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Low-dose aspirin for *in vitro* fertilization: a systematic review and meta-analysis

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Despite recent advances in ovarian stimulation regimens and laboratory techniques, the pregnancy rate of assisted reproduction remains relatively low. New methods that would potentially improve implantation rates are needed. One proposed strategy involves enhancement of blood flow at the implantation site with the use of low-dose aspirin. We conducted a systematic review and meta-analysis to investigate the effect of low-dose aspirin on likelihood of pregnancy in women undergoing *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI). An electronic search of the literature was conducted targeting reports published over the last 26 years. Only randomized controlled trials (RCTs) comparing aspirin with placebo or no treatment in IVF/ICSI women were included in the meta-analysis. A number of relevant outcomes including pregnancy and live birth (LB) rates were investigated. Pooled relative risk (RR) and 95% confidence interval (CI) were calculated using a random-effects model. Inter-study heterogeneity among the trials was assessed using the Cochran's *Q* test. Ten RCTs were identified from the literature search, six of which met the criteria for inclusion in the meta-analysis. Clinical pregnancy (CP) rate per embryo transfer (ET) was not found to be significantly different between patients who received low-dose aspirin and those who received placebo or no treatment (RR 1.09, 95% CI 0.92–1.29). None of the other outcomes, including CP per cycle, spontaneous abortion or ectopic pregnancy per CP and LB rate per cycle or ET was found to differ significantly between the compared groups. On the basis of up-to-date evidence, low-dose aspirin has no substantial positive effect on likelihood of pregnancy and, therefore, it should not be routinely recommended for women undergoing IVF/ICSI.

Key words: aspirin/IVF/implantation/endometrium/pregnancy

Introduction

Low-dose acetylsalicylic acid (aspirin) irreversibly inhibits the enzyme cyclo-oxygenase in platelets, preventing the synthesis of thromboxane (Vane, 1971; Willis, 1974; Pedersen and Fitzgerald, 1984), which is a potent vasoconstrictive agent. The daily administration of aspirin in low doses induces a shift in the balance away from thromboxane A_2 and towards prostacyclin, leading to vasodilatation and increased blood perfusion (Patrono *et al.*, 2005). Aspirin has been found both experimentally and clinically to be cardioprotective, with few adverse effects in doses of 80–160 mg daily (Lorenz *et al.*, 1989). Treatment with low-dose aspirin in prevention of myocardial ischaemia is now widely recognized. Previous studies have shown that low-dose aspirin initiated in the second trimester of pregnancy in high-risk populations decreases the incidence of pre-eclampsia and preterm labour and increases the birth weight of the newborn (Italian Study of Aspirin in Pregnancy, 1993; Collaborative Low-dose Aspirin Study in Pregnancy Collaborative Group, 1994). It has also been demonstrated that women with recurrent spontaneous abortion and antiphospholipid (APL) syndrome may benefit from low-dose aspirin therapy, especially when combined with unfractionated heparin (Kutteh, 1996; Rai *et al.*, 1997; Tulppala *et al.*, 1997).

The main factors that affect the outcome of *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) include the woman's age, number of oocytes retrieved, quality of the embryos transferred, ease of embryo transfer (ET) and endometrial receptivity (Weckstein *et al.*, 1997; Ebner *et al.*, 2000; Terriou *et al.*, 2001; Ziebe *et al.*, 2001; Tomas *et al.*, 2002). Various strategies have been used to improve ovarian response, including the use of higher doses of human menopausal gonadotrophins (hMG) or recombinant follicle-stimulating hormone (Land *et al.*,

1996; De Placido *et al.*, 2000), use of adjuvant growth hormone or growth hormone releasing factor (Dor *et al.*, 1995; Howles *et al.*, 1999), flare-up protocols (Karande *et al.*, 1997), administration of gonadotrophin-releasing hormone (GnRH) agonists (Surrey *et al.*, 1998) and GnRH antagonists (Akman *et al.*, 2001). Despite the introduction of all these interventions, the success of assisted reproductive technology (ART) has not increased markedly, thus leaving avenues for further research (Surrey and Schoolcraft 2000; Tarlatzis *et al.*, 2003).

A large body of evidence shows that APL antibodies, occasionally found in low-risk obstetric populations (Lockwood *et al.*, 1989; Stern *et al.*, 1998), are commonly found in women with reproductive dysfunction such as recurrent pregnancy loss (RPL) (Cowchock *et al.*, 1986; Matzner *et al.*, 1994; Yetman and Kutteh, 1996) and idiopathic infertility (Gleicher *et al.*, 1989, 1994; Birdsall *et al.*, 1996). Nevertheless, there is much controversy with regard to the association between APL antibodies and IVF outcome. Unlike the studies showing benefits after the use of heparin and aspirin in women with RPL (Kutteh, 1996; Rai *et al.*, 1997; Tulppala *et al.*, 1997), there is no consensus regarding its use in IVF patients.

Suboptimal uterine perfusion has been suggested as a possible cause of infertility (Goswamy and Steptoe, 1988). Impaired uterine blood flow may reduce endometrial receptivity resulting in embryo implantation failure (Battaglia *et al.*, 1990; Steer *et al.*, 1992). Since aspirin has been shown to increase uterine perfusion (Kuo *et al.*, 1997), it was not unreasonable to assume that aspirin administration may increase endometrial receptivity and blastocyst implantation. The evidence supporting the effect of low-dose aspirin in women undergoing IVF is, however, inconsistent. Several papers reported a beneficial effect of aspirin, whereas others failed to confirm these findings. Of interest, a retrospective series showed increased spontaneous abortion rate in women taking aspirin pre-conceptually (Li *et al.*, 2003).

In this paper, we present a systematic review and meta-analysis of the available literature on the use of aspirin in ART.

Materials and methods

Objective

The purpose of this review was to determine the effect of low-dose aspirin on the likelihood of pregnancy in women undergoing IVF/ICSI treatment cycles.

Types of studies, interventions and inclusion and exclusion criteria

The systematic review included all types of studies investigating the effect of low-dose aspirin alone or in conjunction with heparin or glucocorticoids on IVF or ICSI outcome. For the purpose of the meta-analysis, all the available randomized controlled trials (RCTs) comparing the use of low-dose aspirin alone versus placebo or no treatment was considered.

Low-dose aspirin was defined as a dosage of 150 mg or less administered orally once a day. Aspirin was commenced at different stages of the treatment cycle (e.g. during down-regulation, during ovarian stimulation, after oocyte collection or on the day of ET) and was continued for a variable length of time (e.g. until confirmation of pregnancy by a positive pregnancy test or by detection of fetal heart activity on ultrasound, during pregnancy up to 34 weeks and up to 6 weeks postpartum). There were no sufficient data to warrant meta-analysis of trials that included specific subgroups of infertile patients, such as oocyte recipients or poor responders (Weckstein *et al.*, 1997; Lok *et al.*, 2004).

Types of outcome measures

The outcome measures assessed in the analysis included pregnancy rate per ET, clinical pregnancy (CP) rate per cycle or ET, CP rate per elective single ET, spontaneous abortion or ectopic pregnancy rate per CP, live birth (LB) rate per cycle or ET, implantation rate and cycle cancellation rate (no embryos available for transfer).

Data collection and statistical analysis

We searched four electronic databases—MEDLINE, EMBASE, Cochrane Controlled Trials Register (CENTRAL) and The UK National Research Register of ongoing and completed research projects undertaken in or for the UK National Health Service—from January 1980 to March 2006 using the key words '(aspirin or acetylsalicylic acid) and (IVF or ICSI)'. All the eligible abstracts were scrutinized in full text to identify those that qualified for this review. We also perused the references of retrieved articles, while additional MEDLINE cross-searches were performed using the names of investigators who were the lead authors of at least one eligible trial. The journals with the highest number of electronically identified trials were hand-searched (Hopewell *et al.*, 2002). The references of retrieved papers and the proceedings of relevant conferences were searched to identify other potentially eligible published or unpublished studies for inclusion in this review. There was no language restriction.

The literature search, the verification of inclusion and exclusion criteria and the extraction of data were undertaken and verified independently and blindly by the two principal investigators (T.A.G., L.G.N.). The results were then compared and a consensus was reached. The methodological quality of all the trials, including those published only in abstract form, was assessed with respect to randomization procedure, concealment of treatment allocation, blinding, co-intervention, sample size estimation, completeness of follow-up and differentiation between subjects and cycles.

Owing to significant heterogeneity among trials, we used the random-effects model (DerSimonian and Laird, 1986) to derive the summary estimates of the effect of treatment. Heterogeneity among studies for every outcome was assessed using the Cochran's Q test (Cochran, 1954). Relative risk (RR) and 95% confidence interval (CI) were calculated using the Revman 4.2 software. Formal statistical exploration for publication bias was not feasible due to the limited number of studies. Data analysis was performed by one of the investigators (M.K.). All authors participated in the review of the contents of the manuscript.

Results

A total of six RCTs (Rubinstein *et al.*, 1999; Urman *et al.*, 2000; Van Dooren *et al.*, 2004; Waldenstrom *et al.*, 2004; Päkkilä *et al.*, 2005; Duvan *et al.*, 2006) were included in this meta-analysis. Two conferences' abstracts (Bordes *et al.*, 2003; Lentini *et al.*, 2003) were excluded as we failed to get a positive reply from the authors. Two more RCTs were excluded as they both involved subgroups of infertile patients—poor responders (Lok *et al.*, 2004) and oocyte recipients (Weckstein *et al.*, 1997). Two trials registered in the UK National Research Register were

identified and the authors contacted. No response was received from the author of the first trial (Zosmer, 1999), whereas the other author (Papaioannou, 2000) confirmed that the trial had not been completed (Fig. 1).

Table I summarizes the descriptive characteristics of the included studies in this systematic review that investigates the effect of low-dose aspirin on IVF/ICSI outcome. A total of 12 studies (10 RCTs and 2 retrospective studies) including 3189 cycles were reviewed. Only the first six trials in the table met the eligibility criteria for the meta-analysis. Aspirin was used in a dose of 75–100 mg per day in all studies.

Table II shows the total effect of the meta-analysis for all the examined outcomes in the eligible IVF/ICSI population. CP per ET was the only outcome to be analysed in all RCTs included in the meta-analysis. This was not found to be different between aspirin and no treatment groups (RR 1.09, 95% CI 0.92–1.29). Low-dose aspirin was not found to be associated with improved outcome in any of the examined parameters. The inter-study heterogeneity just reached statistical significance for one of the outcomes studied—CP/cycle ($P = 0.05$).

The forest plots of the effect of aspirin versus placebo or no treatment on CP rate per ET, spontaneous abortion rate per CP and cycle cancellation rate (no embryos available for transfer) are presented in Figs. 2, 3, 4, respectively. Of note, only one conference abstract (Van Dooren *et al.*, 2004), whose quality measures were obtained in part, was retained in the meta-analysis, but excluding it did not change the overall results.

As shown in Table III, low-dose aspirin did not have any effect on CP per cycle or ET or on cycle cancellation in poor responders undergoing IVF (Lok *et al.*, 2004). In recipients of donated oocytes, low-dose aspirin improved implantation rate (24% versus 9%, RR 2.74, 95% CI 1.13–6.62), but the effects on CP or LB per ET were not statistically significant (Weckstein *et al.*, 1997).

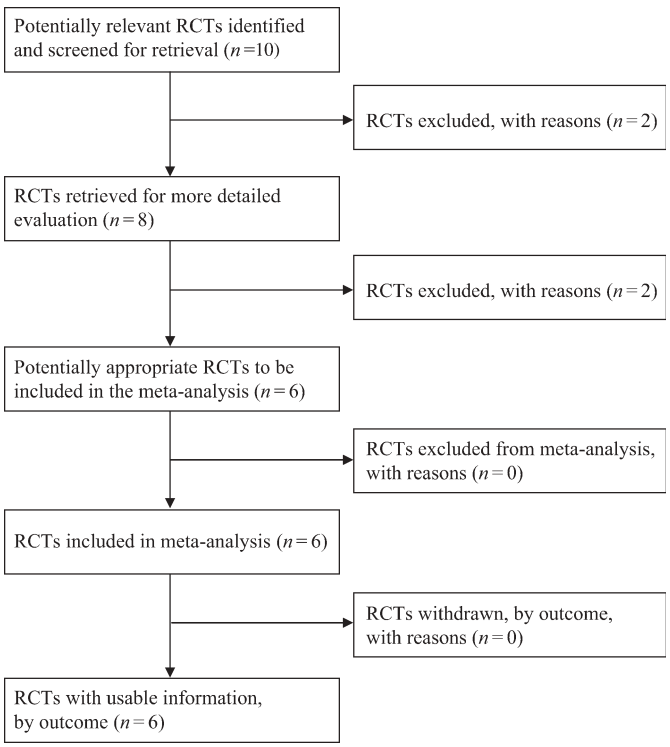

Figure 1. QUOROM statement flow diagram

Discussion

The published evidence regarding the efficacy of aspirin in IVF or ICSI cycles is controversial. The largest published RCT (Waldenstrom *et al.*, 2004) included 1380 cycles and found a marginally higher CP per ET in the aspirin group with no difference in the LB rate. The number of embryos transferred in the aspirin group was significantly higher. Of note, the number of previous cycles was not considered in the inclusion criteria. By considering only the first treatment cycle for individual women (n = 358), similar results were obtained between the two study groups. Rubinstein *et al.* (1999) have reported higher CP and implantation rates, a remarkable increase in the ovarian response to stimulation as well as enhanced uterine and ovarian blood flow in the aspirin group. Other authors have noted higher pregnancy rate in the aspirin group but no significant difference in the other parameters (Bordes *et al.*, 2003). In a RCT, Mollo *et al.* (2003) reported lower first trimester spontaneous abortion rate in the aspirin/prednisone group, while pregnancy and implantation rates were similar between the two groups. Four other RCTs (Urman *et al.*, 2000; Lentini *et al.*, 2003; Van Dooren *et al.*, 2004; Päkkilä *et al.*, 2005) failed to demonstrate any beneficial effect of aspirin on IVF outcome. The four-arm study by Duvan *et al.* (2006) revealed no significant differences in implantation and pregnancy rates among the compared populations—aspirin 100 mg/day, prednisolone 10 mg/day, aspirin 100 mg/day plus prednisolone 10 mg/day and controls. In a retrospective study, Hurst *et al.* (2005) have found a significantly lower implantation rate in the aspirin group (21 versus 30%, $P = 0.01$). However, the retrospective design and the 5-year interval between the compared groups weakened the study conclusion. Another equally flawed, retrospective study (Zhang *et al.*, 2005) showed a significantly increased spontaneous abortion rate (21 versus 51%, $P < 0.01$) in the aspirin group.

The current meta-analysis has shown that low-dose aspirin has no beneficial effect on pregnancy and LB rates or on cycle cancellation. Despite some diversity in the study populations and aspirin therapy regimens, a meta-analysis of the published RCTs was feasible. The treatment dose of aspirin varied slightly among different studies. As a dose of 80–160 mg daily in healthy volunteers (Cerletti *et al.*, 2003) and 0.5–2.0 mg/kg daily in hypertensive pregnant women (Vainio *et al.*, 1999) has been shown to increase the prostacyclin–thromboxane ratio, a dose of ≤150 mg daily should be sufficient to demonstrate the possible benefits of aspirin.

The theory behind the potential positive effects of aspirin is based on the hypotheses that low-dose aspirin enhances implantation and ovarian response to stimulation by increasing uterine and ovarian blood flow, respectively. The current analysis could not provide the data to confirm any of the hypotheses. This is unlikely to be due to the heterogeneity among the studies. In fact, the timing of aspirin administration was appropriate to test the first hypothesis in all but two studies (Waldenstrom *et al.*, 2004; Duvan *et al.*, 2006) as therapy was commenced on day 1 of stimulation or on day 21 of the preceding cycle. The

Table I. Characteristics of controlled trials on low-dose aspirin and IVF outcome included in the systematic review

Author	Study design	Duration of aspirin therapy	Number of ET cycles		Patients' criteria	Comparison
			Aspirin	Placebo/ nothing		
Pakkila *et al.* (2005)	RCT	Day 1 of ovarian stimulation till delivery	174	175	Age <40, <4 previous cycles	Aspirin 100 mg versus placebo
Waldenstrom *et al.* (2004)	RCT	Day of ET till pregnancy test	703	677	Only patients who had ET	Aspirin 75 mg versus nothing
Urman *et al.* (2000)	RCT	Day 1 of ovarian stimulation till FH seen on US	139	136	ICSI for male factor infertility	Aspirin 80 mg versus nothing
Rubinstein *et al.* (1999)	RCT	Day 21 of preceding cycle till 12 weeks	143	136	IVF for tubal factor infertility	Aspirin 100 mg versus placebo
Duvan *et al.* (2006)	RCT	Day of ET till pregnancy test	41	40	Non-selected patients, first ICSI cycle	A. Aspirin 100 mg B. Aspirin 100 mg + prednisone 10 mg C. Prednisone 10 mg D. Placebo
Van Dooren *et al.* (2004) (abstract)	RCT	Day 16 till 10 weeks	85	85	Women <39, first IVF or ICSI	Aspirin 100 mg versus placebo
Bordes *et al.* (2003) (abstract)	RCT	Day 21 till FH seen on US	69	69	Unselected IVF patients	Aspirin 100 mg versus placebo
Lentini *et al.* (2003) (abstract)	RCT	1 month before gonadotrophin till pregnancy test	42	42	Unselected IVF patients	Aspirin 100 mg versus nothing
Lok *et al.* (2004)	RCT	Day 21 of preceding cycle till hCG	17	16	Poor responders <40	Aspirin 80 mg versus placebo
Weckstein *et al.* (1997)	RCT	1 week before estrogen supplementation till 9 weeks	15	13	Recipients of donated oocytes	Aspirin 80 mg versus nothing
Hurst *et al.* (2005)	Retrospective	Day 21 of preceding cycle till pregnancy test	72	244	Unselected IVF patients	Aspirin 80 mg versus nothing
Zhang *et al.* (2005) (abstract)	Retrospective	Day 21 of preceding cycle till 8 weeks	38	45	Patients <40, had no less than 2 good embryos	Aspirin 81 mg versus nothing

Table II. Meta-analysis of all RCTs comparing aspirin versus placebo or no treatment in a standard IVF and/or ICSI population

Outcome	Studies	Participants	With aspirin positive/total (%)	Without aspirin positive/total (%)	Pooled relative risk (95% CI)	Heterogeneity (*P*)
Pregnancy rate/ET	3	1612	303/817 (37.1)	260/795 (32.7)	1.13 (0.97–1.31)	0.35
CP/cycle	4	1142	190/570 (33.3)	174/572 (30.4)	1.08 (0.82–1.44)	0.05
CP/ET	6	2515	450/1273 (35.3)	391/1242 (31.5)	1.09 (0.92–1.29)	0.11
CP/e-SET	1	82	11/40 (27.5)	13/42 (31.0)	0.89 (0.45–1.75)	NA
Miscarriage/CP	3	658	68/348 (19.5)	51/310 (16.5)	1.17 (0.84–1.63)	0.98
Ectopic pregnancy/CP	3	658	15/348 (4.3)	14/310 (4.5)	1.22 (0.34–4.38)	0.10
Live birth/cycle	1	374	32/186 (17.2)	37/188 (19.7)	0.87 (0.57–1.34)	NA
Live birth/ET	2	1729	223/877 (25.4)	194/852 (22.8)	1.08 (0.83–1.40)	0.21
No available embryos for transfer	4	1142	41/570 (7.2)	47/572 (8.2)	0.88 (0.54–1.43)	0.25
Implantation rate	1	348	17/174 (9.8)	19/174 (12.9)	0.89 (0.48–1.66)	NA

NA; Not applicable.

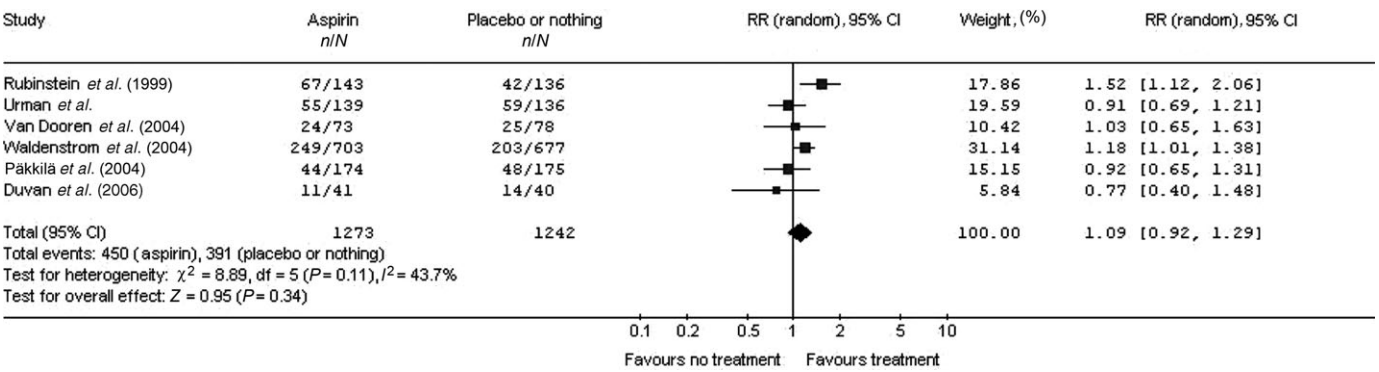

Figure 2. Forest plot of the effect of aspirin versus placebo or no treatment on clinical pregnancy rate per embryo transfer. Review: aspirin versus nothing in IVF. Comparison: aspirin versus placebo or no treatment. Outcome: clinical pregnancy/embryo transfer.

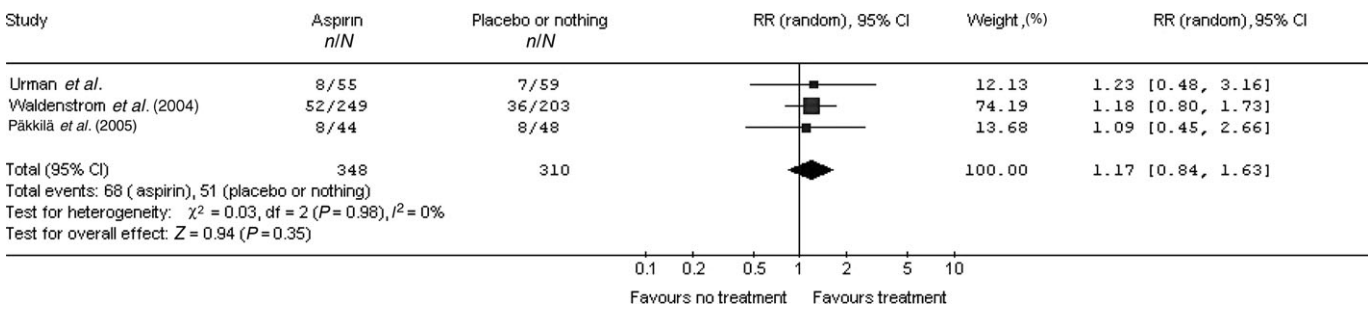

Figure 3. Forest plot of the effect of aspirin versus placebo or no treatment on miscarriage rate per clinical pregnancy. Review: aspirin versus nothing in IVF. Comparison: aspirin versus placebo or no treatment. Outcome: miscarriage/clinical pregnancy.

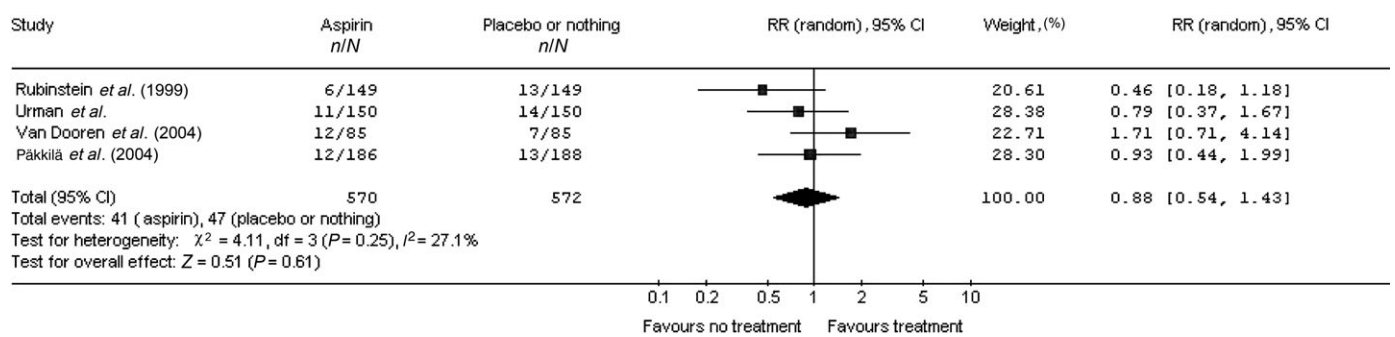

Figure 4. Forest plot of the effect of aspirin versus placebo or no treatment on cycle cancellation rate. Review: aspirin versus nothing in IVF. Comparison: aspirin versus placebo or no treatment. Outcome: no. of cycles cancelled/cycles.

Table III. Main results of the two RCTs comparing aspirin versus placebo in poor responders (Lok *et al.*, 2004) or oocytes recipients (Weckstein *et al.*, 1997)

Study	Outcome measures	Treated group	Untreated group	RR (95% CI)
Lok *et al.* (2004)	CP/cycle	1/30 (3)	2/30 (7)	0.50 (0.05–5.22)
	CP/ET	1/17 (6)	2/16 (13)	0.47 (0.05–4.70)
	No available embryos for transfer	8/30 (27)	10/30 (33)	0.93 (0.53–1.63)
Weckstein *et al.* (1997)	CP/ET	9/15 (60)	4/13 (31)	1.95 (0.78–4.86)
	Live birth/ET	7/15 (47)	4/13 (31)	1.52 (0.57–4.04)
	Implantation rate	15/63 (24)	6/69 (9)	2.74 (1.13–6.62)

hypothesis that improved ovarian stimulation outcome is the result of aspirin treatment was also tested using the same studies.

Undoubtedly, there is lack of strong evidence for the use of low-dose aspirin in frozen embryo replacement (FER) cycles. Wada *et al.* (1994) divided their study population into two groups according to Doppler uterine perfusion—women with normal perfusion did not receive treatment, whereas those with poor perfusion were given aspirin starting on day 13 of the HRT cycle. In the subsequent cycle, women with poor perfusion and some women with normal perfusion received aspirin (150 mg) on day 1 of the cycle. The authors concluded that low-dose aspirin improved uterine perfusion, especially when it was commenced on day 1 of the cycle. The pregnancy rate was similar between untreated women with normal perfusion and those in whom the perfusion improved after aspirin therapy. Of note, women with poor perfusion did not have embryo replacement, thus hampering the accurate assessment of aspirin efficacy in FER cycles. Another small controlled study (Check *et al.*, 1998) of 36 women undergoing FER following failed fresh ET revealed lower CP and implantation rates in the aspirin group compared with controls (11.1 versus 33.3% and 2.9 versus 10.9%, respectively).

As shown by the limited number of studies available in the literature, data are not robust enough to support the use of aspirin in women who respond poorly to ovarian stimulation (Lok *et al.*, 2004) and in those who receive donated oocytes (Weckstein *et al.*, 1997). Further studies are warranted prior to recommending aspirin treatment to these groups of patients.

In an attempt to comprehend the underlying causes of IVF implantation failure, there has been an emerging interest on the role of autoimmune factors. Although a higher prevalence of autoantibodies, especially APL, has been reported in women with recurrent spontaneous abortion (Cowchock *et al.*, 1986; Matzner *et al.*, 1994; Yetman and Kutten, 1996) and idiopathic infertility (Gleicher *et al.*, 1989, 1994; Birdsall *et al.*, 1996), controversy regarding their association with IVF success rates still exists. Proponents of APL antibody-associated immunological dysfunction and infertility have suggested that APL antibodies other than lupus anticoagulant and anticardiolipin have an important effect on the likelihood of pregnancy in IVF (Kaider *et al.*, 1996; Coulam *et al.*, 1997). Other investigators using similarly large APL panel assays have been unable to reveal any relationship between APL antibodies and IVF outcome (Denis *et al.*, 1997; Chilcott *et al.*, 2000). A meta-analysis of seven studies that examined the relationship between APL seropositivity and IVF success also failed to confirm this association (Hornstein *et al.*, 2000).

The efficacy of immunological treatment in APL antibody-positive women undergoing IVF has been investigated, though no consensus has been reached. In a study comprising 307 women positive for antinuclear antibodies and/or APL antibodies, Hasagewa *et al.* (1998) have found a 2-fold increase in pregnancy rate in women treated with prednisone and low-dose aspirin when compared with the untreated population. This is in agreement with another RCT that has demonstrated a significantly higher pregnancy rate in autoantibody-positive women taking the combined treatment compared with those who did not receive therapy (Geva *et al.*, 1998, 2000). Conversely, some authors have reported no beneficial effects following the use of immunological therapy in IVF. A prospective cohort study (Strehler *et al.*, 2002) of 549 women with a history of previous spontaneous abortion or at least two previous failed ET cycles receiving both prednisone and low-dose aspirin or no treatment revealed that pregnancy rates were not affected by treatment. Two studies reported no difference in pregnancy and implantation rates after IVF in APL antibody-positive patients treated with heparin and low-dose aspirin (Schenk *et al.*, 1996; Kutteh *et al.*, 1997). Recently, Stern *et al.* (2003) enrolled 143 autoantibody-positive women who had 10 or more failed ET cycles in a double-blind cross-over RCT. All patients received unfractionated heparin 5000 U and low-dose aspirin 100 mg or placebo from the day of ET until 14 weeks of gestation or fetal demise. Pregnancy rate per transfer, fetal heart implantation rate per embryo and LB rate per embryo were similar between treatment and placebo groups.

A review of the potential risks of aspirin therapy requires re-evaluating the prevailing view that aspirin is well tolerated when administered to women undergoing assisted reproduction. Analysis of the risk of bleeding following administration of diverse doses of aspirin in 192 036 patients enrolled in 31 RCTs revealed that even low-dose aspirin can be associated with bleeding, which may be classified as a major event in a small but significant percentage of patients (Serebruany *et al.*, 2005). Low-dose aspirin also resulted in a 2-fold increase in gastrointestinal bleeding in one study (Patrono *et al.*, 2005). A meta-analysis of 22 studies published between 1971 and 2002 reported that the use of aspirin in the first trimester of pregnancy was associated with a significantly increased risk of central nervous system defects, gastroschisis, cleft lip and palate (Kozer *et al.*, 2002).

This rigorously conducted systematic review and meta-analysis, which throws light upon the use of low-dose aspirin in women undergoing IVF, is mainly intended to provide an up-to-date source of information. By including only RCTs, it helps to make practitioners aware of the quality and quantity of the evidence available. Unfortunately, the heterogeneity of the studies included and the lack of adequately powered analyses may lead to debatable interpretations of some of the results. Any forthcoming RCT needs to be of sufficient statistical power to enable definite conclusions

about aspirin treatment in specific subgroups to be drawn. Future studies should investigate not exclusively the effect of low-dose aspirin on likelihood of pregnancy in IVF cycles but also the relationship with stimulation cycle outcome, maternal and neonatal morbidity.

Conclusion

The concept that better uterine blood flow may improve implantation in ART is attractive, but the evidence evaluating the administration of low-dose aspirin for this purpose does not support its implementation in clinical practice. Currently, accumulating data exist that aspirin is not without side effects to both mother and fetus. Given the lack of proven efficacy and the actual potential for harm, this therapeutic strategy should not be routinely recommended to women undergoing assisted conception.

Couples undergoing ART are often desperate enough to try anything that may boost their fertility performance. Testing of any prescribed pharmacological compound is mandatory, so that potential benefits and risks are clearly presented to both clinicians and patients. Without doubt, randomized controlled studies are difficult to conduct, as couples are often unwilling to be randomly offered treatments that have previously failed. In agreement with Urman *et al.* (2005), we believe that fertility physicians should avoid offering treatment options that are not proven to work and they should always share with patients the available evidence, giving them a realistic view.

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