

Is aspirin effective in women undergoing *in vitro* fertilization (IVF)? Results from an individual patient data meta-analysis (IPD MA)

E. Groeneveld^{1,*}, K.A. Broeze^{2,3}, M.J. Lambers¹, M. Haapsamo⁴, K. Dirckx⁵, B.C. Schoot⁶, B. Salle⁷, C.I. Duvan⁸, R. Schats¹, B.W. Mol^{2,3}, and P.G.A. Hompes¹ for the IPD MARIA study group[†]

¹Centre for Reproductive Medicine, Department of Obstetrics and Gynaecology, VU University Medical Centre, Amsterdam, The Netherlands ²Centre for Reproductive Medicine, Department of Obstetrics and Gynaecology, Academic Medical Centre (AMC), University of Amsterdam, Amsterdam, The Netherlands ³Department of Clinical Epidemiology, Biostatistics and Bio-informatics, Academic Medical Centre (AMC), University of Amsterdam, Amsterdam, The Netherlands ⁴Department of Obstetrics and Gynecology, University Hospital of Oulu, Oulu, Finland ⁵Department of Gynaecology-Obstetrics, Centre for Reproductive Medicine of the University Hospital of Ghent, Ghent, Belgium ⁶Department of Obstetrics and Gynaecology, Catharina Hospital, Eindhoven, The Netherlands ⁷Medecine de la Reproduction, Hôpital Femme Mère Enfants, Bron, France ⁸Department of Obstetrics and Gynecology, Faculty of Medicine, Fatih University, Ankara, Turkey

*Correspondence address. Tel: +31-20-4442793; E-mail: e.groeneveld@vumc.nl

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BACKGROUND: Aspirin is believed to improve the outcome of IVF, but previous conventional meta-analyses on the subject are conflicting. Therefore, we performed a meta-analysis with individual patient data (IPD MA) of randomized clinical trials (RCTs) on the subject.

METHODS: A systematic literature search was conducted to identify RCTs assessing the effectiveness of aspirin in IVF. Authors were asked to share their original data. In a one step meta-analytic approach, the treatment effect of aspirin was estimated with odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression, based on the intention to treat principle.

RESULTS: Ten studies fulfilled the inclusion criteria. Authors of six studies provided IPD, including 1119 patients (562 placebo and 557 aspirin). There were 160 clinical pregnancies in the aspirin (28.8%) and 179 (31.9%) in the placebo group [OR 0.86, 95% CI (0.69–1.1)]. There were 129 ongoing pregnancies in the aspirin (23.6%) and 147 in the placebo group (26.7%) [OR 0.85, 95% CI (0.65–1.1)]. Whereas the conventional meta-analysis limited to studies that could provide IPD showed an OR of 0.89 (95% CI 0.69–1.2), the conventional meta-analysis limited to the eight studies of which method of randomization could be confirmed showed an OR of 0.94

[†] Individual patient data meta-analysis of randomized interventions with aspirin in IVF.

(95% CI 0.76–1.17) and the conventional meta-analysis including all 10 eligible RCTs identified with our search changed the OR to 1.07 (95% CI 0.81–1.41). This difference in direction of effect, derived from the studies not able to share IPD of which quality of randomization could not be confirmed.

CONCLUSIONS: Aspirin does not improve pregnancy rates after IVF.

Key words: *In vitro* fertilization / aspirin / individual patient data meta-analysis

Introduction

IVF is a successful treatment for couples suffering from subfertility. The most important cause of failure of IVF is the loss of embryos after a successful transfer; while over 80% of the patients enrolled in an IVF or ICSI programme reach the phase of embryo transfer, in 60% of these patients implantation does not occur (Levi Setti et al., 2003). One of the causes of this so-called implantation failure may be found in impaired uterine perfusion (Goswamy et al., 1988). It has been suggested that aspirin may help us to increase the uterine blood flow by inhibiting platelet aggregation and reducing vasoconstriction, possibly leading to a more favourable endometrium for embryo implantation (Battaglia et al., 1990; Steer et al., 1992). Aspirin may also suppress negative effects of prostaglandins on implantation, such as the induction of uterine contractions or inflammatory response (Arias, 2000).

In obstetrics, aspirin is known for its potential to prevent pre-eclampsia (Askie et al., 2007). Furthermore, it improves the chance on a live birth in women with antiphospholipid syndrome with a history of recurrent miscarriage (Empson et al., 2005), although recent studies show that it is not effective in women with unexplained recurrent miscarriage (Kaandorp et al., 2010). In the last decade, the use of aspirin during IVF has been investigated in multiple studies (Weckstein et al., 1997; Check et al., 1998; Rubinstein et al., 1999; Urman et al., 2000; Bordes et al., 2003; Lentini et al., 2003; Lok et al., 2004; Pakkila et al., 2005; Duvan et al., 2006; Moini et al., 2007; Dirckx et al., 2009; Lambers et al., 2009a). Whereas some studies could not demonstrate any benefit in IVF outcome, others reported an increase in pregnancy rate, sometimes even statistically significant (Weckstein et al., 1997; Rubinstein et al., 1999; Waldenstrom et al., 2004).

No less than four meta-analyses have been published on the subject thus far (Gelbaya et al., 2007; Khairy et al., 2007; Poustie et al., 2007; Ruopp et al., 2008). Three of these meta-analyses reported a non-significant effect of aspirin, with odds ratios (ORs) and 95% confidence intervals (95% CIs) (calculated from reported relative risks in original articles) of 1.1 (95% CI 0.87–1.5), 1.1 (95% CI 0.72–1.7) and 1.2 (95% CI 0.76–1.7) respectively (Gelbaya et al., 2007; Khairy et al., 2007; Poustie et al., 2007), whereas the fourth meta-analysis even suggested a statistically significant effect of aspirin, with an OR of 1.2 (95% CI 1.1–1.4) (Ruopp et al., 2008). Thus, despite these conventional meta-analyses conducted on the subject, there is still no solid answer to the question of whether aspirin is truly effective in IVF.

Individual patient data meta-analysis (IPD MA) is an alternative to conventional meta-analysis and is thought to provide more reliable estimates of treatment effects (Stewart and Parmar, 1993). Advantages of IPD MA include the ability to check the reliability of the data, to re-analyze outcomes of original trials and to examine

causes for heterogeneity by investigating treatment effect in specific patient subgroups (Piedbois and Buyse, 2004).

In view of the clinical dilemma on aspirin in IVF, we decided to assess the effectiveness of aspirin in IVF using IPD MA.

Methods

Selection of studies and data extraction

We performed a literature search in PubMed, Embase, the Cochrane Library and the WHO International Clinical Trials Registry from 1980 to March 2010. We searched for randomized clinical trials comparing aspirin versus no treatment or placebo in women undergoing IVF. We used the following terms (with synonyms and closely related words): 'trials' or 'systematic reviews' or 'meta-analyses', 'aspirin' or 'salicylic acid' and 'in vitro fertilization'. We did not apply language restrictions. Reference lists of previous meta-analyses on the same subject were also checked for relevant studies. The full list of resources and the search strategy are available from the authors.

Studies were selected if they had a randomized design, if the population under study involved women undergoing IVF or ICSI treatment and if the therapeutic intervention under study was low-dose aspirin (75–150 mg/day) compared with placebo or no drug treatment. Studies addressing the effectiveness of aspirin in predefined patient populations such as poor responders and oocyte donation recipients were not included, as the cause of subfertility in these specific patient groups may differ from that of the general IVF population. We also did not include studies investigating combined treatments of aspirin and another drug—for example, aspirin plus prednisolone.

Two authors (E.G. and M.J.L.) independently screened the electronic searches for eligible articles by reading title and abstract. When it was certain from the abstract that the article was not of use, the article was excluded. From all other studies, we obtained the full article to decide whether the study was potentially eligible. The following information was extracted from the articles: author names, publication year, study design, the method of randomization, blinding, type of comparison group, sample size in each group, duration of follow-up, and duration and dose of aspirin treatment.

Assessment of study quality

The selected studies were assessed independently for methodological quality by two authors (E.G. and M.J.L.) using the Cochrane checklist for the evaluation of RCTs (2010). Furthermore, completeness of the data sets was examined, based on the available data on patient identifiers, type of study medication (aspirin versus placebo/no treatment) and information on clinical and ongoing pregnancy from the published paper and from the data set that we obtained from the authors. Authors were approached for clarification of data that were still missing or discordant after assessment of the second independent reviewer.

Collection of IPD

Contact information from the authors of the studies selected by our search strategy was obtained from PubMed, EMBASE or from the internet. First, second or last authors were approached by e-mail, to inform them about our IPD MA and to ask them whether they were willing to share their data in this collaborative project. Persistent efforts have been made to get their participation; when we could not reach authors by e-mail, the next step was to contact them by phone. Authors who were not able to participate in our project were asked for the reasons why and to convince them of the importance to provide data they were informed that we were obliged to mention their names and reasons why they were not able to share data in our article. Authors who wanted to participate in our project were asked to send their complete original databases.

In order to minimize the work load for the participating authors, we accepted databases in all formats provided that variables and categories were adequately labelled, allowing us to make a selection of the appropriate variables ourselves. Minimal data requirements were: (anonymous) patient identifiers, type of treatment and the occurrence of clinical or ongoing pregnancy. Authors were also asked to provide us with information on the randomization procedure/concealment of allocation. To ensure consistency and quality of randomization, we performed an additional detailed data check in which the comparability of baseline characteristics across aspirin and placebo arms was checked.

The obtained data sets were merged into a summary database when variables were compatible. We were not able to merge variables for embryo quality and indication for IVF because definitions of these variables between the participating clinics were heterogeneous. Clinical pregnancy was defined as a gestational sac and/or heartbeat on ultrasound at 6 weeks of gestational age. Because some databases did not distinguish between intrauterine and ectopic pregnancies, ectopic pregnancies were included in this group. Ongoing pregnancy was defined as an intact intrauterine pregnancy with cardiac activity on ultrasound at 12 weeks gestational age. If data on ongoing pregnancy were not available in the database, we tried to extract this variable based on other data in the database, such as live birth.

Statistical analysis

The primary outcome measure of our study was clinical pregnancy rate. Treatment effect of aspirin was estimated with ORs and 95% CIs, based on the intention to treat principle. Secondary outcome measures were ongoing pregnancy rate and miscarriage rate.

First, we calculated ORs from all available trials separately to see whether these ORs were similar to those reported in the corresponding original articles. Afterwards, the overall effect of aspirin was determined in a database that contained all IPD from all trials using a one step meta-analytic approach (Mathew and Nordstrom, 2010). Such an approach is comparable to a stratified analysis of a multicentre trial and allows for the investigation of treatment effect in predefined patient subgroups. Heterogeneity between trials was determined with interaction terms between trials, and end-points of those trials and in the overall analyses, it was adjusted for trial.

We also conducted three conventional meta-analyses: one based on the 10 eligible RCTs identified with our search, the second based on the eight studies of which the method of randomization could be confirmed and the third limited to studies that could provide their original patient data.

Statistical heterogeneity of the studies in the conventional meta-analyses was examined by checking the results of the I^2 statistic. When the presence of homogeneity could not be rejected, analyses were performed using fixed-effect modelling. If heterogeneity was evident and could not

be explained by means of subgroup-analyses, it was incorporated using random-effects modelling.

Subgroup analyses were performed by incorporating interaction terms between treatment allocation and patient characteristics into our model. We decided to make only subgroups for those variables where at least 50% of the participating studies were able to provide IPD. When, on the basis of the available data, there was no indication to assume a differential effect in one of the subgroups, to minimize the workload for the participating authors, they were not asked to retrieve IPD from medical records.

Data were analyzed using SPSS 15.0 (Statistical package for the Social Sciences: SPSS Inc., Chicago, IL, USA) and RevMan 5 software (Cochrane collaboration).

Results

Included studies

The literature search produced a list of 325 articles, of which 11 studies were potentially eligible based on the title and abstract (see Supplementary data, Fig. S1). One of these 11 studies appeared to be quasi-randomized (Waldenström *et al.*, 2004), as participants were allocated to treatment group according to the day of the week they attended the clinic, and this study was therefore excluded, leaving 10 studies fulfilling the inclusion criteria. We contacted the authors of these studies by phone to ask them whether they could provide us with IPD. Four authors indicated that they could not provide IPD. One author did not have access to the data (Moini *et al.*, 2007), two authors did not have raw data available anymore (Urman *et al.*, 2000; Lentini *et al.*, 2003) and one author could not provide data for unclear reasons (Rubinstein *et al.*, 1999). Authors of the other six trials comparing aspirin with placebo could provide their original data. These data were available for further analysis (Bordes *et al.*, 2003; Van Dooren *et al.*, 2004; Pakkila *et al.*, 2005; Duvan *et al.*, 2006; Dirckx *et al.*, 2009; Lambers *et al.*, 2009a).

Assessment of study quality

Table I shows the methodological quality of all potentially eligible studies. All studies that provided IPD reported on the method of randomization and concealment of allocation, which were performed in a correct manner. From the four studies that did not provide IPD, we were not able to confirm the method of randomization in two studies (Rubinstein *et al.*, 1999; Lentini *et al.*, 2003). Table II presents the study characteristics of all studies potentially eligible for this IPD MA. All studies that provided IPD were published during the last 6 years, started aspirin treatment before embryo transfer and continued aspirin treatment at least until 10 weeks gestational age. Study size varied between 81 and 374 patients. Table III presents the baseline characteristics of the patients in the trials where IPD were available. Data on female age, number of oocytes retrieved and number of developed embryos were available in all participating studies; data on IVF or ICSI were provided in five studies; data on type of infertility (primary/secondary), duration of infertility and number of days of stimulation were available in four studies and data on BMI were provided in three studies.

In two studies, the reported number of patients in their published articles was slightly higher than in their databases (Bordes *et al.*, 2003;

Table I Overview of methodological quality of all potentially eligible studies.

Trial	Method of randomization and allocation of concealment	Blinding	Type of analysis in original article	End-point
Lambers <i>et al.</i> (2009a)	Computerized tables Adequate concealment by third party	Double blind	Intention to treat	Ongoing pregnancy
Dirckx <i>et al.</i> (2009)	Computerized randomization Adequate concealment by third party	Double blind	Intention to treat	Ongoing pregnancy
Duvan <i>et al.</i> (2006)	Envelopes generated by lottery randomization Adequate concealment by sealed envelopes	Double blind	Per protocol	Ongoing pregnancy
Pakkila <i>et al.</i> (2005)	Block randomization, computerized tables Adequate concealment by sealed envelopes	Double blind	Intention to treat	Ongoing pregnancy
van Dooren <i>et al.</i> (2004)	Block randomization, computerized tables Adequate concealment by sealed envelopes	Double blind	Intention to treat	Ongoing pregnancy
Bordes <i>et al.</i> (2003)	Computerized tables Adequate concealment by third party	Double blind	Intention to treat	Ongoing pregnancy
Moini <i>et al.</i> (2007)	Block randomization, method not given Allocation of concealment not given	Double blind	Intention to treat	Clinical pregnancy
Lentini <i>et al.</i> (2003)	Method of randomization not given Allocation of concealment not given	Not blinded	Unreported	Ongoing pregnancy
Urman <i>et al.</i> (2000)	Computerized randomization Adequate concealment by third party	Double blind	Intention to treat	Clinical pregnancy
Rubinstein <i>et al.</i> (1999)	Method of randomization not given Adequate concealment by sealed envelopes	Double blind	Intention to treat	Clinical pregnancy

Inside the black box: studies providing original patient data.

Van Dooren *et al.*, 2004). Furthermore, in four studies, missing data on ongoing pregnancy could be extracted from other variables in the databases, such as live birth (Bordes *et al.*, 2003; Pakkila *et al.*, 2005; Duvan *et al.*, 2006; Dirckx *et al.*, 2009). For this reason, the ORs reported in these articles and obtained from the IPD may show minimal differences (Supplementary data, Table S1).

Statistical analysis

The databases of the six studies from which we obtained IPD included a total of 1119 patients, of whom 556 were allocated to aspirin and 562 to placebo. Interaction terms between trial and end-points of the study were statistically insignificant, indicating that there was no significant heterogeneity. Therefore, for our overall analyses, all IPD were merged into one database.

Data on clinical pregnancy were available for 1118 patients. In the aspirin group, there were 160/556 (28.8%) clinical pregnancies versus 179/562 (31.9%) in the placebo group. The corresponding pooled OR was 0.86 (95% CI 0.67–1.1). In 318 of the 339 patients with a clinical pregnancy, it was known whether they miscarried. The miscarriage rates were 14% (21/150) and 12.5% (21/168) in the aspirin and placebo group, respectively (OR 1.2, 95% CI 0.61–2.3). Data on ongoing pregnancy were available for 1097 patients. In the aspirin group, there were 129 (23.6%) ongoing pregnancies versus 147 (26.7%) in the placebo group. The corresponding pooled OR was 0.85 (95% CI 0.65–1.1). We found no predefined subgroups

with a significant test for interaction (Table IV). There was no evidence that women in any of our prespecified subgroups benefited more from the use of low-dose aspirin.

Figures 1–3 show the results of the three conventional meta-analyses; the first limited to the studies that could provide IPD, the second based on aggregate data from the eight studies of which method of randomization could be confirmed and the third based on aggregate data from the 10 eligible RCTs identified with our search. The studies that provided IPD showed no significant heterogeneity ($I^2 = 2\%$, $P = 0.40$). Therefore, in this meta-analysis, a fixed effect model was applied. The conventional meta-analysis limited to the eight studies of which the method of randomization could be confirmed did not show significant heterogeneity either ($I^2 = 18\%$, $P = 0.28$), therefore we again applied a fixed effect model. The studies in the conventional meta-analysis with aggregate data from all 10 eligible studies, showed significant heterogeneity ($I^2 = 49\%$, $P = 0.04$). This heterogeneity derived from the studies without traceable original patient data, in particular from the two studies in which the method of randomization remained unclear. Therefore, we were not able to examine reasons for this heterogeneity by carrying out subgroup-analyses, and random-effect modelling was used to adjust for this unexplained heterogeneity.

Whereas the conventional meta-analysis limited to studies that could provide IPD showed an OR of 0.89 (95% CI 0.69–1.2), the conventional meta-analysis limited to the eight studies of which the method of randomization could be confirmed showed an OR of

Table II Overview of study characteristics of all potentially eligible studies for this IPD MA.

	Patients' criteria	Aspirin/ placebo	Comparison	Aspirin treatment
Lambers <i>et al.</i> (2009a)	Age <39, at least one previous IVF/ICSI with failed conception and >4 oocytes at oocyte retrieval	84/85	Aspirin 100 mg/daily versus placebo	Start: together with oral contraceptives (prior to stimulation) Until: day of pregnancy test/12 weeks gestation
Dirckx <i>et al.</i> (2009)	First and second IVF/ICSI cycles	97/96	Aspirin 100 mg/daily versus placebo	Start: together with oral contraceptives (prior to stimulation) Until: clinical pregnancy
Duvan <i>et al.</i> (2006)	Non-selected patients, first ICSI cycles	41/40	Aspirin 100 mg/daily versus placebo	Start: embryo transfer Until: clinical pregnancy
Pakkila <i>et al.</i> (2005)	Age <40, <4 previous cycles	186/188	Aspirin 100 mg/daily versus placebo	Start: at first dose of gonadotrophin Until: delivery
van Dooren <i>et al.</i> (2004)	Age <39, first IVF/ICSI cycles	85/85	Aspirin 100 mg/daily versus placebo	Start: at Day 16 of cycle Until: 10 weeks gestation
Bordes <i>et al.</i> (2003)	Unselected IVF patients	69/69	Aspirin 100 mg/daily versus placebo	Start: Day 21 of cycle preceding first dose of gonadotrophin
Moini <i>et al.</i> (2007)	IVF patients with tubal/male or unexplained subfertility	72/73	Aspirin 100 mg/daily versus placebo	Start: Day 21 of cycle preceding first dose of gonadotrophin
Lentini <i>et al.</i> (2003)	IVF patients	42/42	Aspirin 100 mg/daily versus no treatment	Start: month before the first dose of gonadotrophin
Urman <i>et al.</i> (2000)	Unselected ICSI patients	139/136	Aspirin 80 mg/daily versus no treatment	Start: first day of gonadotrophin stimulation Until: cardiac activity on ultrasound
Rubinstein <i>et al.</i> (1999)	IVF patients, infertility due to tubal factor	149/149	Aspirin 100 mg/daily versus placebo	Start: Day 21 of cycle preceding first dose of gonadotrophin

Inside the black box: studies providing original patient data.

Table III Baseline characteristics of studies providing IPD.

	Lambers <i>et al.</i> (2009a)	Dirckx <i>et al.</i> (2009)	Duvan <i>et al.</i> (2006)	Pakkila <i>et al.</i> (2005)	Van Dooren <i>et al.</i> (2004)	Bordes <i>et al.</i> (2003)
Mean age (years)	33.0 ± 3.7	31.2 ± 3.9	30.8 ± 5.6	31.8 ± 4.0	32.5 ± 3.7	32.1 ± 3.5
Mean infertility duration	3.4 ± 1.9	NA	6.3 ± 4.5	4.4 ± 2.7	2.8 ± 1.7	NA
No. days stimulation	11.4 ± 1.9	12.1 ± 3.5	NA	NA	11.9 ± 2.3	11.5 ± 1.5
Total amount FSH	2262.7 ± 898.3	2629.6 ± 1041.8	3943.5 ± 1786.5	2248.4 ± 913.8	1808.5 ± 460.0	2444.3 ± 862.4
IVF/ICSI/both (%)	36.7/63.3	NA	0/100	62.3/32.9/4.8	60.2/39.8	41.2/46.3/5.1
Primary/secondary infertility (%)	23.7/76.3	72.0/28.0	NA	64.2/35.8	81.8/18.2	NA
No. of oocytes	13.6 ± 5.9	12.8 ± 7.7	12.0 ± 6.4	12.3 ± 7.1	9.9 ± 6.6	11.7 ± 6.7
No. of developed embryos	7.5 ± 4.0	NA	5.8 ± 3.2	6.7 ± 4.8	5.3 ± 4.1	7.0 ± 4.5
No. of embryo transfer embryos	1.9 ± 0.3	1.2 ± 0.6	4.4 ± 1.8	1.6 ± 0.7	1.9 ± 0.3	2.1 ± 0.7

NA, not available.

Table IV Effect of aspirin on clinical pregnancy rate in predefined patient subgroups.

Subgroup	Category	Aspirin n/N	Placebo n/N	OR (95% CI)	Interaction P- value
Maternal age (years)	≤32	95/295	108/312	0.90 (0.64–1.3)	0.85
	>32	65/260	70/249	0.85 (0.58–1.3)	
Infertility	Primary	81/276	86/277	0.92 (0.64–1.3)	0.53
	Secondary	55/172	52/175	1.1 (0.71–1.8)	
ART	IVF	57/227	62/224	0.88 (0.58–1.3)	0.67
	ICSI	67/215	83/224	0.77 (0.52–1.1)	
BMI	<20	13/32	11/32	1.3 (0.47–3.6)	0.36
	20–25	47/168	40/150	1.1 (0.65–1.8)	
	≥25	17/72	31/93	0.62 (0.30–1.2)	

OR, odds ratio; 95% CI, 95% confidence interval.

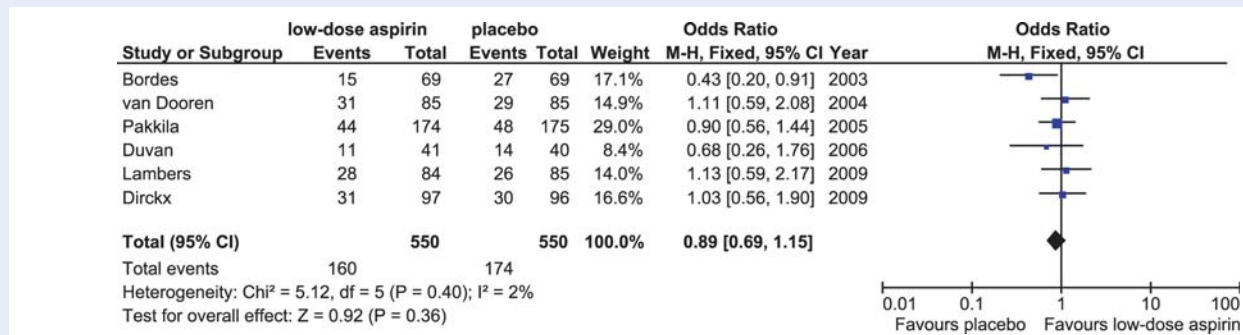


Figure 1 Conventional meta-analysis of studies sharing IPD. Outcome: clinical pregnancy.

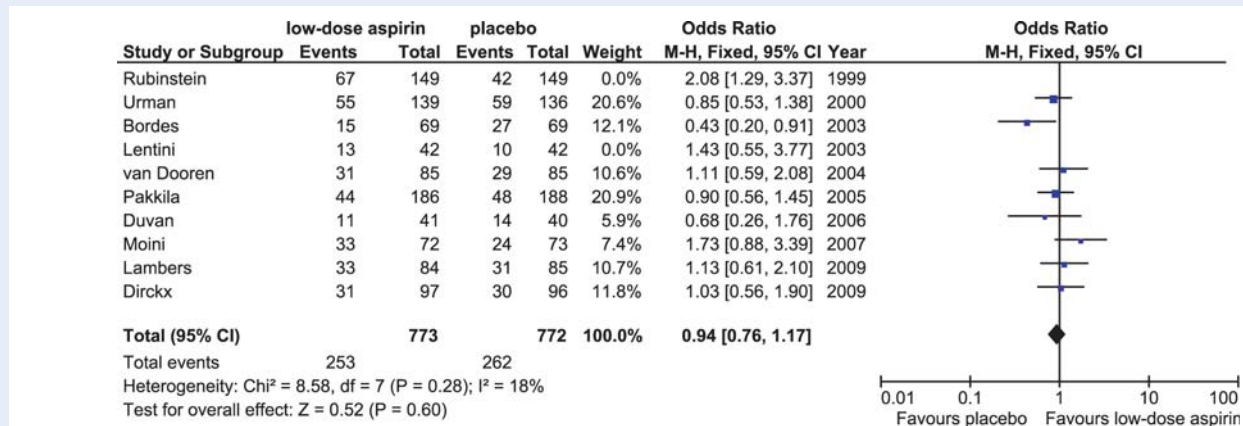


Figure 2 Conventional meta-analysis of studies that were adequately randomized. Outcome: clinical pregnancy.

0.94 (95% CI 0.76–1.17) and the conventional meta-analysis including all 10 eligible RCTs identified with our search changed the OR to 1.07 (95% CI 0.81–1.41).

Table S1 (supplementary data) demonstrates an overview of the treatment effect of aspirin on clinical and ongoing pregnancy rates reported in the original trials and conventional meta-analyses, as well as obtained after re-analysis with IPD. Whereas all previously

performed conventional meta-analyses reported ORs in the direction of a benefit from low-dose aspirin, the modest effect observed from our IPD MA was in the direction of a harm of aspirin. Only two of the published papers that shared IPD, reported on ongoing pregnancy rate in their original articles. A conventional meta-analysis that combined these results showed a pooled OR for ongoing pregnancy rate of 1.04 (95% CI 0.65–1.7) (Forest plot not shown).

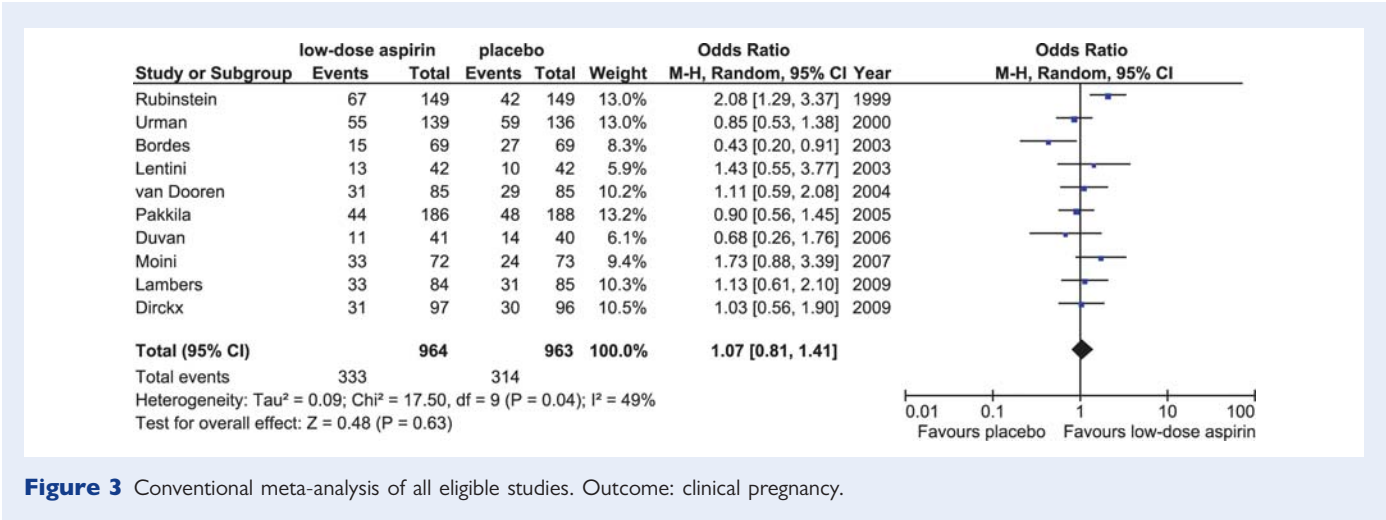


Figure 3 Conventional meta-analysis of all eligible studies. Outcome: clinical pregnancy.

Discussion

In this IPD MA, we found that aspirin does not improve pregnancy rates in IVF patients, nor in specific subgroups. This lack of effect is supported by the pathophysiological data from our previous study, in which it was demonstrated that aspirin does not improve uterine blood flow (Lambers et al., 2009a). Similarly, aspirin was recently found to be ineffective to increase live birth rate in women with unexplained recurrent miscarriage (Kaandorp et al., 2010).

Our conclusion supports three of four previous conventional meta-analyses. In those meta-analyses, the small apparent advantage of aspirin is likely to be based on chance. Our results also indicate that the apparent effect of aspirin is consistent with the chance effect, although the modest effect observed in the IPD MA is in the opposite direction: a harmful effect of aspirin. The difference in the direction of effect reported in previous meta-analyses and obtained with our IPD did not arise from a more sophisticated analysis possible with IPD MA, but from the unavailability of data from older studies.

Since the first report of doubled pregnancy rate in IVF patients after the use of low-dose aspirin (Rubinstein et al., 1997), this treatment is believed to improve the chance of successful implantation during IVF treatment. Of the four conventional meta-analyses that investigated the effectiveness of aspirin in IVF (Gelbaya et al., 2007; Khairy et al., 2007; Poustie et al., 2007; Ruopp et al., 2008), one reported a significant beneficial effect of the use of low-dose aspirin. Different conclusions of meta-analyses on the same topic, even those conducted over the same period, are the result of choices made regarding inclusion criteria and statistical model to adjust for heterogeneity (Lambers et al., 2009c). Instead of adjusting for heterogeneity by applying different statistical models, IPD MA allows for the investigation of heterogeneity through subgroup analysis; there was no benefit of aspirin in any of our prespecified subgroups.

In the present study, we tried to revisit the question of whether daily low-dose aspirin improves the success of IVF by conducting an IPD MA. Unfortunately, the authors of only 60% of the eligible trials were able to share original patient data. Since not all the authors were able to provide IPD, a potential bias could have been created as a result of a difference in the effect of aspirin found in studies with and without traceable data. Even though it is possible that the

studies with traceable data provided the most robust data, a potential bias could still exist.

Three explanations can be offered for the difference in treatment effect between studies with and without traceable data. Firstly, five of the six authors who provided data had published their studies after 2003 (Van Dooren et al., 2004; Pakkila et al., 2005; Duvan et al., 2006; Dirckx et al., 2009; Lambers et al., 2009a), whereas three of the four studies from which we did not receive data were published before that time (Rubinstein et al., 1999; Urman et al., 2000; Lentini et al., 2003). This generates the possibility of publication bias since the initial studies on a subject have a greater chance on publication when they report positive findings (Dickersin, 1990). Secondly, in the study that reported the largest treatment effect and could not provide IPD, there was a lack of detail regarding the method of randomization (Rubinstein et al., 1999). It could therefore have a higher risk of bias, which may have resulted in an overestimated treatment effect. A third explanation for the difference in effect between studies with and without traceable data might be that the authors could not reproduce their reported findings from the original data. This is a particular worry, as this jeopardizes the value that meta-analysts, guideline makers and individual clinicians give to published RCTs. RCTs are considered as the best form of evidence, especially when they are integrated in meta-analyses. On the basis of the ORs in the direction of a benefit of aspirin (albeit not statistically significant) reported in three previous meta-analyses, IVF patients may consider the use of aspirin, in particular because it is a well known, easily accessible drug without major adverse effects. In a previous clinical trial investigating the use of aspirin in IVF, patients also received a questionnaire enquiring whether they would consider the use of aspirin in a next IVF cycle (Lambers et al., 2009a). Almost 25% reported taking aspirin regardless of scientific proof, illustrating the importance of a valid meta-analysis and to demonstrating possible adverse effects. When we omit the data of the trials from which we did not obtain IPD, the modest effect changes in the opposite direction and there seems no reason for patients to use aspirin or to investigate aspirin in IVF in the future.

We have to bear in mind that in the conventional meta-analysis including all eligible studies consistency and randomization could

not be confirmed in two studies (Rubinstein et al., 1999; Lentini et al., 2003) that did not provide IPD and the results may therefore be less reliable. It was however, the best method available to investigate the effect of the studies without IPD on the results, since previous conventional meta-analyses besides the studies included in our IPD MA also included other studies (e.g. matched controlled studies) (Gelbaya et al., 2007; Khairy et al., 2007; Poustie et al., 2007; Ruopp et al., 2008). A third conventional meta-analysis limited to the eight studies that were adequately randomized made clear that the ORs in the direction of favouring aspirin found both in previous conventional meta-analyses and in ours were mostly due to a single study (Rubinstein et al., 1999).

Recently, guidelines for reporting quality criteria of RCTs have been updated to improve transparent reporting of clinical trials (Moher et al., 2010), and prospective trial registration limits the possibility of *post hoc* adjustments in design and analysis of such studies and also addresses the problem of publication bias (Dickersin and Rennie, 2003). In our study, it was difficult to obtain IPD from older studies, while these studies tend to have the largest treatment effect. This highlights the need to create a method to ensure preservation of RCT data sets. Medical journals and their editors should consider handing over the original data as soon as a clinical study is published.

Although we demonstrated that aspirin has no effect on pregnancy rate after IVF, it may have other beneficial effects, for instance, on the outcome of pregnancies after IVF treatment by prevention of pre-eclampsia. In a previous study, we found a lower incidence of hypertensive pregnancy complications in women treated with aspirin; however, this was only a small pilot as it was not powered for this particular outcome (Lambers et al., 2009b). In the Perinatal Antiplatelet Review of International Studies meta-analysis, the authors used IPD to assess the effect of aspirin on pre-eclampsia in women at risk for developing pre-eclampsia. They found a beneficial effect of aspirin in this group of women (Askie et al., 2007). Future studies, including large numbers of IVF patients, are needed to further investigate whether low-dose aspirin is effective in preventing hypertensive pregnancy complications in patients undergoing IVF.

In conclusion, our results demonstrate that aspirin does not improve pregnancy rates after IVF. With this IPD MA, we support the conclusion of three of four previous conventional meta-analyses. We also conclude that aspirin has no added value in specific patient subgroups. This IPD MA could therefore serve as a specific case study, highlighting the need to create a system to save IPD from all published clinical trials

Authors' roles

The work was performed for the IPD MARIA study group (www.ipd-meta-analysis.com). P.G.A.H. and B.W.M. designed the study. E.G., J.C.F.K. and M.J.L. performed the literature search. E.G. coordinated this IPD meta-analysis, approached the original authors and created the summary database. M.J.L., M.H., K.D., B.C.S., B.S. and C.I.D. performed the original data acquisition. E.G. did the analysis, under the supervision of B.W.M. All authors have revised the article and have given final approval of the submitted version.

Supplementary data

Supplementary data are available at <http://humup.oxfordjournals.org/>.

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