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Original article

A new look at low-dose aspirin: Co-administration with tamoxifen in ovulation induction in anovulatory PCOS women

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ABSTRACT

Background: To evaluate the efficacy of co-administration of low-dose aspirin (LDA) and tamoxifen on ovulation rates, endometrial thickness and clinical pregnancy rates in anovulatory PCOS women.
Methods: A randomized clinical trial was conducted among 188 anovulatory PCOS women at Suez Canal University Hospitals, Ismailia – Egypt. Patients were divided into 2 groups. The study group received a daily oral dose of 81 mg of LDA, while the control group received placebo (oral vitamin B12 tablets). Both groups started tamoxifen 10 mg twice daily from 3rd day to 7th day of the cycle. Folliculometry was performed by transvaginal sonography every other day starting from the 9th day of the cycle. Human Chorionic Gonadotrophin 5000 I.U. was given I.M. when at least one dominant follicle was present. The outcome measures included the number of mature follicles (≥18 mm in diameter), endometrial thickness and appearance in addition to the clinical pregnancy rates.
Results: The mean number of follicles per patient was significantly more in the study group (1.4 ± 0.8 vs. 1.1 ± 0.4; *p* value=<0.05). In addition, the endometrium was significantly thicker on study group (9.6 ± 1.4 mm vs. 7.8 ± 1.2 mm; *p* value=<0.01). Significantly, the pregnancy rate was more in the study compared to the control group (37.2% vs. 22.3% respectively; *p* value=<0.03).
Conclusion: Co-administration of LDA with tamoxifen significantly improves ovarian response to stimulation, endometrial thickness and pregnancy rates in anovulatory PCOS patients. This combination is an effective, cheap and safe protocol for infertile PCOS women undergoing ovulation induction.
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Introduction

Tamoxifen – a triphenylethylene derivative – is an anti-estrogenic compound with a structure very similar to clomiphene citrate (CC) [1]. It has been evaluated for ovulation induction (OI) with good results in CC failure cases but fewer side effects such as ovarian hyperstimulation and multiple pregnancies [2]. The reported ovulation rates are between 50–90%; however, pregnancy rates are in the range of 30–50% [2] prompting the search for alternative/adjuvant methods to improve the pregnancy rates.

Low-dose aspirin (LDA) has been shown to increase both ovarian and uterine blood flow through inhibiting the synthesis of thromboxane A2 resulting in vasodilatation and inhibition of platelets aggregation [3]. It was suggested that LDA treatment significantly improves ovarian responsiveness, folliculogenesis, uterine and ovarian blood flow velocity, implantation and pregnancy rates in IVF patients [4,5].

Schisterman et al. [6] in their meta-analysis study regarding LDA in infertility, recommended that more trials are required for meta-analysis and review articles on the effects of LDA on outcomes in infertility to have adequate power to reach definitive findings that could warrant a change in infertility treatment.

Significant number of anovulatory infertile women are resistance to anti-estrogens treatment and need another treatment modality to improve OI results before shifting to other expensive protocols. In the literature, LDA could be added to CC as an adjuvant modality [7]. Meanwhile; the co-administration of both tamoxifen and low-dose aspirin has not been reported in the field of infertility up till now. This has inspired us to evaluate the efficacy of this novel protocol on ovulation rates, endometrial thickness and pregnancy rates in infertile anovulatory PCOS women.

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Participants and methods

After approval of ethics committee of the faculty of medicine, Suez Canal University, this randomized single-blind, clinical trial was conducted during the period from the start of March 2015 to the end of April 2016 at Obstetrics and Gynecology department of Suez Canal University Hospitals. The study included women presented to the outpatient clinic of our department with anovulatory infertility (either primary or secondary) after exclusion of other factors of infertility. The study included women in the reproductive age (20–35 years), BMI < 30 kg/m^2, normal thyroid function tests and prolactin, patent tubes based on normal hysterosalpingogram (HSG) or laparoscopy, and no history of ovulation induction in the previous 3 months to eliminate any post-treatment effect of any ovulation induction drug.

Women eligible for the study (n = 188) were divided into study and control groups by simple randomization method. Each group comprised 94 women, meeting the selection criteria. Randomization of women was performed by using sealed envelopes half of which contained notes labeled as 'study group' and the other half was labeled as 'control group'. Eligible women were asked to choose one of these envelopes to determine the group to which she would be allocated. The study participants received an explanation of the study and signed a consent form. The required sample size was calculated based on a power of the study of 80% and α-error of 0.05 [8] and an expected pregnancy rate of 40% [2].

The study group received a daily oral dose of 81 mg of aspirin (Juspirin®, Julphar CO., U.A.E.), while the control group received vitamin B12 Tab. (Deltavit®, Delta CO., U.A.E.), on the 21st day of their preceding menstrual cycle. After performing transvaginal ultrasonography on 3rd day of the menstrual cycle (for exclusion of any ovarian cysts), induction of ovulation was started in both groups by tamoxifen 10 mg tablet (Tamofen®, Al-Amarya CO., Egypt) twice daily started from 3rd day to 7th day of the cycle, folliculometry was performed by transvaginal sonography (TVS) every other day starting from the 9th day of menstrual cycle. Human Chorionic Gonadotrophin (HCG) at a dose of 5000 IU was administered intramuscularly (Epifassi®, EPICO CO., Egypt) when at least one follicle with a mean diameter ≥18 mm [7]. Endometrial thickness and appearance (triple layer or not) were also assessed prior to HCG administration. Timed intercourse was advised 24 to 36 h after (HCG) injection. All participants received 400 mg of progesterone vaginally (Prontogest®, Marcyl CO.) once daily. Pregnancy was checked by serum beta human chorionic gonadotropin (B-hCG) measurement after two weeks. In cases of positive results, clinical pregnancy was defined as the detection gestational sac by transvaginal ultrasound examination at 6th week of gestation. Patients were advised to continue aspirin or placebo treatment till a positive pregnancy test or at the end of the study (3 months). The study outcome measures included number of mature follicles, endometrial thickness and shape and pregnancy rates after 3 successive cycles of treatment.

Data were processed using SPSS version 16 (SPSS Inc., Chicago, IL, USA). Quantities data were expressed as means ± SD and qualitative data were expressed as numbers and percentages. Student's *t*-test was used to test the significance of difference for quantitative variables while Chi-square and fisher's exact tests were used to test significance for qualitative variables. A probability value (*p*-value) <0.05 was considered statistically significant.

Results

Two hundred and forty-eight women were assessed for eligibility to enroll in the study. Thirty-one were excluded for different reasons in addition to 29 drop out. One hundred eighty-eight completed the follow-up in both arms of the study.

(Table 1) shows the socio-demographic characteristics of all participants. No statistically significant difference was noted between both studied groups regarding women's age, Body Mass Index (BMI), and type and duration of infertility.

The main outcome measures of our study are presented in (Table 2). Significant difference was noted between the studied groups regarding all outcome measures. The mean number of mature follicles ≥18 mm was significantly higher in the study compared to control group [1.4 vs. 1.1 (*p*-value <0.01)]. The endometrial thickness was significantly thicker in the study group [9.6 mm vs. 7.8 mm in the control group (*p*-value <0.01)]. The triple endometrial appearance was more evident in the study group (87% vs. 83%) but without a significant statistical difference. Most importantly, cumulative clinical pregnancy rate after a maximum of 3 cycles of OI was significantly higher in the study compared to the control group (37.2% versus 22.3% respectively; *p* value=<0.03). Of note, more pregnancies occurred in the first treatment cycle in both groups compared to the second and third months (the study group 18, 8 and 9; the control group 9, 7 and 5).

Discussion

In the present study, the co-administration of LDA and tamoxifen appears to be associated with more favorable outcomes compared to tamoxifen alone in ovulation induction. The mean number of follicles, endometrial thickness, and cumulative clinical pregnancy rates are all improved with the addition of LDA to tamoxifen.

Low-dose aspirin has been used for its anti-inflammatory, vasodilator, and platelet aggregation inhibition properties in order to improve blood flow, promote fertility and lead to higher success with IVF regimens [6]. These properties along with the low cost, high availability and minimal side effects of LDA gives it the potential to greatly benefit women who are undergoing ovulation induction.

Low-dose aspirin inhibits the synthesis of thromboxane A2 (TXA2) without affecting the excretion of prostacyclin (PGI2) [9],

Table 1
Baseline characteristics of the studied groups.

Characteristics		Study group (n = 94)		Control group (n = 94)		p-value
Age (Years)	Mean ± SD	26.7 ± 4.8		25.9 ± 6.2		0.3 (NS)
	Range	22–32		21–33		
BMI (kg/m^2)	Mean ± SD	25.6 ± 3.1		26.2 ± 2.8		0.4 (NS)
	Range	20–28		19–28		
Type of infertility	Primary	78	83 %	80	85%	0.8 (NS)
	Secondary	16	17%	14	15%	
Duration of infertility (Years)	Mean ± SD	4.1 ± 2.9		4.3 ± 1.8		0.6 (NS)
	Range	2–7		1.5–7.5		

NS: Not statistically significant difference, BMI: body mass index.

Table 2
Outcome measures in the studied groups.

Characteristics		Study group (n = 94)		Control group (n = 94)		*p*-value
Follicles ≥ 18 mm (N)	Mean ± SD	1.4 ± 0.8		1.1 ± 0.4		<0.05*
	Median	1		1		
Endometrial thickness (mm)	Mean ± SD	9.6 ± 1.4		7.8 ± 1.2		<0.01*
Endometrial appearance		82(87%) 12(13%)		78(83%) 16(17%)		0.45
Triple layer						
Non-Triple layer						
Clinical pregnancy rate**		35	37.2%	21	22.3%	0.03*

* Statistically significant difference.
** Cumulative clinical pregnancy rate after a maximum of 3 cycles of ovulation induction.

thus explaining the increase in blood flow velocity in the ovarian arteries that could result in preferential delivery of gonadotropic hormones or other growth factors or substrates required for steroidogenesis, thus improving folliculogenesis. In addition, prostacyclin has been proposed to modulate the relaxation of vascular smooth muscle of endometrial vessels with vasodilatation of endometrial blood vessels. So, we can postulate that LDA improves the blood supply to both the ovaries and endometrium resulting in a better chance of conception.

Endometrial thickness is one of the essential factors in determining the possibility of success in any ovulation induction program [10]. Of note, at least an endometrial thickness of 8 mm or more is essential for implantation, also preclinical abortions markedly increased in patients whose endometrial thickness was less than 8 mm on the day of HCG administration [11]. So, we can explain the higher pregnancy rate in the study group partly as a result of improved endometrial thickness with the use of LDA. In addition, prostaglandins (PGs) stimulate inflammatory cells and the release of interleukins, which produce inflammation and in turn may diminish the implantation rate. PGF2a stimulates uterine contraction, which may also affect implantation. LDA may avoid these negative effects by irreversibly inhibiting cyclooxygenase, which blocks the synthesis of prostaglandins [12].

Rubinstein et al. [5] reported that LDA treatment significantly improves ovarian responsiveness, uterine and ovarian blood flow, and implantation and pregnancy rates in their patients. However, in contrast to our study; Rubinstein et al. performed their study using low-dose aspirin (100 mg /day) combined with controlled ovarian hyperstimulation for IVF protocol.

In the present study, we opted to use tamoxifen as it is a non-steroidal selective estrogen receptor modulator that has dual action as an ovarian stimulating agent in addition to its estrogenic stimulation effect on the lower genital tract [10]. Furthermore, it improves the endometrial function and receptivity due to increased glycogen content of the endometrial tissue [10]. Regarding LDA, the effects of the different doses ranging from 40 to 324 mg/day on TXA2 and PGI2 have been evaluated. All doses of aspirin suppress TXA2 excretion, however, suppression of PGI2 excretion was more pronounced with the 324 mg or more of aspirin [5].

The study has the following limitations: First, the use of uterine artery Doppler could have been beneficial in elucidating the effect of low dose aspirin on the uterine blood flow and would be an objective measure of its influence. Also, measuring Anti-Mullerian Hormone (AMH) level before ovulation induction could be correlated to both the severity of PCO itself and the outcome of ovulation induction.

In conclusion, our study shows promising results that highlight the potential role for LDA with tamoxifen as an additional co-factor to improve ovarian response; prepare the endometrium to increase the chances of pregnancy. LDA seems to be a useful, effective, cheap and safe treatment in patients who undergo ovulation induction. Further wide scale researches are required to ensure the effectiveness of this co-administration as a novel protocol for ovulation induction.

Conflict of interest

Authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jogoh.2019.02.004.

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