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Metformin Use and Clinical Pregnancy Rate in Women with Unexplained Infertility: Randomized Controlled Trial

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Abstract

Objective: *Unexplained infertility accounts for almost 17% of infertility cases. The aim of this study is to assess the effect of metformin on clinical pregnancy rate as primary outcome in women with unexplained infertility.*
Methodology: *A randomized controlled research trial conducted in infertility clinic, Ain Shams University Maternity Hospital, over a period of six months from June 2017 to November 2018.170 women with unexplained infertility attending outpatient clinic with inclusion criteria were recruited. They were divided into two groups:* ***Group A:*** *the case group, it included 85 cases who received metformin plus clomiphene citrate* ***Group B:*** *the control group, it included 85 control who received placebo plus clomiphene citrate, to evaluate and assess the effect of metformin on clinical pregnancy rate*
Results: *Incidence of clinical pregnancy was not statistically significantly different between both groups. (groupA:14(16.8%), group B: 10 (11.8%)). The number needed to treat (NNT) was estimated to be 21. Also, no statistically significant differences were found between both groups regarding the incidence of complications of induction of ovulation. No significant differences were found between both groups regarding the number of dominant follicles produced during induction of ovulation with clomiphene citrate. On the contrary, endometrial thickness was statistically significantly larger with metformin adjuvant treatment during clomiphene citrate induction of ovulation.*
Conclusion: *The study showed no significant difference in increasing clinical pregnancy rate by adding metformin to clomiphene citrate for ovulation induction in women with unexplained infertility, but it showed a positive effect on endometrial thickness.*

Keywords: *metformin, unexplained, infertility, pregnancy, clomiphene.*

Clinical trial registered: Clinical trials.gov NCT03681197

Introduction

Unexplained infertility is defined as inability to conceive after 1 year of unprotected regular intercourse without known cause in either male or female partner, almost 17% of infertility cases (1).

Metformin is oral hypoglycemic drug used for treatment of type 2 diabetes, especially obese ones as it increase insulin sensitivity (2).

Metformin also augment ovulation by direct effect on ovarian tissue and enhances blood supply to endometrium which is important for implantation,so used for Polycystic ovaries(PCO) (3).

A Cochrane review on PCOs women showed increase in clinical pregnancy rate and decreasing risk of ovarian hyperstimulatoin(OHSS) in using metformin before or during In vitro fertilization (IVF)(4).

A Finnish study using metformin PCOs who received metformin versus placebo for 12 weeks before ovulation induction treatment, continued during treatment and up to 12 weeks gestation. The results showed increasing

pregnancy rate (40.4% versus 53.6%) in placebo group and metformin group respectively, with greater benefit for obese women (5).

Another study used metformin in non-PCOs women with other causes of infertility undergoing IVF after previous failed IVF cycle, it showed increase in clinical pregnancy rate 36.4% with metformin compared to 9.6% in previous cycle (6).

Insulin resistance may be found in unexplained infertility due to other factors such as stress, aging, depression, obesity, also, women with irregular menses are associated with higher insulin resistance than those with regular cycles (7,8).

Based on this theory we assume that women with unexplained infertility may get benefit from using metformin as an adjuvant therapy with clomiphene citrate for ovulation induction in increasing the clinical pregnancy rate. So the target of this study to assess the effect of metformin on clinical pregnancy rate as primary outcome in women with unexplained infertility.

Methodology: A randomized controlled trial was conducted at Ain Shams University infertility clinic in the period from June 2017 and November 2018. 170 infertile women aged 20-35 years with the following inclusion criteria were recruited in the study:Women with unexplained infertility. According to the ESHRE, European Society of Human Reproduction and Embryology guidelines, necessary tests for unexplained infertility are semen analysis, assessment of ovulation and the luteal phase, and assessment of tubal patency by hysterosalpingogram or laparoscopy)(9), previous failed ovulation induction cycle with SERM, aromatase inhibitors or Gonadotropins.Body mass index between 20 and 30,Follicle-stimulating hormone level 12 IU/L or lower (baseline level, cycle day 3),normal transvaginal ultrasound (healthy uterus with no fibroids or other growth and those with the following criteria to be excluded:Women younger than 20 years old or older than 35 years old,uncorrected congenital or acquired uterine anomalies,other causes of infertility rather than unexplained infertility,BMI equal to or more than 30,women with recurrent miscarriage,diabetes mellitus,autoimmune disease.

Methods

- Full history: including age, menstrual history and sexual history, illnesses and infections; surgeries; medications used; exposure to certain environmental agents (chemotherapy, and toxic chemicals); and any previous fertility evaluations (regarding her partner history of medical and surgical history, sexual dysfunction, and any use of medications, tobacco or alcohol).
- Clinical examination: physically examined.
- General examination: for abnormal hair distribution, galactorrhea ,body mass index(B.M.I)., scars of previous surgeries
- Vaginal examination: for any anomalies or pathology
- Pelvic ultrasound: Ultrasound evaluation in the follicular phase day 2 of menstrual cycle was used to identify uterine fibroids, any pathology, and congenital anomalies. At the same time, antral follicle counts were obtained.
- Laboratory investigations including complete blood picture, hematocrit, liver and kidney function tests and coagulation profile,haemoglobin A1c, follicle-stimulating hormone (FSH), leutinizing hormone(LH) and estradiol on day 2 of menstrual cycle to assess how well the ovaries are functioning, TSH to test thyroid function, and prolactin to assess the presence of a benign pituitary tumour and semen analysis for partner.

Hysterosalpingography

Randomization and allocation:

Randomization:

To ensure that there is equivocal chance of participation, using a computergenerated randomization table women participating in the study were given the available number.

Allocation and concealment:

Numbers of participating women were written on sequentially numbered opaque sealed envelope that contains the assignment code. At the time of procedure, the responsible investigator opened the envelope to reveal the assignment code, and explained the planned method. Monitoring and follow up document was done by another person. After enrollment, the cases were randomly allocated into two groups each group 85 women:

Group A: the case group, it included 85 cases who received metformin plus clomiphene citrate, metformin 850 mg tablets were started twice daily started immediately at booking time and continued with the induction protocol, it was stopped once pregnancy confirmed, Clomiphene citrate (100 mg) starting on day2 till day6 of the cycle.

Group B: the control group, it included 85 control who received placebo plus clomiphene citrate. (100 mg) starting on day 2 till day 6 of the cycle. Folliculometry by transvaginal ultrasound was done on day 9 followed by serial folliculometry every other day till reaching dominant follicle 18mm or more where we gave HCG of 10000 IU intramuscular injection. Then timed sexual intercourse was instructed 36-48 hr. after HCG injection and for next 3 days. Serum pregnancy test was done after 16 days. Transvaginal ultrasound was done on day 35 for women with positive pregnancy test to visualize gestational sac (clinical pregnancy rate) as primary outcome. Searching for secondary outcomes as chemical pregnancy rate, presence of ovulation induction complications such as OHSS, ovarian cyst and multiple pregnancy rates, endometrial thickness difference in both groups when adding metformin to clomiphene citrate, effect of adding metformin on number of dominant follicles.

Blinding: the principal investigator prepared the envelopes of both groups containing either (metformin and clomiphene citrate) or (placebo structure similar to metformin and clomiphene citrate). After enrollment women were given the envelope. Responsible investigator instructed her regarding administration dose and timing

and recorded the outcomes. The responsible investigator is different from the one who prepared the envelopes.

Ethical consideration:

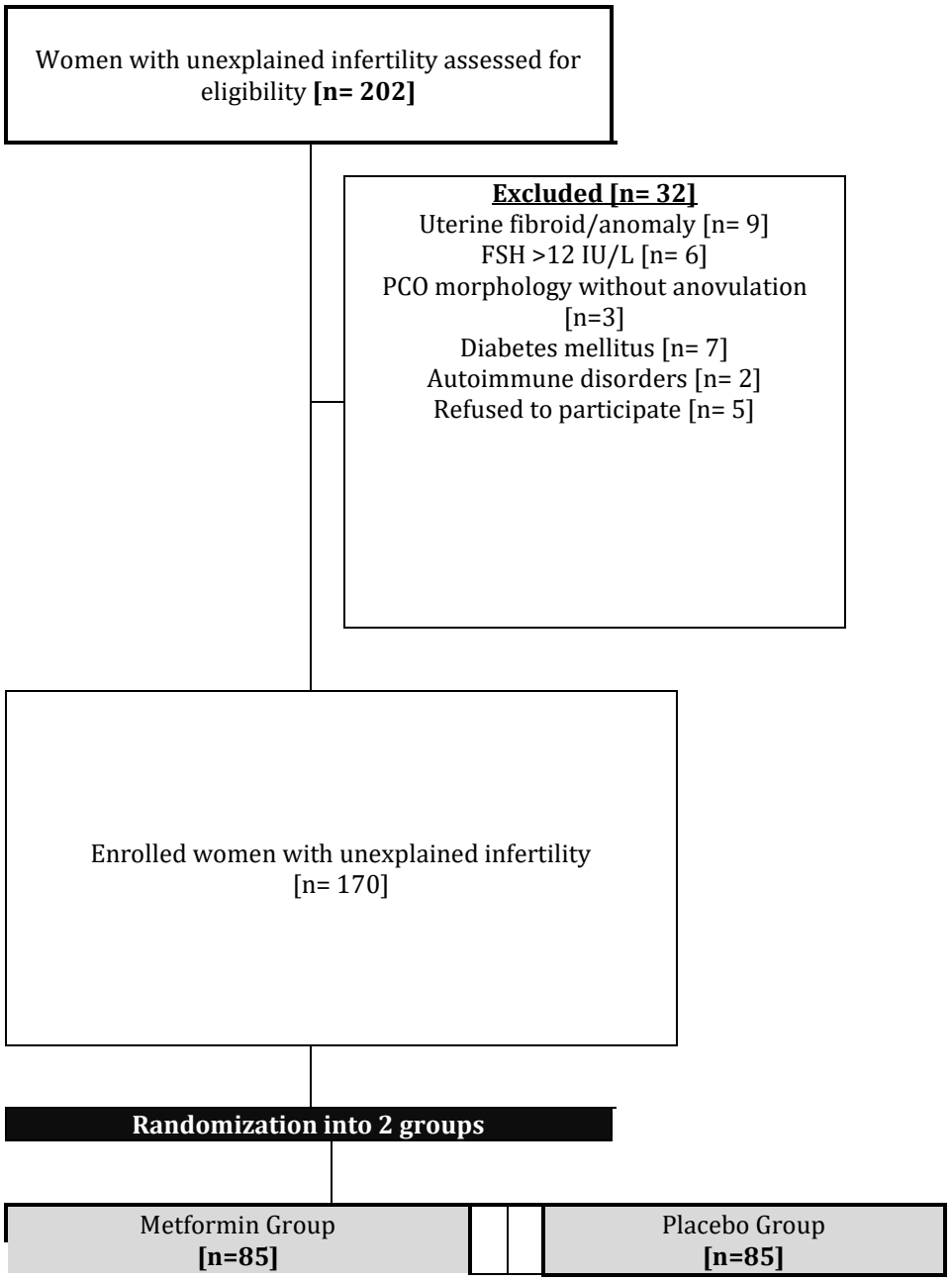
All patients had an informed consent: their right to self-determination and the right to know, understand to make informed decisions, right to privacy and confidentiality.

Sample size justification

Sample size was calculated using PASS version 15.0, setting the power (β) at 0.02 and the significance level (α) at 0.05. Data from a previous report (10), indicated that clinical pregnancy rate in women with unexplained infertility undergoing induction of ovulation using clomiphene citrate was 28.3% assuming that metformin adjuvant therapy improves clinical pregnancy rate by 20% calculation according to these values produced a minimal sample size of 154 women. Assuming a dropout rate of 10%, this yielded a drop out inflated total sample size of 170 women with unexplained infertility to be randomized into two groups with 85 women in each arm.

Statistical analysis:

Statistical analysis was performed using Microsoft Excel 2007 and statistical package for social sciences (SPSS VERSION 15.0). Data were prescribed as range, mean and standard deviation (for parametric variables), range, median and interquartile range (for non-parametric variables), and number and percentage (for categorical variables). Difference between variables of two groups was analyzed using student t- test (for non-parametric variables) and Chi-squared test (for categorical variables). Difference between variables of more than two groups was analyzed using one way ANOVA test (for parametric variables), Kruskal Wallis test (for non-parametric variables) and Chi-squared test (for categorical variables). Correlation between two variables was estimated using Pearson correlation coefficient (for parametric variables) and Spearman rank correlation coefficient (for non-parametric variables).



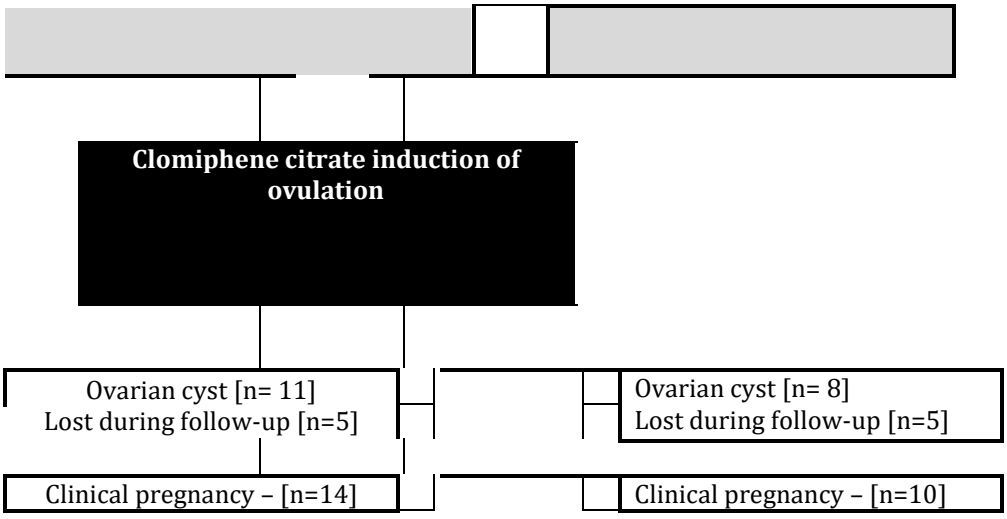


Figure 1: CONSORT 2010 flow diagram showing the recruitment and handling of the study population during the course of the study.

Results

The current study was conducted in Ain Shams University Maternity Hospital in the period between June 2018 and November 2018. A total of 170 women were enrolled in the study. Basic demographic and clinical characteristics of the study groups. No statistically significant differences between women of both groups regarding age, body mass index, parity, number of abortions, duration or type of infertility.

Table 1: Comparison between study groups regarding basic demographic and clinical characteristics.

	Metformin Group	Placebo Group	P
Age (Yrs) Range Mean±SD	 21.0 – 37.0 28.21 ± 3.56	 20.0 – 35.0 28.38 ± 3.95	 0.76
BMI (Kg/m²) Range Mean ± SD	 20.3 – 29.9 26.93 ± 2.00	 20.1 – 29.8 26.72 ± 2.19	 0.52
Parity Range Median (IQR)	 0 – 2 0 (0 – 1)	 0 – 3 0 (0 – 1)	 0.48
No. of abortions Range Median (IQR)	 0 – 2 0 (0 – 1)	 0 – 3 0 (0 – 1)	 0.66
Infertility Duration Type *Primary* *Secondary*	 3.04 ± 1.90 37 (43.5%) 48 (56.5%)	 3.43 ± 1.78 34 (40.0%) 51 (60.0%)	 0.16 0.75

Basal hormonal profile in the study groups. No statistically significant differences between women of both groups regarding basal FSH and LH levels.

Table 2: Comparison between study groups regarding basal hormonal profile.

	Metformin Group	Placebo Group	P
Basal FSH (IU/L) Range Mean ± SD	 3.20 – 11.20 5.28 ± 1.50	 2.90 – 10.90 5.52 ± 1.97	 0.35

Basal LH (IU/L) Range Mean ± SD	 1.70 – 7.10 2.94 ± 0.99	 1.80 – 6.30 3.09 ± 1.19	0.39

Analysis of the Outcomes of Clomiphene Citrate Induction of Ovulation in the Study Groups. No significant differences were found between both groups regarding the number of dominant follicles produced during induction of ovulation with clomiphene citrate. On the contrary, endometrial thickness was statistically significantly larger with metformin adjuvant treatment during clomiphene citrate induction of ovulation.

Table 3: Comparison between study groups regarding number of dominant follicles and endometrial thickness during induction of ovulation.

	Metformin Group [n=85]	**Placebo Group [n=85]**	**P**
No. of dominant follicles 1 2 3	 55 (64.7%) 13 (15.3%) 1 (1.2%)	 58 (68.2%) 13 (15.3%) 1 (1.2%)	0.94
Endometrial thickness (mm) Range Mean ± SD 95%CI of mean	 6.80 – 10.20 8.84 ± 0.85 8.63 – 9.04	 6.20 – 9.0 7.59 ± 0.75 7.41 – 7.77	**<0.001**
Difference in mean (95%CI)	1.24 (0.98 – 1.51)		

Comparison of chemical and clinical pregnancy rates in the study groups. Incidence of clinical pregnancy was not statistically significantly different between both groups. Analysis of relative incidence of clinical pregnancy revealed marked inconsistency on examining the 95% confidence interval; i.e. ranging from 0.83 to 1.06. The number needed to treat (NNT) was estimated to be 21.25; meaning about 21 women with unexplained infertility should receive adjuvant metformin treatment during clomiphene citrate induction of ovulation, so that one extra women achieve clinical pregnancy.

Table 4: Comparison of chemical and clinical pregnancy rates in the study groups.

	Metformin Group [n=85]	**Placebo Group [n=85]**	**P**	**RR (95%CI)**	**NNT**
Clinical pregnancy rate	14 (16.5%)	10 (11.8%)	0.50	0.94 (0.83 – 1.06)	21.25
Chemical Pregnancy Rate	16(18.8)	14(16.5)	0.84	0.97(0.84 -1.11)	42.5

Comparison between study groups regarding the complications of induction of ovulation. No statistically significant differences were found between both groups regarding the incidence of complications of induction of ovulation, namely multiple pregnancy and ovarian cyst. No recorded cases of ovarian hyperstimulation syndrome.

Table 5: Comparison between study groups regarding the complications of induction of ovulation.

	Metformin Group [n=85]	**Placebo Group [n=85]**	**P**
Multiple pregnancy	0 (0 %)	1 (1.17%)	0.99
Ovarian cyst	11 (12.9%)	8 (9.4%)	0.62

Discussion

Unexplained infertility accounts for almost 17% of infertility cases, using empirical treatment for unexplained infertility like observation with timed intercourse and lifestyle changes, clomiphene citrate and intrauterine insemination (IUI), controlled ovarian hyperstimulation (COH) with IUI, and IVF.

Metformin as an insulin sensitizer is used together with ovulation induction drugs in women with PCOs as they have insulin resistance.It can also be used in other cases of infertility due to its direct effect on ovarian tissue, endometrial and subendometrial layer.

In the current study metformin was used in women with unexplained infertility. This study is a randomized controlled trial which was conducted in Ain Shams Maternity hospital this study included 170 women who were diagnosed as unexplained infertility and were revised according to the mentioned inclusion and exclusion criteria, after they were well informed about the purpose and course

of the study from the medical investigator and had provided the written consent.

In the current study, there was no significant difference between the study groups A&B regarding the demographic data regarding age, body mass index, parity, number of abortions, duration or type of infertility where ($p < 0.05$).

Regarding hormonal profile there was no statistically significant differences between women of both groups regarding basal FSH and LH levels.

The current study demonstrated that women included had no significant differences were found between both groups regarding the number of dominant follicles produced during induction of ovulation with clomiphene citrate.

On the contrary, endometrial thickness was statistically significantly larger with metformin adjuvant treatment during clomiphene citrate induction of ovulation (8.84±0.85 ;p value<0.001) compared to (7.59±0.75 ;p value 0.94) in clomiphene only group.

Incidence of clinical pregnancy was not statistically significantly different between both groups (16.5% and 11.8% ;p value0.5) in group A and group B respectively.

Also, no statistically significant differences were found between both groups regarding the incidence of complications of induction of ovulation, namely multiple pregnancy (7.1 in group A and 4.7 in group B ;p value 0.74), ovarian cyst(12.9 in group A and 9.4 in group B; p value 0.62). No recorded cases of ovarian hyperstimulation.

Tso et al., (2014) study partially agreed with us and found no conclusive evidence that metformin treatment before or during assisted reproductive techniques (ART) cycles improved live birth rates in women with PCOS. However, the use of this insulin-sensitising agent increased clinical pregnancy rates and decreased the risk of OHSS. (4)

When metformin was compared with placebo or no treatment, clinical pregnancy rates were higher in the metformin group, for the woman with 31% chance of achieving clinical pregnancy using placebo or no treatment, the corresponding chance with metformin use would be 32%-49%. The risk of ovarian hyperstimulation syndrome was lower in the metformin group (OR 0.29; 95% CI 0.18 to 0.49).

Gill et al., (2014) assessed whether metformin combined with clomiphene citrate improve fertility related outcomes in clomiphene resistant women with PCOS or not also disagreed with our study. Metformin and Clomiphene Citrate have been shown to improve ovulation and pregnancy rates in the treatment of infertile patients with PCOS who are clomiphene resistant.

This difference in results between our study and previous two studies, they included women with PCO. (11) Papunen and colleagues (2012) study, a multicenter double-blind trial, on 320 women with PCO also disagreed with our study and found that metformin significantly improved pregnancy rate (vs. placebo) in the whole study population (PR: 53.6 vs. 40.4%, P< 0.006) and PR in obese women (49.0 vs. 31.4%, P<0.04), and there was a similar trend in non-obese (PR: 58.6 vs. 47.6%, p<0.09) with better improvement in obese women. Difference in results as women included are diagnosed as PCO, obese, received dose of 1500-2000 mg daily and continued till 12 weeks of gestation (5).

Abu Hashim (2016) disagreed with us and proved that in women with PCOS undergoing gonadotrophin ovulation induction, metformin significantly increased pregnancy and live birth rates (P < 0.0001 and P = 0.020, respectively) with reduced risk of cancelled cycles.

A beneficial effect of metformin co-treatment in increasing clinical pregnancy rates and reducing the risk of OHSS in PCOS patients undergoing assisted reproduction techniques has been shown, but these results are limited to women with PCO who are undergoing ART (12).

In contrast, Al-Ruthia et al (2017) that evaluated the effect of metformin use on pregnancy rates among polycystic ovary syndrome patients undergoing in vitro fertilization found metformin co-treatment during IVF might negatively affect pregnancy rates. A total of 210 women with PCOS, 109 of them received metformin in addition to gonadotropins.Patients who received metformin were 16% less likely to be pregnant in comparison with those who did not receive metformin (OR = 0.840; 95% CI = 0.710–0.993; P = 0.0415). This study is retrospective cohort study which included different doses and duration of metformin administration (13).

Finally, our study results disagreed with Jinno M and colleagues (2010) study which assessed the role of metformin use in non PCO women with other causes of infertility (tubal factor, endometriosis and male factor) who had failed at least twice to conceive by previous IVF, and found that Low-dose metformin improved pregnancy rate (14).

Metformin use improved significantly clinical pregnancy rate compared with previous IVF (36.4% and 9.6% respectively) but there was no statistical difference in endometrial thickness in both groups (10.9 ±0.3 in metformin group and 10.3 ±0.2 with the previous IVF). This study is different from ours as it includes all types of infertility except PCO, using low dose metformin 500 mg for longer period 8-12 weeks before and during ovulation induction and using IVF technique (6).

While regarding endometrial thickness our study agrees with study for Khalaf et al., (2018) which was conducted in Ain Shams university hospital on 85 patients with PCO who received metformin 500 mg three times daily for three months. Endometrial thickness was significantly increased by use of metformin (14).

No previous studies assessed the role of metformin on clinical pregnancy rate in women with unexplained infertility. Points of strength in the current study, the interventions for all participants were done after randomization and blinding, correlation and multiple logistic regression analysis was done to confirm the results,

all participants were diagnosed as unexplained infertility with no other external factors could affect the results.

Points of weakness of the current study the relatively small sample size for looking at some parameters, variation in duration of metformin usage according to the booking time in relation to starting time of clomiphene citrate, excluding obese women from the study who mostly get higher benefit from metformin and short period of metformin administration and follow up for one cycle.

Conclusion

Although, The study showed no significant difference in increasing clinical pregnancy rate by adding metformin to clomiphene citrate for ovulation induction in women with unexplained infertility, it showed a positive effect on endometrial thickness. We are still recommending use of metformin for women with unexplained infertility as it was found that 21 women needed to be treated with metformin in addition to clomiphene citrate to get one pregnant woman, since metformin is a cheap, available, easily administered drug and non-invasive method, so worthy to be added to clomiphene citrate to get one pregnant woman among 21 women as other options for treatment of infertility would be either costy or difficult administration as injection.

Compliance with ethical standards:

Disclosure statement
No potential conflict of interest was reported by the authors.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Ethical approval: All procedures performed in studies involving human participants were in accordance with ethical standards of the Ethical committee of the department of obstetrics and gynecology faculty of medicine, Ain Shams University.

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