Journal of Assisted Reproduction and Genetics, Vol. 17, No. 3, 2000

GYNECOLOGY

Low-Dose Aspirin for Infertile Women with Thin Endometrium Receiving Intrauterine Insemination: A Prospective, Randomized Study

YAO-YUAN HSIEH,[1] HORNG-DER TSAI,[1,2] CHI-CHEN CHANG,[1] HUI-YU LO,[1] and CHING-LUN CHEN[1]

Submitted: August 10, 1999
Accepted: November 19, 1999

Purpose: *The objective was to evaluate the effect of aspirin on infertile women with thin endometrium.*
Methods: *Patients who had thin endometrium (≤ 8 mm) and intrauterine insemination were divided into the aspirin and nonaspirin groups. Endometrial pattern (trilaminar and nontrilaminar) and thickness, the pulsatility index (PI) and resistance index (RI) of the uterine artery, spiral artery, and ovarian dominant follicles, and pregnancy rates of both groups were measured.*
Results: *A total of 114 and 122 women were included in the aspirin and nonaspirin groups, respectively. There were significantly higher percentages of trilaminar endometrium (46.5% vs. 26.2%) and pregnancy rate (18.4% vs. 9.0%) after aspirin therapy. There was nonsignificant difference in the endometrial thickness, and PI/RI values of the uterine artery, spiral artery, and ovarian dominant follicle between both groups.*
Conclusions: *Higher pregnancy rate and better endometrial pattern were achieved in patients with thin endometrium after aspirin administration. Aspirin therapy could not significantly increase the endometrial thickness and the resistance of uterine and ovarian flow.*

KEY WORDS: Aspirin; intrauterine insemination; spiral artery; thin endometrium; uterine artery.

INTRODUCTION

Lower pregnancy rates were noted in patients with thin endometrium (1,2) or low uterine flow (3). Abdalla *et al.* (1) demonstrated that pregnancy is less likely when the endometrium is <7.5 mm thick and does not occur when thickness is <5 mm. Because implantation requires dilation of endometrial blood vessels, it is possible that the reduced pregnancy rate in patients with thin endometrium could be improved by increasing the resistance of uterine flow (3). Numerous studies suggested that treating women with aspirin might improve the pregnancy rates with artificial reproductive technique (ART) (2,4,5). Kuo *et al.* (4) demonstrated that aspirin may improve uterine flow in women with unexplained infertility. Wada *et al.* (5) demonstrated an improvement in the resistance of uterine flow, pregnancy rate, and lower miscarriage rate in patients with low uterine flow after aspirin treatment.

However, few investigators have demonstrated the value of aspirin in patients receiving the intrauterine insemination (IUI). In this series, we tried to determine whether the addition of low-dose aspirin could improve the endometrial pattern and thickness, resistance of uterine flow, and pregnancy in patients with thin endometrium after IUI. To our knowledge, this is the first and largest prospective series aiming to evaluate the role of aspirin in patients with thin endometrium and receiving IUI.

MATERIALS AND METHODS

From January 1996 through March 1999, all infertile women with thin endometrium (≤8 mm, on the day of IUI in the previous cycle) and receiving IUI in China Medical College Hospital were recruited in this

[1] Department of Obstetrics and Gynecology, China Medical College Hospital, Taichung, Taiwan.
[2] To whom correspondence should be addressed.

1058-0468/00/0300-0174$18.00/0

series. Couples with female age ≥38 years, poor parameter of semen analysis, hydrosalpinx, uterine cavity abnormality, and male factor infertility were excluded from this series. All cases were assigned randomly to one of the two groups: aspirin group and nonaspirin group. Patients in the aspirin group received low-dose aspirin (Bokey, 100 mg/day, oral, Yung Shin Co, Taiwan, ROC) from menstrual day 1 through pregnancy test.

All patients received the similar ovarian hyperstimulation protocol: combined clomiphene citrate (CC) and human menopausal gonadotropin (hMG) (Pergonal, Serono, Rome, Italy). An oral dose of CC (100 mg/day) was given on cycle day 3 through cycle day 7 and three doses of hMG (150 IU/day) were administered on cycle day 6, 8, and 10. Follicular survey was done on cycle day 3, 10, and 14. Human chorionic gonadotropin (hCG) (500 IU; Pregnyl; Organon, Oss, the Netherlands) was given when two follicles ≥16 mm in diameter were found. The semen was prepared with the Enhance (Percoll) method using three different density (95%, 70%, 50% Percoll) gradient centrifugation. All patients received IUI 34–36 hr after hCG injection.

All patients underwent sonography and Doppler surveys on menstrual day 3 and the day of IUI. Sonographic and Doppler assessment were performed transvaginally with a 5-MHz endovaginal probe using the Acuson 128 unit (Acuson, Mountain View, CA). The endometrial thickness, pattern and vascular impedance [pulsatility index (PI) and resistance index (RI)] of the spiral, bilateral uterine, and ovarian dominant follicle were measured. Endometrial thickness was measured at the greatest anterioposterior dimension of the endometrium under a longitudinal section. There were two endometrium patterns: trilaminar and nontrilaminar. A trilaminar pattern was identified as a hypoechoic layer with a central hyperechoic line or an isoechoic layer with a central echogenic line. A nontrilaminar pattern was described as a single homogeneous layer.

The spiral artery for checking was located near the junction of endometrium and myometrium. The Doppler evaluation of the uterine artery was focused on the ascending branch of the uterine arteries. The perifollicular flows of the bilateral follicle ≥16 mm represent the impedance of the dominant follicle. If there were more than one follicle ≥16 mm, their mean value represented the impedance of the dominant follicle. If all follicles were <16 mm, the largest one was checked and taken as the dominant follicle.

Progesterone (Duphaston, 15mg/day, oral, Solvay Co, Holland) was administered since day 3 post-IUI. Clinical pregnancy was defined as a positive urine pregnancy test 2 weeks post-IUI and confirmed by transvaginal ultrasonography of intrauterine gestational sac. If a pregnancy was achieved, patients were instructed to continue the aspirin through 6 weeks after IUI. Further statistic analyses were performed by using the SAS statistical package. Patients' age, endometrial thickness and pattern, vascular impedance of the uterine artery, spiral artery, and ovarian dominant follicle, as well as clinical pregnancy rates of the two groups

Table I. The Comparison of Age, Endometrial Thickness, and Patterns, Vascular Impedances of Uterine Artery, Spiral Artery, and Dominant Follicle, and Pregnancy Rate in Aspirin and Nonaspirin Groups

	Aspirin group	Nonaspirin group	*P* value
Number	114	122	
Age (year)	33.1 ± 2.8	32.4 ± 3.6	NS[b]
Endometrium[a]			
Thickness (previous cycle) (mm)	5.8 ± 1.1	5.7 ± 1.5	NS
Thickness (this cycle) (mm)	7.2 ± 1.8	5.8 ± 1.4	NS
Trilaminar pattern (previous cycle)	23.7% (27/114)	24.6% (30/122)	NS
Trilaminar pattern (this cycle)	46.5% (53/114)	26.2% (32/122)	0.001
Uterine artery[a]			
PI	2.63 ± 0.58	2.71 ± 0.72	NS
RI	0.73 ± 0.21	0.78 ± 0.31	NS
Spiral artery[a]			
PI	1.1 ± 0.31	1.3 ± 0.38	NS
RI	0.61 ± 0.15	0.68 ± 0.19	NS
Ovarian dominant follicle flow[a]			
PI	0.65 ± 0.21	0.74 ± 0.22	NS
RI	0.50 ± 0.08	0.52 ± 0.10	NS
Pregnancy rate	18.4% (21/114)	9.0% (11/122)	0.036

[a] Measurement on the day of IUI.
[b] NS, nonsignificant difference.

were compared. A P value of $< .05$ was considered statistically significant.

RESULTS

A total of 114 and 122 women were included in the aspirin and nonaspirin treatment groups, respectively. The mean age and endometrial thickness of the two groups showed nonsignificant difference (33.1 ± 2.8 year vs. 32.4 ± 3.6 year; 5.8 ± 1.1 mm vs. 5.7 ± 1.5 mm) (Table I). After the aspirin therapy, the endometrium became thickened in the aspirin group (7.2 ± 1.8 mm vs. 5.8 ± 1.4 mm), which showed nonstatistical difference (Table I).

Regarding the vascular impedance, there were nonsignificant differences in the PI/RI of the uterine artery flow (2.63 ± 0.58/0.73 ± 0.21 vs. 2.71 ± 0.72/0.78 ± 0.31), spiral artery flow (1.1 ± 0.31/0.61 ± 0.15 vs. 1.3 ± 0.38/0.68 ± 0.19), and ovarian dominant follicle (0.65 ± 0.21/0.50 ± 0.08 vs. 0.74 ± 0.22/0.52 ± 0.10) between the aspirin and nonaspirin groups, respectively (Table I). The endometrial trilaminar layer in the aspirin group was significantly higher than that in the nonaspirin group (46.5% vs. 26.2%). The clinical pregnancy rate was 18.4% (21/114) in the aspirin group and 9.0% (11/122) in the nonaspirin group, showing statistical difference (Table I).

DISCUSSION

Thin endometrium associated with poor uterine receptivity and lower embryo implantation has been demonstrated (1,6). As for the management of the patients with thin endometrium, aspirin administration was shown to increase embryo implantation rate in animal study (7). However, the real value of aspirin remains controversial in the patients with thin endometrium and receiving ART. Weckstein *et al.* (8) observed that the oocyte donation recipients with a thin endometrium got improved implantation rate and better pregnancy outcomes after the low-dose aspirin supplement. They also demonstrated that the possible mechanism of aspirin is through improving the resistance of uterine flow by shifting local production of thromboxane toward prostacyclin. In contrast, Check *et al.* (9) demonstrated the absence of positive effect of aspirin therapy on pregnancy rates following frozen embryo transfer.

It also remains controversial whether aspirin can improve the resistance of uterine or ovarian flow. It has been demonstrated that women with high uterine vascular impedance could benefit from aspirin administration by reducing uterine vascular resistance and increasing uterine blood flow (5). Kuo *et al.* (4) demonstrated that aspirin improved the uterine flow and increased the pregnancy rate of women with unexplained infertility or impaired uterine blood flow. In contrast, Check *et al.* (9) observed nonsignificant changes in the endometrial PI/RI values after the aspirin therapy. In this series, we also observed nonsignificant changes in the vascular impedance of uterine, spiral arteries, and dominant follicle after aspirin administration. As for the effect of aspirin on endometrial thickness, several investigators have demonstrated nonstatistical change in the endometrium after the aspirin supplement (2,9). In our series, we also observed nonsignificant changes in the endometrial thickness after aspirin administration.

In conclusion, higher pregnancy rate and better endometrial pattern were achieved in the infertile patients with thin endometrium after aspirin administration. Aspirin therapy could not obviously increase endometrial thickness or the resistance of uterine and ovarian flow. However, the nonsignificant difference may be due to the case number limitation. A larger series is necessary to clarify the real value of aspirin in women with thin endometrium.

REFERENCES

1. Abdalla HI, Brooks AA, Johnson MR, Kirkland A, Thomas A, Studd JWW: Endometrial thickness: A predictor of implantation in ovum recipients? Hum Reprod 1994;9:363–365
2. Weckstein LN, Jacobson A, Galen D, Hampton K, Hammel J: Low-dose aspirin for oocyte donation recipients with a thin endometrium: Prospective, randomized study. Fertil Steril 1997; 68:927–930
3. Steer CV, Tan SL, Dillon D, Mason BA, Campbell S: Vaginal color Doppler assessment of uterine artery impedance correlates with immunohistochemical markers of endometrial receptivity required for the implantation of an embryo. Fertil Steril 1995; 63:101–108
4. Kuo HC, Hsu CC, Wang ST, Huang KE: Aspirin improves uterine blood flow in the peri-implantation period. J Formos Med Assoc 1997;96:253–257
5. Wada I, Hsu CC, Williams G, Macnamee MC, Brinsden PR: The benefits of low-dose aspirin therapy in women with impaired uterine perfusion during assisted conception. Hum Reprod 1994; 9:1954–1957
6. Shapiro H, Cowell C, Casper RF: The use of vaginal ultrasound

for monitoring endometrial preparation in a donor oocyte program. Fertil Steril 1993;59:1055–1058
7. Testart J, Gauthier A: The action of anti-inflammatory drugs on the fertility of female rats with intrauterine contraceptive devices. J Reprod Fertil 1991;63:257–261
8. Weckstein LN, Jacobson A, Galen D, Hampton K, Hammel J: Low-dose aspirin for oocyte donation recipients with a thin endometrium: Prospective, randomized study. Fertil Steril 1997; 68:927–930
9. Check JH, Dietterich C, Lurie D, Nazari A, Chuong J: A matched study to determine whether low-dose aspirin without heparin improves pregnancy rates following frozen embryo transfer and/or affects endometrial sonographic parameters. J Assist Reprod Genet 1998;15:579–582