Low-dose acetylsalicylic acid plus prednisolone as an adjuvant treatment in IVF: a prospective, randomized study

Alberto Revelli, M.D., Ph.D.,[a] *Elisabetta Dolfin, M.D.,*[a] *Gianluca Gennarelli, M.D., Ph.D.,*[a] *Teresa Lantieri, M.D.,*[a] *Marco Massobrio, M.D.,*[a] *Jan Gunnar Holte, M.D., Ph.D.,*[b] *and Ilan Tur-Kaspa, M.D.*[c]

[a] Reproductive Medicine and IVF Unit, Department of Obstetrical and Gynecological Sciences, S. Anna Hospital, University of Turin, Turin, Italy; [b] Carl von Linné Kliniken, Uppsala, Sweden; and [c] Institute for Human Reproduction and Reproductive Genetics Institute, Chicago, Illinois

Objective: To test whether adjuvant therapy with acetylsalicylic acid (ASA) and prednisolone (ASA+Pred) could improve the outcome of IVF in good–pregnancy prognosis patients.
Design: Prospective, randomized study.
Setting: University hospital.
Patient(s): Three hundred ninety-five infertile couples undergoing IVF.
Intervention(s): Patients were randomized to receive ASA+Pred (n = 97) or nothing (n = 298), in addition to the routinely used IVF medications.
Main Outcome Measure(s): The primary endpoint was implantation rate (IR). Secondary endpoints were number of retrieved oocytes and pregnancy rate (PR). The blood flow in uterine arteries and subendometrial vessels also was measured.
Result(s): Patients who received ASA+Pred had significantly more retrieved oocytes. The PR and IR in the study group and in controls were 50.5% and 40.6% and 25.1% and 19.4%, respectively, values that were not significantly different from one another. Uterine blood flows were not significantly different between treated and nontreated patients. A statistically significantly lower incidence of severe ovarian hyperstimulation syndrome was noted among treated patients who were at high risk of developing ovarian hyperstimulation syndrome (1.7% vs. 6.5%).
Conclusion(s): Adjuvant treatment with ASA+Pred improves ovarian responsiveness but does not significantly improve uterine blood fluxes, PR, and IR. It may be effective in preventing the onset of severe ovarian hyperstimulation syndrome. (Fertil Steril® 2008;90:1685–91. ©2008 by American Society for Reproductive Medicine.)

Key Words: Acetylsalicylic acid, prednisolone, in vitro fertilization, ovarian hyperstimulation syndrome, uterine blood fluxes, embryo implantation

Low doses (75–100 mg/d) of acetylsalicylic acid (ASA) and/or prednisone (Pred) treatment have been suggested to improve pregnancy and assisted reproductive technology outcome for selected groups of patients. These effects were attributed mainly to improved blood perfusion to the ovaries and endometrium and the induction of a more favorable immune tolerance toward the transferred embryos.

Low doses (75–100 mg/d) of ASA selectively inhibit thromboxane A2 synthesis without affecting prostacyclin production and coagulation times (1). In women with recurrent miscarriages, ASA administration was shown to increase the live-birth rate, probably by improving endometrial blood perfusion (2). This effect on endometrial circulation was tested during IVF also, and it was reported that ASA increased pregnancy rates in patients with impaired uterine perfusion who were undergoing cryopreserved embryo transfer (ET) (3). In addition, when it was given with heparin, ASA was demonstrated to improve IVF outcome in women with antiphospholipid antibody syndrome (4).

Other investigators administered ASA from the beginning of ovarian stimulation for IVF to increase ovarian perfusion and, consequently, ovarian responsiveness to gonadotropins. A prospective, randomized, placebo-controlled study obtained a significantly better ovarian response in ASA-treated patients, including a higher number of follicles, more retrieved oocytes, and higher E_2 levels at oocyte pickup (5). Increased uterine perfusion, as measured by color Doppler ultrasound examination, and a significant increase in the pregnancy and implantation rates also were reported (5). The improvement in IVF results, however, was not confirmed by others who treated a subgroup of IVF patients, the poor responders, with the same ASA protocol (6, 7).

A positive influence of ASA on the endometrial receptivity toward transferred embryos also was proposed. A large, randomized prospective study reported a significantly increased live birth rate in unselected IVF patients who received ASA for 2 weeks after ET (8). This finding, however, was not

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Reprint requests: Alberto Revelli, M.D., Reproductive Medicine and IVF Unit, Department of Obstetrical and Gynecological Sciences, S. Anna Hospital, University of Turin, Via Ventimiglia 3, 10126, Torino, Italy (FAX: 390116964022; E-mail: fertisave@yahoo.com).

confirmed in another prospective randomized study in unselected IVF patients (9).

Combination of corticosteroid hormones and ASA also was proposed to try to increase embryo implantation by inducing a better tolerance of the immune system toward the embryo and by lowering the local inflammatory reaction to the transfer procedure. In fact, methylprednisolone alone was reported to increase the pregnancy and implantation rates when used for a short period of 4 days after ET in unselected IVF patients (10). A similar finding was reported in women with antinuclear antibodies who received Pred for 4 days after ET (11). The combined use of low doses of Pred and ASA (ASA+Pred) was found to significantly improve the outcome of IVF in women with autoantibodies (12, 13), as well as of uterine perfusion in patients with repeated implantation failure during IVF (14). Further, ASA and Pred in association were reported to improve the reproductive outcome in women with idiopathic recurrent miscarriage (15). However, when the combination of ASA+Pred was administered from the beginning of ovarian stimulation and tested in a prospective randomized study on unselected IVF patients, the pregnancy and implantation rates showed no difference with respect to those observed in subjects who were treated with ASA alone (16).

All of the studies mentioned in the previous paragraph used ASA and corticosteroids in a fixed scheme throughout the treatment period (whether during the whole stimulation cycle or just in the post-ET days). In our study, we tested a new protocol of ASA+Pred administration that was targeted to increase ovarian responsiveness in the follicular phase (low doses of both drugs) and to yield the highest immunosuppressive effect in the 5 days around ET (higher Pred doses for 5 d). The outcome of IVF (ovarian responsiveness to gonadotropins, pregnancy and implantation rates), as well as the woman's compliance with the therapy (tolerance, complications), were assessed by a prospective randomized study.

MATERIALS AND METHODS

Patients

The internal local ethical committee authorized the study. According to a power calculation analysis based on the primary endpoint (implantation rate), a total number of 395 infertile couples was included. The study was performed between October 2002 and April 2006. According to the Italian law on assisted reproduction, after March 2004, only three oocytes per cycle were inseminated, and no embryo selection was made before transfer; this methodological change obviously affected both ASA+Pred–treated patients and controls in the same way, because randomization was continued using the same criteria as before.

We aimed to study a group of unselected IVF patients with a good pregnancy prognosis, so inclusion criteria were the following: [1] treatment was conducted by standard IVF-ET or intracytoplasmic sperm injection; [2] this was only the patient's first treatment cycle; [3] only ET with fresh embryos was used; [4] patient age was $\geq$40 years; and [5] the patient had normal ovarian reserve (normal or good responders), as estimated by antral follicle count and basal FSH.

Patients were excluded from the study who were >40 years of age or who had a reduced ovarian reserve (antral follicle count of <5 follicles per ovary, basal FSH of >10 IU/mL), autoimmune diseases (including hypothyroidism with autoantibodies), or antiphospholipid or antinuclear antibodies.

Before starting ovarian stimulation, patients signed an informed consent and were assigned by a computer-generated, 1:3 randomization to receive ASA+Pred therapy (n = 97) or nothing (n = 298), in addition to the medications that were used routinely in our IVF program.

Ovarian Stimulation

Pituitary desensitization was achieved by administering a GnRH analogue (buserelin acetate, 1,200 μg/d intranasally) in a mid-follicular long protocol. Superovulation was obtained by using recombinant FSH (daily SC injections; either Gonal F [Serono, Geneve, Switzerland] or Puregon [Organon, Oss, the Netherlands]) at appropriate doses (75–225 IU), which were estimated according to women's age, antral follicle count, and basal FSH level. Ovarian response to gonadotropins was monitored by transvaginal ultrasound and serum E_2 every other day, from stimulation day 7. Final oocyte maturation was induced by using hCG (10,000 IU, IM; either Profasi HP [Serono] or Gonasi HP [Amsa, Italy]) when the leading follicle reached 20 mm, with appropriate serum E_2 levels.

Oocyte pickup was performed by using transvaginal ultrasound-guided puncture 36 hours after hCG injection. Oocyte insemination, intracytoplasmic sperm injection, and in vitro embryo culture were performed according to standard criteria.

Embryo transfer was performed with a Sydney catheter (Cook, Adelaide, Australia) 48 hours after oocyte pickup, and the same four operators (A.R., G.G., J.G.H., Dr. Federica Moffa) performed all ETs, to minimize any operator-based interference on the IVF results.

The luteal phase was supported by transvaginal P (400 mg/d for 15 d, Crinone 8; Serono) in all patients; after 14 days from ET, serum hCG was assayed, and in the case of positive hCG, pregnancy was confirmed by transvaginal ultrasound that was aimed at detecting the presence of one or more gestational sacs.

Acetylsalicylic Acid with Pred Treatment

Patients randomized to be treated with ASA+Pred received a daily dose of ASA (100 mg), from the 1st day of ovarian stimulation until the day of the pregnancy test. Acetylsalicylic acid was stopped for 24 hours before oocyte pickup. Those patients also received Pred in the following doses: 10 mg/d (in 2 separate administrations of 5 mg each), from the 1st day of ovarian stimulation until the day before ET; 30 mg/d (in 3 administrations of 10 mg each), for 5 days starting from the day of ET; and 10 mg/d again, until the day of the pregnancy test.

Patients in the control group did not receive any treatment in addition to the standard drugs used (buserelin, FSH, hCG, and P).

A placebo was not administered because the variables that were chosen as primary and secondary endpoints were objective ones and thus not likely to be influenced by the patient's will.

Patients with a positive pregnancy test and a clinically confirmed pregnancy continued the ASA+Pred regimen until 10 weeks of pregnancy.

Ultrasound Color-Doppler Evaluation

Transvaginal color-Doppler blood flow measurements were taken the 1st day of ovarian stimulation and again on the day of oocyte pickup, using a transvaginal probe (7.5 MHz); a pulsed Doppler system for blood flow analysis was used, with wall filters (50 Hz) to eliminate low-frequency signals.

Uterine artery blood flow was measured at the level of the internal uterine os. All measures were adjusted for the measurement angle (never $>30^{\circ}$). Subendometrial vessels were visualized at the periphery of the endometrium, at a 5-mm distance from the myometrium.

The recording was considered satisfactory when at least five consecutive waveforms were obtained, each demonstrating the maximum shift. The resistance index (calculated as peak systolic velocities – peak diastolic velocities/peak systolic velocities) was calculated on three consecutive uniform heartbeats.

Endpoints and Statistics

The primary endpoint of the study was the implantation rate; a difference of >8% in the implantation rate between the treatment and the control groups was considered clinically significant and was used to calculate the power of the study.

Secondary endpoints were the following: [1] number of retrieved oocytes, [2] fertilization rate, [3] pregnancy rate, [4] ongoing pregnancy rate (>13 wk), and [5] incidence of adverse effects and complications.

Data were analyzed by using JMP software (JMP; SAS Institute Inc., http://www.JMPdiscovery.com), and because distribution of variables was found to be normal, the two-tailed Student's *t*-test, χ^2 test, and Fisher's exact test were used for comparisons. The $P<.05$ level was considered statistically significant.

RESULTS

No dropouts from the study protocol were registered because all patients in the treatment and in the control group completed the IVF cycle. In the ASA+Pred group, no relevant adverse effects (gastrointestinal bleeding, for example) were observed; some patients experienced a mild increase in euphoria, probably linked to Pred.

The ovarian responsiveness to FSH was found to be higher in patients who received ASA+Pred. They had significantly higher E_2 levels the day of hCG administration and significantly more recovered oocytes at oocyte pickup (Table 1). As a consequence, they also had more metaphase II oocytes used for fertilization and significantly more fertilized oocytes and transferred embryos (Table 1). We do clarify that the relatively high mean number of embryos transferred is a result of the fact that some of the cycles included in the study were performed under the new Italian law that forces the transfer of all embryos available ($\leq$3 embryos). None of the patients included in the study had complete fertilization failure, so all had at least one embryo transferred in utero.

The pregnancy rate and the implantation rate were high overall and were not significantly different between treated patients and controls; they were slightly, but not significantly, higher in patients receiving ASA+Pred (Table 1). The abortion rate was quite similar in the two groups, and the ongoing pregnancy rate was not significantly different in treated and nontreated subjects, although it was slightly higher in treated patients (Table 1).

The Doppler ultrasound analysis of uterine blood flows showed no significant differences between treated and nontreated patients, either in the uterine artery or in the subendometrial vessels (Table 2). Moreover, the flow indexes did not significantly change longitudinally, from day 1 of ovarian stimulation to the day of oocyte pickup (Table 2).

As an incidental finding, when we considered only patients who were at high risk of ovarian hyperstimulation syndrome (OHSS; women <35 y of age, with polycystic or multifollicular ovaries at antral follicle count and with >15 follicles of size >12 mm at oocyte pickup), a significantly lower incidence of severe OHSS was noted in ASA+Pred–treated patients in comparison to their matched controls; no cases of severe OHSS were observed among the low-risk patients (Table 3). Considering only patients who were at high risk for OHSS, no significant differences were found between treated women and controls as far as the ovarian response to FSH or as far as the pregnancy, implantation, and abortion rates were concerned. By contrast, severe OHSS requiring hospital care was significantly more frequent in the control group (7/107, 6.5%) than in the ASA+Pred group (1/57, 1.7%; Table 3).

DISCUSSION

The use of ASA, corticosteroids, or a combination of the two as an adjuvant therapy in IVF has been proposed by several investigators and has become a rather widely diffused practice, despite the lack of solid evidence for its benefits.

The aim of this prospective randomized study was to evaluate the effectiveness of an adjuvant treatment with low-dose ASA+Pred in good-prognosis IVF patients. We chose to study a homogeneous good-prognosis population to minimize, as much as possible, any patient-related variation in results and to concentrate on the effects of the treatment. Thus, women with serum autoantibodies, who were >40

TABLE 1

Characteristics and IVF outcome of patients submitted to IVF with or without adjuvant treatment with low-dose ASA + Pred.

Parameter	ASA + Pred patients	Control patients	*P*
No. of patients	97	298	—
Age (y)	34.2 ± 0.4	34.2 ± 0.2	NS
Length of infertility (y)	4.1 ± 2.8	3.8 ± 2.1	NS
Body mass index	21.9 ± 0.7	21.8 ± 0.7	NS
Basal FSH (mUI/mL)	6.5 ± 3.1	6.8 ± 2.8	NS
Antral follicle count	11.3 ± 5.8	12.0 ± 5.4	NS
Total administered FSH (IU)	2,875 ± 1,476	3,183 ± 1,676	NS
Stimulation length (d)	11.4 ± 1.8	11.9 ± 1.8	NS
E_2 at hCG (pg/mL)	2,082 ± 741	1,728 ± 672	< .001
Endometrium at oocyte pickup (mm)	10.5 ± 1.8	10.4 ± 2.0	NS
No. of recovered oocytes	14.0 ± 6.5	10.5 ± 5.1	< .001
No. of mature metaphase II oocytes	11.1 ± 5.5	8.3 ± 4.5	< .001
No. of fertilized oocytes	7.3 ± 4.0	5.5 ± 3.3	< .001
Fertilization rate (%)	67.1	67.1	NS
No. of transferred embryos	251	622	—
Transferred embryos per cycle	2.6 ± 0.4	2.1 ± 0.5	< .001
No. of clinical pregnancies	49	121	—
No. of gestational sacs	63	150	—
Pregnancy rate (%)	50.5	40.6	NS
Twinning rate (%)	26.5	22.3	NS
Implantation rate (%)	25.1	19.4	NS
No. of abortions	8	23	—
Abortion rate (%)	16.3	19.0	NS
Ongoing pregnancy rate (%)	42.2	32.8	NS

Note: Data are mean ± SD unless otherwise indicated.

Revelli. ASA plus prednisolone therapy in IVF. Fertil Steril 2008.

TABLE 2

Uterine blood fluxes measured by transvaginal Doppler ultrasound in patients submitted to IVF with or without adjuvant treatment with low-dose ASA + Pred.

Parameter	ASA + Pred	Controls
Uterine artery PI (stimulation d 1)	1.7 ± 0.15	2.6 ± 0.19
Uterine artery PI (at oocyte pickup)	2.0 ± 0.22	2.1 ± 0.30
Subendometrial RI (stimulation d 1)	0.8 ± 0.18	0.8 ± 0.19
Subendometrial RI (at oocyte pickup)	0.9 ± 0.10	1.0 ± 0.13

Note: Data are mean ± SD unless otherwise indicated. *P* values comparing the two groups were statistically nonsignificant across all parameters. PI = pulsatility index; RI = resistance index.

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years of age, or who had basal FSH and ultrasound parameters indicating a low ovarian reserve were not included in the study. Further, only first treatment cycles with fresh ETs were considered. As a result of these inclusion criteria, no patient had fewer than five retrieved oocytes at oocyte pickup, and all cycles resulted in the transfer of at least one embryo. Although the ovarian response was significantly better in the ASA+Pred group, the overall results were good both in the treatment and in the control groups, with comparable implantation and pregnancy rates. No significant adverse effects linked to ASA and Pred were observed.

The ultrasound Doppler evaluations were performed at 8:00 AM on both day 1 of ovarian stimulation and the day of oocyte pickup, according to a standard technique (17). The observed improvement in ovarian response in the ASA+Pred group could not be explained by the Doppler measurements.

The computer-generated randomization led to well-matched comparable groups of IVF patients. No significant differences were observed in variables able to affect IVF results (age, body mass index, smoking habit, ovarian reserve indexes).

TABLE 3

Characteristics and IVF outcome of patients submitted to IVF with or without adjuvant treatment with low-dose ASA+Pred, subdivided according to the high or low risk of developing OHSS.

	High-risk OHSS			Low-risk OHSS		
Parameter	**ASA+Pred**	**Controls**	***P***	**ASA+Pred**	**Controls**	***P***
No. of patients	57	107		39	192	—
Age (y)	33.0 ± 0.5	32.1 ± 0.4	NS	35.7 ± 2.7	35.5 ± 3.1	NS
Length of infertility (y)	4.1 ± 0.3	3.0 ± 0.2	NS	4.2 ± 2.8	4.2 ± 2.1	NS
Body mass index	21.5 ± 0.4	22.2 ± 0.3	NS	20.8 ± 0.6	21.2 ± 0.7	NS
Basal FSH (mUI/mL)	4.7 ± 1.7	5.5 ± 2.1	NS	6.6 ± 1.9	6.7 ± 1.6	NS
Antral follicle count	17.3 ± 6.8	16.4 ± 7.1	NS	10.5 ± 4.4	11.3 ± 4.2	NS
Total administered FSH (IU)	2,490 ± 160	2,410 ± 117	NS	3,416 ± 1,827	3,615 ± 1,714	NS
Stimulation length (d)	11.4 ± 0.2	11.6 ± 0.1	NS	11.4 ± 1.8	12.1 ± 1.6	NS
E_2 at oocyte pickup (pg/mL)	2,840 ± 797	2,756 ± 774	NS	1,885 ± 662	1,649 ± 528	NS
Endometrium at oocyte pickup (mm)	10.5 ± 1.6	10.5 ± 2.0	NS	10.6 ± 2.1	10.4 ± 2.1	NS
No. of recovered oocytes	17.3 ± 6.3	14.2 ± 6.2	NS	9.1 ± 2.6	8.4 ± 2.9	NS
Mature metaphase II oocytes	13.4 ± 0.7	11.2 ± 0.5	NS	7.5 ± 2.8	6.8 ± 3.1	NS
No. of fertilized oocytes	8.9 ± 0.5	7.4 ± 0.3	NS	5.0 ± 2.4	4.5 ± 2.4	NS
Fertilization rate (%)	68.8	68.1	NS	66.0	66.6	NS
No. of transferred embryos	149	267		77	466	—
No. of transferred embryos per cycle	2.6 ± 0.3	2.5 ± 0.4	NS	2.0 ± 0.4	2.4 ± 0.4	NS
No. of clinical pregnancies	36	56		12	65	—
No. of gestational sacs	47	70		15	80	—
Pregnancy rate (%)	63.2	52.3	NS	30.0	33.8	NS
Twinning rate (%)	25.0	23.2	NS	25.0	23.0	NS
Implantation rate (%)	31.5	26.2	NS	19.4	17.3	NS
No. of abortions	4	9		3	11	—
Abortion rate (%)	7.0	8.4	NS	25.0	16.9	NS
Ongoing pregnancy rate (%)	56.1	43.9	NS	23.0	28.1	NS
Severe OHSS (%)	1 (1.7)	7 (6.5)	.03	0.0	0.0	—

Note: Data are mean ± SD unless otherwise indicated.

Revelli. ASA plus prednisolone therapy in IVF. Fertil Steril 2008.

The ASA+Pred–treated women showed a significantly better ovarian response to FSH; a significant increase was observed in their E_2 levels at hCG and in their numbers of retrieved oocytes. Because before the new Italian law, all mature oocytes were used for fertilization, more oocytes were available (and were used) in the treatment group, and even if the fertilization rate was the same in both groups, more fertilized eggs were obtained in ASA+Pred women, and more fresh embryos were available for transfer. The better ovarian response to FSH in treated patients is not a result of the fact that in this group, there is a higher proportion of young women with polycystic or multifollicular ovaries and high antral follicle count than in the control group (57/97 vs. 107/298); in fact, the same significant difference in favor of the ASA+Pred group is seen even if the comparison is made excluding these high responders (Revelli A, et al., unpublished data). Better ovarian responsiveness to gonadotropins in patients treated with ASA was reported elsewhere by Rubinstein et al. (5), who administered ASA at the same dose that we did, starting on day 21 of the preceding menstrual cycle. This finding, however, was not confirmed by other studies in which the same dose (7) or lower doses of ASA (6) were used. Cortisol was reported to positively affect oocyte maturation in unstimulated (18) and stimulated (19) IVF cycles: it is possible that the enhancing effect of ASA+Pred on ovarian responsiveness could be partially due to P.

The implantation rate was chosen as the primary endpoint of this study, with a difference of >8% between groups considered to be clinically significant. Because this was the primary endpoint, all four doctors performed the ETs according to a standard procedure, to minimize any operator-related bias. Furthermore, ASA+Pred were administered in a way that was aimed to enhance the possible positive effects of the treatment on implantation. In fact, Pred dose was relevantly increased (≤30 mg/d) on the day of ET and the 4 following

days, which represent the so-called implantation window. This Pred dose was, however, lower than the one used elsewhere by other investigators (11), and it therefore was likely to be harmless to the patients. Acetylsalicylic acid was given from the beginning of ovarian stimulation, at a dose (100 mg/d) that was similar to that given in other published studies (5, 9, 16). As in other published studies (8, 16), a placebo was not administered to patients in the control group.

The pregnancy and implantation rates were slightly (but not significantly) higher in the treatment group. The implantation rate was higher in the ASA+Pred patients, but the difference was not statistically significant and was lower than the one (8%) that was a priori considered clinically relevant. No significant effect of ASA+Pred over uterine blood fluxes, either longitudinally inside the same group (1st day of stimulation vs. day of hCG) or between the two groups, was observed. The abortion rate was slightly lower in treated women, leading to a higher ongoing pregnancy rate in ASA+Pred patients, although the difference did not reach statistical significance. Higher pregnancy and implantation rates with ASA adjuvant therapy were reported elsewhere in unselected IVF patients (5, 8), but this finding was not confirmed in other studies that included all IVF patients (7, 9) or only poor responders (6). Even the finding of increased ovarian and endometrial perfusion in ASA-treated women (5) was not confirmed in other clinical trials (6) and was not observed in the present study. Uterine blood flow measurements are not considered a fully reliable index of endometrial receptivity in IVF, and their predictive value for implantation is limited (17, 20, 21). As far as the ASA+Pred association is concerned, its influence was proven to be positive for IVF patients with autoimmune antibodies (13, 12) or women with recurrent abortion (15), but its use in unselected IVF patients was found to be useless in comparison with ASA alone (16). In a previous non-randomized study, methylprednisolone given in large doses (60 mg/d) for 4 days after ET was found to support the implantation of zona-dissected embryos (10), and in association with ASA it was shown to increase endometrial vascularization (14). We did not get evidence of a positive effect of ASA+Pred therapy on the pregnancy and implantation rates. It must be noted, however, that in the present study, the influence of a better ovarian response and of the consequent more abundant embryo availability in ASA+Pred group over the pregnancy rate could not be observed because transfers with thawed embryos that were frozen in the treatment cycle were not calculated.

The so-called high responders are known to have a good chance of pregnancy and to produce embryos with high implantation potential. When we considered only high responders (young women with polycystic or multifollicular ovaries and $\geq$15 follicles at oocyte pickup), no significant effects of ASA+Pred were observed on IVF effectiveness. However, we incidentally noted that the incidence of severe OHSS in the ASA+Pred group was relevantly lower than expected in these high-risk patients (22) and was significantly lower than in controls. Because severe OHSS may have some features in common with the inflammatory response (leukocytosis, circulating C-reactive protein, and interleukin increase, etc.) (23, 24), an anti-inflammatory treatment may be useful for preventing the onset of OHSS or to decrease its severity. If further, more targeted trials confirm the effectiveness of ASA+Pred in this context, adjuvant treatment with ASA+Pred could be used to reduce the incidence of severe OHSS in high-risk patients without negatively affecting IVF outcome.

In conclusion, this prospective randomized trial shows that the adjuvant treatment with low doses of ASA+Pred is able to improve ovarian responsiveness to gonadotropins in good-prognosis IVF patients but does not significantly improve uterine blood fluxes and pregnancy and implantation rates. It is possible that ASA+Pred treatment could be effective in preventing the onset of severe OHSS in high-responder patients during IVF.

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