCP) and metformin leads to a decrease in ovarian stromal vascularity in PCOS women possibly through different mechanisms and this reduction is more pronounced with OCP.[19]

The addition of myo-inositol and metformin to the treatment of infertile PCOS women with letrozole resistance improves ovarian function;[20] However, it is insignificant. Of note, inositol was more effective than metformin in patients with normal BMIs.[20]

The addition of ALC therapy is superior to metformin plus pioglitazone in improving insulin resistance, polycystic ovaries, menstrual irregularities, and hypoadiponectinemia in women with PCOS.[3]

Combination Therapy

In some studies, the use of metformin combined with other drugs to get maximum improvement results when compared to single metformin, some agents used as a combination in therapy are myo-inositol[2,1,20], pioglitazone[3], progestins[16], L-carnitine[4], clomiphene citrate[4], ethinylestradiol+cyproterone acetate[19].

CONCLUSION

Clinical studies of metformin interventions both single and in combination have been conducted in several countries where most studies show that metformin can improve clinical and laboratory improvements in PCOS patients, which can improve the fertility rates of women with PCOS.

REFERENCES

1. Shokrpour M, Foroozanfard F, Afshar Ebrahimi F, et al. Comparison of myo-inositol and metformin on glycemic control, lipid profiles, and gene expression related to insulin and lipid metabolism in women with polycystic ovary syndrome: a randomized controlled clinical trial. *Gynecol Endocrinol*. 2019;35(5):406-411. doi:10.1080/09513590.2018.1540570
2. Agrawal A, Mahey R, Kachhawa G, Khadgawat R, Vanamail P, Kriplani A. Comparison of metformin plus

E-ISSN: 2528-410X

myoinositol vs metformin alone in PCOS women undergoing ovulation induction cycles: randomized controlled trial. *Gynecol Endocrinol*. 2019;35(6):511-514. doi:10.1080/09513590.2018.1549656

3. Tauqir S, Israr M, Rauf B, et al. Acetyl-l-Carnitine Ameliorates Metabolic and Endocrine Alterations in Women with PCOS: A Double-Blind Randomized Clinical Trial. *Adv Ther*. 2021;38(7):3842-3856. doi:10.1007/s12325-021-01789-5

4. El Sharkwy I, Sharaf El-Din M. l-Carnitine plus metformin in clomiphene-resistant obese PCOS women, reproductive and metabolic effects: a randomized clinical trial. *Gynecol Endocrinol*. 2019;35(8):701-705. doi:10.1080/09513590.2019.1576622

5. Zhai J, Yao GD, Wang JY, et al. Metformin Regulates Key MicroRNAs to Improve Endometrial Receptivity Through Increasing Implantation Marker Gene Expression in Patients with PCOS Undergoing IVF/ICSI. *Reprod Sci*. 2019;26(11):1439-1448. doi:10.1177/1933719118820466

6. Foda AA, Foda EA, El-Negeri MA, El-Said ZH. Serum chemerin levels in Polycystic Ovary Syndrome after metformin therapy. *Diabetes Metab Syndr Clin Res Rev*. 2019;13(2):1309-1315. doi:10.1016/j.dsx.2019.01.050

7. Zheng S, Liu E, Zhang Y, et al. Circulating zinc-α2-glycoprotein is reduced in women with polycystic ovary syndrome, but can be increased by exenatide or metformin treatment. *Endocr J*. 2019;66(6):555-562. doi:10.1507/endocrj.EJ18-0153

8. Liu Y, Li J, Yan Z, Liu D, Ma J, Tong N. Improvement of Insulin Sensitivity Increases Pregnancy Rate in Infertile PCOS Women: A Systemic Review. *Front Endocrinol (Lausanne)*. 2021;12. doi:10.3389/fendo.2021.657889

9. Mohamed S. Can Insulin Sensitizer Drugs Enhance the Result of Assisted Reproductive Cycles when Used for PCOS Women Undergoing ART? Meta-Analysis and …. *EC Gynaecol*. Published online 2022. https://ecronicon.org/assets/ecgy/pdf/ECGY-11-00728.pdf

10. Cabrera-Cruz H, Oróstica L, Plaza-Parrochia F, Torres-Pinto I, Romero C, Vega M. The insulin-sensitizing mechanism of myo-inositol is associated with AMPK activation and GLUT-4 expression in human endometrial cells exposed to a PCOS environment. *Am J Physiol - Endocrinol Metab*. 2020;318(2):E237-E248. doi:10.1152/ajpendo.00162.2019

11. Soldat-Stanković V, Popović-Pejičić S, Stanković S, et al. The effect of metformin and myoinositol on metabolic outcomes in women with polycystic ovary syndrome: role of body mass and adiponectin in a randomized controlled trial. *J Endocrinol Invest*. 2022;45(3):583-595. doi:10.1007/s40618-021-01691-5

12. Sohrevardi SM, Heydari B, Azarpazhooh MR, et al. Therapeutic Effect of Curcumin in Women with Polycystic Ovary Syndrome

E-ISSN: 2528-410X

Receiving Metformin: A Randomized Controlled Trial. *Adv Exp Med Biol*. 2021;1308:109-117. doi:10.1007/978-3-030-64872-5_9

13. Chang HH, Hsueh YS, Cheng YW, Ou HT, Wu MH. Association between polymorphisms of OCT1 and metabolic response to metformin in women with polycystic ovary syndrome. *Int J Mol Sci*. 2019;20(7). doi:10.3390/ijms20071720

14. Abdalmageed OS, Farghaly TA, Abdelaleem AA, Abdelmagied AE, Ali MK, Abbas AM. Impact of Metformin on IVF Outcomes in Overweight and Obese Women With Polycystic Ovary Syndrome: A Randomized Double-Blind Controlled Trial. *Reprod Sci*. 2019;26(10):1336-1342. doi:10.1177/1933719118765985

15. Ali DES, Shah M, Ali A, et al. Treatment with Metformin and Combination of Metformin plus Pioglitazone on Serum Levels of IL-6 and IL-8 in Polycystic Ovary Syndrome: A Randomized Clinical Trial. *Horm Metab Res*. 2019;51(11):714-722. doi:10.1055/a-1018-9606

16. Acosta-Torres S, Murdock T, Matsuno R, et al. The addition of metformin to progestin therapy in the fertility-sparing treatment of women with atypical hyperplasia/endometrial intraepithelial neoplasia or endometrial cancer: Little impact on response and low live-birth rates. *Gynecol Oncol*. 2020;157(2):348-356. doi:10.1016/j.ygyno.2020.02.008

17. Erensoy H, Niafar M, Ghafarzadeh S, Aghamohammadzadeh N, Nader ND. A pilot trial of metformin for insulin resistance and mood disturbances in adolescent and adult women with polycystic ovary syndrome. *Gynecol Endocrinol*. 2019;35(1):72-75. doi:10.1080/09513590.2018.1498476

18. Alhussain F, Alruthia Y, Al-Mandeel H, et al. Metformin improves the depression symptoms of women with polycystic ovary syndrome in a lifestyle modification program. *Patient Prefer Adherence*. 2020;14:737-746. doi:10.2147/PPA.S244273

19. Sahu A, Tripathy P, Mohanty J, Nagy A. Doppler analysis of ovarian stromal blood flow changes after treatment with metformin versus ethinyl estradiol-cyproterone acetate in women with polycystic ovarian syndrome: A randomized controlled trial. *J Gynecol Obstet Hum Reprod*. 2019;48(5):335-339. doi:10.1016/j.jogoh.2018.10.006

20. Pourghasem S, Bazarganipour F, Taghavi SA, Kutenaee MA. The effectiveness of inositol and metformin on infertile polycystic ovary syndrome women with resistant to letrozole. *Arch Gynecol Obstet*. Published online 2019. doi:10.1007/s00404-019-05064-5

21. Andræ F, Abbott D, Stridsklev S, et al. Sustained maternal hyperandrogenism during pcos pregnancy reduced by metformin in non-obese women carrying a male fetus. *J Clin Endocrinol Metab*. 2020;105(12):3762-3770. doi:10.1210/clinem/dgaa605

22. Xing C, Li C, He B. Insulin

E-ISSN: 2528-410X

Sensitizers for Improving the Endocrine and Metabolic Profile in Overweight Women with PCOS. *J Clin Endocrinol Metab*. 2020;1051. Xing(9):2950-2963. doi:10.1210/clinem/dgaa337