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Low-dose aspirin treatment improves ovarian responsiveness, uterine and ovarian blood flow velocity, implantation, and pregnancy rates in patients undergoing in vitro fertilization: a prospective, randomized, double-blind placebo-controlled assay

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Objective: To determine the effects of low-dose aspirin on ovarian response, uterine and ovarian blood flow velocity, and implantation and pregnancy rates in patients undergoing IVF.

Design: Prospective, randomized, double-blind placebo-controlled assay.

Setting: Department of Reproductive Medicine, CER Medical Institute, Buenos Aires, Argentina.

Patient(s): Two hundred ninety-eight infertile patients (mean [± SD] age, 35.6 ± 4.09 years) undergoing IVF cycles.

Intervention(s): In the treatment group, 149 patients underwent controlled ovarian hyperstimulation and received a daily dose of 100 mg of aspirin. In the control group, 149 patients underwent controlled ovarian hyperstimulation in association with placebo.

Main Outcome Measure(s): Number of follicles, number of oocytes retrieved, serum E_2 levels, uterine and ovarian pulsatility index, cancellation rate, number of embryos transferred, and implantation and pregnancy rates.

Result(s): There were statistically significant differences between the treatment group and the control group, respectively, in the number of follicles (19.8 ± 7.2 versus 10.2 ± 5.3), number of oocytes retrieved (16.2 ± 6.7 versus 8.6 ± 4.6), serum E_2 levels (2,923.8 ± 1,023.4 versus 1,614.3 ± 791.7 pg/mL), uterine pulsatility index (1.22 ± 0.34 versus 1.96 ± 0.58), ovarian pulsatility index (1.18 ± 0.31 versus 1.99 ± 0.56), pregnancy rate (45% versus 28%), and implantation rate (17.8% versus 9.2%).

Conclusion(s): Low-dose aspirin treatment significantly improves ovarian responsiveness, uterine and ovarian blood flow velocity, and implantation and pregnancy rates in IVF patients. (Fertil Steril® 1999;71:825–9. ©1999 by American Society for Reproductive Medicine.)

Key Words: Aspirin, IVF-ET, implantation, pregnancy rate, uterine and ovarian blood flow velocity, Doppler ultrasound

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Acetylsalicylic acid was synthesized in 1897. The product was called aspirin. In 1971, Vane (1) described the mechanism of action of aspirin, showing that it inhibits the enzyme cyclooxygenase, thus avoiding prostaglandin (PG) synthesis.

Because PGs participate in almost all human body systems, it is not surprising that a drug with a mechanism of action related to them should have multiple therapeutic uses. Since its beginnings, aspirin has been used as an analgesic, an antiinflammatory, and an antipyretic agent.

It is well known that low-dose aspirin is effective in the prevention and treatment of cardiovascular diseases (2–6). Furthermore, it has been demonstrated that low-dose aspirin increased the weight of newborns in pregnant patients with fetal growth retardation; it is also

used to prevent recurrent idiopathic fetal growth retardation and to improve placental and fetal blood flow in women with preeclampsia (7–9).

Currently, low-dose aspirin treatment is also used as an effective therapy for women with antiphospholipid syndrome and recurrent miscarriages. Several studies have compared patients with antiphospholipid antibody seropositivity who were receiving heparin and aspirin with untreated seronegative patients; these studies showed high fecundity rates after IVF-ET in antiphospholipid antibody–seropositive women treated with heparin and aspirin (10).

Several studies are being performed to determine whether aspirin inhibits the replication of human immunodeficiency virus and also whether aspirin diminishes the incidence of mortality in patients with colon cancer (11, 12). The aim of this study was to evaluate the effect of low-dose aspirin treatment in infertile patients to improve the outcome of IVF cycles.

MATERIALS AND METHODS

This was a prospective, randomized, double-blind placebo-controlled study. Randomization was performed by drawing a sealed envelope, which contained instructions on how each patient would be treated (aspirin or placebo). Both patients and clinical staff were blinded to the treatment.

We analyzed 298 couples whose infertility was due to a tubal factor and who underwent consecutive IVF cycles. The couples had previously signed informed consent forms. The study was performed in accordance with the ethical standards of the CER Medical Institute ethics committee, the ethical statements of the Argentine Society for Sterility and Fertility, and the Helsinki declaration of 1975 (as revised in 1983).

The 298 patients were randomly divided into treatment and control groups. The treatment group (149 patients; mean [± SD] age, 35.9 ± 4.2 years) received a daily oral dose of 100 mg of aspirin, and the control group (149 patients; mean age, 35.4 ± 3.9 years) received placebo. Both groups started aspirin or placebo cotreatment on the 21st day of their preceding menstrual cycle.

Controlled ovarian hyperstimulation was initiated in all patients with the GnRH analogue leuprolide acetate (Lupron; Abbott, Buenos Aires, Argentina), starting in the midluteal phase of the previous cycle. Subcutaneous injections (2 mg/d) were given until pituitary desensitization was achieved, which was confirmed by serum E_2 levels <27 pg/mL and by basal ultrasonography. Then, gonadotropin therapy was given using highly purified FSH or recombinant FSH and hMG (Gonal F, Metrodine and Pergonal, Serono Laboratories, Buenos Aires, Argentina; Puregon and Humegon, Organon, Buenos Aires, Argentina). GnRH analogue injection (1 mg/d) was continued up to and including the day of hCG administration (Profasi 10,000 IU, Serono Laboratories; Pregnyl, Organon).

Cycle monitoring was performed with serial transvaginal ultrasonography and serum E_2 levels, as published previously (13). Moreover, transvaginal color Doppler ultrasonography was used to measure uterine and ovarian blood flow velocity on day 2 of the preceding cycle and on the day of hCG administration of the ovarian-stimulated cycle. All scans were performed by one operator using a Medison 7700 (Ekhoson, Buenos Aires, Argentina) with a transvaginal probe of 7.5 MHz.

Blood flow velocity expressed as pulsatility index (PI), which is an angle-independent parameter, was calculated automatically according to the following formula: PI = [(peak systolic velocity/mean velocity) − (end-diastolic velocity/mean velocity)]. This variable is currently the most accurate method of assessing blood flow velocity and can even be used when there is absent or reversed flow in diastole. Furthermore, the pulsatility index not only uses maximum peak flow velocity, but also takes into account the mean flow during the whole cardiac cycle. The mean pulsatility indices of the left and right uterine arteries and the left and right ovarian arteries were calculated and used as an index of uterine and ovarian flow velocity, respectively.

Transvaginal follicular aspiration and IVF-ET were performed after our standard procedure (14). The luteal phase was supported by vaginal micronized P (300 mg/d, Utrogestan; Rontag, Buenos Aires, Argentina) and IM P (100 mg/d, Prolution; Schering, Buenos Aires, Argentina).

Clinical pregnancies were detected by increasing serum β-hCG levels in at least two determinations 14–16 days after ET and were confirmed by ultrasonographic screening of the gestational sac showing fetal heart activity 7 days after the last β-hCG determination. Pregnant patients continued the medication, which included aspirin or placebo cotreatment, through 12 weeks' gestation.

The ovarian responsiveness and IVF outcome variables analyzed included number of follicles of >15 mm, number of oocytes retrieved, serum E_2 levels on the day of hCG administration, mean pulsatility index of the left and right uterine and ovarian arteries, cancellation rate, number of embryos transferred, implantation rate, and pregnancy rate (PR). The data were analyzed with the use of the two-tailed Student's *t*-test, Mann-Whitney rank-sum test, and Fisher's exact test. $P<.05$ was considered statistically significant.

RESULTS

The results of this study are summarized in Table 1. The mean (± SD) age was similar in the treatment and control groups (35.9 ± 4.2 versus 35.4 ± 3.9 years, respectively).

The mean number of embryos transferred was identical in

TABLE 1

IVF-ET outcome in the treatment and control groups.

Variable	Treatment group (n = 35)	Control group (n = 39)	*P* value
Mean age (y)	35.9 ± 4.2	35.4 ± 3.9	NS
Cancellation rate (%)	4	9	<.05
No. of follicles	19.8 ± 7.2	10.2 ± 5.3	<.05
No. of oocytes retrieved	16.2 ± 6.7	8.6 ± 4.6	<.05
E_2 level (pg/mL)	2,923.8 ± 1,023.4	1,614.3 ± 791.7	<.05
No. of embryos transferred	3.3	3.3	NS
Implantation rate (%)	17.8	9.2	<.05
Clinical PR (%)	45	28	<.05

Note: Values are means ± SD unless otherwise indicated. PR = pregnancy rate. NS = not significant.

TABLE 2

Doppler ultrasound measurements in the treatment and control groups.

Variable	Pulsatility index: Treatment group	Pulsatility index: Control group	*P* value
Uterine arteries			
Day 2 of a previous cycle	1.98 ± 0.48	2.01 ± 0.54	NS
Day of hCG administration	1.22 ± 0.34	1.96 ± 0.58	<.05
P value	<.05	NS	
Ovarian arteries			
Day 2 of a previous cycle	2.10 ± 0.45	2.16 ± 0.57	NS
Day of hCG administration	1.18 ± 0.31	1.99 ± 0.56	<.05
P value	<.05	NS	

Note: Values are means ± SD. NS = not significant.

both groups (3.3 embryos; range, 2–5). At least two good-quality embryos were transferred in all patients.

Ovarian responsiveness was expressed as the number of follicles of >15 mm on the day of hCG administration, the number of oocytes retrieved, and serum E_2 levels on the day of hCG administration.

The mean (± SD) number of follicles of >15 mm on the day of hCG administration was 19.8 ± 7.2 versus 10.2 ± 5.3 for the treatment and control groups, respectively ($P<.05$). The mean (± SD) number of oocytes retrieved for the treatment group was 16.2 ± 6.7, versus 8.6 ± 4.6 for the control group ($P<.05$). The mean (± SD) level of serum E_2 on the day of hCG administration was also significantly higher in the treatment group than in the control group (2,923.8 ± 1,023.4 versus 1,614.3 ± 791.7 pg/mL, respectively; $P<.05$). Therefore, the three indices used to determine ovarian response were significantly higher in the treatment group than in the control group.

The aspirin-treated group had a significantly lower cancellation rate than the control group (4% versus 9%, respectively; $P<.05$).

The implantation rate and PR were significantly higher in the group of patients who received aspirin treatment as compared with those who received placebo. The implantation rate was 17.8% in the treatment group and 9.2% in the control group ($P<.05$). The clinical PR was 45% versus 28% for the treatment and control groups, respectively ($P<.05$) (Table 1).

We performed transvaginal color Doppler ultrasonography to compare uterine and ovarian blood flow velocity in the two groups. Patients who received aspirin (treatment group) showed an increased blood flow velocity as compared with the control group. Pulsatility index values of the uterine and ovarian arteries in patients included in the treatment group were significantly lower on the day of hCG administration as compared with the pulsatility index on day 2 of a previous cycle (pulsatility index in uterine arteries: 1.22 ± 0.34 versus 1.98 ± 0.48, respectively, $P<.05$; pulsatility index in ovarian arteries: 1.18 ± 0.31 versus 2.10 ± 0.45, respectively, $P<.05$). The control group showed no significant difference between the pulsatility index in the uterine and ovarian arteries on the day of hCG administration and the pulsatility index on day 2 of a previous cycle (1.96 ± 0.58 versus 2.01 ± 0.54 and 1.99 ± 0.56 versus 2.16 ± 0.57, respectively).

Moreover, the pulsatility index values on day 2 of a previous cycle were similar in both groups (1.98 ± 0.48 and 2.01 ± 0.54 in the treatment and control groups, respectively), but when we analyzed the pulsatility index on the day of hCG administration, the treatment group showed a significantly lower pulsatility index in the uterine and ovarian arteries as compared with the control group (1.22 ± 0.34 versus 1.96 ± 0.58, respectively, in uterine arteries and 1.18 ± 0.31 versus 1.99 ± 0.56, respectively, in ovarian arteries) (Table 2).

When analyzing the uterine pulsatility index in those patients who got pregnant and those patients who did not, the pulsatility index was found to be significantly lower in the group of pregnant patients (1.23 ± 0.36 versus 2.6 ± 0.54, respectively; $P<.05$).

No side effects were observed in patients treated with aspirin, and bleeding was similar for both groups.

DISCUSSION

The number of follicles, number of oocytes retrieved, serum E_2 levels on the day of hCG administration, implantation rate, and PR were significantly higher in patients who received aspirin cotreatment during the IVF cycles (Table 1). Furthermore, patients treated with aspirin showed increased blood flow velocity in the uterine and ovarian arteries with lower pulsatility index values (Table 2).

These results could be explained by the pharmacologic

properties of aspirin. First, several substances such as collagen, thrombin, thromboxane A_2 (TXA_2), adenosine diphosphate (ADP), and dense and alpha granules from the platelets produce platelet activation. Activated platelets release calcium from the dense granules into the cytoplasm. Calcium causes platelet contraction with a further release of serotonin, ADP, and arachidonate. Arachidonate is converted into TXA_2 by the cyclooxygenase enzyme. When this enzyme is irreversibly inhibited by low-dose aspirin treatment, vasoconstriction and platelet aggregation may be avoided (14, 15), which in turn may improve folliculogenesis and implantation.

As regards the dose determination, the effects of a range of very low doses of aspirin (40–324 mg/d) on TXA_2 and prostacyclin (PGI_2) have been evaluated (16). All doses of aspirin suppressed TXA_2 excretion by >80%. Suppression of PGI_2 excretion was more pronounced with the 324-mg dose of aspirin than with other doses.

Low doses of aspirin seem to be more platelet-selective than high doses, with an optimal effect at approximately 100 mg/d without affecting the bleeding time (17). Although the vascular store of cyclooxygenase is renewable, kinetic studies have shown that platelet TXA_2 production is inhibited for the lifespan of the platelet (8–11 days) (15–18). Cyclooxygenase enzyme is responsible for the conversion of arachidonic acid to TXA_2 in the platelet; in cells of the vascular wall it is responsible for the conversion of arachidonic acid to PGI_2 (14, 19, 20). TXA_2 induces platelet aggregation and vasoconstriction; PGI_2 inhibits platelet aggregation and induces vasodilation (21, 22).

Thus, aspirin has the potential to be both antithrombotic and thrombogenic. The thrombogenic effect occurs only with high doses because platelet cyclooxygenase is more selective than vascular cyclooxygenase. Therefore, low-dose aspirin inhibits the synthesis of TXA_2 without affecting the excretion of PGI_2 (23–25), thus explaining the increase in blood flow velocity in the uterine and ovarian arteries.

Prostacyclin has been proposed to modulate the relaxation of vascular smooth muscle of endometrial vessels. As low-dose aspirin treatment shifts local production of TXA_2 toward PGI_2, we can postulate that this therapy may improve embryo implantation because of its effect on the endometrium.

Moreover, PGs stimulate inflammatory cells (monocytes, lymphocytes, neutrophils, and macrophages) and the release of interleukin, which produces inflammation (26, 27) and in turn may diminish the implantation rate. $PGF_{2\alpha}$ stimulates uterine contraction, which may also affect implantation. Aspirin may avoid these negative effects by irreversibly inhibiting cyclooxygenase, which blocks the synthesis of PGs (1).

The appearance, number, and size of blood vessels that could be detected inside the ovaries increased with follicular development. Vascularization of the follicles may play a role in their maturation from the early follicular phase. Aspirin seems to increase this vascularization because of a vasodilation effect that could result in preferential delivery of gonadotropic hormones or other growth factors or substrates required for steroidogenesis, thus improving folliculogenesis.

Hence, aspirin increases blood flow in the ovaries, which may improve folliculogenesis and increase the number of oocytes retrieved. Our results showed a statistically significant increase in the uterine blood flow velocity in patients who were treated with aspirin, with a mean pulsatility index in the uterine arteries on the day of hCG administration of 1.22 in the treated group versus 1.96 in the control group. Because implantation requires dilation of endometrial blood vessels, the increase in the uterine blood flow velocity resulting from low-dose aspirin treatment may improve implantation.

Wada et al. (28) performed a prospective trial that revealed a significant improvement in blood flow and PRs after aspirin therapy. Aspirin treatment may have decreased TXA_2 excretion of endometrial cells, improving implantation in the treated group. In agreement with Battaglia et al. (29), we conclude that TXA_2 plays a role in embryo implantation and that Doppler flow analysis of the uterine arteries in infertile patients may be important in the management of ovarian stimulation cycles.

A reduced PR has been reported in IVF patients with low uterine blood flow (28, 30). It is possible that the reduced PR in patients with a thin endometrium could be improved by increasing uterine blood flow (31). We think that low-dose aspirin treatment is a useful way to achieve this objective.

It has been shown that the blood flow velocity in the uterine and ovarian arteries increased significantly after ovulation induction (32, 33). The pulsatility index was also significantly lower in women with a high endocrine response compared with those with a low response, having a negative linear correlation with the number of follicles >15 mm on the day of hCG administration. Those changes occurred because of a marked decrease in the vascular impedance and, therefore, an increase in the diastolic blood flow velocity (34). The changes in vessel compliance are responsible for alterations in blood flow during cycle stimulation. Ovarian steroids alter the function of periarterial sympathetic nerves through changes in α-1-adrenergic receptor numbers, leading to marked changes in blood flow (35).

In our study, pregnant patients showed significantly lower uterine pulsatility index values than those patients who did not get pregnant. These data confirm that the decrease in peripheral impedance in the uterine vascular bed, reflected by a low pulsatility index, is a consequence of increased blood flow and tissue perfusion, which may improve uterine receptivity (29, 36–38).

In conclusion, this study demonstrated that low-dose aspirin treatment significantly improves ovarian response, uter-

ine and ovarian blood flow velocity, implantation rate, and PR in patients undergoing IVF. Aspirin seems to be a useful, effective, and safe treatment in patients who undergo assisted reproductive technologies.

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