

# Does low-dose aspirin improve pregnancy rate in IVF/ICSI? A randomized double-blind placebo controlled trial

K. Dirckx<sup>1</sup>, P. Cabri, A. Merien, L. Galajdova, J. Gerris, M. Dhont, and P. De Sutter

Department of Gynaecology–Obstetrics, Centre for Reproductive Medicine of the University Hospital of Ghent, 9000 Ghent, Belgium

<sup>1</sup>Correspondence address. Tel: +32-9-332-69-37; Fax: +32-9-332-49-72; E-mail: kaatje.dirckx@ugent.be

**BACKGROUND:** It has been suggested in the literature that low-dose aspirin leads to an increased number of oocytes in IVF/ICSI as well as a higher pregnancy rate. The aim of the present study was to investigate the effect of daily administration of low-dose aspirin, compared with placebo, on pregnancy rate in IVF and ICSI.

**METHODS:** This study was a prospective, randomized, double-blind placebo controlled trial, performed in the fertility centre of the University Hospital of Ghent. Concealed allocation by computerized randomization was done by the central pharmacy of the hospital. Daily oral administration of aspirin 100 mg or placebo started before stimulation and was continued until confirmation of pregnancy by detection of fetal heart activity on ultrasound. The primary outcome measure assessed in this trial was clinical pregnancy rate per cycle.

**RESULTS:** Two hundred and one couples were included in this study, 193 women (aspirin group  $n = 97$ , placebo group  $n = 96$ ) started treatment and 181 underwent an embryo transfer. There were 31 clinical pregnancies (31/97 or 32%) in the aspirin group versus 30 (30/96 or 31%;  $P = 0.916$ ; OR 1.033; 95% CI 0.565–1.890) in the placebo group.

**CONCLUSIONS:** This randomized controlled trial could not show a significant difference in clinical pregnancy rate between the aspirin and the placebo group in a first or second IVF/ICSI cycle. Given the lack of evidence for a beneficial effect of low-dose aspirin, it appears that low-dose aspirin should not be prescribed routinely in IVF/ICSI treatment.

ClinicalTrials.gov Identifier: NCT00644085.

**Key words:** IVF/ICSI / low-dose aspirin / placebo

## Introduction

Aspirin (acetylsalicylic acid) is well known to have analgesic, anti-inflammatory and antipyretic properties. Aspirin and other salicylates act as inhibitors of the enzyme cyclo-oxygenase, resulting in the direct inhibition of the biosynthesis of prostaglandins and thromboxanes from arachidonic acid (Martindale, 1999). In blood platelets, such inhibition prevents the synthesis of thromboxane, which is a vasoconstrictor that causes platelet aggregation and is thus potentially thrombotic. In blood vessel walls, the enzyme inhibition prevents the synthesis of prostacyclin, which is a vasodilator that has anti-aggregation properties and is potentially anti-thrombotic. Aspirin therefore appears to have paradoxical biological effects (Martindale, 1999). The duration of these effects, however, is shorter in vascular

cells, which regain the ability to regenerate prostacyclin in a few hours. In platelets, cyclo-oxygenase is irreversibly inhibited, rendering them unable to re-synthesize new thromboxane. In this way, aspirin has an antiplatelet effect and causes a shift toward an increase in the synthesis of prostacyclin, responsible for vasodilatation and an improved blood perfusion in many organs. Low daily doses of aspirin, in the range of 75–325 mg, appear to have an equally antiplatelet effect (Martindale, 1999).

Aspirin's antiplatelet activity has led to its use and investigation in a variety of disorders.

There is evidence that low-dose aspirin plays an important role in the initial treatment and secondary prevention of myocardial infarction and ischemic stroke (Keller *et al.*, 2007). The combination of low-dose aspirin and unfractionated heparin appears to be of benefit in pregnant

women with antiphospholipid antibodies and recurrent pregnancy loss not related to other causes (Empson *et al.*, 2005). Pre-eclampsia is associated with deficient intravascular production of prostacyclin and excessive production of thromboxane. The administration of low-dose aspirin to women at risk leads to a significant reduction in the likelihood of developing pre-eclampsia, preterm birth, fetal or neonatal death and small-for-gestational age babies (Duley *et al.*, 2007).

The above-mentioned facts have led to the hypothesis that low-dose aspirin may improve uterine and ovarian perfusion and that aspirin might enhance endometrial receptivity and ovarian responsiveness as well, which could result in better implantation and pregnancy rates after IVF or ICSI treatment. It has also been suggested in the literature that low-dose aspirin would lead to an increased number of oocytes in IVF/ICSI as well as a higher pregnancy rate (Rubinstein *et al.*, 1999). The aim of the present study was to investigate the potential benefits of daily administration of low-dose aspirin, compared with placebo, on pregnancy rates in first and second IVF and ICSI cycles. The effect on the number of oocytes, embryo quality and miscarriage rate was also examined. Despite existing trials and even recent meta-analyses, there is still controversy about the use of low-dose aspirin in IVF/ICSI treatment. Therefore, our study contributes further to the existing literature.

## Materials and Methods

This study was a prospective, randomized, double-blind placebo controlled trial, performed in the Centre for Reproductive Medicine of the University Hospital of Ghent. Patients were included and randomized at the first consultation in our centre, before the start of the treatment. All patients could enter the study only once. Concealed allocation by computerized randomization was done by the central pharmacy of the hospital.

Daily oral administration of aspirin 100 mg or placebo was started together with the oral contraceptive pill prior to stimulation, and was continued until confirmation of pregnancy by detection of fetal heart activity on vaginal ultrasound at 6 weeks and 3 days of amenorrhoea.

Stimulation was performed with the short gonadotrophin-releasing hormone agonist protocol (Decapeptyl<sup>®</sup>, Ipsen, Paris, France), 0.1 mg daily for 7 days, started on Day 5 after pill stop) and human menopausal gonadotrophin (hMG) (Menopur<sup>®</sup>, Ferring, Saint-Prex, Switzerland) or recombinant follicle-stimulating hormone (rFSH) (Puregon<sup>®</sup>, Organon, Oss, The Netherlands or Gonal-F<sup>®</sup>, Merck-Serono, Geneva, Switzerland) 150–300 IU daily from Day 7 after pill stop until human chorionic gonadotrophin (hCG) administration. The choice of gonadotrophin was made by the clinician, although the majority of patients were treated with hMG. The dose was decided by the clinician, but age of the patient was taken into account. When at least half of the follicles were 18–20 mm in diameter, hCG (Pregnyl<sup>®</sup>, Organon, Oss, The Netherlands) 5000 IU was given subcutaneously. Our centre uses these criteria since it appears that the number of adequate size follicles is more important than the size of the leading follicle(s) (Wittmaack *et al.*, 1994). Oocyte retrieval took place 35 h after hCG administration. The oocytes were fertilized by routine IVF or ICSI technique. The quality of the embryos was scored on the day of transfer (Day 3) and was based on the number of blastomeres, fragmentation rate and the absence of multinucleated blastomeres (Van Royen *et al.*, 1999). Top embryos were described as having seven or more blastomeres on Day 3, 20% fragmentation or less and no multinucleated blastomeres. One or two embryos were transferred on Day 3 following oocyte retrieval. The number of embryos transferred was based on age of the patient and embryo quality. As luteal support, hCG (Pregnyl<sup>®</sup>)

1500 IU was given subcutaneously on Days 5, 8 and 11 post-oocyte retrieval. When there was a risk of ovarian hyperstimulation syndrome (OHSS), i.e. when more than 20 oocytes were retrieved, progesterone (Utrogestan<sup>®</sup>, Besins, Brussels, Belgium) 3 × 200 mg was given transvaginally daily.

Measurement of serum hCG was performed 12 days after embryo transfer. Transvaginal ultrasound was done at 6 weeks and 3 days amenorrhoea to confirm clinical pregnancy by fetal heart activity and number of gestational sacs.

## Inclusion and exclusion criteria

Dutch-speaking women starting a first or second IVF/ICSI cycle could participate in the trial.

Women who were suffering from platelet dysfunction, thrombopenia, gastrointestinal ulcers, recurrent gastritis, aspirin hypersensitivity or who were on treatment with anticoagulants or aspirin were excluded from participation.

## Outcome measures

The primary outcome measure assessed in this trial was clinical pregnancy rate per cycle.

Secondary outcome measures were number of oocytes retrieved, embryo quality, twins rate, miscarriage rate and live birth rate per cycle.

## Statistical analysis

Anticipating an increase in pregnancy rate of 20% (Rubinstein *et al.*, 1999), with 80% power at the 5% significance level, 93 patients had to be included in each group. This meant that 186 patients had to be randomized in total according to the sample size calculation.

Statistical comparisons were performed by  $\chi^2$  test and *t*-test where appropriate and the level of statistical significance was set at  $P = 0.05$ .

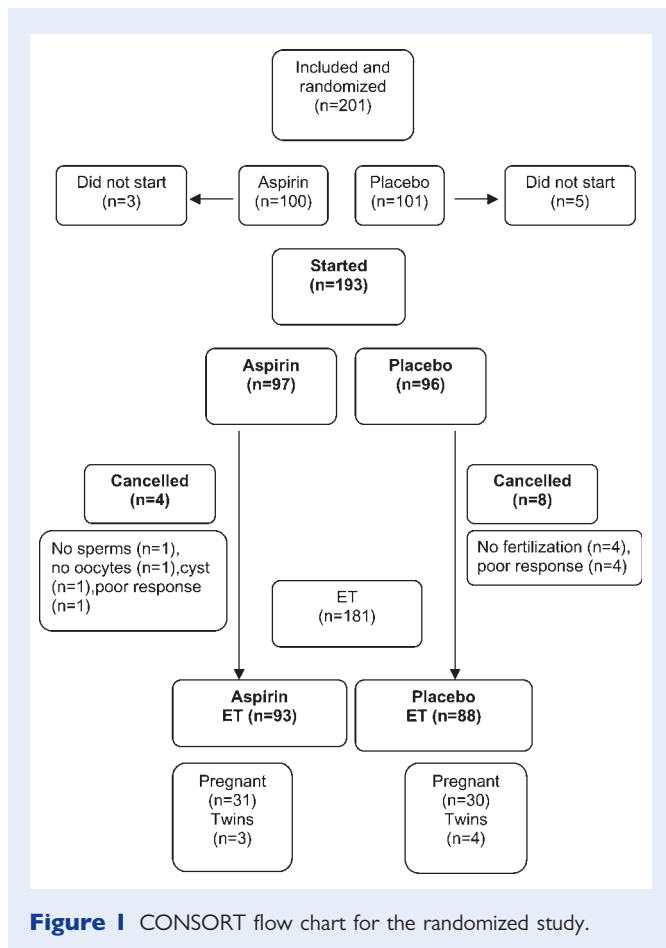
## Results

Taking into account a dropout of  $\pm 10\%$  of included patients, we included 201 patients (Fig. 1). Eight of them (three in the aspirin and five in the placebo group) did not start the treatment for unknown reasons, 193 couples (the aspirin group  $n = 97$ , the placebo group  $n = 96$ ) effectively participated and were further analyzed. Twelve of them were cancelled during stimulation or received no transfer (the aspirin group  $n = 4$ , the placebo group  $n = 8$ ). The main reasons for cancellation were poor response or failure of fertilization (Fig. 1). The number of cancelled patients during stimulation or before transfer was not significantly different between the two groups. Finally, 181 women (the aspirin group  $n = 93$ , the placebo group  $n = 88$ ) underwent an embryo transfer (Fig. 1).

The two groups did not differ significantly regarding age, cycle number or subfertility status. Also the use of different gonadotrophins, the variable starting dose of gonadotrophins and the use of different forms of luteal support was, due to the randomization, equally divided between the groups. Mean duration of stimulation and mean total dose of gonadotrophins were not different for the two groups (Table I).

More than 20 oocytes were retrieved in 29 out of 193 patients who started (16 patients or 16% in the aspirin group versus 13 patients or 13% in the placebo group). These patients were considered to be at risk for OHSS and received progesterone as luteal support.

The mean number of oocytes ( $12.6 \pm 7.6$  in the aspirin group versus  $12.9 \pm 7.9$  in the placebo group) did not differ significantly



between the two groups. Also the quality of the embryos (65 or 67% top embryos in the aspirin group versus 58 or 60% in the placebo group) and the number of embryos transferred (65 or 67% single-embryo transfer in the aspirin group versus 60 or 62% in the placebo group) was comparable for both groups (Table II).

There were 31 clinical pregnancies (31/97 or 32%) in the aspirin group versus 30 (30/96 or 31%) in the placebo group. This difference was not significant ( $P = 0.916$ ; OR 1.033; 95% CI 0.565–1.890). In the aspirin group, 24 live births (including three twins) out of 29 pregnancies with known outcome were obtained versus 27 live births (including four twins) out of 28 pregnancies with known outcome in the placebo group. This lower live birth rate in the aspirin group (25%) versus controls (28%) is not statistically different.

## Discussion

The data of this prospective, randomized, double-blind placebo controlled trial show that low-dose aspirin does not improve clinical pregnancy rate in first or second IVF or ICSI cycles. As mentioned above, potential shortcomings of our study could have been the use of different forms of gonadotrophins, different starting doses of gonadotrophins or different forms of luteal support. Also the criteria for hCG administration for triggering the final oocyte maturation may be subject to discussion. However, due to a correctly performed randomization both the aspirin and the placebo groups were quite comparable which is reassuring with regard to the results (Tables I and II).

**Table 1** Characteristics of both groups (patients who started a cycle  $N = 193$ )

	Aspirin group ( $n = 97$ )	Placebo group ( $n = 96$ )
Mean age in years (SD)	31.1 (3.9)	31.3 (3.8)
First cycle (%)	84 (86%)	87 (91%)
Mean cycle number (SD)	1.2 (0.6)	1.1 (0.3)
Primary subfertility (%)	66 (68%)	72 (75%)
No. of patients used (%)		
Menopur <sup>®</sup>	89 (92%)	84 (87%)
Puregon <sup>®</sup>	7 (7%)	7 (8%)
Gonal F <sup>®</sup>	1 (1%)	5 (5%)
Mean starting dose FSH (SD)	220 IU (61.2)	221.1 IU (54.7)
No. of patients starting FSH		
$\leq 150$ IU (%)	23 (24%)	20 (21%)
$\geq 200$ IU (%)	74 (76%)	76 (79%)
Mean duration of stimulation in days (SD)	12.1 (3.8)	12 (3.2)
Mean total dose of FSH in IU (SD)	2666.5 (1116.5)	2564.8 (994.7)

Although our study was not sufficiently powered to show a smaller difference, according to our test hypothesis (with an arbitrary power calculation of 20%), these results are consistent with the conclusions derived from some recent meta-analyses (Gelbaya et al., 2007; Khairy et al., 2007; Poustie et al., 2007). These indicate a lack of evidence for the routine use of low-dose aspirin in IVF/ICSI treatment. The review of Poustie et al. (2007) for the Cochrane database of Systematic Reviews analyzed nine RCTs (including 1449 women) and the authors concluded that, due to a lack of adequate trial data, low-dose aspirin cannot currently be recommended for women undergoing *in vitro* fertilization. On the basis of the seven included RCTs, Khairy et al. (2007) concluded that the currently available evidence does not support the routine use of low-dose aspirin in IVF or ICSI treatment. However, they noted a trend, but with insufficient power, suggesting improvement in clinical pregnancy rates. Their review also showed no effect of aspirin on miscarriage or ectopic pregnancy rate. Gelbaya et al. (2007) included six RCTs in a meta-analysis and concluded that low-dose aspirin does not improve pregnancy and live birth rates in IVF/ICSI cycles. These authors also cited a review of the potential risks of aspirin therapy and mentioned its potential harm during pregnancy. In contrast with this conclusion, a further meta-analysis, which is in fact a re-analysis of the data used by Gelbaya et al. (2007), concludes that aspirin may increase clinical pregnancy rates in IVF/ICSI treatment. These authors stated that without adequate proof of a lack of effect on outcomes in IVF/ICSI, there is no reason to discontinue the use of aspirin in current practice (Ruopp et al., 2008). In view of the controversy that still exists, our study adds qualitative data to the ongoing meta-analyses.

In particular, our study could not replicate the results of the trial performed by Rubinstein et al. (1999) showing impressive outcomes regarding ovarian responsiveness (mean number of 16 oocytes in the aspirin group versus 8 in the placebo group) and pregnancy

**Table II Outcome measures for both groups (patients who started a cycle N = 193)**

	Aspirin group (n = 97)	Placebo group (n = 96)	P-values** or OR (95% CI)
Mean No. of oocytes (SD)	12.6 (7.6)	12.9 (7.9)	P = 0.788
No. of patients with ≥20 oocytes (%)	16 (16%)	13 (13%)	OR = 1.261 (0.578–2.752)
No. of patients with no transfer (%)	4 (4)	8 (8)	OR = 0.473 (0.146–1.536)
Single-embryo transfer (%)	65 (67%)	60 (62%)	OR = 1.219 (0.676–2.196)
Mean No. of embryos transferred (SD)	1.2 (0.5)	1.2 (0.5)	P = 1.000
N° of top quality embryos* (day 3) (%)	65 (67%)	58 (60%)	OR = 1.331 (0.741–2.391)
Clinical pregnancy (heart activity/cycle) (%)	31 (32%)	30 (31%)	OR = 1.033 (0.565–1.890)
Mean No. of gestational sacs (SD)	1.1 (0.4)	1.1 (0.3)	P = 1.000
Live birth rate/cycle (%)	24 (25%) (incl. 3 twins)	27 (28%) (incl. 4 twins)	OR = 0.840 (0.445–1.587)
Miscarriage	5	1	
Missing data	2	2	

\*The quality of the embryos was scored on the day of transfer (Day 3). Top embryos were described as having seven or more blastomeres 20% fragmentation or less and no multinucleated blastomeres.

\*\*P>0.05 are statistically not significant (NS).

rates (45% in the aspirin group versus 28% in the placebo group, an improvement of 17%) in IVF treatment with low-dose aspirin compared with placebo. These authors analyzed 298 couples with tubal factor infertility who underwent consecutive IVF cycles. However, there is no mention of timing of randomization, previous cycles, primary or secondary infertility and dosage of stimulation. It may well be that some bias regarding these parameters explains these marked results.

A recent randomized placebo controlled trial evaluated the benefits of daily low-dose aspirin administration in patients who had at least one previous failed attempt (Lambers *et al.*, 2007). In agreement with our own results, that study could not demonstrate higher pregnancy rates in the aspirin-treated group compared with placebo. Also the other outcomes did not differ significantly.

However, in some groups of infertility patients, e.g. pregnant women with antiphospholipid syndrome and recurrent miscarriages, aspirin therapy during pregnancy, in combination with unfractionated heparins, has already proven its benefits (Empson *et al.*, 2005), although it is not clear yet exactly when it should commence.

At present, there are no adequate trials or data about the use of aspirin in other selected groups, including recurrent pregnancy loss without antiphospholipid syndrome or with inherited thrombophilias (Di Nisio *et al.*, 2005), repeated implantation failure, and poor responders (Lok *et al.*, 2004; Fratrarrelli *et al.*, 2008).

Moreover, it has been shown that the use of aspirin in combination with other drugs, e.g. steroids, is of no proven benefit in routine IVF or ICSI treatment (Duvan *et al.*, 2006).

In addition, aspirin is not harmless (Martindale, 1999). The most common adverse effects of aspirin are gastrointestinal disturbances such as nausea, dyspepsia and vomiting. Slight gastrointestinal blood loss is quite common, often asymptomatic and of no clinical significance. The risk of major bleeding is low. Some persons (with asthma, chronic urticaria or chronic rhinitis) exhibit hypersensitivity to aspirin which may provoke various reactions. Aspirin increases bleeding time and reduces platelet aggregation. It may cause other blood disorders,

especially in large doses. There is evidence suggesting that gastrointestinal toxicity of aspirin is dose-related. Doses of 300 mg or less carry a risk of ulcer bleeding or acute gastric mucosal damage, although very small doses like 75 mg are probably safe (Martindale, 1999; Serebruany *et al.*, 2005). In our study, unfortunately there was no systematic registration of adverse reactions; nevertheless, no serious adverse events regarding gastrointestinal symptoms or blood loss were reported. None of the above-mentioned trials reported important side effects with low-dose aspirin.

It has been suggested that aspirin might increase the risk of congenital central nervous system defects, gastroschisis or cleft lip and palate in the fetus (Kozer *et al.*, 2002). On the other hand, the authors of another meta-analysis concluded that there is no evidence for teratogenicity or long-term adverse effects of low-dose aspirin used in the first trimester of pregnancy (Coomarasamy *et al.*, 2003).

There is also conflicting evidence about the potential risk of miscarriage in early pregnancy when using aspirin (Nielsen *et al.*, 2001; Coomarasamy *et al.*, 2003; Li *et al.*, 2003). Nielsen *et al.* (2001) concluded in a population-based cohort study and case-control study (Denmark) that the use of non-steroidal anti-inflammatory drugs (NSAIDs) during pregnancy did not seem to increase the risk of adverse birth outcome, although there was an increased risk of miscarriage. Coomarasamy *et al.* (2003) criticized the results of the study of Nielsen and concluded that, due to bias concerning the indication for the use of NSAIDs, the evidence of association between NSAIDs during early pregnancy and miscarriage was unreliable. On the other hand, Li *et al.* (2003) concluded in a population-based cohort study in the USA that the prenatal use of NSAIDs and aspirin increased the risk of miscarriages. This study was controlled for potential confounding by indication for use (Li *et al.*, 2003). In our study, more miscarriages were observed in the aspirin group. Since our sample size was not chosen to analyze miscarriage rates, this difference is not statistically significant but confirmed that the risk of miscarriage when using aspirin pre-conceptually or in early pregnancy might be a reason for concern.

In conclusion, our randomized placebo controlled trial could not show better pregnancy rates, nor an increase in the number of oocytes, with the use of low-dose aspirin in first or second IVF/ICSI cycles.

We acknowledge that this study was not sufficiently powered to show smaller differences than our test hypothesis, which had an arbitrary power calculation of 20%. To show smaller differences regarding the potential benefits of low-dose aspirin in IVF/ICSI, more studies with greater power are needed.

There is also a need for randomized controlled trials investigating the use of low-dose aspirin for several specific patient subgroups undergoing *in vitro* fertilization. However, in view of the lack of evidence, it appears that low-dose aspirin should not be recommended routinely in IVF/ICSI treatment.

## Funding

Petra De. Sutter is holder of a fundamental clinical research mandate by the National Fund for Scientific Research [Fonds Wetenschappelijk Onderzoek (FWO) Vlaanderen].

## References

- Coomarasamy A, Honest H, Papaioannou S, Gee H, Saeed Khan K. Aspirin for prevention of preeclampsia in women with historical risk factors: a systematic review. *Am Coll Obstet Gynecol* 2003;**101**: 1319–1332.
- Di Nisio M, Peters L, Middeldorp S. Aspirin and anticoagulants for the treatment of recurrent miscarriage in women without antiphospholipid syndrome. *Cochrane Database Syst Rev* 2005;2:CD004734, doi:10.1002/14651858.CD004734.pub2.
- Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev* 2007;2:CD004659, doi:10.1002/14651858.CD004659.pub2.
- Duvan CI, Ozmen B, Satiroglu H, Atabekoglu CS, Berker B. Does addition of low-dose aspirin and/or steroid as a standard treatment in nonselected intracytoplasmic sperm injection cycles improve *in vitro* fertilization success? A randomized, prospective, placebo-controlled study. *J Assist Reprod Genet* 2006;**23**:15–21.
- Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. *Cochrane Database Syst Rev* 2005;2:CD002859, doi:10.1002/14651858.CD002859.pub2.
- Frattarelli JL, McWilliams GD, Hill MJ, Miller KA, Scott RT. Low-dose aspirin use does not improve *in vitro* fertilization outcomes in poor responders. *Fertil Steril* 2008;**89**:1113–1117.
- Gelbaya TA, Kyrgiou M, Li TC, Stern C, Nardo LG. Low-dose aspirin for *in vitro* fertilization: a systematic review and meta-analysis. *Hum Reprod Update* 2007;**13**:357–364.
- Keller TT, Squizzato A, Middeldorp S. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular disease. *Cochrane Database Syst Rev* 2007;3:CD005158, doi:10.1002/14651858.CD005158.pub2.
- Khairy M, Banerjee K, El-Toukhy T, Coomarasamy A, Khalaf Y. Aspirin in women undergoing *in vitro* fertilization treatment: a systematic review and meta-analysis. *Fertil Steril* 2007;**88**:822–831.
- 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**: 1623–1630.
- Lambers MJ, Hoozemans DA, Homburg R, Schats R, Lambalk CB, Hompes PGA. Low-dose acetylsalicylic acid (aspirin) is not beneficial in a selected group of *in vitro*-fertilisation (IVF) and intra-cytoplasmic-sperm-injection (ICSI)-patients with previous implantation failure. Oral presentations ASRM 2007. *Fertil Steril* 2007;**88**(Suppl 1):S3.
- Li DK, Liu L, Odouli R. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *BMJ* 2003;**327**:368.
- 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**:556–561.
- Martindale. *The Complete Drug Reference*, 32nd edn. Pharmaceutical Press, London, UK, 1999.
- Nielsen GL, Sørensen HT, Larsen H, Pedersen L. Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study. *BMJ* 2001;**322**:266–270.
- Poustie VJ, Dodd S, Drakeley AJ. Low-dose aspirin for *in vitro* fertilisation. *Cochrane Database Syst Rev* 2007;4:CD004832, doi:10.1002/14651858.CD004832.pub2.
- 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**:825–829. Erratum in: *Fertil Steril* 1999;**72**:755.
- Ruopp MD, Collins TC, Whitcomb BW, Schisterman EF. Evidence of absence or absence of evidence? A reanalysis of the effects of low-dose aspirin in *in vitro* fertilization. *Fertil Steril* 2008;**90**: 71–76.
- Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Baggish JS, Bhatt DL, Topol EJ. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. *Am J Cardiol* 2005;**95**:1218–1222.
- Van Royen E, Mangelschots K, De Neubourg D, Valkenburg M, Van de Meerssche M, Ryckaert G, Eestermans W, Gerris J. Characterization of a top quality embryo, a step towards single-embryo transfer. *Hum Reprod* 1999;**14**:2345–2349.
- Wittmaack FM, Kreger DO, Blasco L, Tureck RW, Mastroianni L Jr, Lessey BA. Effect of follicular size on oocyte retrieval, fertilization, cleavage, and embryo quality in *in vitro* fertilization cycles: a 6-year data collection. *Fertil Steril* 1994;**62**:1205–1210.

Submitted on April 28, 2008; resubmitted on December 2, 2008; accepted on December 10, 2008