Low-dose aspirin does not improve ovarian stimulation, endometrial response, or pregnancy rates for in vitro fertilization

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Published: 31 May 2005

Received: 21 February 2005

Accepted: 31 May 2005

Abstract

**Background:** The purpose of this study is to determine if low-dose aspirin improved ovarian stimulation, endometrial response, or IVF pregnancy rates in our program.

**Methods:** Retrospective analysis of 316 consecutive IVF cycles from 1995 through 2001. Aspirin 80 mg daily was initiated at the start of luteal leuprolide in 72 cycles. The 244 controls received no aspirin during treatment.

**Results:** The live birth rate in aspirin users was 29%, slightly lower compared to 41% in the no aspirin control group (p = 0.07). Implantation rates were 21% with aspirin and 30% in the control population (p = 0.01). There was no difference in the maximal endometrial thickness between aspirin and non-aspirin groups. The two groups were similar regarding age, gonadotropin ampules, embryos, number of embryos transferred, prior parity, diagnosis, use of intracytoplasmic sperm injection, and stimulation protocol.

**Conclusion:** Low-dose aspirin was not beneficial to IVF patients in our program. Aspirin does not enhance endometrial thickness, augment the ovarian response, or improve pregnancy rates.

**Background**

Numerous measures have been employed in an attempt to increase implantation and pregnancy rates in assisted reproduction. Aspirin has been utilized as one such potential therapy. This drug has been shown to increase uterine blood flow [1], hence clinicians have postulated that aspirin could improve the receptiveness of the endometrium, thereby increasing implantation and birth rates.

Our institution at one time used aspirin routinely during IVF cycles, based on the work of studies which showed that low-dose aspirin increased implantation and pregnancy rates in women undergoing IVF [2,3]. Contrary data from Urman and co-investigators found no improvement
in IVF outcomes with low-dose aspirin [4]. Subsequently, the use of aspirin was stopped in our program early in 2000. Since conflicting results have been reported in the literature, we sought to compare pregnancy rates along with other IVF outcome variables retrospectively in the two groups of women (aspirin vs. non-aspirin) at our institution.

**Methods**

This study was a retrospective analysis of 316 consecutive IVF cycles from 1995 – 2001 at Carolinas Medical Center comparing women who were treated with low-dose aspirin versus those who did not receive aspirin treatment. Aspirin was used in all initial cycles from 1995, and excluded from most, but not all cycles beginning early in 2000 at the discretion of the attending physician. Demographic data including age, parity, cycle number, basal FSH, diagnosis, method of stimulation, and use of intracytoplasmic sperm injection was obtained from our database. For the purpose of this study, we divided method of stimulation into GnRH antagonists, long luteal leuprolide, and micro-dose flare. The infertility diagnoses were categorized into male factor, endometriosis, tubal factor, ovulatory dysfunction, unexplained, and other, which included uterine factors and immunological causes. The pregnancy and delivery rates were stable in our program from 1995 to 2001.

Seventy-two aspirin cycles were reviewed along with 244 non-aspirin cycles. For the aspirin cycles, 80 mg of aspirin daily was initiated at the start of down-regulation with luteal leuprolide. Aspirin was started on the first day of leuprolide in microdose flare stimulations. Patients were instructed to continue aspirin until they received the results of their pregnancy tests. The controls received no aspirin at any point during treatment. The outcome measures from the completed cycles were then reviewed. Of interest were the number of gonadotropin ampules used, endometrial thickness, number of eggs fertilized, number of embryos transferred, implantation rate, pregnancy rate, and live birth rate.

**Statistics**

The main independent variable was treatment with aspirin (yes/no). Demographic and clinical characteristics for each treatment group were reported and compared with two-tailed t-test, Wilcoxon Rank Sum test, Chi-Square or Fisher’s Exact tests, as appropriate. The study outcomes were analyzed in two stages: the first with Chi-Square tests followed by a confirmatory analysis using a regression method generalized estimating equations (GEE). Further analysis of the outcomes assessed their association with aspirin treatment after controlling for other patient and clinical characteristics. The power of the study to determine a difference in pregnancy rates with and without aspirin based on previous studies was approximately 60–72% with an alpha of 0.05 [2,3].

**Results and Discussion**

There was no significant difference between age, previous pregnancy, infertility diagnosis, prior IVF, basal FSH, and method of stimulation between the aspirin and non-aspirin groups. (Table 1) More women in the non-aspirin group had been pregnant before (15.9% v. 9.7%) compared to the aspirin group, but this did not achieve statistical significance (p = 0.06).

Low-dose aspirin did not improve any IVF outcomes analyzed in this study, even though more embryos were transferred to women who used aspirin (p = 0.03) (Table 2). In fact, the pregnancy rate in aspirin users was 48%, slightly lower compared to non-users, 57% (p = 0.18). Clinical pregnancy rates were 45% and 54% for users and non-users, respectively.

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**Table 1: Demographic Data**

|                      | Aspirin | No aspirin | p  |
|----------------------|---------|------------|----|
| Number patients      | 72 (23%)| 244 (77%)  |    |
| Age                  | 34 ± 4  | 34 ± 4     | 0.7|
| Previously pregnant  | 7 (10%) | 39 (16%)   | 0.06|
| Diagnosis            |         |            |    |
| Unexplained          | 4 (6%)  | 12 (5%)    |    |
| Male factor          | 23 (32%)| 51 (21%)   |    |
| Endometriosis        | 9 (13%) | 51 (21%)   |    |
| Tubal factor         | 13 (18%)| 54 (22%)   |    |
| Ovulatory dysfunction| 12 (17%)| 24 (10%)   |    |
| Other                | 6 (8%)  | 17 (7%)    |    |
| Multiple diagnoses   | 4 (6%)  | 54 (22%)   |    |
| Prior IVF            | 32%     | 22%        | 0.12|
| Basal FSH (mIU/mL)   | 7 ± 2   | 7 ± 8      | 0.14|
| Stimulation method   |         |            |    |
| Antagonist           | 0       | 2 (1%)     |    |
| Long luteal leuprolide| 62 (86%)| 195 (80%)  |    |
| Flare                | 8 (11%) | 34 (14%)   |    |

**Table 2: Results**

|                      | Aspirin | No Aspirin | P   |
|----------------------|---------|------------|-----|
| Ampules (75 IU)      | 42 ± 15 | 44 ± 17    | 0.35|
| Endometrial thickness| 12 ± 2  | 12 ± 2     | 0.26|
| ICSI                 | 23 (32%)| 67 (28%)   | 0.46|
| Oocytes fertilized   | 9 ± 4   | 9 ± 6      | 0.7 |
| Embryos transferred  | 4 ± 1   | 3 ± 1      | 0.03|
| Pregnancy rate       | 48%     | 57%        | 0.18|
| Live birth rate      | 29%     | 41%        | 0.07|
| Implantation rate    | 21%     | 30%        | 0.01|
ponents of aspirin consider treatment to be a simple, inex-
sible explanation of how aspirin is beneficial, even in the
attenuates placental apoptosis, and this could be a possi-
patients [9-13]. In vitro studies have shown that aspirin
[8]. Other studies have also found a beneficial effect with
not to women with negative antiphospholipid antibodies
repeat IVF failures and antiphospholipid antibodies, but
noglobulin therapy was administered to women with
controlled study found that IVF outcome was significantly
rate was 27% with aspirin and 23% in the control popu-
ning embryo transfer found an 11% pregnancy rate with
aspirin compared to 33% in controls, although the results
were not statistically different [16]. Implantation rates
were also lower with aspirin therapy, 2.9%, compared to
10.9% in untreated patients in this study. An uncontrolled
study of IVF likewise found that outcomes were not
improved with aspirin and heparin compared to conventional therapy [17]. Finally, a prospective, rand-
onized, double-blind, placebo-controlled trial of poor
responders by Lok et al found no benefit with daily aspir-
in 80 mg for cancellation rates, total dose of hMG used,
number of mature follicles, or number of oocytes retrieved [18]. Furthermore, there was no difference in
intraovarian or uterine artery pulsatility index with daily
aspirin.

Our results conflict with several studies that have shown that aspirin is beneficial for infertility therapy. Rubenstein et al found that aspirin 100 mg starting in the luteal phase of the preceding cycle improved blood flow velocity, ovar-
ian responsiveness, implantation and pregnancy rates in a
randomized, controlled trial of 149 patients undergoing
IVF compared to 149 placebo-treated controls [2,5]. Weckstein et al also found enhanced uterine blood flow and significantly higher implantation and clinical preg-
nancy rates with low-dose aspirin in women who had a
thin endometrium undergoing embryo transfer from oocyte donation in a randomized controlled study [3].

Interestingly, endometrial thickness was not improved
with aspirin. In an prospective, randomized insemination
study of women with a thin endometrium undergoing
insemination, aspirin improved the percentage of trilami-
nar endometrium and pregnancy rates from 9 to 18%, but
not endometrial thickness or ultrasound flow patterns [6].

Waldenstrom et al randomized 1380 unselected IVF cycles
on alternate days to receive aspirin 75 mg or no aspirin
starting on the day of embryo transfer and continuing
until 18 days after retrieval [7]. In this study, the live birth
rate was 27% with aspirin and 23% in the control popu-
lation, with an odds ratio 1.2 (95% CI 1.0–1.6). A non-
controlled study found that IVF outcome was significantly
improved when aspirin, heparin, and intravenous immu-
noglobulin therapy was administered to women with
repeat IVF failures and antiphospholipid antibodies, but
not to women with negative antiphospholipid antibodies
[8]. Other studies have also found a beneficial effect with
aspirin/heparin, and aspirin plus prednisolone in IVF
patients [9-13]. In vitro studies have shown that aspirin
attenuates placental apoptosis, and this could be a possi-
ble explanation of how aspirin is beneficial, even in the
absence of endometrial or oocyte improvement [14]. Pro-
ponents of aspirin consider treatment to be a simple, inex-
pensive, and harmless means to improve IVF outcomes
[7].

However, some studies have shown anticoagulation ther-
apy to be ineffective, and sometimes detrimental, during
IVF. A large randomized controlled trial of low-dose aspir-
in by Urman et al found no difference in implantation or
pregnancy rates in patients undergoing ICSI [4]. A higher
incidence of ectopic pregnancy was found in the aspirin
group. A prospective, randomized, placebo-controlled IVF
trial by Stern and colleagues found no benefit with aspirin
and heparin for women with prior IVF implantation fail-
ure and antiphospholipid or antinuclear antibodies [15].
Another small matched study of women undergoing fro-
zen embryo transfer found an 11% pregnancy rate with
aspirin compared to 33% in controls, although the results
were not statistically different [16]. Implantation rates
were also lower with aspirin therapy, 2.9%, compared to
10.9% in untreated patients in this study. An uncontrolled
study of IVF likewise found that outcomes were not
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intraovarian or uterine artery pulsatility index with daily
aspirin.

Randomized controlled trials have repeatedly shown that
combined aspirin plus heparin improves pregnancy out-
comes for women with recurrent pregnancy losses attrib-
uted to antiphospholipid antibodies [19,20]. This benefit
is also shown in a prospective series [21]. Outcomes are
better with aspirin plus heparin therapy than with aspirin
alone in most [20,21], but not all studies [22,23]. Aspirin
plus corticosteroid therapy, on the other hand, may be
harmful. Combined low-dose aspirin plus prednisone
increased the risk of preterm birth in two randomized
controlled trials [24,25]. With a minimal benefit of aspi-
rin alone for women with recurrent pregnancy losses
and antiphospholipid antibodies, it is not surprising that we
failed to find a beneficial effect of aspirin therapy in our
general IVF population.

In our study, we did not test for uterine blood flow or rou-
tinely test for antiphospholipid antibodies. Therefore, we
were not able to sub-divide the women in our study into
groups that might be more responsive to aspirin. How-
ever, an ASRM Practice Committee Report in 1999 con-
cluded that antiphospholipid antibodies do not affect IVF
success, and therapy is not justified [26]. Furthermore, we
believe that implantation rates, pregnancy rates, and live
birth rates are more important indicators of IVF outcome

compared to indirect measurements such as endometrial blood flow. In our study, pregnancy, implantation, and live birth rates were higher in the non-aspirin control group.

Another weakness in our study is the six-year period over which our IVF cycles were reviewed. It is possible that subtle differences could bias results in the aspirin and control groups in a retrospective analysis. Additionally, the small study population yields a limited statistical power to detect minor differences in pregnancy outcomes with aspirin. There are actual and sometimes large differences between the two groups of women, which could affect the outcomes. The differences are not significant, but might be due to the small population studied. There certainly could be minor changes in treatment protocols over that span of time, but our age-related pregnancy and live birth rates remained stable during the years of this study.

Based on the results from our study and the prospective randomized trials by Urman and colleagues [4] and Stern et al [15], aspirin is not beneficial for a general IVF population. Since implantation, pregnancy, and delivery rates are higher for non-aspirin users, our study raises the possibility that aspirin may lower IVF success. A potential fertility reducing effect of aspirin is plausible, since prostaglandins affect ovulation, fertilization, and implantation [27]. Since aspirin inhibits prostaglandin synthesis, implantation could be compromised. Clearly, a larger, prospective randomized study with adequate power would be needed to determine if low-dose aspirin reduced IVF success.

There is some risk associated with aspirin therapy for infertility, although the extent of the risk for a healthy infertility population is unclear. One population based cohort study found that aspirin and nonsteroidal anti-inflammatory agents increased the risk of miscarriage, although a recent meta-analysis showed no increased risk of miscarriage with aspirin [28,29]. Although aspirin does not appear to alter the risk of congenital anomalies, first trimester aspirin consumption may increase the incidence of gastroschisis [30]. Acetylsalicylic acid may reach the fetal circulation and exert antiplatelet effects in the fetus and newborn, although the incidence of neonatal bleeding does not appear to be increased with maternal aspirin [31,32]. However, maternal aspirin may raise the risk of placental abruption and antenatal, intrapartum, and postpartum hemorrhage [32,33]. Additionally, there is at least one reported maternal death due to complications of cerebral hemorrhage in a woman treated with aspirin and heparin after IVF [34]. Although these risks may be small, treatment with aspirin is not justified in the absence of a proven benefit.

**Conclusion**

Low-dose aspirin did not enhance endometrial thickness, augment the ovarian response, or improve pregnancy rates in our study. There is no apparent benefit in the routine use of aspirin during IVF cycles, and this practice should be abandoned.

**Competing interests**

The author(s) declare that they have no competing interests.

**Authors’ contributions**

* BSH conceived of the study, participated in the analysis and interpretation of the data, and drafting and revising the manuscript. JTB made substantial contributions to the design and acquisition of data, and drafting the manuscript. PBM, MAP, TAL, and MLM made substantial contributions to the acquisition of data and revising the manuscript. All authors read and approved the final manuscript.

**Acknowledgements**

We thank Howell Sasser, Ph.D., Director of Research Epidemiology, Dickson Institute at Carolinas Medical Center for his assistance with statistical evaluation.

**References**

1. 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, 9:1954-7.

2. Rubinstein M, Marazzi A, Polak de Fried E: 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. *Fertil Steril* 1999, 71:825-9.

3. Weckstein LN, Jacobson A, Galen D, Hampson K, Hammel J: Low-dose aspirin for oocyte donation recipients with a thin endometrium: prospective, randomized study. *Fertil Steril* 1997, 68:927-30.

4. Urman B, Mercan R, Alatas C, Balaban B, Isiklar A, Nuhoglu A: Low-dose aspirin does not increase implantation rates in patients undergoing intracytoplasmic sperm injection: a prospective randomized study. *J Assisted Reprod Genet* 2000, 17:586-90.

5. Polak de Fried E: Errata. *Fertil Steril* 1999, 72:755.

6. Hsieh YY, Tsai HD, Chang CC, Lo HY, Chen CL: Low-dose aspirin for infertile women with thin endometrium receiving intrauterine insemination: a prospective, randomized study. *J Assist Reprod Genet* 2000, 17:1-7.

7. Waldenstrom U, Hellberg D, Nilsson S: Low-dose aspirin in a short regimen as standard treatment in vitro fertilization: a randomized, prospective study. *Fertil Steril* 2004, 81:1560-4.

8. Sher G, Zouves C, Feinman P, Maassarani G, Matzner W, Chong P, Ching W: A rational basis for the use of combined heparin/aspirin and IVIG immunotherapy in the treatment of recurrent IVF failure associated with antiphospholipid antibodies. *Am J Reprod Immunol* 1998, 39:391-4.

9. Hasegawa I, Hamamoto Y, Suzuki M, Murakawa H, Kurabayashi T, Takakawa K, Tanaka K: Prednisolone plus low-dose aspirin improves the implantation rate in women with autoimmune conditions who are undergoing in vitro fertilization. *Fertil Steril* 1998, 70:1044-8.

10. Sher G, Matzner W, Feinman P, Maassarani G, Zouves C, Chong P, Ching W: The selective use of heparin/aspirin therapy, alone, or in combination with intravenous immunoglobulin G, in the management of antiphospholipid antibody-positive
women undergoing in vitro fertilization. *Am J Reprod Immunol* 1998, 40:74-82.

11. Sher G, Amar A, Lerner-Geva L, Yaron Y, Daniel Y, Schwartz T, Azem F, Yovel I, Lessing JB: Prednisone and aspirin improve pregnancy rate in patients with reproductive failure and autoimmune antibodies: a prospective study. *Am J Reprod Immunol* 2000, 43:36-40.

12. Geva E, Ami T, Lerner-Geva L, Yaron Y, Matzner W, Ching W, Chong P: High fecundity rates following in-vitro fertilization and embryo transfer in antiphospholipid antibody seropositive women treated with heparin and aspirin. *Hum Reprod* 1994, 9:2278-83.

13. Geva E, Lerner-Geva L, Yaron Y, Scholl JS, Hobart JM, Neerhof MG, Ragin A: The use of combined heparin/aspirin and immunoglobulin G therapy in the treatment of in vitro fertilization patients with antithyroid antibodies. *Am J Reprod Immunol* 1998, 39:223-5.

14. Sher G, Feinman M, Zouves C, Feinman M, Sohn S, Matzner W, Ching W, Chong P: High fecundity rates following in-vitro fertilization and embryo transfer in antiphospholipid antibody seropositive women treated with heparin and aspirin. *Hum Reprod* 1994, 9:2278-83.

15. Stern C, Chamley LW, Birdsall M, Zanderigo AM, Liddell HS, Pattison NS: Adjuvant low-dose aspirin therapy in poor responders undergoing in vitro fertilization: a prospective, randomized, double-blind, placebo-controlled trial of heparin and aspirin for women with in vitro fertilization implantation failure and antiphospholipid or antinuclear antibodies. *Fertil Steril* 2003, 80:376-83.

16. Check JH, Dietterich C, Lurie D, Nazzari 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 sono graphic parameters. *J Assist Reprod Genet* 1998, 15:579-82.

17. Kutteh WH, Yetman DL, Chantilis SJ, Crain J: Effect of antiphospholipid antibodies in women undergoing in-vitro fertilization: role of heparin and aspirin. *Hum Reprod* 1997, 12:1711-5.

18. Lok IH, Yip SK, Cheung LP, Yin Leung PH, Haines CJ: Adjuvant low-dose aspirin therapy in poor responders undergoing in vitro fertilization: a prospective, randomized, double-blind, placebo-controlled trial. *Fertil Steril* 2004, 81:556-61.

19. Triolo G, Ferrante A, Ciccia F, Accardo-Palumbo A, Perino A, Castelli A, Giarratano A, Licata G: Randomized study of subcutaneous low molecular weight heparin plus aspirin versus intravenous immunoglobulin in the treatment of recurrent fetal loss associated with antiphospholipid antibodies. *Arthritis Rheum* 2003, 48:728-283-4.

20. Rai R, Cohen H, Dave M, Regan L: Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BJM* 1997, 314(7076):253-7.

21. Kutteh WH: Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. *Am J Obstet Gynecol* 1996, 174:1584-9.

22. Farquharson RG, Quenby S, Greaves M: Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. *Obstet Gynecol* 2002, 100:408-13.

23. Parsonson NS, Chamley LW, Birdsall M, Zanderigo AM, Liddell HS, McDougall J: Does aspirin have a role in improving pregnancy outcome for women with the antiphospholipid syndrome? A randomized controlled trial. *Am J Obstet Gynecol* 2000, 183:1008-12.

24. Laskin CA, Bombardier C, Hannah ME, Mandel FP, Ritchie JW, Farewell V, Farine D, Spitzer K, Fielding L, Solonника CA, Yeung M: Prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss. *NEJM* 1997, 337:148-53.

25. Silver RK, MacGregor SN, Sholl JS, Hobart JM, Neerhof MG, Ragan A: Comparative trial of prednisone plus aspirin versus aspirin alone in the treatment of anticolidipin antibody-positive obstetric patients. *Am J Obstet Gynecol* 1993, 169:1411-7.

26. Practice Committee Report: Antiphospholipid antibodies do not affect IVF success. *American Society for Reproductive Medicine* 1999.

27. Rock JA, Hurst BS: Clinical significance of prostanoid concentration in women with endometriosis. *Prog Clin Biol Res* 1990, 23:61-80.

28. Li DK, Liu L, Oudou R: Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *BMJ* 2003, 327(7411):368.

29. Kozer E, Nikfar S, Costei A, Boskovic R, Nulman I, Koren G: Aspirin consumption during the first trimester of pregnancy and congenital anomalies: a meta-analysis. *Am J Obstet Gynecol* 2002, 187:1623-30.

30. Kozer E, Costei AM, Boskovic R, Nulman I, Nikfar S, Koren G: Effects of aspirin consumption during pregnancy on pregnancy outcomes: meta-analysis. *Dev Res Repro Toxicology* 2003, 68:70-84.

31. Leonhardt A, Bernert S, Watzer B, Schmitz-Zeigler G, Seyberth HW: Low-dose aspirin in pregnancy: maternal and neonatal aspirin concentrations and neonatal prostanoid formation. *Pediatrics* 2003, 111:e77-81.

32. Sibai BM, Caritis SN, Thom E, Klebanoff M, McNellis D, Rococo L, Paul RH, Romero R, Witter F, Rossen M, et al.: Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *NEJM* 1993, 329:1213-8.

33. Golding J: A randomized trial of low dose aspirin for primiparae in pregnancy. The Jamaica Low Dose Aspirin Study Group. *Br J Obstet Gynaecol* 1998, 105:293-9.

34. Centers for Disease Control and Prevention: Pregnancy-related death associated with heparin and aspirin treatment for infertility, 1996. *JAMA* 1998, 279:1860-1.