Does standard adjuvant low-dose aspirin therapy improve the outcome of in vitro fertilization?

A systematic review

By

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Background

- Many changes have occurred in the techniques of assisted reproduction since 1978, when the first “test tube baby” was born. Louise Brown was the product of an embryo created following fertilization of a mature oocyte collected by timing the endogenous luteinizing hormone (LH) surge in a natural menstrual cycle.

- Treatment options available to infertile couples have tremendously expanded to include simple ovulation induction, intrauterine insemination (IUI), as well as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI).

Background continued

- The most important factors governing the chances of successful IVF include the patient's age and response to superovulation.

- Several factors involved in optimizing the success of embryo transfer have been studied. They include:
  - Time and stage of embryo transfer
  - Choice of the transfer catheter
  - Position of the patient during the procedure
  - Ultrasonographic guidance during the procedure
  - The use of certain medications: progesterone, sildenafil, low-dose aspirin...

(Sallam, 2005)

Background continued

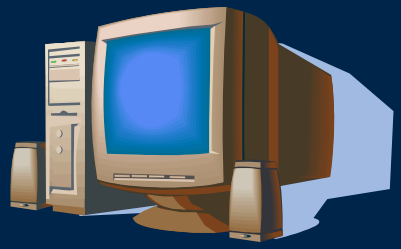
- Low-dose aspirin irreversibly inhibits the enzyme cyclo-oxygenase in platelets, preventing the synthesis of thromboxane A2, a potent vasoconstrictor and enhancer of platelet aggregation.

- Low-dose aspirin may, therefore, increase uterine and ovarian blood flow and tissue perfusion, and hence, improve the results of IVF and ICSI.

(Vane, 1971; Willis, 1974; Wada et al., 1994)

Objectives

The objective of this review is to evaluate the effect of adjuvant low-dose aspirin (75-100 mg/d) as a standard therapy in non-selected patients undergoing IVF-ET, irrespective of underlying conditions.



Search strategy

- Different electronic databases including PubMed, Embase, the Reproductive Health Library, the Cochrane Library and Google were searched for randomized controlled trials.
- Keywords: aspirin, in vitro fertilization, intracytoplasmic sperm injection, embryo transfer.
- Different resources of the WHO library and the library of the Faculty of Medicine of the University of Geneva were consulted throughout the preparation of this review.

Criteria for considering studies for this review

- Inclusion criteria: randomized controlled trials comparing the use versus the non-use of low-dose aspirin as an adjuvant therapy to IVF-ET.
- Types of participants: Infertile women undergoing IVF-ET, with GnRH analog mid-luteal pituitary downregulation and controlled ovarian stimulation with recombinant FSH or hMG.
- Type of intervention: aspirin in a dose of 75-100 mg/d was administered as an adjuvant therapy to IVF-ET in the treatment group, while no aspirin was administered in the control group.

- Types of outcome measures:
  - Number of oocytes retrieved
  - Number of embryos transferred
  - Serum estradiol level on the day of hCG administration
  - Pulsatility index of uterine and ovarian arteries
  - Implantation rate
  - Clinical pregnancy rate
  - Miscarriage rate per clinical pregnancy
  - Extrauterine pregnancy rate per clinical pregnancy
  - Birth rate per embryo transfer

Search results

- The search strategies identified 7 randomized controlled trials of which two were excluded for selecting patients with antiphosholipid syndrome and poor responders, respectively.

- 5 randomized controlled trials with a total of 2054 patients are included in this review:
  - Duvan *et al*. (2006) with 81 participants
  - Päkkilä *et al.* (2005) with 374 participants
  - Waldenström *et al.* (2004) with 1022 participants
  - Urman *et al.* (2000) with 279 participants
  - Rubinstein *et al*. (1999) with 298 participants

Characteristics of the included studies

Study, year; number of patients	Country	Intervention	Outcome measures	Allocation conceal.
Duvan et al., 2006; 81	Turkey	Group A: 100 mg aspirin from day of ET. Group B: placebo	Nb of oocytes, nb of embryos, serum E2, IR, clinical PR,	
Päkkilä et al., 2005; 374	Finland	Group A: 100 mg aspirin with onset of controlled ovarian stimulation. Group B: placebo	Nb of oocytes, nb of embryos, clinical PR, miscarriage & ectopic pregnancy rate/clinical pregnancy	√
Rubinstein et al., 1999; 298	Argentina	Group A: 100 mg aspirin from 21st day of preceding cycle. Group B: placebo	Nb of oocytes, nb of embryos, serum E2 level, uterine & ovarian PI, IR, clinical PR	√

Characteristics of the included studies
continued

Study, year; number of patients	Country	Intervention	Outcome measures	Allocation conceal.
Urman et al., 2000; 279	Turkey	Group A: 80 mg aspirin with onset of controlled ovarian stimulation. Group B: no treatment	Nb of oocytes, nb of embryos, serum E2, IR, clinical PR, miscarriage & ectopic pregnancy rate/clinical pregnancy	√
Waldenström et al., 2004;1022	Sweden	Group A: 75 mg aspirin from day of ET. Group B: no treatment	Nb of oocytes, nb of embryos, clincal PR, birth rate/ET	

IR= implantation rate, PR= pregnancy rate, E2 = estradiol, ET = embryo transfer

Methodological quality of included studies

- ✓ All of the studies were approved by ethics committees.
- ✓ 2 studies were conducted in university hospitals.
- ✓ All of the studies provide data on patient characteristics, including age and etiology of infertility.
- ✓ All of the studies provide data on the protocols used for controlled ovarian stimulation.
- ✓ Randomization methods are reported in all of the studies.
- ✓ Tools for data analysis are reported in all of the studies.

Results

- The number of oocytes retrieved was significantly higher in the treatment group in the study by Rubinstein *et al.*, while no statistically significant difference was reported in the other studies.

Study, number of participants	Treatment group	Control group	*P*-value
Duvan, 81	11.52 ± 6.46	12.41 ± 6.41	NS
Päkkilä, 374	12.0 ± 7.0	12.7 ± 7.2	NS
Rubinstein, 298	16.2 ± 6.7	8.6 ± 4.6	< 0.05
Urman, 279	10.9 ± 6.0	11.7 ± 6.5	NS
Waldenström, 1022	8.4	8.3	NS

Results continued

- The number of embryos transferred was significantly higher in the treatment group in the study by Waldenström *et al.*, while no statistically significant difference was reported in the other studies.

Study, number of participants	Treatment group	Control group	*P*-value
Duvan, 81	4.3 ± 1.8	4.3 ± 1.7	NS
Päkkilä, 374	1.64 ± 0.64	1.63 ± 0.71	NS
Rubinstein, 298	3.3	3.3	NS
Urman, 279	3.1 ± 1.5	3.2 ± 1.4	NS
Waldenström, 1022	2.1	2.0	0.0001

Results continued

- Rubinstein *et al.* reported a significantly higher serum estradiol level on the day of hCG administration in the treatment group while Duvan *et al*. and Urman *et al*. reported no statistically significant difference in this outcome measure.

Study, number of participants	Treatment group	Control group	*P*-value
Duvan, 81	1800.4 ± 1172.2	2628.3 ± 1351.0	NS
Rubinstein, 298	2923.8 ± 1023.4	1614.3 ± 791.7	< 0.05
Urman, 279	2107.8 ± 1293.9	2505.8 ± 1562.3	NS

Results continued

- Rubinstein *et al.* reported a significantly higher implantation rate in the treatment group while Duvan *et al.* and Urman *et al.* reported no statistically significant difference in this outcome measure.

Study, number of participants	Treatment group	Control group	*P*-value
Duvan, 81	9.8	10.9	NS
Rubinstein, 298	17.8	9.2	< 0.05
Urman, 279	15.6	15.1	NS

Results continued

- Two studies reported significantly higher clinical pregnancy rates in the treatment group (Rubinstein *et al.*, Waldenström *et al.*), while no statistically significant difference was reported in the other studies.

Study, number of participants	Treatment group	Control group	*P*-value	OR (95% CI)
Duvan, 81	27	35	NS	
Päkkilä, 374	25.3	27.4	NS	
Rubinstein, 298	45	28	< 0.5	
Urman, 279	39.6	43.4	NS	
Waldenström, 1022	35.4	30		1.3 (1.0 - 1.6)

Results continued

- Three studies reported that there is no statistically significant difference in miscarriage and extrauterine pregnancy rates between both study groups (Päkkilä *et al.*; Urman *et al.*; Waldenström *et al.*).

Study	Treatment group	Control group	*P*-value	OR (95% CI)
Päkkilä	18.2 (9)	16.7 (6.3)	NS	
Urman	14.5 (9.1)	11.9 (1.6)	NS	
Waldenström	20.9 (2.4)	17.7 (4.9)		1.2 (0.8-2.0) 0.5 (0.2-1.3)

Results continued

- Waldenström *et al*. reported a significantly increased birth rate in the treatment group as compared with the control group.

Study, number of participants	Treatment group	Control group	OR (95% CI)
Waldenström, 1022	27.2	23.2	1.2 (1.0 – 1.6)

Discussion

The explanation of discordant results may lie within the dosage (75, 80 or 100 mg/d) and the duration of aspirin administration (initiation at the luteal phase, with the onset of controlled ovarian stimulation or on the day of embryo transfer).

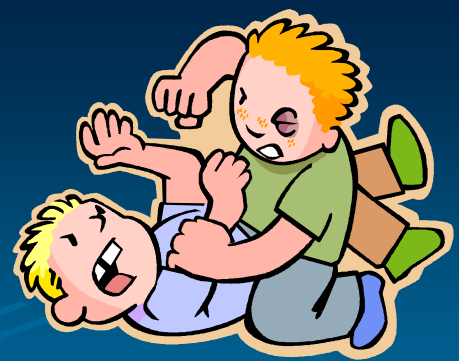
Discussion continued

Waldenström *et al.* (2004) reported an increased birth rate per ET in the treatment group as compared with the control group. However, some points need to be taken into consideration:

- In the aspirin group, the number of embryos transferred was significantly higher than in the control group, which could contribute to the higher pregnancy rate in the aspirin group.
- The study was open and not placebo controlled, both of which may increase the risk for study bias.
- As the lower confidence intervals included 1.0, there is a possibility that aspirin treatment has no effect on IVF.

Conclusion

It seems that there is a controversy concerning the use of low-dose aspirin as an adjuvant therapy in non-selected IVF patients. While some authors do recommend its use, others claim it has no beneficial effects for this particular population. More randomized controlled trials need to be undertaken in order to reach more conclusive results, especially for the dosage and duration of treatment.



Louise Brown

on her 25th birthday

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Merci

Vielen Dank

World Health Organization


Thank you