# A Comparative Study between the Effect of Pentoxifylline and Low Dose Aspirin on Uterine Artery Blood Flow in Patients with Unexplained Infertility


## Abstract

**Background:** Infertility is customarily defined as the inability to conceive after 1 year of regular unprotected intercourse. The Practice Committee of the American Society for Reproductive Medicine (ASRM) has published guidelines for a standard infertility evaluation. It includes a semen analysis, assessment of ovulation, a hysterosalpingogram, and, if indicated, tests for ovarian reserve and laparoscopy. The aim of this study was to compare the possible changes in uterine artery doppler indices after the use of pentoxifylline and low dose aspirin in patients with unexplained fertility.

**Methods:** This prospective comparative clinical study was conducted on patients age between 20 and 35 years old, body mass index (BMI) from 18 – 25 $kg/m^2$, with unexplained infertility. Patients were divided into two equal groups: low dose aspirin group and pentoxifylline group. All patients were subjected to personal, husband, sexual and menstrual history taking, clinical examination, routine infertility investigations [Husband semen analysis, Hormonal investigation (FSH, LH, midluteal progesterone, prolactin, TSH)], hysterosalpingogram, laparoscope and transvaginal ultrasound.

**Results:** There was no significant difference between both groups regarding age, BMI, occupation, residency, parity, type/duration of infertility, menstrual regularity/amount, dysmenorrhea, sexual intercourse frequency, using of lubricant or vaginal douching. There was no significant difference between the studied groups regarding FSH, LH, TSH, basal uterine artery RI and PI and S/D ratio at one and three months.

**Conclusions:** In women with unexplained infertility, there was no significant difference between the effect of pentoxifylline and low dose aspirin on the uterine artery blood flow or Doppler indices (RI, PI and S/D ratio).

**Keywords:** Pentoxifylline, Low dose aspirin, Uterine artery, Blood flow, Infertility.

## Introduction:

Infertility is customarily defined as the inability to conceive after 1 year of regular unprotected intercourse. The Practice Committee of the American Society for Reproductive Medicine (ASRM) has published guidelines for a standard infertility evaluation. It includes a semen analysis, assessment of ovulation, a hysterosalpingogram, and, if indicated, tests for ovarian reserve and laparoscopy. When the results of a standard infertility evaluation are normal, practitioners assign a diagnosis of unexplained infertility. Although estimates vary, the likelihood that all such test results for an infertile couple are normal (i.e., that the couple has unexplained infertility) is approximately 15% to 30% [1].

A good blood supply towards the endometrium is usually considered to be an essential requirement for implantation and therefore assessment of endometrial blood flow in has attracted a lot of attention in recent year [2].

Abnormal uterine perfusion may be a contributing factor to etiopathology of unexplained infertility. Transvaginal Doppler pulsed ultrasound is an important tool for examining the female reproductive system and is a noninvasive method to assess the uterine perfusion.

It was found that Peri-implantation endometrial perfusion is impaired in women with unexplained infertility as the uterine artery PI ($P = 0.003$) and RI ($P = 0.007$) were significantly increased in patients with un explained infertility [3].

Pentoxifylline and its metabolites improve the flow properties of blood by decreasing its viscosity. In patients with chronic peripheral arterial disease, this increases blood flow to the microcirculation and enhances tissue oxygenation, lowering blood viscosity, and improving erythrocyte flexibility. Pentoxifylline has been shown to increase leukocyte deformability and to inhibit neutrophil adhesion and activation. Tissue oxygen levels have been shown to be significantly increased by therapeutic doses of pentoxifylline in patients with peripheral arterial disease [4].

Low-dose aspirin irreversibly blocks the formation of thromboxane A2 in platelets, producing an inhibitory effect on platelet aggregation This antithrombotic property makes aspirin useful for improving the blood flow [5].

In this study we discussed the possible effect of pentoxifylline and low dose aspirin on the uterine artery blood flow in patients with unexplained infertility. The aim of this study was to compare the possible changes in uterine artery doppler indices after the use of pentoxifylline and low dose aspirin in patients with unexplained fertility.

## Patients and Methods:

This prospective comparative study was conducted on sixty patients in the department of Obstetrics and Gynecology at Tanta University Hospital, from period of January 2018 to December 2020. Women with age between 20 and 35 years old, body mass index (BMI) from 18 – 25 kg/m$^2$, with unexplained infertility [normal semen analysis with absence of any sexual disorder and normal sexual relation, ovulatory midluteal progesterone value, tubal patency as evaluated in HSG or laparoscope, absence of any endocrinal abnormalities] were included.

Women with any systemic disease, women with a history of pelvic or abdominal surgery, women with previous pelvic inflammatory disease, women with pelvic pathology (ovarian cysts, PCOS, fibroid and endometrial polyp), women suggested to have endometriosis clinically (heavy painful periods, dyspareunia) or proved with laparoscope, smoker woman, drug intake especially hormones were excluded.

Informed consent was obtained from all participants in this research. The study was done after approval from the Ethical Committee, Faculty of Medicine, Egypt.

Patients were subdivided randomly into two equal groups: Pentoxifylline group: patients received pentoxifylline tablets in dose 400mg twice daily for three months. Low dose aspirin group: patients received low dose aspirin in dose of 81 mg once daily for three months.

**All patients were subjected to the following:**

Personal history, husband history and sexual history [coital frequency, timing in relation to the cycle, use of vaginal lubricant before, or vaginal douching after, coitus, as well as any associated problems as difficult or painful coitus] was taken. Past history: medical diseases, abdominal surgeries, drug therapy or allergy. Menstrual history: menarche, regularity, duration, amount, and associated pain.

General and Local clinical examination: to exclude general diseases, local causes of infertility.

Routine infertility investigations were done if not done before: Husband semen analysis, Hormonal investigation (FSH, LH, midluteal progesterone, prolactin, TSH),

Hysterosalpingogram HSG: to ensure tubal patency, Laparoscope: may be used to exclude any apparent cause of infertility, TVS: to detect masses or lesions in uterus, adnexa and pelvis.

After exclusion of causes of infertility by the previous investigation: Mid-luteal TVS color doppler was applied to each patient as initial evaluation of uterine artery blood flow before receiving any treatment.

**Technique used:**

On the day of mid-luteal phase (day 21-22 of menstrual cycle), TVS examination was performed for patient in both groups in the lithotomy position using a 6.5-MHz Transvaginal transducer with CD facility between 12 :4.00 PM. All US scans over a period of minutes to ensure that the analysis spanned several cardiac cycles and exclude circadian effect of blood flow. All women are rested for at least 20 minutes before being scanned to minimize the effect of exercise on uterine blood flow [6].

When a longitudinal view of the uterus was obtained, the color Doppler mode was activated. Doppler sonography was then performed on the vessels with the highest color intensity

within the innermost endometrial subendometrial area. The insonation angle was kept at 0° because the course of the small spiral arteries could not be determined.

After confirming that waveforms were continuous, an average of three to five cardiac cycles was selected for calculation of (RI), (PI), maximum peak systolic blood flow velocity (V max), and (V mean). The vessel with the lowest PI was considered for further statistical analysis. Uterine circulation was assessed simultaneously in each examination; bilateral uterine arteries were sampled lateral to the cervix near the internal os. Mean levels of both uterine RI and PI were used for analysis.

The endometrial thickness pattern visualized was designated as a multilayered or a non-multilayered endometrium. A multilayered endometrium presented as a triple-line pattern in which hyperechogenic outer lines and a well-defined central echogenic line were seen with hypoechogenic or black areas between these lines. A non-multilayered endometrium consisted of homogeneous endometrial patterns characterized by either hyperechogenic or iso-echogenic endometrium [7].

After initial evaluation of all patients by Doppler US the two groups started receiving treatment.

Reevaluation of uterine artery blood flow done to all patients included in the study using Doppler us and data collected.

**Statistical analysis**

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test and within the same group by paired Student's t-test. 95% CI was expressed. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed P value $< 0.05$ was considered statistically significant.

## Results:

Demographic characters, type of infertility and parity, menstrual history and sexual history were insignificantly different between both groups. (Table 1)

**Table 1: Demographic characters, type of infertility and parity, menstrual history and sexual history of the studied groups**

| | | Aspirin group (n= 30) | Pentoxifylline group (n= 30) | 95% CI | P |
|---|---|---|---|---|---|
| **Age** | | 25.80 ± 4.072 | 27.70 ± 6.069 | -4.57, 0.77 | 0.160 |
| **BMI** | | 30.15 ± 2.021 | 29.86 ± 2.098 | -0.78, 1.35 | 0.589 |
| **Occupation** | **Housewife** | 57% (17) | 63% (19) | -0.18, 0.31 | 0.79 |
| | **Worker** | 43% (13) | 37% (11) | | |
| **Residency** | **Rural** | 27% (8) | 33% (10) | -0.17, 0.3 | 0.78 |
| | **Urban** | 73% (22) | 67% (20) | | |
| **Parity (for secondary infertility)** | | 1.25 ± 0.5 | 1 ± 0 | - 0.79, 1.29 | 0.8 |
| **Type** | **Primary** | 87% (26) | 93% (28) | -0.08, 0.22 | 0.67 |
| | **Secondary** | 13% (4) | 7% (2) | | |
| **Menarche** | | 10.87 ± 1.57 | 11.13 ± 1.98 | - 1.19, 0.66 | 0.57 |
| **Menstrual history** | | | | | |
| **Regularity** | **Regular** | 67% (20) | 77% (23) | -0.18, 0.31 | 0.57 |
| | **Irregular** | 33% (10) | 23% (7) | | |
| **Amount** | **Small** | 17% (5) | 13% (4) | - | 0.78 |
| | **Normal** | 77% (23) | 77% (23) | | |
| | **Large** | 7% (2) | 10% (3) | | |
| **Dysmenorrhea** | | 17% (5) | 7% (2) | -0.26, 0.06 | 0.42 |
| **Sexual history** | | | | | |
| **Weekly frequency** | | 2.03 ± 0.67 | 2.33 ± 0.61 | - 63, 0.03 | 0.1 |
| **Lubricant use** | | 40% (12) | 33% (10) | -0.31, 0.18 | 0.79 |
| **Vaginal douching** | | 13% (4) | 17% (5) | -0.15, 0.21 | 1 |

Data is expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between groups. P is significant when < 0.05.

Duration of infertility was statically insignificant different between both groups. (Table 2)

**Table 2: Duration of infertility of the studied groups:**

| | Aspirin group (n= 30) | Pentoxifylline group (n= 30) | 95% CI | P |
|---|---|---|---|---|
| **Duration (months)** | 17.63 ± 5.1 | 16.1 ± 1.94 | - 0.46, 3.53 | 0.13 |

Data is expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between groups. P is significant when < 0.05.

FSH, LH and TSH were insignificantly different between both groups. (Table 3)

**Table 3: Infertility work up in the studied groups:**

| | Aspirin group (n= 30) | Pentoxifylline group (n= 30) | 95% CI | P |
|---|---|---|---|---|
| **FSH** | 4.36 ± 0.219 | 4.31 ± 0.398 | -0.12, 0.21 | 0.58 |

| | | | | |
|---|---|---|---|---|
| **LH** | 10.23 ± 0.332 | 10.39 ± 0.600 | -0.41, 0.09 | 0.22 |
| **TSH** | 2.96 ± 1.385 | 3.55 ± 2.459 | -1.62, 0.44 | 0.26 |

Data is expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between groups. P is significant when < 0.05. FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, TSH: thyroid stimulating hormone.

**Table 4: Resistance index (RI) and pulsatility index (PI) of the studied groups:**

| RI | Aspirin group (n= 30) | Pentoxifylline group (n= 30) | 95% CI | P |
|---|---|---|---|---|
| **Basal** | 0.67 ± 0.086 | 0.69 ± 0.104 | -0.07, 0.03 | 0.369 |
| **One month** | 0.60 ± 0.080 | 0.61 ± 0.076 | -0.05, 0.03 | 0.610 |
| **P1** | **0.002*** | **0.001*** | ---- | |
| **Three months** | 0.57 ± 0.079 | 0.57 ± 0.083 | -0.05, 0.03 | 0.750 |
| **P2** | **<0.001*** | **<0.001*** | ---- | |
| **PI** | | | | |
| **Basal** | 1.26 ± 0.382 | 1.35 ± 0.369 | -0.28, 0.11 | 0.375 |
| **One month** | 1.12 ± 0.297 | 1.15 ± 0.292 | -0.19, 0.12 | 0.647 |
| **P1** | 0.119 | **0.023*** | ---- | |
| **Three months** | 1.14 ± 0.300 | 1.17 ± 0.292 | -0.19, 0.12 | 0.674 |
| **P2** | 0.181 | **0.041*** | ---- | |

Data is expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between groups. P is significant when < 0.05.

**Table 5: S/D ratio of the studied groups:**

| S/D ratio | Aspirin group (n= 30) | Pentoxifylline group (n= 30) | 95% CI | P |
|---|---|---|---|---|
| **Basal** | 2.89 ± 0.600 | 3.06 ± 0.577 | -0.47, 0.14 | 0.290 |
| **One month** | 2.58 ± 0.453 | 2.64 ± 0.469 | -0.31, 0.17 | 0.574 |
| **P1** | 0.005 | **0.003*** | ---- | |
| **Three months** | 2.56 ± 0.450 | 2.62 ± 0.470 | -0.30, 0.18 | 0.621 |
| **P2** | **0.003*** | **0.002*** | ---- | |

Data is expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between groups. P is significant when < 0.05.

Spontaneous pregnancy was insignificantly different between both groups. (Table 6)

**Table 6: Spontaneous pregnancyinthe studied groups:**

| | Aspirin group (n= 30) | Pentoxifylline group (n= 30) | 95% CI | P |
|---|---|---|---|---|
| **Spontaneous pregnancy** | 13.3% (4) | 16.7% (5) | 0.40, 1.89 | 1 |

Data is expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between groups. P is significant when < 0.05.

## Discussion

The uterine artery pulsatility index(PI) and resistance index(RI) were considerably elevated in patients with unexplained infertility, indicating that peri-implantation endometrial perfusion is compromised in women with unexplained infertility [8].

Pentoxifylline is a methyl xanthine derivative that alters blood rheology by inhibiting phosphodiesterase. It enhances blood flow by improving the elasticity of erythrocytes and leukocytes. It also prevents platelets from clumping together [9].

Low-dose aspirin, commonly known as acetylsalicylic acid (ASA), inhibits platelet aggregation by irreversibly blocking the synthesis of thromboxane A2 in platelets. Aspirin is useful for increasing blood flow because of its antithrombotic properties [10].

Regarding **infertility work up**; statistical analysis of current results showed that there was no significant difference between both groups regarding FSH, LH, TSH, basal uterine artery RI and PI and S/D ratio at one and three months.

**Yao-Yuan et al (2000)** evaluated the effect of aspirin on infertile women with thin endometrium. Patients who had thin endometrium (<8mm) and intrauterine insemination were divided into the aspirin and non-aspirin groups. A total of 114 and 122 women were included in the aspirin and non-aspirin groups, respectively. Endometrial pattern (tri-laminar and non-tri-laminar) and thickness, the pulsatility index (PI) and resistance index (Rl) of the uterine artery, spiral artery, and ovarian dominant follicles, and pregnancy rates of both groups were measured. They disagreed with current study and stated that there was no significant difference in the endometrial thickness, and PI/RI values of the uterine artery; spiral artery, and ovarian dominant follicle between both groups but there were significantly higher percentages of tri-laminar endometrium (46.5% vs. 26.2%) and pregnancy rate (18.4% vs. 9.0%) after aspirin therapy.

**Ledee-Bataille et al (2002)** didn't evaluate the effect of pentoxifylline on the uterine artery Doppler indices. On the other hand, they stated that treatment by pentoxifylline (PTX) appears to improve the pregnancy rate in patients with a thin endometrium by increasing the endometrial thickness and improving ovarian function. This was especially noticeable in patients who had previously received total body irradiation. They evaluated the effect of an anti-fibrotic treatment by a combination of PTX and tocopherol (vitamin E) in patients with a thin endometrium who were enrolled in an oocyte donation program. Eighteen oocyte

recipients who failed to develop a pre-ovulatory endometrial thickness of at least 6 mm after receiving vaginal micronized estradiol were enrolled in the study. The patients received a combination of PTX (800 mg/day) and vitamin E (1000 lU/day) for 6 months.[11]

**Élène Letur-Konirsch and Delanian (2003)** stated that in women with premature ovarian failure (POF) and uterine resistance to HRT; combined PTX-Vit.E reduces fibro-atrophic uterine lesions and improves the uterine response to hormonal replacement therapy (HRT), thus allowing embryo implantation and ongoing pregnancy. They assessed whether treatment with combined pentoxifylline (PTX) and tocopherol (Vit.E) can improve uterine parameters in HRT-resistant women with POF, for whom the outcome of assisted reproductive technology is usually negative. Three women with POF (ages 36 ± 2 years) using HRT exhibited uterine hormone-resistance, although they had high E2 plasma levels. Their mean endometrial thickness was 4.9 mm, and they had an echogenic endometrium and thin uterine crosses. Treatment consisted of 800 mg of PTX combined with 1,000 IU of Vit.E daily for at least 9 months. PTX-Vit.E treatment was well tolerated and induced improvements in endometrial thickness, echogenicity, and pulsatility index of the uterine arteries assessed by ultrasound and Doppler before and after treatment, and embryo implantation by IVF oocyte donation.[12]

**Acharya et al (2009)** didn't evaluate the effect of pentoxifylline on the uterine artery Doppler indices. On the other hand, a retrospective analysis was carried out to investigate the use of pentoxifylline and tocopherol in improving the endometrial thickness in cases that are unresponsive to conventional therapy. Twenty women with thin endometrium (56 mm) undergoing either ovulation induction or frozen embryo transfer cycles were prescribed 800 mg of PTX and 1000 IU of Vit E daily. The mean duration of treatment was 8.1 months (+4.5, range 1–18 months). The mean thickness of endometrium before and after treatment was 4.37 mm (+1.5 mm) and 6.05 mm (+1.83 mm), respectively. Overall, 14 (73.7%) women showed improvement in endometrial thickness which was the primary outcome. Pregnancy occurred in eight women (40%) of which three were natural, one had ovulation induction and another five had frozen embryo transfers.[13].

**Haapsamo et al (2009)** [14] stated that in unselected IVF/ICSI women, low-dose aspirin therapy, when started concomitantly with controlled ovarian stimulation, did not affect UtA vascular impedance on the day of embryo transfer. However, the incidence of non-optimal uterine hemodynamics was significantly lower in the aspirin group than in the placebo group. A total of 122 women who underwent IVF/ICSI were randomized to receive 100 mg aspirin (n = 61) or placebo (n = 61) daily, starting on the first day of gonadotrophin

stimulation. Doppler ultrasonography was performed on the day of embryo transfer. Embryo transfer took place in 57 women in the aspirin group and in 56 women in the placebo group. UtA mean PI values did not differ significantly between the groups. The incidence of non-optimal uterine hemodynamics was lower in the aspirin group than in the placebo group (P = 0.03). Other secondary outcome measures did not differ between the groups.

**Aleyasin et al (2009)**[15] showed that PTX plus tocopherol could improve the ZIFT outcome in infertile couples. Local effects and anti-oxidative characteristics of these drugs may be the cause of better results however they didn't assess their effects on uterine artery Doppler indices. They aimed to determine whether combined PTX and tocopherol treatment can improve clinical pregnancy rate or not. One hundred twelve infertile women undergoing standardized controlled ovarian hyperstimulation for ICSI- ZIFT entered this randomized clinical trial. Patients were randomized to equal groups of combined PTX and tocopherol therapy or none (not receiving PTX and tocopherol). These drugs were administered to the intervention group for two cycles before starting ICSI-ZIFT cycle. The clinical pregnancy was higher in the intervention (combined PTX and tocopherol) group in comparison to the other group (57.14% vs 39.29%, p=0.01). However, there was no difference in the mean endometrial thickness, number of retrieved oocytes, the number of metaphase II oocytes and grade of them in both groups.

**Akbari-Fakhrabadi et al (2018)** **[16]**aimed to summarize the available findings regarding the effect of pentoxifylline (PTX) and tocopherol combination on improving endometrial thickness that wasn't assessed in our study. The review included interventional studies, including randomized controlled trials (RCTs) and quasi-experimental studies, assessing PTX and vitamin E (Tocopherol) combination in women with thin endometrium. A meta-analysis of three quasi-experimental studies showed a significant difference in endometrial thickness after treatment (MD: 1.96 mm; 95% CI: 0.94–2.98, p<.001) but there was no difference in the mean of endometrial thickness between case and control groups (10.8 vs. 10.48 mm, p5.467) in aforementioned RCT. Although the effect of intervention was seen in quasi experimental studies but this finding was not confirmed in the only retrieved RCT.

Finally, **Wang et al (2020)** **[17]**stated that unexplained recurrent pregnancy loss (URPL) patients had impaired uterine perfusion. Doppler parameters are valuable in predicting women at high risk of URPL. Low-dose aspirin (LDA) could be effective in improving endometrial receptivity. They evaluated differences in Doppler parameters and pregnancy outcomes and determined the predictive accuracy of such indices, as well as the

effects of LDA in URPL. An observational study was conducted on 190 cases. The endometrial thickness, pulsatility index (PI), resistive index (RI), and systolic-to- diastolic ratio (S/D) values of endometrial and uterine artery blood flow were collected. A second ultrasonography examination was performed in URPL patients who had received daily LDA for 2 months. There were 190 URPL patients and 35 control patients. Endometrial thickness was significantly thinner in URPL patients than control patients ($P$=0.005). The PI, RI, and S/D values for endometrial blood flow and the mean PI, RI, and S/D values for uterine arteries were significantly higher in URPL patients ($P$<0.001). The predictive accuracy of the indices mentioned above were 0.660, 0.802, 0.852, 0.837, 0.784, 0.929, and 0.929, respectively. Following LDA supplementation, URPL patients showed a significant reduction in resistance to endometrial and uterine artery blood flow ($P$<0.001).

The limitations of current study were due to COVID 19 pandemic, relatively small sample size and blinding wasn't done.

**Conclusions:**

In women with unexplained infertility, there was no significant difference between the effect of pentoxifylline and low dose aspirin on the uterine artery blood flow or Doppler indices (RI, PI and S/D ratio).

**Financial support and sponsorship:** Nil

**Conflict of Interest:** Nil

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