Journal of Thrombosis and Haemostasis, **10**: 2075–2085 DOI: 10.1111/j.1538-7836.2012.04886.x

ORIGINAL ARTICLE

Low-dose aspirin for *in vitro* fertilization or intracytoplasmic sperm injection: a systematic review and a meta-analysis of the literature

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To cite this article: Dentali F, Ageno W, Rezoagli E, Rancan E, Squizzato A, Middeldorp S, Margaglione M, Grandone E. Low-dose aspirin for *in vitro* fertilization or intracytoplasmic sperm injection: a systematic review and a meta-analysis of the literature. *J Thromb Haemost* 2012; **10:** 2075–85.

Summary. *Background:* It was hypothesized that low-dose aspirin could improve implantation rates in subsequent pregnancies in women undergoing *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI). Previous studies have shown inconclusive results or focused on surrogate endpoints. We therefore conducted a systematic review and meta-analysis of the literature investigating the effect of low-dose aspirin on hard outcomes, including live birth rate, pregnancy rate and miscarriage. *Methods:* MEDLINE and EMBASE databases were searched up to November 2011. Randomized controlled trials comparing low-dose aspirin with placebo/no treatment in IVF/ICSI women were included. Pooled odds ratios (ORs) and 95%confidence intervals (CIs) were calculated. *Results:* Seventeen studies with 6403 patients were included. The use of aspirin did not improve live birth pregnancy rate compared with placebo or no treatment (1.08; 95% CI, 0.90, 1.29). Pregnancy rates were significantly increased in patients randomized to low-dose aspirin (OR, 1.19; 95% CI, 1.01, 1.39), but miscarriage rates were not (OR, 1.18; 95% CI, 0.82, 1.68). Results of sensitivity analyses including high-quality studies did not show statistically significant differences in all considered endpoints. *Conclusions:* The results of this study do not show a substantial efficacy of aspirin inwomen undergoing IVF/ICSI and do not support the use of low-dose aspirin to improve the success of IVF/ICSI in terms of pregnancy outcomes. Further high-quality studies evaluating the possible efficacy of aspirin in selected groups of patients are warranted.

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Received 4 May 2012, accepted 9 August 2012

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Keywords: aspirin, *in vitro* fertilization or intracytoplasmic sperm injection.

Introduction

Despite their current popularity, success rates of *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) remain low [1]. The clinical pregnancy rate among women undergoing fresh embryo transfer (ET) after IVF or ICSI varies from 20% to 35% per transfer [1]. The main factors that affect the outcome of IVF and ICSI treatments are age, number of oocytes retrieved, quality of the embryos, number of embryos transferred, success of embryo transfer and endometrial receptiveness [2–6].

Suboptimal uterine perfusion has been suggested as a possible cause of infertility [7]. Impaired uterine blood flow may reduce endometrial receptivity, resulting in embryo implantation failure [8,9]. It has been hypothesized that low-dose aspirin may enhance uterine and ovarian blood flow and tissue perfusion by decreasing platelet aggregation and inhibiting vasoconstriction [10,11]. This effect could improve the results of IVF and ICSI treatments [12,13] by increasing endometrial receptivity and blastocyst implantation. However, the evidence supporting the efficacy of low-dose aspirin in women undergoing IVF is inconsistent. A number of papers reported a beneficial effect of aspirin, but many others failed to confirm these findings. Previous randomized controlled trials (RCTs) and meta-analyses have shown inconclusive or inconsistent results or were focused on indirect endpoints such as the implantation rate or the artery pulsatility index [10–16]. To better explore the role of low-dose aspirin in this setting, we carried out a systematic review and meta-analysis of the literature to investigate its effects on hard outcomes only, including rate of live birth, pregnancy rate and rate of miscarriage in women undergoing IVF or ICSI.

Methods

A protocol was prospectively developed, detailing the specific objectives, criteria for study selection, approach used to assess study quality, outcomes and statistical methods. This systematic review was performed according to the guidelines for Quality of Reporting of Meta-analysis (PRISMA) [17].

Study identification

We tried to identify all published studies that evaluated the role of aspirin in the improvement of live birth and pregnancy rates and in the reduction of miscarriages in women undergoing IVF or ICSI, using the MEDLINE (1948 to November 2011, week 3) and EMBASE (1980–2011, week 51) electronic databases. The search strategy was developed without any language restriction and used the subject headings and key words presented in Appendix 1. We supplemented our search by manually reviewing the reference lists of all retrieved articles for additional published or unpublished trials and by searching the abstracts of the International Society of Thrombosis and Haemostasis (ISTH) and of European Society of Human Reproduction and Embryology Scientific Meetings (ESHRE) (from 2003 to 2011).

Study selection

Study selection was performed independently by two reviewers (ERe, ERa), with disagreements resolved through discussion and the opinion of a third reviewer (FD), if necessary. RCTs in women undergoing IVF or ICSI were included if they met the following criteria: (i) low-dose aspirin ($<$ 150 mg) was compared either with placebo or no therapy; and (ii) at least one of the following outcomes was assessed: live birth, pregnancy rate and miscarriage rate.

Studies not including a control group drawn from the same population, animal studies, *in vitro* studies or trials that exclusively reported other clinical outcomes were excluded. Case reports, editorials, commentaries, letters, review articles, guidelines or secondary prevention trials were also excluded. To assess the agreement between reviewers for study selection, we used the kappa (k) statistic, which measures agreement beyond chance [18]. When multiple papers for a single study had been published, we decided to use the latest publication and to supplement it, if necessary, with data from the earlier publications.

Data extraction

Two reviewers (ERa, ERe) independently extracted data on study (year of publication, design, study centre) and patient characteristics (number of subjects enrolled, mean or median age) and on the aforementioned outcomes (pregnancy rate, rate of live birth and miscarriage).

Study validity assessment

Two unmasked investigators (ERa, ERe) independently completed the assessment of study validity.

We planned quality assessment by means of Jadad's scale, which evaluates the following three study characteristics: method of randomization, method of blinding and follow-up [19]. To stratify RCTs, we applied the following cut-offs: a total of three points or more defined high-quality studies, whereas studies with two or less points were defined as low-quality studies.

The following additional quality items were also considered for our assessment: the total number of patients lost to follow-up ($<$ 5% of patients, more than 20%, or between 5 and 20%); the use of a commonly accepted definition of clinical pregnancy (increased levels of urinary or plasma β-HCG confirmed by ultrasonography (gestational sac and/or fetal cardiac activity)); and the publication of the study in peer-reviewed journals as opposed to studies only published as an abstract.

Subgroup analyses

We planned *a priori* a list of subgroup analyses according to the following characteristics of the study populations:

1 cause of infertility;
2 type of induction protocol (short vs. long term);
3 type of assisted reproduction techniques (IVF, ICSI);
4 time of aspirin introduction and duration of aspirin therapy (at least 1 day before ET or after ET, during the entire period of the pregnancy); and
5 history of ET failure

Type of induction protocol was defined according to recent guidelines [20] or according to the definition of single studies if not further specified.

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each outcome. The data were pooled using a random-effects model (the DerSimonian and Laird method) [21]. For treatment effects that were statistically significant, we determined the number needed to treat (NNT). Statistical heterogeneity was evaluated using the Cochran's Q and I^2 statistic, which assesses the appropriateness of pooling the individual study results [22]. When heterogeneity was present, we repeated the analysis removing one study at a time to assess the source of heterogeneity. Presence of publication bias was explored using funnel plots of effect size against standard error [23]. The software Review Manager (RevMan, version 5.0.16 for Windows, Oxford, UK; The Cochrane Collaboration, 2008] supported the analysis. Sensitivity analyses including high-quality studies only were performed.

Results

Study identification and selection

We identified 780 potentially relevant studies from the following databases: 569 from EMBASE and 211 from MEDLINE. We excluded 750 studies after title and abstract screening using the predefined inclusion and exclusion criteria; the remaining

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30 studies were retrieved in full for detailed evaluation [3,11,13,14,24–49]. Agreement between reviewers for study selection was optimal ($K = 0.91$). Of the retrieved studies, 16 were excluded for the following reasons: 10 did not match inclusion criteria [13,24–32], three were editorials or commentaries [33–35], and three [11,44,49] reported duplicate data. Furthermore, 19 abstracts from ISTH and from ESHRE were found using 'in vitro fertilization' and 'intracytoplasmic sperm injection' search terms. Sixteen abstracts did not meet inclusion criteria, leaving only three for inclusion [50–52].

Seventeen studies were therefore included in this systematic review: 14 were published as full text [3,14,36–43,45–48] and three [50–52] as abstracts. The study identification and selection progression is detailed in Fig. 1.

Study characteristics

Baseline characteristics of patients included in the studies are summarized in Table 1. Study size ranged from 28 [3] to 2425 [47] patients, for a total of 6610 patients. Ten RCTs were placebo controlled whereas the other seven [3,36–38,40,47,51] compared low-dose aspirin with no treatment. In six studies, aspirin was started at least 1 day before the ET, whereas in the other studies it was started at the time of IVF or ICSI. Aspirin was maintained until the pregnancy test in four studies [39,40,42,46], until ultrasound detection of gestational sac and/or embryonic cardiac activity in three studies [37,45,47], until the 9–12th week of pregnancy in four studies [3,14,43,50] and during the entire period of the pregnancy in three studies [36,41,48], whereas the duration of treatment with aspirin was not specified in three studies [38,51,52].

Live birth

The effect of low-dose aspirin on rate of live births was evaluated in six studies for a total of 2600 patients. A live birth occurred in 330 of 1312 (25.2%) patients randomized to low-dose aspirin and in 306 of 1288 (23.8%) patients randomized to placebo or no treatment. The use of low-dose aspirin was not effective in increasing the rate of live birth compared with placebo or no treatment (OR, 1.08; 95% CI, 0.90, 1.29; $P = 0.43$; $I^2 = 0\%$), Fig. 2A. A funnel plot of OR vs. standard error appeared asymmetric with an absence of studies in the right hand corner (Appendix 2a).

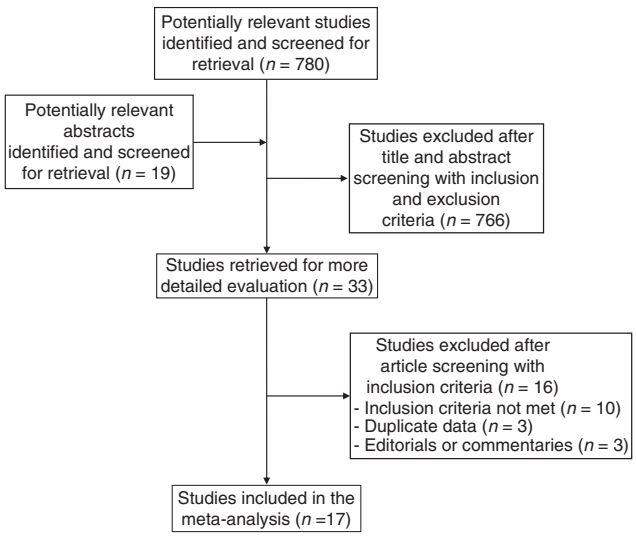

Fig. 1. Selection process.

Pregnancy rate

The effect of low-dose aspirin on pregnancy rate was evaluated in 17 studies for a total of 6403 patients. Pregnancy occurred in 1139 of 3506 (32.5%) women randomized to low-dose aspirin and in 850 of 2897 (29.3%) women randomized to placebo or no treatment. The use of low-dose aspirin was associated with a significantly higher pregnancy rate in comparison to placebo or no treatment (OR, 1.19; 95% CI, 1.01, 1.39; $P = 0.03$; $I^2 = 29\%$), Fig. 2B. The absolute increase in pregnancy rates was estimated at 3.2% with an NNT of 31 (95% CI, 18, 118). A funnel plot of OR vs. standard error appeared symmetric, suggesting the absence of publication bias (Appendix 2b).

Miscarriage

The effect of low-dose aspirin on miscarriage was evaluated in six studies for a total of 904 patients. Miscarriages occurred in 86 of 471 (18.3%) women randomized to low-dose aspirin and in 67 of 433 (15.5%) randomized to placebo or no treatment. The use of low-dose aspirin did not result in a statistically significant higher rate of miscarriage as compared with placebo or no treatment (OR, 1.18; 95% CI, 0.82, 1.68; $P = 0.75$; $I^2 = 0\%$), Fig. 2C. A funnel plot of OR vs. standard error appeared symmetric, suggesting the absence of publication bias (Appendix 2c).

Study quality and sensitivity analyses

Quality assessment items according to the Jadad scale are summarized in Table 2. Of the 17 studies included in the analysis, seven [14,37,39,45,46,48,50] were defined as high quality, whereas the other 10 [3,36,38,40–43,47,51,52] were defined as low quality. The total number of patients lost to follow-up was $< 5\%$ in all the included studies.

In the high-quality studies according to the Jadad scale, the use of low-dose aspirin did not result in any improvement, as compared with placebo or no treatment, in the rates of live birth (OR, 0.91; 95% CI, 0.66, 1.24), pregnancy rates (OR, 1.13; 95% CI, 0.86, 1.47) or miscarriages (OR 1.12; 95% CI, 0.60, 2.09).

When the analysis was restricted to studies that used a commonly accepted definition of clinical pregnancy only, the use of low-dose aspirin was again not associated with any statistically significant effect on live birth rate (OR, 1.07; 95% CI, 0.89, 1.28), pregnancy rate (OR, 1.16; 95% CI, 0.97, 1.39) and miscarriage rate (OR, 1.18; 95% CI, 0.82, 1.68) as compared with placebo or no treatment. Similar findings were

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Table 1 Baseline characteristics and treatment of patients included in the studies

Study, year (ref)	Included patients	Mean age, years ± SD	Inclusion criteria	Primary outcome	Treatment and dose	Onset of therapy and continuation
Weckstein, 1997 [3]	28	41.8 ± 3.4 (ASA group) 39.4 ± 4.5 (Placebo)	Oocyte donation recipients who failed to develop an endometrial thickness of at least 8 mm during a test cycle receiving oral micronized E_2; normal uterine cavity	Clinical pregnancy rate, delivery rate, implantation rate	15 pts ASA (81 mg) vs. 13 pts Control group	1 week before starting estrogen treatment. Pts treated until 9 weeks after ET.
Check, 1998 [36]	36	All the subjects enrolled in the study were at most 42 years old	Pts who had not conceived following transfer of embryos in the retrieval cycle, using their own oocytes, not taking any concomitant medications increasing blood flow, such as heparin	Implantation and clinical pregnancy rates	18 pts ASA (81 mg) vs. 18 pts Control group	On day 2 of the frozen ET cycle. ASA was continued through the pregnancy if the beta-HCG level was positive.
Rubistein, 1997 [14]	298	ASA: 35.9 ± 4.2 Placebo: 35.4 ± 3.9	Infertility for tubal factor; >1 IVF cycle	No. follicles, no. oocytes retrived, serum E2 levels, uterine and ovarian pulsatility index, cancellation rate, no. ET, implantation and pregnancy rates	Aspirin (100 mg) vs. placebo	21st day of precedent menstrual cycle. Pregnant patients continued medication through 12 weeks' gestation
Urman, 2000 [37]	300	32.5 ± 4.8 (ASA group) 32.4 ± 4.7 (control group)	300 pts undergoing their first ICSI cycle with ejaculated spermatozoa for male infertility	Clinical pregnancies and clinical pregnancy rate; implantation and implantation rate	139 pts ASA (80 mg) vs. 136 pts Control group	Beginning on the 1st day of the gonadotropin stimulation. ASA was continued until the ultrasonographic detection of fetal cardiac activity and it was stopped if the HCG test was negative.
Matassa, 2001 [38]	91	32.07 ± 3.98 (ASA group) 32.62 ± 3.71 (Control group)	91 pts undergoing controlled ovaric hyperstimulation	Determine if the use of low-dose ASA and trans-abdominal ecography can modify outcome in IVF-ET procedures to improve: implantation rate; pregnancy rate	46 pts ASA (100 mg) vs. 45 pts Control group	Cycle day 21 before stimulation. Not specified until aspirin continued.
Lentini, 2003 [52]	84	34.6 ± 3.5 (ASA group) 34.2 ± 4.6 (control group)	84 pts undergoing IVF from January to December 2002.	Oocyte quality; fertilization, implantation and pregnancy rate	42 pts ASA (100 mg) vs. 42 pts Control group	A month before the first dose of gonadotropin. Not specified until aspirin continued.
Bordes, 2003 [51]	138	Mean age similar in both groups	138 women undergoing IVF cycles and who underwent controlled ovarian hyperstimulation with a long protocol.	Implantation and pregnancy rate	69 pts ASA (100 mg) vs. 69 pts Placebo	On the 21st day of the menstrual cycle preceding the introduction of the GnRH analogue. Not specified until the medication continued
Lok, 2004 [39]	60	36.0 [33.8–37.3 years] (ASA group) 36.9 [33.0-38.8 years] (Placebo group)	Poor responders: pts who had previous IVF cycles cancelled because of the recruitment of fewer than three mature follicles (>o = 17 mm); pts with repeated high basal levels of FSH (>10 IU L^{-1})	To determine if supplementation with low-dose ASA improves utero-ovarian blood flow and ovarian responsiveness (mature follicles; oocytes for retrieval) to gonadotropin stimulation in poor responders undergoing IVF	30 pts ASA (80 mg) vs. 30 pts Control group	Beginning at the time of commencement of GnRHa in the preceding cycle and continuing until the day of HCG administration or cancellation

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Table 1 Continued.

Study, year (ref)	Included patients	Mean age, years ± SD	Inclusion criteria	Primary outcome	Treatment and dose	Onset of therapy and continuation
Van Dooren, 2004 [50]	170	32.0 [22–44 years] (ASA and Placebo groups)	Women younger than 39 years with regular cycle, according to national guidelines	Determine effect of ASA 100 mg, in patients undergoing their first IVF or ICSI cycle, on: ovarian response (number of oocytes); pregnancy rates	85 pts ASA (100 mg) vs. 85 pts Placebo	Cycle day 16. Continued until menstruation or, in case of pregnancy, up till 10 weeks pregnancy
Waldenström, 2004 [40]	1022	33.5 (ASA group) 33.3 (Control group)	Pts neding IVF for: tubal factor; endometriosis; hormonal factor; male factor; unknown cause	Live births and live birth rate	703 pts Aspirin (75 mg) vs 677 pts Control group	From the day of ET until the pregnancy test was administered (18 days after oocyte retrieval). A placebo was not used but the pts were randomized into the treatment group by giving ASA to all pts that accepted inclusion in the study every 2nd day and giving no treatment the other day. Aspirin was discontinued after the pregnancy test irrespective of whether it was positive or negative
Pakkila, 2005 [41]	374	ASA: 32 Placebo: 31.3		No. oocytes, no. and quality embryos, clinical pregnancy and pregnancy outcome (clinical pregnancy rate per cycle randomized).	ASA 100 mg vs. placebo 186 pts Aspirin (100 mg) vs. 188 pts Placebo	1st day of ovarian stimulation; Pts continued until delivery, menstruation or negative hCG test
Duvan, 2006 [42]	187	31.2 ± 5.6 (ASA group) 30.2 ± 5.6 (Placebo) 31.6 ± 6.1 (Prednisolone group) 33.5 ± 6.2 (ASA + prednisolone group)	Non-selected infertile pts who were undergoing their first ICSI cycle at Faculty of Medicine	Determine the effects of short-term low-dose aspirin and/or steroid use on implantation and pregnancy rates	41 pts ASA (100 mg) vs. 50 pts Prednisolone (10 mg/die) vs. 56 pts (ASA 100 + prednisolone 10) vs 40 pts Placebo	On embryo transfer day. Pts continued until confirmed clinical pregnancy test
Moini, 2007 [43]	145	29.3 ± 4.1 (ASA group) 29.9 ± 4.9 (Placebo)	Infertility for tubal, male or unexplained factors. No medication for at least 3 months before the study	Determine the effect of low-dose ASA on: ovarian response, implantation and pregnancy rates in pts undergoing IVF	72 pts ASA (100 mg) vs 73 pts Placebo	On the 21st of their preceding menstrual cycle and continued until menstruation or a negative pregnancy test. Pts with clinical pregnancy go on until 12 weeks
Lambers, 2009 [46]	169 IVF	ASA: 33.04 Placebo:32.96	Age < 39, FSH < 10 3rd day cycle, previous IVF or ICSI failed, no contraindication ASA, no previous ongoing pregnancy	Pregnancy rate, pulsatility index in uterine artery	84 pts ASA 100 mg vs. 85 pts placebo 100 mg.	1st day stimulation to day pregnancy. Daily medication continued until the day of pregnancy test
Dirckx, 2009 [45]	193	31.3 ± 3.9 (ASA group) 31.3 ± 3.8 (Placebo group)	Dutch-speaking women starting a first or second IVF/ICSI cycle	Clinical pregnancy rate per cycle	97 pts ASA 100 mg vs. 96 pts Placebo	Started together with the oral contraceptive pill prior to stimulation and continued until confirmation of pregnancy at 6 weeks and 3 days of amenorrhea

Table 1 Continued.

Study, year (ref)	Included patients	Mean age, years ± SD	Inclusion criteria	Primary outcome	Treatment and dose	Onset of therapy and continuation
Varnagy, 2010 [47]	2425	Not specified	Superovulation cases between 2000 and 2006	Determine if the administration of aspirin can be recommended as a prophylactic measure for ovarian hyperstimulation syndrome (OHSS)	1503 ASA (100 mg) vs. 922 control group	1st day of controlled ovarian stimulation. Aspirin was continued until menstruation, a negative pregnancy test or the ultrasonographic detection of embryonic cardiac activity
Haapsamo, 2010 [48]	487	< 40 years	Age < 40 years, < 4 previous ovarian stimulations, no contraindications for ASA	Incidence of hypertensive pregnancy complications	242 ASA VS 245 Placebo	Started on the first day of gonadotropin stimulation. Pregnant women continued the medication until delivery

ASA, acetylsalicylic acid; ET, embryo transfer; FSH, follicle-stimulating hormone; GnRH, gonadotropin releasing hormone; HCG, human chorionic gonadotropin; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; no., number; pts, patients.

obtained when the analysis was restricted to studies published in peer-reviewed journals only (OR 1.08, 95% CI 0.90, 1.29; OR 1.15, 95% CI 0.97, 1.36; and OR 1.18, 95% CI 0.82, 1.68, respectively).

Subgroup analyses

Table 2 reports in detail the studies included in each subgroup, the total number of patients, and the main results of each subgroup analysis. We could not perform a subgroup analysis according to the cause of infertility because, in most studies, patients with different causes of infertility were included. However, pregnancy and live birth rates were not significantly different between treatment groups in a study that only included patients with male infertility [37], whereas pregnancy rates were significantly increased by the use of aspirin in a study that only included patients with infertility secondary to tubal causes [14].

The use of low-dose aspirin was again associated with a higher pregnancy rate as compared with placebo when only patients undergoing IVF were considered. Similar results were obtained in the subgroup of studies in which aspirin was administered to patients at least 1 day before the ET. All the other subgroup analyses were not statiscally significant.

Discussion

In this systematic review and meta-analysis of the literature, we assessed the effect of low-dose aspirin on hard endpoints in women undergoing IVF or ICSI. Using data from 17 RCTs for a total of more than 6000 patients, we found no benefit with the use of aspirin for the most relevant outcome (i.e. live birth). Although a small but statistically significant increase in the rate of pregnancies was found with aspirin, when compared with placebo or no treatment, this effect was probably offset by the lack of protection against miscarriage. Furthermore, when the analysis was restricted to high-quality studies only, there was no statistically significant difference in any of the selected outcomes, including pregnancy rates, between treatment groups.

Previous meta-analyses assessing the efficacy of aspirin have shown apparently conflicting results [15,16,53]. Khairy *et al.* [15] and Gelbaya *et al.* [16] included only six and seven RCTs in their analyses, respectively, and did not find any statistical difference in the rates of pregnancy, miscarriage and live birth between women treated with low-dose aspirin and those treated with placebo or no treatment. In another meta-analysis, Ruopp *et al.* [12] pooled, using a fixed-effect model, the results of 10 RCTs for a total of about 2800 patients. In this meta-analysis, the use of low-dose aspirin was associated with a significantly increased rate of pregnancies without any significant effect on the rate of miscarriage. However, when the analysis was repeated using the random-effect model, a more conservative approach that takes into account the variance among the studies, the statistical significance for the rate of pregnancies was not reached. Last, a very recent meta-analysis performed

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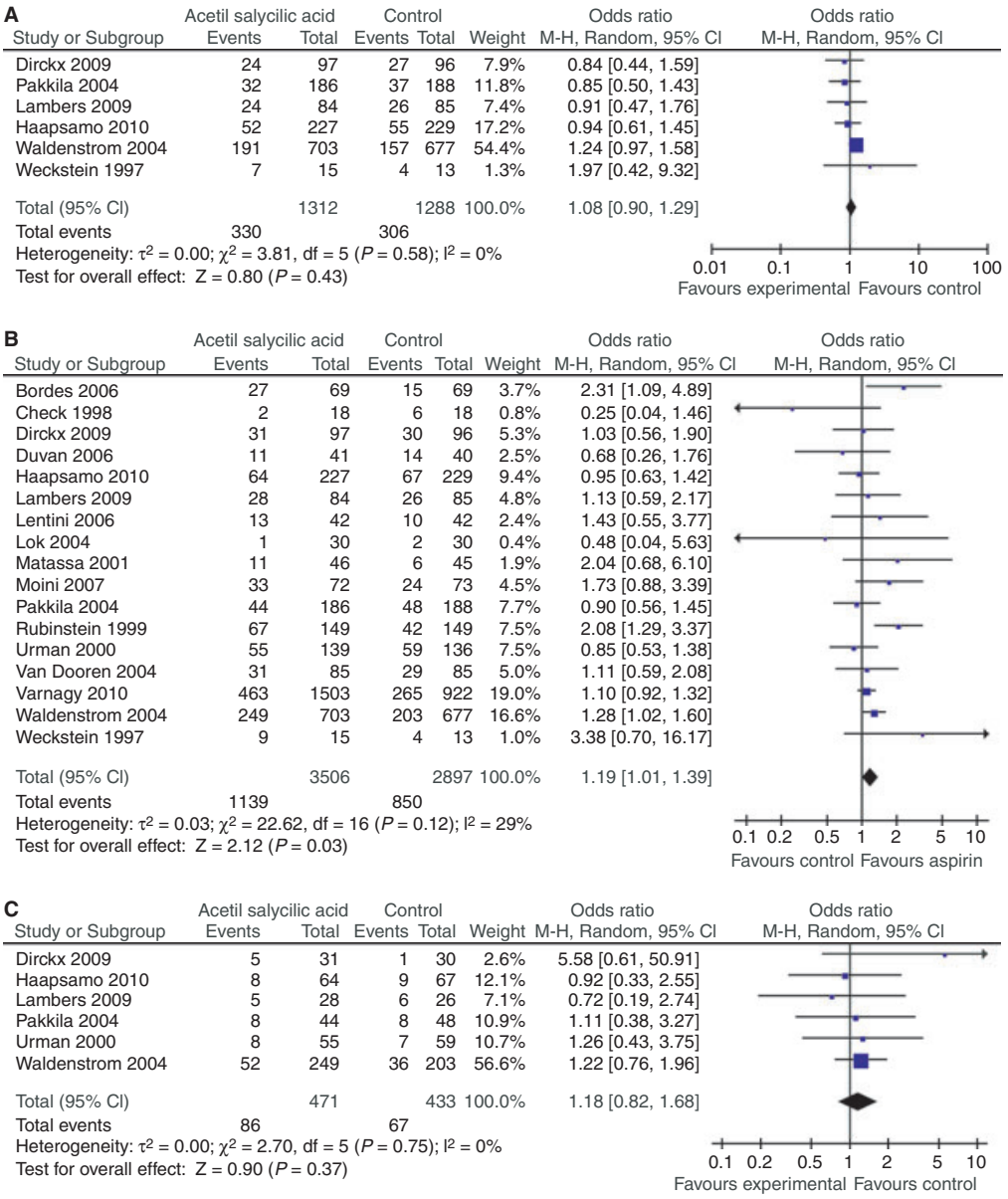

Fig. 2. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of the association between low-dose aspirin/placebo or no treatment and live birth (2a), pregnancy rate (2b) and miscarriage (2c).

on an individual patient basis that included six studies for a total of about 1100 patients failed to find increased pregnancy rates with the use of low-dose aspirin [53].

Overall, the results of the previous studies, as well as the results of this meta-analysis, with a more updated search strategy, with different inclusion and exclusion criteria, and with the inclusion of twice the number of patients, do not support the use of low-dose aspirin in general patients undergoing IVF/ICSI. It may be argued that IVF/ICSI treatment success rates are likely to be variable according to several factors, including age, number of previous cycles, treatment indication and type of protocol. In this study, we observed that the timing of introduction of low-dose aspirin, especially when introduced at least 1 day before ET, may contribute to the efficacy of this approach. Similarly, we observed that the use of aspirin appeared to be potentially more effective in specific subgroups of patients, such as patients undergoing IVF and patients with a previous ET failure, because the observed association seems to be more robust than in the general study population. Although the results of these analyses suggest the possibility that, within well-defined target populations, aspirin may truly be an effective strategy to improve pregnancy rates, we found no signs of an effect in terms of miscarriages and life birth rates in these subgroups, thus making the hypothesis of a true benefit in these specific populations unlikely.

Potential indications for IVF treatment include: male factor fertility problems where medical/surgical management and

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Table 2 Sensitivity and subgroup analyses

Patients	Number of studies	Total patients	Endpoint	Odds ratios (95% CI)
Sensitivity analyses				
High-quality studies (JADAD scale)	3	819	Live birth	0.91 (0.66–1.24)
	7	1621	Pregnancy	1.13 (0.86–1.47)
	4	360	Miscarriage	1.12 (0.60–2.09)
Clinical pregnancy diagnosed with pregnancy test and US	12	5970	Pregnancy	1.16 (0.97–1.39)
	5	2572	Live birth	1.07 (0.89–1.28)
	6	904	Miscarriage	1.18 (0.82–1.68)
All studies without abstracts	14	6011	Pregnancy	1.15 (0.97–1.36)
	6	2600	Live birth	1.08 (0.90–1.29)
	6	904	Miscarriage	1.18 (0.82–1.68)
Subgroup analyses				
Only IVF patients	3	1577	Live birth	1.20 (0.96–1.51)
	12	5024	Pregnancy	1.35 (1.11–1.65)
	2	506	Miscarriage	1.15 (0.74–1.80)
Aspirin administered at least 1 day before ET	5	1220	Live birth	0.91 (0.70–1.19)
	14	4906	Pregnancy	1.21 (1.01–1.44)
	5	452	Miscarriage	1.12 (0.65–1.92)
At least one preceding ET failure	2	197	Live birth	1.02 (0.56–1.88)
	6	736	Pregnancy	1.47 (0.91–2.37)
	1	54	Miscarriage	0.72 (0.19–2.74)
Long induction protocol	4	2379	Live birth	1.09 (0.90–1.32)
	11	3546	Pregnancy	1.20 (0.98–1.47)
	5	843	Miscarriage	1.13 (0.79–1.62)
Use of Aspirin during the entire period of pregnancy	2	830	Live birth	0.90 (0.65–1.26)
	3	866	Pregnancy	0.89 (0.65–1.22)
	2	223	Miscarriage	1.01 (0.48–2.11)

intrauterine insemination (IUI) have not resulted in a live birth; tubal disease where tubal surgery has not resulted in a live birth or is judged to be inappropriate [54]; and endometriosis where surgery and IUI have not resulted in a live birth. Younger maternal age and the possibility to cryopreserve embryos seem to be determinants of pregnancy after an IVF cycle [55,56]. Unfortunately, in most of the studies included in our systematic review, the indication for IVF was not clearly described and women of different ages were included. Furthermore, only one study reported the use of frozen embryos [36]. Thus, we were unable to analyze the results according to age, IVF/ICSI indication and cryopreservation of embryos, and if low-dose aspirin really is effective in certain subgroups of patients, this remains to be firmly established.

Our meta-analysis has some potential limitations. First, the studies included in our meta-analysis had different inclusion and exclusion criteria. However, the heterogeneity among the studies, calculated using the I^2 statistic, was generally low. Furthermore, to partially overcome the existence of clinical heterogeneity among the studies, we decided to pool the results of original studies using the random effect model, an approach that takes into account the potential sources of heterogeneity among the studies. Second, as already discussed above, due to the limitation of a meta-analytic approach we were unable to conclusively explore the possible effects of aspirin in some subgroups of patients.

However, as low-dose aspirin is widely used in clinical practice in assisted conception clinics despite a lack of evidence, the aim of our MA was to assess the evidence sustaining this approach in general patients undergoing assisted reproduction. Furthermore, with a series of hypothesis-generating subgroup analyses, we explored the possibility of a different efficacy of low-dose aspirin in many subgroups of patients according to baseline characteristics, differences in aspirin therapy and types of induction protocol and of assisted reproduction techniques. Unfortunately, to date, notwithstanding the amount of original literature on this topic, only a few studies have properly addressed the efficacy of low-dose aspirin in other subgroups, preventing an adequate evaluation in this meta-analysis.

Finally, because it is recognized that publication bias can affect the results of meta-analyses, we attempted to assess this potential bias using a funnel plot. However, funnel plots appeared symmetric, suggesting the absence of publication bias in the analysis that considered pregnancy and miscarriage rates. In the funnel plot analysis that evaluated differences in live births in patients randomized to low-dose aspirin or placebo/no treatment we observed asymmetry, with an absence of studies in the right corner of the plot. This suggests that unpublished studies likely to demonstrate an efficacy of low-dose aspirin in increasing the rate of live birth were probably not included in our meta-analysis. However, inclusion of these studies and elimination of this bias, if it really existed, would not significantly affect our results.

In conclusion, our results do not support the use of low-dose aspirin in improving the success of IVF/ICSI in terms of pregnancy outcomes. Studies aimed at evaluating the possible effect of aspirin on rate of pregnancy or live births in well-defined settings of patients (with a defined infertility diagnosis, definite induction protocol or definite age) are warranted.

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Addendum

F. Dentali handled conception and design, analyzed and interpreted the data, drafted the article, critically revised the article for important intellectual content, gave final approval of the article, provided administrative, technical or logistic support, and collected and assembled the data. W. Ageno handled conception and design, analyzed and interpreted the data, drafted the article, critically revised the article for important intellectual content, and gave final approval of the article. E. Rezoagli analyzed and interpreted the data, drafted the article, gave final approval of the article, and collected and assembled the data. E. Rancan drafted the article, gave final approval of the article, and collected and assembled the data. E. Grandone, A. Squizzato, M. Margaglione and S. Middeldorp handled conception and design, drafted the article, critically revised the article for important intellectual content, and gave final approval of the article.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interests.

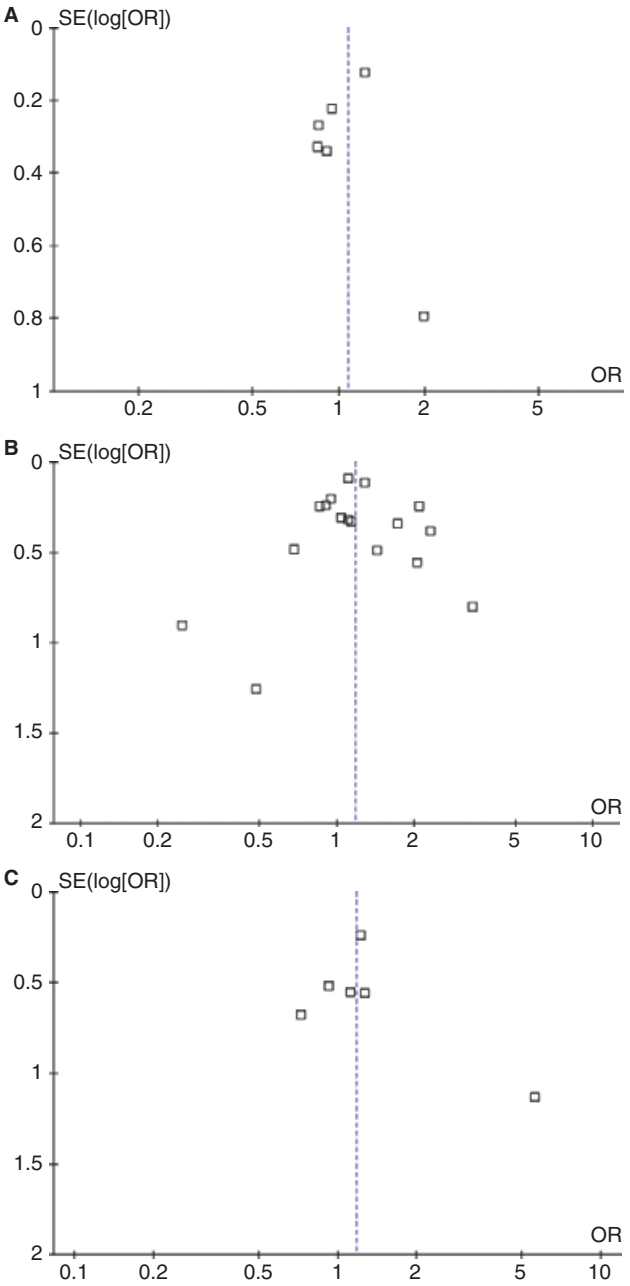
Appendix 1

Database: Ovid MEDLINE(R) <1948 to November Week 3 2011>

Search Strategy:

1 Embryo Implantation/(8365)
2 Fertilization *in vitro*/(22994)
3 Embryo Transfer/(11538)
4 Ovulation Induction/(8100)
5 Sperm Injections, Intracytoplasmic/(3817)
6 Heparin, Low-Molecular-Weight/(6181)
7 Heparin/(46857)
8 Anticoagulants/(46963)
9 Aspirin/(35572)
10 Platelet Aggregation Inhibitors/(22908)
11 6 or 7 or 8 or 9 or 10 (131341)
12 1 or 2 or 3 or 4 or 5 (40560)
13 11 and 12 (211)
14 from 13 keep 1-211 (211)

Appendix 2



References

1 Nygren KG, Andersen AN, European IVF-monitoring programme (EIM). Assisted reproductive technology in Europe, 1998. Results generated from European registers by ESHRE. European Society of Human Reproduction and Embryology. *Hum Reprod* 2001; **16**: 2459–71.
2 Harlin J, Aanesen A, Csemiczky G, Wramsby H, Fried G. Delivery rates following IVF treatment, using two recombinant FSH preparations for ovarian stimulation. *Hum Reprod* 2002; **17**: 304–9.
3 Weckstein LN, Jacobson A, Galen D, Hampton K, Hammel J. Low-dose aspirin for oocyte donation recipients with a thin endometrium: prospective, randomised study. *Fertil Steril* 1997; **68**: 927–30.
4 Ebner T, Yaman C, Moser M, Sommergruber M, Feichtinger O, Tews G. Prognostic value of first polar body morphology on fertilization rate and embryo quality in intracytoplasmic sperm injection. *Hum Reprod* 2000; **15**: 427–30.
5 Terriou P, Sapin C, Giorgetti C, Hans E, Spach JL, Roulier R. Embryo score is a better predictor of pregnancy than the number of transferred embryos or female age. *Fertil Steril* 2001; **75**: 525–31.
6 Ziebe S, Loft A, Petersen JH, Andersen AG, Lindenberg S, Petersen K, Andersen AN. Embryo quality and developmental potential is compromised by age. *Acta Obstet Gynecol Scand* 2001; **80**: 169–74.
7 Tomás C, Tikkinen K, Tuomivaara L, Tapanainen JS, Martikainen H. The degree of difficulty of embryo transfer is an independent factor for predicting pregnancy. *Hum Reprod* 2002; **17**: 2632–5.

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8 Goswamy RK, Williams G, Steptoe PC. Decreased uterine perfusion–a cause of infertility. *Hum Reprod* 1988; **3**: 955–9.
9 Battaglia C, Artini PG, Giulini S, Salvatori M, Maxia N, Petraglia F, Volpe A. Colour Doppler changes and thromboxane production after ovarian stimulation with gonadotrophin-releasing hormone agonist. *Hum Reprod* 1997; **12**: 2477–82.
10 Steer CV, Campbell S, Tan SL, Crayford T, Mills C, Mason BA, Collins WP. The use of transvaginal color flow imaging after *in vitro* fertilization to identify optimum uterine conditions before embryo transfer. *Fertil Steril* 1992; **57**: 372–6.
11 Haapsamo M, Martikainen H, Räsänen J. Low-dose aspirin and uterine haemodynamics on the day of embryo transfer in women undergoing IVF/ICSI: a randomized, placebo-controlled, double-blind study. *Hum Reprod* 2009; **24**: 861–6.
12 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**: 71–6.
13 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.
14 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.
15 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**: 822–31.
16 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**: 357–64.
17 Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; **151**: 264–9.
18 McGinn T, Wyer PC, Newman TB, Keitz S, Leipzig R, Guyatt G, Evidence-Based Medicine Teaching Tips Working Group. Tips for learners of evidence-based medicine: 3. Measures of observer variability (kappa statistic). *CMAJ* 2004; **171**: 1369–73.
19 Jadad AR, Moore AR, Carrol D. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12.
20 National Collaborating Centre for Women's and Children's Health (UK). *Fertility: Assessment and Treatment for People with Fertility Problems [Internet]*. London, UK: RCOG Press, 2004.
21 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–88.
22 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–60.
23 Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001; **323**: 101–5.
24 Revelli A, Dolfin E, Gennarelli G, Lantieri T, Massobrio M, Holte JG, Tur-Kaspa I. Low-dose acetylsalicylic acid plus prednisolone as an adjuvant treatment in IVF: a prospective, randomized study. *Fertil Steril* 2008; **90**: 1685–91.
25 Geva E, Amit 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 andautoimmune antibodies: a prospective study. *AJRI* 2000; **43**: 36–40.
26 Qublan H, Amarin Z, Dabbas M, Farraj A-E, Beni-Merei Z, Al-Akash H, Bdoor A-n, Nawasreh M, Malkawi S, Diab F, Al-Ahmad N, Balawneh M, Abu-Salim A. Low-molecular weight heparin in the treatment of recurrent IVF-ET failure and thrombophilia: a prospective randomized placebo-controlled trial. *Hum Fertil*, 2008; **11**: 246–53.
27 Urman B, Ata B, Yakin K, Alatas C, Aksoy S, Mercan R, Balaban B. Luteal phase empirical low molecular weight heparin administration in patients with failed ICSI embryo transfer cycles: a randomized open-labeled pilot trial. *Hum Reprod* 2009; **24**: 1640–7.
28 Stern C, Chamley L, Norris H, Hale L, Baker HWG. A randomized, double-blind, placebocontrolled trial of heparin and aspirin for women with *in vitro* fertilization implantation failure and antiphospholipid or antinuclear antibodies. *Fertil Steril* 2003; **80**: 376–83.
29 Sher G, Maassarani G, Zouves C, Feinman M, Sohn S, Matzner W, Chong P, Ching W. The use of combined Heparin/Aspirin and immunoglobulin G therapy in the treatment of *in vitro* fertilization patients with antithyroid antibodies. *AJRI* 1998; **39**: 223–5.
30 Sher G, Zouves C, Feinman M, Maassarani G, Matzner W, Chong P, Ching W. A rationale basis for the use of combined Heparin/Aspirin and IVIG immunotherapy in the treatment of recurrent IVF failure associated with antiphospholipid antibodies. *AJRI* 1998; **39**: 391–4.
31 Sher G, Matzner W, Feinman M, 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. *AJRI* 1998; **40**: 74–82.
32 Sher G, Feinman M, Zouves C, Kuttner G, Maassarani G, Salem R, 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.
33 Bronson R. Immunology and reproductive medicine. *Hum Reprod* 1995; **10**: 755–7.
34 Yehia M. Luteal phase support in assisted reproduction. Debate. *Middle East Fertil Soc J* 2007; **12**: 158–60.
35 Cheung LP, Yip SK, Lok IH, Haines CJ. Aspirin and reproductive performance? *Fertil Steril* 1999; **72**: 754–5.
36 Check JH, Dietterich C, Lurie D, Nazari 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 sonographic parameters. *J Assist Reprod Genet* 1998; **15**: 579–82.
37 Urman B, Mercan R, Alatas C, Balaban Bisiklar A, Nuhoglu A. Low-dose aspirin does not increase implantation rates in patients undergoing intracytoplasmic sperm injection: a prospective randomized study. *J Assist Reprod Genet* 2000; **17**: 586–90.
38 Matassa I, Morana T, Perino A, Pane A, Castelli A, Natale E, Venezia R. Terapia con aspirina ed embryo-transfer eco guidato nella IVF-ET. *Giorn It Ost Gin* 2001; **3**: 98–9.
39 Lok IH, Yip SK, Cheung LP, Leung PHY, 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.
40 Waldenstrom U, Hellberg D, Nilsson S. Low-dose aspirin in a short regimen as standard treatment in *in vitro* fertilization: a randomized, prospective study. *Fertil Steril* 2004; **81**: 1560–4.
41 Pakkila M, Rasanen J, Heinonen S, Tinkanen H, Tuomivaara L, Makikallio K, Hippelainen M, Tapanainen JS, Martikainen H. Low-dose aspirin does not improve ovarian responsiveness or pregnancy rate in IVF and ICSI patients: a randomized,placebo-controlled double-blind study. *Hum Reprod* 2005; **20**: 2211–4.
42 Duvan CI, Ozmen B, Satıroglu 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.
43 Moini A, Zafarani F, Haddadian S, Ahmadi J, Honar H, Riazi K. Effect of low-dose aspirin therapy on implantation rate in women undergoing *in-vitro* fertilization cycles. *Saudi Med J* 2007; **28**: 732–6.
44 Haapsamo M, Martikainen H, Rasanen J. Low-dose aspirin reduces uteroplacental vascular impedance in early and mid gestation in IVF and ICSI patients: a randomized, placebo-controlled double-blind study. *Ultrasound Obstet Gynecol* 2008; **32**: 687–93.

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45 Dirckx K, Cabri P, Merien A, Galajdova L, Gerris J, Dhont M, De Sutter P. Does low-dose aspirin improve pregnancy rate in IVF/ICSI? A randomized double-blind placebo controlled trial. *Hum Reprod* 2009; **24**: 856–60.
46 Lambers MJ, Hoozemans DA, Schats R, Homburg R, Lambalk CB, Hompes PGA. Low-dose aspirin in non-tubal IVF patients with previous failed conception: a prospective randomized double-blind placebo-controlled trial. *Fertil Steril* 2009; **92**: 923–9.
47 Varnagy A, Bodis J, Manfai Z, Wilhelm F, Busznyak C, Koppan M. Low-dose aspirin therapy to prevent ovarian hyperstimulation syndrome. *Fertil Steril* 2010; **93**: 2281–4.
48 Haapsamo M, Martikainen H, Tinkanen H, Heinonen S, Nuojua-Huttunen S, Rasanen J. Low-dose aspirin therapy and hypertensive pregnancy complications in unselected IVF and ICSI patients: a randomized, placebo-controlled, double-blind study. *Hum Reprod* 2010; **25**: 2972–7.
49 Lambers MJ, Groeneveld E, Hoozemans DA, Schats R, Homburg R, Lambalk CB, Hompes PGA. Lower incidence of hypertensive complications during pregnancy in patients treated ith low-dose aspirin during *in vitro* fertilization and early pregnancy. *Hum Reprod* 2009; **24**: 2447–50.
50 van Dooren IM, Schoot BC, Dargel E, Maas P. Low-dose aspirin demonstrates no positive effect on clinical results in the first *in vitro* fertilization (IVF) cycle. *Fertil Steril* 2004; **82**(Suppl 1): S18.
51 Bordes A, Bied Damon VA, Hadj S, Nicollet B, Chomier M, Salle B. Does aspirin improve IVF results? *Hum Reprod* 2003; **18**(Suppl 1): 119.
52 Lentini GM, Falcone P, Guidetti R, Mencaglia L. Effects of low-dose aspirin on oocyte quality, fertilization rate, implantation and pregnancy rates in unselected patients undergoing IVF. *Hum Reprod* 2003; **18**(Suppl 1): 40.
53 Groeneveld E, Broeze KA, Lambers MJ, Haapsamo M, Dirckx K, Schoot BC, Salle B, Duvan CI, Schats R, Mol BW, Hompes PG, for the IPD MARIA study group. Is aspirin effective in women undergoing *in vitro* fertilization (IVF)? Results from an individual patient data meta-analysis (IPD MA). *Hum Reprod Update* 2011; **17**: 501–9.
54 Kontoravdis A, Makrakis E, Pantos K, Botsis D, Deligeoroglou E, Creatsas G. Proximal tubal occlusion and salpingectomy result in similar improvement in invitro fertilization outcome in patients with hydrosalpinx. *Fertil Steril* 2006; **86**: 1642–9.
55 Heffner LJ. Advanced maternal age – how old is too old? *N Engl J Med* 2004; **351**: 1927–9.
56 Lambers MJ, Mager E, Goutbeek J, McDonnell J, Homburg R, Schats R, Hompes PG, Lambalk CB. Factors determining early pregnancy loss in singleton and multiple implantations. *Hum Reprod* 2007; **22**: 275–9.

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