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Low-dose aspirin for oocyte donation recipients with a thin endometrium: prospective, randomized study

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Objective: To evaluate the effect of low-dose aspirin use in oocyte donation recipients with an endometrial thickness of <8 mm.
Design: A prospective, randomized study.
Setting: An oocyte donation program in a private infertility practice.
Patient(s): Twenty-eight recipients undergoing oocyte donation who failed to develop an endometrial thickness of at least 8 mm in a previous evaluation cycle.
Intervention(s): Fifteen recipients received low-dose aspirin (81 mg/d) in addition to standard hormone replacement for an oocyte donation cycle. The remaining 13 recipients did not receive aspirin.
Main Outcome Measure(s): Clinical pregnancy rates, delivery rates, implantation rates, and change in endometrial thickness were compared in the aspirin and nonaspirin groups.
Result(s): There was no demonstrable increase in endometrial thickness in the aspirin-treated group. However, there was a statistically significant increase in implantation rates in the aspirin-treated group (24% versus 9%) and in implantation rates and clinical pregnancy rates in the aspirin-treated group when the final endometrial thickness was <8 mm.
Conclusion(s): Low-dose aspirin therapy improves implantation rates in oocyte donation recipients with a thin endometrium. (Fertil Steril® 1997;68:927–30. © 1997 by American Society for Reproductive Medicine.)

Key Words: Aspirin, oocyte donation, thin endometrium, implantation

We and other investigators have observed a decreased pregnancy rate in recipients of oocyte donation when the endometrial thickness is <8 mm. Alam et al. (1) reported that only one of eight recipients achieved a pregnancy when the endometrium was <8 mm. Abdalla et al. (2) reported only 2 of 15 recipients conceived when endometrial thickness was <7.5 mm. Recently, we confirmed these observations with a report of only one of seven recipients conceiving with an endometrium of <8 mm (3). Other investigators have reported reduced conception with egg donation when the endometrium is <6 mm (4).

Because implantation requires dilation of endometrial blood vessels and a reduced pregnancy rate has been reported in IVF patients with low uterine blood flow (5), it is possible that the reduced pregnancy rate in patients with a thin endometrium could be improved by increasing uterine blood flow. Recently, Wada et al. (6) studied the use of aspirin treatment for cryopreserved ET cycles in patients with high Doppler pulsatility index (low uterine perfusion). They reported an improvement in the pulsatility in-

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dex with aspirin treatment, a trend toward an improvement in the pregnancy rate when aspirin was begun on day 1 of treatment versus at the time of ET, and a lower miscarriage rate.

In the present study, we evaluated the effect of aspirin on endometrial receptivity in oocyte donation recipients who had an endometrium that had not reached 8 mm with a standard dose and duration of estrogen during a test cycle.

MATERIALS AND METHODS

From September 1993 through January 1995, 28 oocyte donation recipients were identified who failed to develop an endometrial thickness of at least 8 mm during a test cycle receiving oral micronized E_2 (2 mg for 4 days, 4 mg for 4 days, and 6 mg for 4 days). All patients had a normal uterine cavity that was evaluated by hysteroscopy or hysterosalpingogram. Some patients received additional estrogen (increased dose, transdermal estrogen, or IM estrogen) for an additional 5–7 days to assess whether an improved endometrium could be achieved.

Women who had continuing ovarian function were down-regulated with leuprolide acetate (LA) before estrogen therapy. For the ET cycle the study group was randomized prospectively by sealed envelopes to receive low-dose aspirin (81 mg/d) beginning 1 week before starting estrogen treatment. Both groups received an identical hormone regimen except that additional estrogen was given in some instances according to their test cycle response. Therapy with progesterone (100 mg IM daily and 50 mg twice daily vaginally) was started 2 days before ET. If a pregnancy was achieved, recipients were instructed to continue the aspirin through 9 weeks after ET, and exogenous estrogen and P were continued until approximately 60 days after ET.

The endometrium was measured by a single ultrasonographer with a 7.5-mHz transvaginal probe (Siemens, Issaquah, WA), in the longitudinal plane at the point of maximal thickness. Endometrial measurements at the end of standard estrogen replacement, after additional estrogen, and during the ET cycle were measured.

Clinical pregnancy rates, delivery rates, and implantation rates were compared in the aspirin and nonaspirin groups using Fisher's exact test. Recipients' age, endometrial thickness, and change in endometrial thickness with treatment were compared in the two groups with a paired *t*-test.

We do not have an institutional review board at our hospital, but patients gave their informed consent for participation in the study with the understanding that not participating would not compromise their care. A thorough discussion of the potential risks of low-dose aspirin was part of the informed consent process.

RESULTS

From September 1993 through January 1995 we completed 125 fresh oocyte donation cycles in our oocyte donation program (including those cycles randomized in this study) with a 42% delivery rate per ET. During this period 28 fresh oocyte donation cycles were randomized to aspirin and no aspirin treatment groups.

Fifteen cycles were randomized to aspirin treatment, and 13 cycles were randomized to no aspirin treatment groups. The mean age of oocyte donation recipients between the two groups (mean, 41.8 years, ±3.4 SD, ±.86 SE versus mean, 39.4 years, ±4.5 SD, ±1.24 SE) was not significantly different. The mean endometrial thickness obtained during the test cycle in the aspirin versus the nonaspirin group was not statistically significant (mean, 6.6 mm, ±0.66 SD, ±0.17 SE versus mean, 6.0 mm, ±1.0 SD, ±0.28 SE) nor was there a difference in the change in endometrial thickness from the test cycle to the transfer cycle between the two groups (mean, 1.6 mm, ±1.5 SD, ±0.39 SE versus mean, 0.9 mm, ±0.8 SD, ±0.22 SE).

There were a higher number of embryos transferred in the nonaspirin group (mean, 5.3, ±0.85 SD, ±0.24 SE) compared with the aspirin-treated group (mean, 4.2, ±0.86 SD, ±0.22 SE), significant at the $P < 0.01$ level. The implantation rate in aspirin cycles was 24% versus 9% in nonaspirin cycles, which is a statistically significant difference at the $P < 0.05$ level (Table 1).

There were nine clinical pregnancies in the aspirin-treated group (60%) and four clinical pregnancies in the nonaspirin-treated group (31%); seven of

Table 1 Comparison of Results of Oocyte Donation Cycles in Low-Dose Aspirin and Nonaspirin Treatment Groups

Groups	No. of patients	Clinical pregnancy rate	Delivery rate	Implantation rate*
Low-dose aspirin	15	9/15 (60)	7/15 (47)	15/63 (24)
Nonaspirin	13	4/13 (31)	4/13 (31)	6/69 (9)
P value		NS	NS	$P < 0.05$

Note: Values in parentheses are percentages. NS = not significant.

* Gestational sacs per embryos transferred.

the nine pregnancies in the aspirin-treated group delivered and four pregnancies in the nonaspirin-treated group delivered (not statistically significant).

There were four multiple pregnancies in the aspirin-treated group: two sets of twins and two sets of triplets. Both sets of twins were delivered. One set of triplets was lost at 12 weeks and the other set was lost at 22 weeks, secondary to an incompetent cervix. There were two multiple pregnancies in the nonaspirin group, both twins, all of which delivered.

We further looked at oocyte donation cycles in which the endometrial thickness was <8 mm in the transfer cycle because these are the patients whom we identified previously to have a decreased pregnancy rate (Table 2). There were six cycles in the aspirin-treated group and 12 cycles in the nonaspirin-treated group in which recipients did not develop an endometrium of at least 8 mm during the real oocyte donation cycle.

There was no significant difference between the mean endometrial thickness in these two groups; the clinical pregnancy rate was 83% in the aspirin-treated group and 25% in the nonaspirin-treated group, which is statistically significant at the level of $P < 0.05$. There was a statistically significant difference between the 38% implantation rate in the aspirin-treated group and the 8% implantation rate in the nonaspirin-treated group ($P < 0.01$).

Table 2 Results of Oocyte Donation Cycles With Endometrium <8 mm in Transfer Cycle in Low-Dose and Nonaspirin Treatment Groups

	No. of patients	Mean endometrial thickness (mm)	Clinical pregnancy rate	Delivery rate	Implantation rate*
Low-dose aspirin	6	7.1	5/6 (83)	3/6 (50)	10/26 (38)
Nonaspirin	12	6.8	3/12 (25)	3/12 (25)	5/65 (8)
P value		NS	$P < 0.05$	NS	$P < 0.01$

Note: Values in parentheses are percentages. NS = not significant.
* Gestational sacs per embryos transferred.

DISCUSSION

We have previously reported that oocyte donation recipients with an endometrial thickness of <8 mm had a significantly lower pregnancy rate (3). In the present study, we performed a prospective randomized evaluation of low-dose aspirin on cycle outcome in 28 recipients whose test cycle revealed an endometrium of <8 mm with standard estrogen stimulation. The use of aspirin was associated with an increased rate of implantation, and in those women whose endometrium remained <8 mm in spite of augmented estrogen stimulation, the increase in the pregnancy rate was statistically significant.

The pregnancy rates while receiving aspirin were similar to our overall oocyte donation program. The achievement of statistical significance with a relatively small study group suggests a pronounced treatment effect.

Aspirin has previously been shown to reduce uterine vascular resistance, thus increasing uterine blood flow in women undergoing IVF who had a high Doppler pulsatility index (6). Therefore, we speculate that the reduced pregnancy outcome in egg donation recipients with a poorly developed endometrium is attributable to decreased uterine blood flow, which is corrected by aspirin. Aspirin may act to improve blood flow by shifting local production of thromboxane toward prostacyclin.

Doppler studies to measure uterine blood flow were not done because we did not have Doppler ultrasound availability at the time of this study. Information from Doppler studies would be of benefit to substantiate the hypothesis that low-dose aspirin increases uterine blood flow in patients with a thin endometrium. Previously, Wada et al. (6) reported a benefit of low-dose aspirin in women with decreased uterine perfusion.

Sher et al. (7) reported an increased pregnancy rate with low-dose aspirin and heparin for women who underwent IVF and who had circulating antiphospholipid antibodies, presumably by inhibiting hypercoagulability in the choriodecidual space. However, these researchers also found an increased pregnancy rate in these treated patients compared with patients who did not have positive antiphospholipid antibodies, suggesting other mechanisms of the effect of aspirin, such as on uterine blood flow.

At the time of this study we did not measure antiphospholipid antibodies in these patients. It is, however, possible that the improved implantation rates in aspirin-treated patients also may be related to a beneficial effect for patients with positive antiphospholipid antibodies. Furthermore, we did not include a placebo-treated group in this study; therefore, we cannot rule out a placebo effect of the aspirin.

In conclusion, low-dose aspirin restored the reduced pregnancy outcome in oocyte donation recipients with a poorly developed endometrium to normal levels. These findings suggest that all oocyte donation recipients should undergo a test cycle so that this subgroup can be identified and offered this simple and highly successful adjunctive treatment.

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