International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Laila R et al. Int J Reprod Contracept Obstet Gynecol. 2024 Dec;13(12):3484-3490
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20243578

Original Research Article

Pretreatment with ethinylestradiol-drospirenone and metformin enhances ovulation and pregnancy in women with polycystic ovary syndrome

Rawnok Laila, T. M. Fahad Nasif, S. M. Munira, Tahmida Islam, Farzana Deeba, Shakeela Ishrat*

Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Received: 06 October 2024
Accepted: 07 November 2024

***Correspondence:**
Dr. Shakeela Ishrat,
E-mail: shakeelaishrat@bsmmu.edu.bd

ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a major cause of anovulatory infertility and affects 5-10% women of reproductive age. High serum anti-mullerian hormone (AMH) is associated with lack of ovulation in PCOS women. Combined oral contraceptives containing ethinylestradiol and drospirenone suppress androgen production and reduce AMH concentration which may optimize the women with PCOS for better response to ovulation induction. This study aimed to assess the effects of ethinylestradiol-drospirenone (EE-DRSP) and metformin combination as pretreatment for ovulation induction in polycystic ovary syndrome in comparison to metformin only pretreatment.
Methods: This was a randomized controlled trial conducted on a total 62 subfertile PCOS women having high serum AMH (≥5 ng/dl). They were randomly assigned into 2 groups. In group A 31 participants received EE-DRSP and metformin combination and in group B 31 participants received only metformin for 3 months. After 3 months the participants had ovulation induction with letrozole for 3 cycles. The outcome variables were the rates of ovulation and pregnancy.
Results: Ovulation rate per cycle was higher in group A than group B. Cumulative ovulation rate per participant was also 1.36 times higher in group A than B (100.0% versus 73.3%). Cumulative pregnancy rate was 1.91 times higher in combination group than metformin alone group (67.7% versus 35.5%).
Conclusions: Pretreatment with ethinylestradiol-drospirenone and metformin for three months before ovulation induction is more effective than metformin only in terms of higher ovulation and pregnancy rate in subfertile PCOS women.

Keywords: Ethinylestradiol-drospirenone, Metformin, Ovulation induction, PCOS

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common female endocrinopathy of reproductive age group as well as a major cause of anovulatory infertility.[1] It is a heterogeneous condition and affects about 5-10% of female populations.[1-3] Currently, it is thought that PCOS is a multifactorial disorder, that emerges from a complex interaction of genetic and environmental traits.[4]

PCOS is responsible for 55% to 70% of infertility cases resulting from chronic anovulation, thus, it is among the most common causes of infertility due to ovulation dysfunction.[5] Excessive androgen release in PCOS patients leads to increased granulosa cell synthesis of estrogen precursors. In these patients luteinizing hormone receptors, in presence of hyperinsulinemia, appear earlier in granulosa cells, causing activation of aromatase in these cells. This results in increased estrogen production, with

positive feedback on LH and negative feedback on FSH and ultimately disruption of folliculogenesis.[6] PCOS is characterized by hyperandrogenism (hirsutism and/or biochemical hyperandrogenemia) and oligo/anovulation and also highly associated with obesity and insulin resistance.[7]

Anti-mullerian hormone (AMH), a dimeric glycoprotein is a member of the transforming growth factor beta (TGF-β) superfamily of regulatory proteins.[8,9] It is exclusively produced by granulosa cells (GCs) of developing pre-antral and small antral follicles and has been found to play an important role in chronic anovulation by inhibiting the initial recruitment of primordial follicles and by prompting follicular arrest.[10-12] Serum AMH is 2-4-fold higher in women with PCOS than in healthy women.[13] It is due to increased production of AMH per follicle, not due to increased follicular pool. It has been shown that serum AMH is a more reliable diagnostic tool for PCOS than antral follicle count (AFC). Higher AMH in PCOS has been associated with relatively poor response to ovulation induction. It is useful for establishing treatment protocol and defining the best strategy for ovulation induction in infertile women with PCOS.[14-16]

Combined oral contraceptives are known to normalize menstrual function, to ameliorate hirsutism and acne as well as reduce serum AMH in women with PCOS. On the opposite, treatment with metformin is beneficial for weight reduction and correction of insulin resistance, but still the effect on menstrual cycle and hyperandrogenism is rather weak.[17] Few data are available on the impact of the treatment modalities on high serum AMH levels in women with PCOS.

Combination oral contraceptives (COCs) are currently advised as the first line of treatment for female hirsutism for lowering ovarian androgen production. Their pregestational activity reduces luteinizing hormone (LH) secretion and, in turn, LH-mediated ovarian androgen release. The beneficial effect of the estrogenic component is mainly attributable to its SHBG elevating ability, which decreases the amount of free testosterone (T) available.[18] Drospirenone (DRSP), is an analogue of spironolactone with antimineralocorticoid and antiandrogenic properties. DRSP neither reduces the estrogen-induced rise in SHBG nor prevents androgens from binding to SHBG which is a crucial characteristic.[19] Further, DRSP has various favorable metabolic effects, including the potential to reduce blood pressure and body weight.

Different studies showed that, OCP reduces the AMH level.[20] This could be explained by the suppression of LH secretion by OCP, as luteinizing hormone (LH) is responsible for the overexpression of AMH and AMH-specific type 2 receptors (AMHRII) in lutein GCs in anovulatory PCOS. So reduced LH may directly impact on AMH secretion.[21] OCP significantly reduces serum AMH levels by decreasing androgens and suppression of serum LH.[7] OCP use for two months before repeating CC treatment in CC-resistant women produced effective ovulation and pregnancy rates.[22] Pretreatment with COC for 42 days before ovulation induction with letrozole improved ovulation and pregnancy rates in CC resistant patients.[23]

Letrozole is a potent, reversible, highly selective aromatase inhibitor (AI), that prevents androgen to estrogen conversion. It is now recommended as first line treatment for ovulation induction in anovulatory PCOS women as it does not decrease estrogen receptors in target tissues with less negative impact on endometrium and cervical mucus.[24] Letrozole appears to have superior ovulation rates, pregnancy, and live birth rates compared to CC in PCOS women.[25] A large randomized controlled trial reported that the comparative ovulation rate for CC and letrozole was 48.3% versus 61.7% with a live birth rate of 19.1 versus 27.5% respectively.[26]

It is indeed a challenging matter to induce ovulation in anovulatory PCOS patients with high serum AMH. So, the present study aimed to assess the effects of pretreatment oral contraceptives (ethinylestradiol-drospirenone) and metformin combination in a goal to reduce serum AMH and to restore ovulation in anovulatory infertile PCOS patients.

METHODS

This was a randomized controlled trial study carried out in the department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from July 2022 to June 2023. In our study, we included 62 diagnosed patients of PCOS women with subfertility having high serum AMH (≥5 ng/dl) levels. Patients were randomized into two groups: group A (experimental group) and group B (comparator group). Inclusion criteria were diagnosed cases of PCOS women according to Rotterdam criteria, age: 18-35 years, body mass index (BMI):18-29.9 kg/m^2, infertility for ≥1 year and serum AMH level ≥5 ng/ml. Exclusion criteria were endocrine disorders (hyperprolactinemia, diabetes mellitus, hypothyroidism), known case of pulmonary, cardiac, liver, or renal diseases, history of metformin and other drug treatment within three months, endometriosis, bilateral tubal block, and severe male factor abnormality or any contraindications to EE-DRSP i.e. obesity, thromboembolism, breast cancer, etc.

In experimental group A, 31 participants were given tab. ethenylestradiol-drospirenone (tablet Rosen 28, Incepta Pharmaceuticals Ltd.) once daily and tablet metformin (tablet Nobesit, Incepta Pharmaceuticals Ltd.) 500 mg thrice daily for 3 months before ovulation induction with letrozole. In comparator group, 31 participants were given 500 mg tablet metformin thrice daily for 3 months before letrozole induction. Group A received pretreatment with 0.030 mg of ethinylestradiol (EE) and 3 mg drospirenone (DRSP) for 3 (three) months cyclically and metformin 500 mg daily for 1 week, 1000 mg for next 1 week and 1500

mg in 3 divided doses for last 10 weeks. On the other hand, group B participants received only metformin in the same dose and duration. After 3 months ovulation induction was started from day 2/3 of menstruation with letrozole 2.5 mg, two tablets daily for 5 days. Participants of both groups come on day 12 to do TVS for folliculometry. The hCG injection of 5,000 IU was given intramuscularly when at least one follicle measured ≥18 mm. Timed intercourse was advised every other day for 1 (one) week from 36 hours after the night of hCG administration. Confirmation of ovulation was seen on TVS findings by collapsed follicle with appearance of echogenicity within follicular fluid and collection of fluid in pouch of Douglas 36 hours after trigger and/or mid-luteal (day 21) serum progesterone measurement. Serum progesterone ≥3 ng/ml was considered suggestive of ovulation. Pregnancy was confirmed by serum β-hCG measurement and/or ultrasonographic visualization of gestational sac. In case of ovulation in the initial cycle without pregnancy, letrozole induction was repeated in the same dose in next 2 cycle. Follow up was the same as described before.

All data were recorded systematically in preformed data collection form. Quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. Chi-square test was used to analyse the categorical variables. Student t-test, Mann-Whitney U test and paired t-test was used for continuous variables. A p value <0.05 was considered as significant. Statistical analysis was performed by using Statistical Package for Social Sciences version 26.0. The study was approved by the Ethical Review Committee of Bangabandhu Sheikh Mujib Medical University.

RESULTS

In group A, 31 participants received EE-DRSP and metformin combination and in group B, 31 participants received tab. metformin for 3 months before letrozole ovulation induction. In group B,1 case was pregnant before starting ovulation induction. So, a total 61 patients started ovulation induction.

Table 1: Demographic characteristics of the study population (n=62).

Demographic characteristics	Group A (n=31)		Group B (n=31)		P value
	N	%	N	%	
Age (years)					
18-21	6	19.4	8	25.8	
22-25	12	38.7	14	45.2	
26-29	10	32.3	6	19.4	
30-35	3	9.7	3	9.7	
Mean±SD	25.4±3.7		24.2±3.9		0.220
Range (min-max)	20.0-35.0		19.0-34.0		
Infertility					
Primary	19	61.3	21	67.7	0.596
Secondary	12	38.7	10	32.3	
Duration of infertility					
≤3 years	26	83.9	28	90.3	0.354
>3 years	5	16.1	3	9.7	
BMI (kg/m^2)					
18.5-24.9	11	35.5	7	22.6	
5.0-29.9	20	64.5	24	77.4	
Mean±SD	25.9±2.9		26.5±2.6		0.332
Range (min-max)	19.4-29.8		20.0-29.9		
Waist circumference(cm)	86.1±8.1		87.2±7.1		0.595
Range (min-max)	76.0-107.0		76.0-110.0		
Oligomenorrhea	26	83.9	28	90.3	0.354
Hirsutism	24	77.4	25	80.6	0.500
Acanthosis nigricans	30	96.8	27	87.1	0.177
Polycystic ovaries	24	77.4	20	64.5	0.201

Table 1 shows that the differences between the base line characteristics of the two groups were not statistically significant. Table 2 shows that mean serum AMH was 10.7 ng/ml in group A and 10.1±4.0 ng/ml in group B. There was no significant difference in AMH, LH and testosterone levels between the two groups.

Table 2: Baseline hormonal parameters of study population (n=62).

Variables	Group A (n=31)	Group B (n=31)	P value
	Mean±SD	Mean±SD	
Serum AMH (ng/ml)	10.7±1.9	10.1±4.0	0.415
Serum LH (mIU/ml)	11.9±4.1	10.8±4.7	0.343
Serum testosterone (ng/ml)	60.0±15.6	61.1±25.7	0.846
Serum FSH (mIU/ml)	5.3±1.5	5.4±1.6	0.909
Serum TSH (mIU/ml)	2.4±1.0	2.3±1.9	0.898
Serum prolactin (ng/dl)	12.3±4.7	12.6±3.4	0.768

Table 3: Comparison of ovulation rate (by TVS findings and/or day 21 serum progesterone) between two groups.

Ovulation rate	Group A		Group B		RR (95%CI)	P value
	N	%	N	%		
1st cycle	(n=31)		(n=30)			
Yes	27	87.1	14	46.7	1.87 (1.24 to 2. 80)	0.001
2nd cycle	(n=20)		(n=25)			
Yes	18	90.0	13	52.0	1.73 (1.15 to 2.59)	0.006
3rd cycle	(n=11)		(n=20)			
Yes	10	90.9	06	30.0	3.03 (1.51 to 6.07)	0.001
Cumulative ovulation rate	(n=31)		(n=30)			
Yes	31	100.0	22	73.3	1.36 (1.10 to 1.69)	0.002

Table 4: Comparison of pregnancy rate between two groups (by serum β-hCG and/or sonographic findings).

Pregnancy rate	Group A		Group B		RR (95%CI)	P value
	N	%	N	%		
Before cycle	(n=31)		(n=31)			
Yes	0	0.0	1	3.2	0.33 (0.01 to 7.88)	0.500
1st cycle	(n=31)		(n=30)			
Yes	10	32.3	5	16.7	1.93 (0.75 to 4.50)	0.157
2nd cycle	(n=20)		(n=25)			
Yes	9	45.0	4	16.0	2.81 (1.01 to 7.80)	0.033
3rd cycle	(n=11)		(n=20)			
Yes	2	18.2	1	5.0	3.64 (0.37 to 35.73)	0.281
Cumulative pregnancy rate	(n=31)		(n=31)			
Yes	21	67.7	11	35.5	1.91 (1.12 to 3.25)	0.011

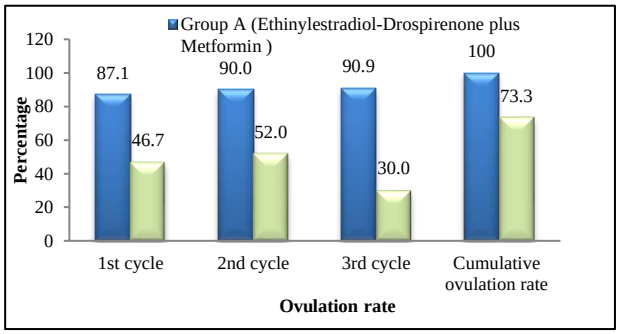

Figure 1: Comparison of ovulation rate (determined by sonographic features and/or serum progesterone) between the two groups.

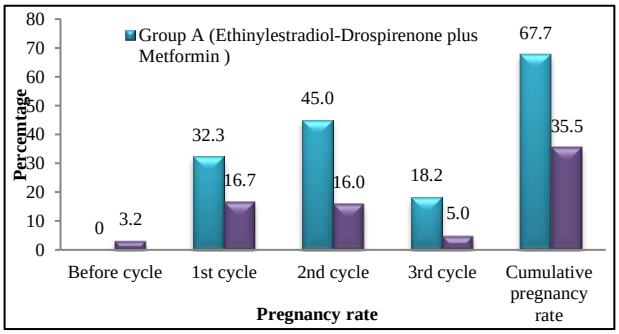

Figure 2: Comparison of pregnancy rate (by serum β-hCG and/or sonographic findings) between two groups.

Table 3 shows that the ovulation rate per cycle and cumulative ovulation rate per participant was significantly

higher in group A than in group B. All the women in group A achieved ovulation by third cycle. Cumulative ovulation rate per participant was also 1.36 times higher in group A than B (100.0% versus 73.3%). Table 4 shows that cumulative pregnancy rate was significantly higher in group A than group B (67.7% versus 35.5%) with relative ratio 1.91.

DISCUSSION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting reproductive age women. Combined oral contraceptive has long been considered a first line of therapy for PCOS woman because it regulates menstrual cycle and reduces hyperandrogenism. The COC users have lower pituitary LH and AMH. Metformin is an insulin sensitizer frequently used in PCOS. Several studies reported that metformin improves menstrual pattern, increase ovulation and reduce serum androgen levels.[27,28] With above concept, these combined drugs were investigated in our study as pretreatment to ovulation induction in women with polycystic ovary syndrome and high serum AMH.

The objective of our study was to evaluate the effectiveness of ethinylestradiol-drospirenone and metformin pre-treatment combination compared to metformin only pretreatment before ovulation induction with letrozole in polycystic ovary syndrome. The findings are that the cumulative ovulation rate per participant and ovulation rate per cycle are significantly higher in the women who received three months of pre-treatment with EE-DRSP and metformin.

Branigan and Estes were the first to address the concept of pre-treatment with drospirenone containing oral contraceptive pills before ovulation induction in PCOS women.[22] There are many studies available now regarding the effects of pretreatment with combined hormonal pills in IVF cycles. But there are few studies on pre-treatment with OCP and metformin combination prior to ovulation induction in the selected population of PCOS women and high serum AMH.

A prospective randomized study conducted on clomiphene (CC)-resistant women with polycystic ovarian syndrome concluded that pretreatment with drospirenone-containing COC before letrozole ovulation induction improve ovulation rates.[23] Ovulation was significantly higher (84.5%) compared to those having no treatment (66.7%). Another randomized controlled trial was done on women with PCOS and high AMH having pre-treatment with cyproterone acetate-ethinyl estradiol or not for three months before ovulation induction with letrozole.[29] The ovulation rate was higher (82.4%) in pre-treatment group compared to letrozole only group (43.0%). Our study found much higher ovulation rate in both experimental and comparator group (100% and 73.3%) because we added metformin in both groups. A prospective before-after study evaluated the efficacy of sequential treatment of metformin and incremental doses of letrozole in induction of ovulation in CC-resistant PCOS patients.[30] Ovulation occurred in 62.96% where as in ours it was 73.3%. The difference may be due to different baseline BMI.

One study investigated the role of anti mullerian hormone (AMH) level in the management of polycystic ovary syndrome (PCOS) and assessed the impact of metformin and oral contraceptives (OC) on serum AMH levels in a cohort of adolescents with PCOS.[31] Those who received oral contraceptives plus metformin had greater decrease in AMH and LH than those who received metformin alone. Metformin administration in women with polycystic ovary syndrome is associated with reduced serum AMH levels. Pretreatment with EE-DRSP and metformin combination before ovulation induction cause further reduction in serum AMH level and this in turn results in greater ovulation rates.

Cumulative pregnancy rate per participant and per cycle in our study was much higher in women who received EE-DRSP and metformin pre-treatment before ovulation induction then those who received metformin only. This result is in agreement with other studies.[23] Clinical pregnancy rate was significantly higher (27.6% versus 14.4%) with sequential treatment of metformin and incremental doses of letrozole in induction of ovulation in cases of CC-resistant PCOS patients.[30] The study showed 13.33% of patients conceived with metformin alone before ovulation induction. Pregnancy rate per ovulatory cycle was 30%. Cumulative pregnancy rate was 57.14%. This study strongly supports my findings.

A randomized controlled trial used oral contraceptives containing CPA (cyproterone acetate) and EE for three months before ovulation induction with letrozole.[29] Pregnancy rate was higher in (23.5%) in pre-treatment group than letrozole only (8.8%) group. Our study found higher pregnancy rate 67.7% (EE-DRSP and metformin combination group) versus 35.5% (metformin only group). This is explained by the addition of metformin pretreatment before letrozole induction in both groups.

Another study compared letrozole and metformin with letrozole alone in ovulation induction in terms of pregnancy rate in PCOS patients.[33] The study administered metformin before and during ovulation induction. They concluded that combination of letrozole plus metformin is superior as to letrozole alone for induction of pregnancy in polycystic ovarian syndrome.

In summary, EE-DRSP and metformin combination appears promising as pre-treatment in enhancing fertility outcomes for PCOS women undergoing ovulation induction by improving hormonal parameters. Metformin acts as insulin sensitizer whereas the estrogen progestin pill reduces androgen, AMH and LH, an effect leading to enhanced response to ovulation induction in infertile PCOS women.

However, it is important to acknowledge limitations identified in this study. First, the present study was conducted over a short period of time. Another limitation was the relatively small sample size. Both participants and investigators were not blinded to the treatment allocation after randomization, which could introduce bias into the results. Lastly, the participants were recruited from one location of a single hospital, so our findings may not be generalized as there are genetic, racial and geographical variations in people and that might not represent the whole community; so further multicentre studies are warranted to consolidate the evidence provided in this study.

CONCLUSION

Pretreatment with ethinylestradiol-drospirenone and metformin for three months before ovulation induction is more effective than metformin only in terms of higher ovulation and pregnancy rate in sub fertile PCOS women.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet. 2007;370:1828-31.
2. Franks S. Polycystic ovary syndrome in adolescents. Int J Obes. 2008;32(7):1035-41.
3. Orio F, Palomba S. Endocrinology: new guidelines for the diagnosis and treatment of PCOS. Nat Rev Endocrinol. 2014;10:130-2.
4. Williams T, Mortada R, Porter S. Diagnosis and treatment of polycystic ovary syndrome. Am Fam Phys. 2016;94(2):106-13.
5. Hajishafiha M, Dehghan M, Kiarang N, Sadegh-Asadi N, Shayegh SN, Ghasemi-Rad M. Combined letrozole and clomiphene versus letrozole and clomiphene alone in infertile patients with polycystic ovary syndrome. Drug Des Devel Ther. 2013:1427-31.
6. Palomba S, Orio F, Zullo F. Ovulation induction in women with polycystic ovary syndrome. Fertil Steril. 2006;86:S26-7.
7. Panidis D, Georgopoulos NA, Piouka A, Katsikis I, Saltamavros AD, et al. The impact of oral contraceptives and metformin on anti-Müllerian hormone serum levels in women with polycystic ovary syndrome and biochemical hyperandrogenemia. Gynecol Endocrinol. 2011;27(8):587-92.
8. Dewailly D, Andersen CY, Balen A, Broekmans F, Dilaver N, Fanchin R, et al. The physiology and clinical utility of anti-Müllerian hormone in women. Hum Reprod Update. 2014;20(3):370-85.
9. Mumford SL, Legro RS, Diamond MP, Coutifaris C, Steiner AZ. Baseline AMH level associated with ovulation following ovulation induction in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2016;101(9):3288-96.
10. Weenen C, Laven JS, Von Bergh AR, Cranfield M, Groome NP, Visser JA, et al. Anti-Müllerian hormone expression pattern in the human ovary: potential implications for initial and cyclic follicle recruitment. Mol Hum Reprod. 2004;10(2):77-83.
11. Knight PG, Glister C. TGF-β superfamily members and ovarian follicle development. Reproduction. 2006;132(2):191-206.
12. La Marca A, Broekmans FJ, Volpe A, Fauser BC, Macklon NS. Anti-Müllerian hormone (AMH): what do we still need to know? Hum Reprod. 2009;24(9):2264-75.
13. Villarroel C, Merino PM, Lopez P, Eyzaguirre FC, Van Velzen A, Iniguez G, et al. Polycystic ovarian morphology in adolescents with regular menstrual cycles is associated with elevated anti-Müllerian hormone. Hum Reprod. 2011;26(10):2861-8.
14. Jacob SL, Field HP, Calder N, Picton HM, Balen AH, Barth JH. Anti-Müllerian hormone reflects the severity of polycystic ovary syndrome. Clin Endocrinol. 2017;86(3):395-400.
15. Casadei L, Madrigale A, Puca F, Manicuti C, Emidi E, Piccione E, et al. The role of serum anti-Müllerian hormone (AMH) in the hormonal diagnosis of polycystic ovary syndrome. Gynecol Endocrinol. 2013;29(6):545-50.
16. Dumont A, Robin G, Catteau-Jonard S, Dewailly D. Role of anti-Müllerian hormone in pathophysiology, diagnosis and treatment of polycystic ovary syndrome: a review. Reprod Biol Endocrinol. 2015;13:1-10.
17. Banu J, Ishrat S, Deeba F, Anowary S, Alamgir CF, Darmini M. Impact of cyproterone acetate and ethinylestradiol on clomiphene resistant PCOS patient with high serum AMH level. J Shaheed Suhrawardy Med Coll. 2020;12(1):38-44.
18. Murphy AA, Cropp CS, Smith BS, Burkman RT, Zacur HA. Effect of low-dose oral contraceptive on gonadotropins, androgens, and sex hormone binding globulin in nonhirsute women. Ferti Steril. 1990;53(1):35-9.
19. Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. Contraception. 2000;62(1):29-38.
20. Kallio S, Puurunen J, Ruokonen A, Vaskivuo T, Piltonen T, Tapanainen JS. Anti-Müllerian hormone levels decrease in women using combined contraception independently of administration route. Fertil Steril. 2013;99(5):1305-10.
21. Van den Berg MH, Van Dulmen-den Broeder E, Overbeek A, Twisk JW, Schats R, Van Leeuwen FE, et al. Comparison of ovarian function markers in users of hormonal contraceptives during the hormone-free interval and subsequent natural early follicular phases. Hum Reprod. 2010;25(6):1520-7.
22. Branigan EF, Estes MA. A randomized clinical trial of treatment of clomiphene citrate-resistant anovulation with the use of oral contraceptive pill

suppression and repeat clomiphene citrate treatment. Am J Obstet Gynecol. 2003;188(6):1424-30.
23. Salama M, Hamza H. Drospirenone containing combined oral contraceptive premedication before letrozole ovulation induction in clomiphene resistant PCOS, is it worth the wait. Gynecol Reprod Health. 2019;3(2):1-6.
24. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Hum Reprod. 2018;33(9):1602-18.
25. Mes-Krowinkel MG, Louwers YV, Mulders AG, de Jong FH, Fauser BC, Laven JS. Influence of oral contraceptives on anthropomorphometric, endocrine, and metabolic profiles of anovulatory polycystic ovary syndrome patients. Fertil Steril. 2014;101(6):1757-65.
26. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Eng J Med. 2014;371(2):119-29.
27. Palomba S, Falbo A, Giallauria F, Russo T, Tolino A, Zullo F, et al. Effects of metformin with or without supplementation with folate on homocysteine levels and vascular endothelium of women with polycystic ovary syndrome. D Care. 2010;33(2):246-51.
28. Palomba S, Falbo A, Zullo F, Orio Jr F. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. Endocr Rev. 2009;30(1):1-50.
29. Chowdhury P, Banu J, Deeba F, Debnath RC, Rani C, Sultana S, et al. Pre-treatment with cyproterone acetate plus ethinylestradiol enhances ovarian response in women with polycystic ovary syndrome. Int J Reprod Contracept Obstet Gynecol. 2023;12(10):2320-70.
30. Azargoon A, Toussy JA, Darbanan FF. Pregnancies following the use of sequential treatment of metformin and incremental doses of letrozole in clomiphenresistant women with polycystic ovary syndrome. Iran J Reprod Med. 2012;10(1):33.
31. Dursun F, Güven A, Yursun F, Güven A, Yıldız M. Assessment of anti-Müllerian hormone level in the management of adolescents with polycystic ovary syndrome. J Clin Res Pediatr Endocrinol. 2016;8(1):55.
32. Medeiros LR, Colonetti T, Nagib EC, Uggioni ML, Junior JC, Ceretta L, et al. Anti-Müllerian hormone levels after metformin treatment in polycystic ovary syndrome: a systematic review and meta-analysis. Obes Res Clin Pract. 2023;17(4):288-97.
33. Mohsin RA, Saeed AS, Baig MM, Khan M. Role of letrozole and metformin versus letrozole alone in ovulation induction in patients of polycystic ovarian syndrome. Pak J Med Health Sci. 2019;13(1):350-2.

Cite this article as: Laila R, Nasif TMF, Munira SM, Islam T, Deeba F, Ishrat S. Pretreatment with ethinylestradiol-drospirenone and metformin enhances ovulation and pregnancy in women with polycystic ovary syndrome. Int J Reprod Contracept Obstet Gynecol 2024;13:3484-90.