Does addition of low-dose aspirin and/or steroid as a standard treatment in nonselected intracytoplasmic sperm injection cycles improve in vitro fertilization success? A randomized, prospective, placebo-controlled study

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Purpose: To investigate the effects of short-term low-dose aspirin and/or steroid use on implantation and pregnancy rates in nonselected intracytoplasmic sperm injection (ICSI) cycles.

Methods: Two-hundred patients undergoing ICSI for their first cycle were enrolled in this study. Participants were then randomized into four groups on the embryo transfer day. Aspirin (100 mg/day) in group A, prednisolone (10 mg/day) in group B, aspirin along with prednisolone in group C were given while placebo was administered to group D.

Result: There were no statistically significant differences recorded in the demographic, ovulation induction cycle characteristics between groups. Mean transferred embryo number and mean top quality embryo number were similar among study groups. There were no statistical differences in implantation and pregnancy rates between study groups.

Conclusion: Administration of low-dose aspirin and prednisolone alone or concomitant as a standard treatment have no positive effects on implantation and/or pregnancy rates.

KEY WORDS: aspirin; prednisolone; implantation rate; pregnancy rate.

INTRODUCTION

Implantation process was the most crucial step comprising many cell–cell and cell–cytokines interactions for determining in vitro fertilization (IVF) success. Despite the advanced success in fertilization rates approaching up to 80% in in vitro fertilization techniques, the implantation rates are still not in desired ranges mainly lower than 20–25% for per

embryo transfer. However there has been a great diversity between countries and clinicians in administration of aspirin and/or steroid among infertile patients to improve the IVF success, some controversial studies reported conflicting results leading a debate in use of aspirin or steroid increasing the implantation and pregnancy rates in IVF as a standard or optional treatment in selective infertile patients.

Low-dose aspirin has been widely used in obstetrics to increase uteroplacental perfusion especially in preeclampsia and to prevent idiopathic intrauterine growth retardation (1). Particularly, on the basis of the similar effects of anti-aggregant agents on reproductive organs, it has been hypothesized that insufficient uterine blood flow could be diminished IVF outcomes due to alterations implantation mechanism

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and environment. Subsequently, one can hypothesize that increased uterine blood flow by administration of anti-aggregant agents can improve the IVF outcomes leading a favorable environment. In a study exploring Wada *et al.* reported that administration of aspirin, an anti-aggregant agent, in cryopreserved cycles of patients with impaired uterine perfusion (high pulsatility index) improved the IVF outcomes by increasing the pregnancy rates (2). They claimed that improved outcomes were a result of increased uterine perfusion (2). Likewise, Sher *et al.* reported that concomitant use of aspirin and heparin in IVF patients with positive anti-phospholipid antibodies increased pregnancy rates (3). In addition, concomitant administration of aspirin and prednisolone, a steroid, in IVF patients with positive auto-antibodies resulted in favorable outcomes (4).

However, the administration of corticosteroids in nonselective IVF patients is controversial, steroid administration was also shown to increase pregnancy rates in IVF patients with embryonal assisted hatching (5). Nevertheless these improved results of corticosteroid administration in those patients with micro-manipulated embryos did not solely support the idea of routine usage of immunosuppressive agents in IVF-ET patients because of possible effect of micromanipulation. Therefore, regardless of increased pregnancy rates, there was no consensus achieved whether routine usages of immunosuppressive agents without any other clinical or laboratory procedure do improve the IVF outcomes or not?

In this prospective randomized study we aimed to investigate the possible positive effect of aspirin and/or prednisolone on implantation and pregnancy rates among nonselected infertile patients undergoing ICSI in whom no additional clinic and/or laboratory procedure was performed.

MATERIALS AND METHODS

Two hundred nonselected infertile patients who were undergoing their first ICSI cycle at Faculty of Medicine, Department of Obstetrics and Gynecology, Ankara University, IVF Unit between the years 2001 and 2002 were enrolled in this prospective study. The study was approved by the local ethical committee of the Faculty of Medicine, Ankara University, and an informed consent was taken from all participants. One patient with asthma bronchial

was excluded from the study after standard routine questionnaire given to all participants for detecting systemic diseases in which anti-aggregants and/or steroid administrations are contraindicated. Laboratory tests comprising day 3 serum hormone levels, markers for TORCH infections was studied routinely in all participants. Subsequent to laboratory tests a standard long-luteal GnRH agonist with triptorelin acetate (0.1 mg/day/sc). Erkim Pharmacy, Turkey) ovulation induction regimen along with fixed dose (225–450 IU/day) of recombinant gonadotropin (follitropin β , PuregonTM; Organon group, Turkey) concerning age, BMI, day 3 hormone profile was implemented to all participants. Ovulation induction monitorization of cycles was made by serial folliculometry, serum estradiol (E₂) and/or luteinization hormone (LH) levels studied. Among these 199 patients who undergone ovulation induction regimen totally five patients with poor response to ovulation induction (days 5–6 E₂ levels <100 mg/mL), five patients with premature LH surge (LH levels >10 IU/mL) and two patients with severe ovarian hyperstimulation syndrome (E₂ levels >4300 mg/mL) in whom ovulation triggering was not conducted were excluded from the study. Ovulation triggering was made by 10,000 IU urinary hCG (PregnylTM 5000 IU; Organon group, Turkey) as soon as three >17 mm or two >18 mm follicle was measured. Oocyte aspiration procedures (OPU) were performed after 35–36 h from hCG triggering with 17 G double lumen aspiration needle (SwemedTM; PM Group, Turkey). Subsequently, 187 patients were reached to embryo transfer step after ovulation induction. On embryo transfer day these participants were then randomized into four groups based on a lottery randomization with the help of envelopes and initial letters of the groups regardless of measured endometrial thickness on the same day; group A (41 patients) was given 100 mg/day aspirin, group B (50 patients) was given 10 mg/day prednisolone, group C (56 patients) was given aspirin (100 mg/day) along with prednisolone (10 mg/day) while group D (40 patients) was taken as a control group. Same sequential media (GII series, VitrolifeTM; Colorado, USA) was used for embryo culturing. Embryo scoring was done according to zonal thickness, cytoplasmic fragmentation, blastomeres number, and morphology. All embryo transfers were performed by the same clinician under ultrasound guidance with a soft embryo transfer catheter (WallaceTM, California, USA) in all compared cycles on day 3. Luteal phase was supported by administration of 3 × 200 mg/day

vaginal micronised progesterone (ProgestanTM; Koçak Pharmacy, Turkey) in all cycles.

Pregnancy was determined as positive β -hCG levels after 12 days from embryo transfer and doubling levels after 2 days from the initial serum β -hCG levels. Clinical pregnancy was confirmed by observing the gestational sac and/or detecting fetal heart beats. Aspirin and/or steroid therapy was continued until the clinical pregnancy test was confirmed. In cases with no increase in β -hCG levels and/or no observation of gestational sac was classified as biochemical pregnancy.

Statistical Tests

The statistical analysis was carried out by the SPSS for Windows Version 9.0. For the measurement of comparison among groups one-way variance analysis, Kruskal–Wallis variance analysis, Student's test, and for counted data chi-square test was used. A p value <0.05 was considered as statistically significant. To achieve 80% power with a type I error $p = 0.05$ for observing a 20% difference in implantation and pregnancy rates between the groups, 200 subjects ($n = 50$ each group) were planned to enroll to the current study.

RESULTS

A total of 187 patients' first ICSI cycle in which embryo transfer was performed were enrolled in this prospective randomized study. After randomization 100 mg/day aspirin was given to 41 patients in group A, 10 mg/day prednisolone was given to 50 patients in group B, aspirin (100 mg/day) along with prednisolone (10 mg/day) was given to 56 patients in group C, and placebo was given to 40 patients in group D (control group). No adverse side effects due to aspirin and/or steroid therapy were detected during the study. The mean age of patients in the study was 31.8 ± 6.0 . There were no significant differences between the groups in demographic characteristics concerning age, infertility period, infertility etiology, mean serum E_2 , and FSH hormone levels (Table I).

There were also no statistically significant differences observed in ovulation induction characteristics of the patients among the study groups regarding mean total gonadotropin dose (IU), mean stimulation period, mean serum E_2 levels on hCG day, mean number of follicles >14 mm and >17 mm on the triggering day, mean number of picked-up oocytes, mean number of M_2 oocytes (Table II). There were

also no significant differences observed in patients' pre-embryo transfer ICSI characteristics, comprising also the mean endometrial double wall thickness (EDWT) on embryo transfer day, between the study groups (Table III). The mean number of transferred embryos and the number of top quality transferred embryos among the groups were similar (Table III).

Implantation rates were calculated as 9.8% in group A, 13.3% in group B, 9.3% in group C, and 10.9% in control group, respectively ($p > 0.05$). There was no statistically significant difference between pregnancy rates and clinical pregnancy rates among groups (Table III). Clinical pregnancy rates were calculated as 27% in group A, 38% in group B, 28.6% in group C, and 35% in control group, respectively. The rates seemed to be higher in groups 2 and 4, but there was no statistically significant difference ($p > 0.05$) (Table III).

DISCUSSION

In 1991, an animal study on rats suggested for the first time that aspirin, an anti-inflammatory drug, is a potential agent to increase embryo implantation rates due to increased uterine blood flow (7). Principally aspirin inhibits cyclooxygenase, an enzyme which produces prostaglandins (PG) from arachidonic acid, which leads an increase in prostacyclin (PI_2)/thromboxane (TXA_2) ratio at tissue step. TXA_2 predominantly causes vasoconstriction and thrombocyte aggregation whereas PI_2 has vasodilator and anti-aggregant effects. Subsequent to these alterations in favor of PI_2 , aspirin thus predominantly regulates the tissue perfusion by increasing peripheral vasodilatation and blood flow. In regard of this animal study one can assume that aspirin has positive effects on implantation and pregnancy rates in infertile women. However uterine malperfusion has not been reported as a cause of implantation failure, decreased endometrial thickness (<6 mm) has been widely claimed in implantation failure among infertile women and in infertility treatment. No report of a successful pregnancy in the literature in women with endometrial thickness lower than 6 mm suggested that implantation process is directly related with endometrial thickness and receptivity. Therefore one can hypothesize that along with ovulation induction regimens in infertile managements adjunctive medical therapies for improving endometrial receptivity and environments could improve the outcomes of artificial reproductive techniques.

Table I. Demographic Characteristics of the Study Groups

	Group A (<i>n</i> = 41)	Group B (<i>n</i> = 50)	Group C (<i>n</i> = 56)	Group D (<i>n</i> = 40)	<i>p</i> value
Mean age (years)	31.2±5.6	31.6±6.1	33.5±6.2	30.2±5.6	ns
Mean infertility duration (years)	6.1±4.1	7.6±5.8	8.0±5.1	6.4±4.8	ns
Mean basal FSH levels (IU/mL)	7.8±3.6	6.9±4.3	7.4±4.2	7.1±3.9	ns
Mean basal E ₂ levels (mg/mL)	35.3±12.8	33.7±15.4	36.1±17.2	38.2±19.3	ns
Etiology (%)					
Male infertility	46.3 (19/41)	38 (19/50)	51.8 (29/56)	57.5 (23/40)	
Tubal infertility	22 (9/41)	14 (7/50)	12.5 (7/56)	10 (4/40)	
Unexplained infertility	24.4 (10/41)	44 (22/50)	28.6 (16/56)	32.5 (13/40)	
Ovulatory infertility	4.9 (2/41)	4 (2/50)	3.6 (2/56)	–	
Endometriosis	2.4 (1/41)	–	3.6 (2/56)	–	

Note. *n*: number of patients; ns: not significant. A *p* value <0.05 was considered as statistically significant.

Table II. The Cycle Characteristics of the Study Groups

	Group A (<i>n</i> = 41)	Group B (<i>n</i> = 50)	Group C (<i>n</i> = 56)	Group D (<i>n</i> = 40)	<i>p</i> value
Mean total gonadotropin dose (IU)	3462.1±1357.8	3262.5±1796.1	3478.5±1556.6	2905.0±1260.1	ns
Mean simulation period (days)	13.1±2.1	12.7±2.2	12.7±2.3	12.8±2.3	ns
Mean serum E ₂ levels (mg/mL)	1800.4±1172.2	2218.4±1339.9	2232.5±1734.6	2628.3±1351.0	ns
Mean number of follicle >14 mm	12.0±6.1	11.6±7.2	10.6±5.2	13.0±6.1	ns
Mean number of follicle >17 mm	6.0±2.4	6.7±2.6	7.1±1.9	6.4±2.8	ns
Mean number of oocytes	11.52±6.46	10.97±7.59	9.62±5.36	12.41±6.41	ns
Mean number of M ₂ oocytes	9.6±6.7	9.1±6.2	9.2±5.8	10.2±4.5	ns

Note. *n*: number of patients; ns: not significant. A *p* value <0.05 was considered as statistically significant.

Table III. The Characteristics and the Cycle Outcomes of the Study Groups

	Group A (<i>n</i> = 41)	Group B (<i>n</i> = 50)	Group C (<i>n</i> = 56)	Group D (<i>n</i> = 40)	<i>p</i> value
EDWT (mm)	11.4±2.6	11.1±2.18	11.7±3.1	11.0±2.5	ns
Mean number of transferred embryo(s)	4.3±1.8	4.0±1.2	3.9±1.6	4.3±1.7	ns
Grade A transferred embryo(s) (%)	21.8 (38/174)	19.7 (37/188)	18.5 (40/216)	17.2 (30/174)	ns
Outcomes (%)					
Implantation rate	9.8 (17/174)	13.3 (25/188)	9.3 (20/216)	10.9 (19/174)	ns
Pregnancy rate	29.3 (12/41)	44 (22/50)	33.9 (19/56)	40 (16/40)	ns
Clinical pregnancy rate	27 (11/41)	38 (19/50)	28.6 (16/56)	35 (14/40)	ns

Note. EDWT: endometrial double wall thickness (mm); *n*: number of patients; ns, not significant. A *p* value < 0.05 was considered as statistically significant.

In 1997, Weckstein *et al.* reported that concomitant use of aspirin with standard hormone replacement therapy in donor oocyte recipients who has thin endometrium has a potential to increase implantation rates by increasing endometrial receptivity (8). Furthermore, there are some other reports indicating increased pregnancy rates with concomitant administration of aspirin with heparin or steroid in IVF patients especially with positive auto-antibodies (4,9). However, these studies conducted among special infertile populations, described positive effects of aspirin on these patients led to the idea of possible similar effects can also be observed on unselected patients. In parallel to above theory, in 1999, Rubinstein *et al.* reported that low-dose aspirin use initiated at day 21 of preceding cycle related with significantly increased implantation and pregnancy rates in 298 IVF cycles (10). On contrary in a retrospective study Hurst *et al.* concluded that low-dose aspirin does not enhance endometrial thickness, augment the ovarian response, and/or improve pregnancy rates (6). However the dose of aspirin is differs in the studies, it was shown that 80–150 mg/day minimum 50 mg dose of aspirin inhibits solely trombocytes' cyclo-oxgenase without affecting on PI_2 synthesis leading only alterations in TXA_2 levels. Urman *et al.* reported that 80 mg/day aspirin begun on the first day of ovarian hyperstimulation in non-selected patients undergoing ICSI does not increase implantation rates (11). Even duration of aspirin administration differs between the current and the study of Urman *et al.* both studies were unable to detect positive effects of aspirin on outcomes of ART. On the other hand, in parallel with Rubinstein *et al.*, Waldenstrom *et al.* recently showed a 4% positive effect on clinical and chemical pregnancy rates of short-term low-dose aspirin administration to pregnancy rates in large population comprising 1380 nonselected IVF patients on contrary to Hurst *et al.* (12). However they included some patients who had undergone their second and third IVF cycles, and they also did not screen for anti-phospholipid syndrome. Another particular concern for this study is the calculated confidential intervals and odds ratio located closely to 1.0. In addition it is interesting that improved results were also similar after exclusion of patients with recurrent IVF attempts. It was also reported in this study that almost 39% of the study population were on their second and third cycle whereas 16.7% of them undergone their fourth-eight cycles. It was well known that implantation failure is directly related with recurrent IVF failures, and on contrary couples have subsequently improved

chance for achieving pregnancy up to three cycles. In the current study, likewise to Waldenstrom *et al.*'s study, aspirin was administered on the day of transfer until pregnancy testing date. In parallel with the studies of Hurst *et al.*, the current study also failed to show any advanced outcomes in regard of implantation and pregnancy rates in ICSI cycles among unselected infertility population when aspirin-treated and control group were compared. Therefore it still remains controversial that anti-aggregant agents have a role in increasing ART outcomes in unselected patients.

Another major concern is that however the dose and duration of the administration of aspirin does not affect outcomes, aspirin might impair the physiopathology of implantation. Increased concentrations of PGs are thought to play role in early phases of implantation. In animal and human studies it was shown that blastocyst produces PGs and embryo secretes PGs in pre-implantation phase. In addition there are strong evidences supporting that complex serial immune mechanisms regulate implantation process (13). Many molecules such as cytokines, growth factors, and hormones play major roles in the communication of embryo and endometrium in peri-implantation phase. Particularly, PGE_2 and Platelet Activating Factor (PAF) mainly involved in this pathway and play a key role in increasing vascular permeability. Therefore another hypothesis is that inhibiting cyclooxygenase pathway which produces prostanoids might also impair implantation process. It has been shown that inhibition of cyclooxygenase by indomethacin has a potential to decrease implantation rates in mice (14). Therefore, although enhancing of implantation and pregnancy rates were shown in some human studies, late administration of aspirin such as on transfer day might not impair communication between embryo and endometrium. Thus short-term administration of aspirin gives an advantage to prevent potential adverse effects even when no positive effects were observed in the current study.

It has been postulated that concomitant glucocorticoid use in patients managed with IVF-ICSI improve the negative clinical results due to hyperandrogenism by decreasing adrenal gland hyperactivity. By far the mechanism of glucocorticoids positive effects on implantation is still an obscure. However it has been thought that glucocorticoids are supporting implantation by causing a direct or progesterone induced release of immunosuppressive factors from endometrium. This is also a hypothetical

mechanism for preventing early pregnancy losses. It has also been postulated that glucocorticoids support implantation by increasing the release of a group of fibronectin, that function as tropho-utero-nectin (supports implantation of conception and attachment of placenta to uterine wall), from different type of cells (15). Another reason for using immunosuppression by glucocorticoids to enhance implantation is suspect in light of recent studies describing the pivotal role of T-lymphocytes in implantation (16). The necessity of the presence of uterine lymphocytes for successful pregnancy has been demonstrated in recent studies. Furthermore the proponent of corticosteroid treatment for immunosuppression diminishes the presence of uterine lymphocytes, thereby leading a normal embryo development.

Among all these mechanisms for possible benefits of immunosuppression in implantation, no consensus has been achieved for glucocorticoid administration in IVF cycles. In 1990, the first study in which glucocorticoids were used in IVF cycles reported the positive effect of immunosuppression with 16 β -methylprednisolone on the frequency of pregnancy in IVF patients after zona dissected embryos were replaced (5). In parallel, Polak *et al.* also showed in a prospective and nonrandomized study that administration of immunosuppressive dosage (60 mg/day) corticosteroid (methyl prednisolone) for a short period (4 days) subsequently to oocyte collection to patients with non-micromanipulated embryos increases implantation and pregnancy rates in IVF cycles (17). On the contrary, a prospective, randomized study reported that concomitant use of low-dose prednisolone with standard protocol does not increase implantation and pregnancy rates in also ICSI cycles (18). However, the studies on this topic differ among dosage of corticosteroid and duration of administration, no additional positive effects of steroids on outcomes of ART have been proved in majority of the studies. Thus with lack of rationale for treatment and controversial results of clinical trials, use of immunosuppression with corticosteroids to enhance implantation rates is questioned.

However, the results of the administration of anti-aggregants or steroids alone are still controversial; one can assume that concomitant therapies comprising both of them could improve the outcomes. In a study, low-dose aspirin along with prednisolone therapy that initiated with ovulation induction has been shown to increase implantation rates especially in patients with positive auto-antibodies and prior to unsuccessful results (4). Nevertheless in solely ad-

ministration of aspirin or steroids the improved outcomes were also reported in patients with positive auto-antibodies. Thus these results cannot be generalized for unselected population. Furthermore in the current study no additional benefits on outcomes of ICSI were observed in the concomitant administration group (Group C). In statistical analysis, because of no observational statistical differences among groups both in implantation and pregnancy rates, calculated impact factors were found to be lower than expected initially. Therefore a type II error of the statistics for a value of $\alpha=0.05$ was encountered in the current study in regard of initially planned power calculations. To defeat this type II error that encountered in the current study, subject number of a planned further study on this topic should be increased because of nondifferent results among selected groups. However the current study should be accepted as a detailed and a unique pilot study on this topic.

Conclusively, the current study that investigated the short-term administration effects of aspirin or steroid alone and concomitant usage of them was failed to show positive effects on outcome of ICSI in nonselected population. However, the advantage of anti-aggregants administration to special IVF patients, such as with anti-phospholipid syndrome or with thrombophilic disorders, cannot be generalized to the nonselected population undergoing ART. To defeat the controversies in the literature, initiation and application dosages of anti-aggregants and/or steroid in the studies should be standardized. To our knowledge the current study is unique as it investigated and compared the effects of short-term use of aspirin or steroid alone, and aspirin along with steroid on implantation and pregnancy rates in nonselected patients undergoing their first ICSI procedures. Therefore it can be claimed that neither aspirin or prednisolone nor concomitant administration of both in nonselected IVF patients regardless of auto-antibody status and unsuccessful IVF trials have no additional effects on outcomes of ICSI in favor of increased implantation and pregnancy rates.

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