6

Preconceptional Low-Dose Aspirin for the Prevention of Hypertensive Pregnancy Complications and Preterm Delivery After IVF: A Meta-Analysis with Individual Patient Data

HUM REPROD. 2013 JUN;28(6):1480-8

Study question
Does preconceptionally started low-dose aspirin prevent hypertensive pregnancy complications and preterm delivery in IVF patients?

Summary answer
The current data do not support the use of preconceptionally started low-dose aspirin treatment for the prevention of hypertensive pregnancy complications and preterm delivery in IVF women.

What is known already
Studies starting low-dose aspirin treatment as prevention in the second trimester of pregnancy found no or only moderate reductions in the relative risk of developing pre-eclampsia. Low-dose aspirin was possibly started too late, that is after the first episode of trophoblast invasion.

Study design, size, duration
We performed a meta-analysis with individual patient data (IPD), in which four authors could provide IPD on a total of 268 pregnancies (n = 131 treated with aspirin, n = 137 placebo). Data on hypertensive pregnancy complications and preterm delivery were collected.

Participants/materials, setting, methods
All separate databases were merged into a summary database. Treatment effect of aspirin on the incidence of hypertensive pregnancy complications (n = 187) and preterm delivery (n = 180) were estimated with odds ratios (OR) and 95% confidence intervals (95% CI) using multivariable confidence logistic regression.

Main results and the role of chance
There were significantly fewer twin pregnancies in the aspirin group (OR 0.55 95% CI 0.30–0.98), but no significant differences for hypertensive pregnancy complications and preterm delivery: for singletons OR 0.62 (95% CI 0.22–1.7) and OR 0.52 (95% CI 0.16–1.7), respectively, as well as for twin pregnancies OR 1.2 (95% CI 0.35–4.4) and OR 1.6 (95% CI 0.51–5.0), respectively.

Limitations, reasons for caution
We have to bear in mind that the included studies showed clinical heterogeneity; there was variation in the duration of low-dose aspirin therapy and degree of hypertension between the different studies. Although we combined IPD from four studies, we have to realize that the studies were not powered for the outcome of the current IPD meta-analysis.

Wider implications of the findings
Based on the current meta-analysis with IPD we found no confirmation for the hypothesis that preconceptionally started low-dose aspirin reduces the incidence of hypertensive pregnancy complications or preterm delivery in IVF women. Larger studies are warranted.
INTRODUCTION

Hypertensive pregnancy disorders are the most important cause of maternal and neonatal morbidity and mortality. Pre-ecclampsia (PE) has its origin in abnormal implantation and placental development in early pregnancy. Shallow trophoblast invasion of the maternal spiral arteries leads to decreased placental perfusion resulting in placental ischemia and infarction. As a consequence, platelets and the clotting system are activated resulting in an imbalance between prostacyclin (a vasodilator) and thromboxane A2 (a vasoconstrictor and stimulant of platelet aggregation).

As an inhibitor of the cyclo-oxygenase (COX) enzyme, aspirin inhibits thromboxane A2 and reduces vasoconstriction and platelet aggregation. Therefore, it has been hypothesized that aspirin treatment during pregnancy improves trophoblast invasion of the uterine spiral arterioles, leading to more optimal placental perfusion and reduced chances of developing pregnancy-induced hypertension (PIH) and PE. It has also been suggested that aspirin treatment should be started early in pregnancy, with a crucial time before 16 or even 12 weeks of gestational age, since the cytotrophoblast invades maternal spiral arterioles as early as 8 weeks of gestation.

Studies that started low-dose aspirin treatment in the second trimester of pregnancy found no benefit or only moderate reductions in the relative risk of developing PE. Low-dose aspirin treatment was possibly started too late, that is after the completion of the first episode of trophoblast invasion. This hypothesis was supported by a recently published meta-analysis demonstrating a significant diminution of PE in a subgroup of women who began intervention at 16 weeks of gestational age or earlier. This meta-analysis also reported a significant decrease of preterm birth in this patient subgroup.

Many studies have indicated that IVF patients have an increased risk of developing obstetric complications, such as PIH, PE and preterm delivery. A growing body of evidence suggests that defective placentation may not only play a role in the genesis of hypertensive pregnancy disorders, but also in preterm birth indicating that those disorders share a similar mechanism of disease. The increased risk of placental dysfunction in IVF patients may be the result of the hormonal environment induced during IVF or the pre-existing metabolic-vascular state of patients undergoing IVF. Therefore, low-dose aspirin prophylaxis may especially be effective in IVF. Follow up of one placebo controlled trial on preconceptional low-dose aspirin treatment in IVF found a lower incidence of hypertensive pregnancy complications in the aspirin-treated group, but these
results could not be confirmed by a second study. A meta-analysis reported a significant decrease in preterm births, but unfortunately did not report whether these were medically induced because of maternal complications. Therefore, it is impossible to make a reliable estimation of the value of low-dose aspirin prophylaxis in the prevention of preterm births.

These contradictory and inconclusive findings prompted us to carry out a further evaluation in a larger series of IVF patients by employing IPD Meta-Analysis (IPD-MA) from published randomized trials on the preconceptional use of aspirin in IVF. IPD-MA is an alternative for conventional meta-analysis and is thought to provide more reliable estimates of treatment effect. Advantages of IPD-MA include the ability to check the reliability of the data and to examine causes for heterogeneity by investigating treatment effect in different subgroups. In addition, IPD-MA limits the risk for publication bias, since also non-published (follow-up-) data could be discovered. The aim of this IPD-MA was to investigate whether preconceptional low-dose aspirin treatment influences the incidence of hypertensive pregnancy complications and preterm delivery in IVF patients.
MATERIAL AND METHODS

Sources
To identify trials comparing aspirin versus no treatment/placebo in IVF we conducted a literature search in PubMed, Embase, the Cochrane Library and the international World Health Organization clinical trial registry from March 1980 to January 2011. We used the following terms (with thesaurus terms, synonyms and closely related words): ‘trials’ or ‘systematic reviews’ or ‘meta-analysis’, ‘aspirin’ or ‘salicylic acid’ and ‘in vitro fertilization’. Because we wanted to collect all IPD on hypertensive pregnancy complications and preterm delivery (also non-published data and data from studies investigating aspirin in IVF) we did not add specific terms for hypertensive pregnancy complications and preterm delivery to avoid publication bias.

For this IPD-MA we selected both RCTs and studies reporting follow-up data of RCT’s on aspirin in IVF. Due to the limited number of studies investigating aspirin therapy in IVF, no restrictions were applied to risk criteria that might contribute to the development of pre-eclampsia or the duration of low-dose aspirin therapy.

Study selection
Two authors [E.G. and M.J.L.] screened the electronic searches for eligible articles by reading the title and abstract. A final selection was made by reading the complete article. In case of disagreement regarding the selection of studies a third reviewer (P.G.A.H.) made the final decision. The studies were then assessed for their quality using the Cochrane checklist for the evaluation of RCTs. The following information was extracted from the articles: author names, publication year, study design, method of randomization, concealment of allocation, blinding, type of comparison group, sample size in each group, number of pregnant women in each group, duration of follow-up and duration and dose of aspirin treatment. Studies that used an inadequate method of randomization or concealment of allocation and studies of which the authors could not confirm the method of randomization or concealment of allocation were excluded from the IPD-MA.

The authors of the eligible studies were approached and asked to provide us with IPD of patients with an ongoing pregnancy (12 weeks of gestational age) in the original clinical trial. We asked for routinely registered variables of the IVF treatment, the course and outcome of pregnancy and the occurrence of pregnancy complications, such as hypertensive pregnancy complications and preterm delivery. Pregnancies terminated because of congenital abnormalities were excluded.

Minimal data requested were [anonymous] patient identifiers, treatment with aspirin or placebo/no treatment, presence or
absence of hypertensive pregnancy complications and type of pregnancy (singleton/twin). To analyse the incidence of preterm birth, we also asked for data regarding gestational age at delivery. PIH was defined according to international guidelines as diastolic blood pressure ≥90 mmHg or systolic blood pressure ≥140 mmHg, or both, on repeated measurements detected after 20 weeks of gestation. PE was defined as PIH and proteinuria (≥300 mg/24 h). In the case of haemolysis, elevated liver enzymes and low–platelet patients were diagnosed with HELLP syndrome. Because not all databases distinguished the degree of hypertensive pregnancy complications (e.g. PIH, PE, HELLP) \(^{21-22}\), all hypertensive pregnancy complications were joined in one group.

All separate data sets were merged into a summary database (the Statistical Package for the Social Sciences version 15.0, Inc. Chicago, IL, USA). All cases were included, also those with incomplete data (i.e. intention to treat analysis). Statistical heterogeneity between the studies was assessed with interaction terms between aspirin and trial. The primary end-point of this follow-up study was the incidence of hypertensive pregnancy complications. Secondary end-points were preterm delivery.

Treatment effect of aspirin on the incidence of hypertensive pregnancy complications and preterm delivery was estimated with odds ratios (OR) and 95% confidence intervals (95% CI) using multivariable logistic regression. Because multiple pregnancies could modify the effect of aspirin on hypertensive pregnancy complications and preterm delivery, subgroups of singleton and twin pregnancies were made \(^{23-25}\). In the calculation of OR for hypertensive pregnancy we adjusted for trial. In the analysis for preterm delivery, in addition to adjusting for trial we adjusted for hypertensive pregnancy complications as pregnancies with hypertensive complications may require earlier termination of pregnancy \(^{26}\).
RESULTS

The literature search produced a list of 532 reports. Based on our selection criteria 13 studies were potentially eligible (FIGURE 1 and Supplementary data, FIGURE S1). One report was excluded because it was quasi-randomized. Two RCTs already published their follow-up data on hypertensive pregnancy complications. To prevent redundancy in the data these two follow-up studies were therefore excluded and we only included the original RCTs. Finally, 10 reports were potentially eligible for this IPD-MA, corresponding with the trials identified in our IPD MARIA on the effect of aspirin on pregnancy rates after IVF. Of these reports, six authors also participated in our previous IPD-MA, and four of those were able to provide us with IPD on (hypertensive) pregnancy complications, course and outcome of pregnancy and preterm delivery.

In one of the participating studies data on hypertensive pregnancy complications were derived directly from medical records. In a second study data on hypertensive complications were obtained from questionnaires. In the other two studies patients first received a questionnaire inquiring about the pregnancy and possible complications. These data were linked with data from medical records, which were checked for hypertensive pregnancy complications during pregnancy and delivery. In these two studies 91 and 90% of the data in the questionnaires, respectively, could be linked with medical records.
FIGURE 1 Selection of trials

IPD, individual patient data. References of reports identified with the literature search: A Bordes et al. [2003]; Dirckx et al. [2009]; Duvan et al. [2006]; Lambers et al. [2009a]; Lentini et al. [2003]; Moini et al. [2007]; Pakkila et al. [2005]; Rubinstein et al. [1999]; Urman et al. [2000]; van Dooren et al. [2004]; Waldenstrom et al. [2004]; Lambers et al. [2009b]; Haapsamo et al. [2010]. B Waldenstrom et al. [2004]. C Lambers et al. [2009b]; Haapsamo et al. [2010]. D Bordes et al. [2003]; Dirckx et al. [2009]; Duvan et al. [2006]; Lambers et al. [2009a]; Lentini et al. [2003]; Moini et al. [2007]; Pakkila et al. [2005]; Rubinstein et al. [1999]; Urman et al. [2000]; van Dooren et al. [2004]. E Dirckx et al. [2009]; Lambers et al. [1999]; van Dooren et al. [2000]. F Lentini et al. [2003]; Pakkila et al. [2005]. G Bordes et al. [2003]; Duvan et al. [2006]. H Dirckx et al. [2009]; Lambers et al. [2009a]; van Dooren et al. [2004]; Pakkila et al. [2005].
An overview of the methodological quality of the potentially eligible trials is shown in TABLE I. All IPD were derived from trials in which the method of randomization and concealment of allocation were adequate. TABLE II shows an overview of the study characteristics of the included studies. In all studies aspirin treatment had been started preconceptionally and continued at least until 10 weeks of gestational age. Study size of the original clinical trials varied between 169 and 487 patients. TABLE III shows the patient and pregnancy characteristics of the included studies. Data on maternal age, number of transferred embryos, parity, gestational age at delivery, mode of delivery and birth weight were provided in all participating studies; data on duration of infertility were available in three studies.

Of the 269 ongoing pregnancies, one pregnancy was terminated at 16 weeks of gestational age because of trisomy 18 and was therefore excluded. For all remaining patients gestational age at delivery was after 20 weeks of gestational age. Of the 268 patients with an ongoing pregnancy, 131 patients were treated with aspirin and 137 patients were treated with placebo. There were 196 singleton pregnancies, 66 twin pregnancies and 6 pregnancies with an unknown number of fetuses. Among patients treated with aspirin there was a significant lower number of twin pregnancies: 25 (19.7%) compared with 41 (30.4%) twins in the placebo group (OR 0.55, 95% CI 0.30–0.98) (the number of fetuses in six cases was unknown). TABLE IV shows the number of patients with hypertensive pregnancy complications and preterm delivery in the different studies. Although in our analysis the interaction terms between aspirin and trial were not significant \( P = 0.43 \) and \( P = 0.88 \) for hypertensive pregnancy complications and preterm delivery respectively, indicating no significant heterogeneity, we adjusted for trial to provide the most reliable estimates of treatment effect. Unfortunately, we could not investigate the effect of aspirin on the degree of hypertension, owing to the limited number of patients with hypertensive pregnancy complications and incomplete reports on the degree of the disease.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Method of randomisation &amp; allocation of concealment</th>
<th>Blinding</th>
<th>Type of analysis in original article</th>
<th>End point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lambers 2009a</td>
<td>Computerized tables Adequate concealment by third party</td>
<td>Double blind</td>
<td>Intention to treat</td>
<td>Ongoing pregnancy</td>
</tr>
<tr>
<td>Dirckx 2009</td>
<td>Computerized randomization Adequate concealment by third party</td>
<td>Double blind</td>
<td>Intention to treat</td>
<td>Ongoing pregnancy</td>
</tr>
<tr>
<td>Pakkila 2005</td>
<td>Block randomization (computerized tables) Adequate concealment by sealed envelopes</td>
<td>Double blind</td>
<td>Intention to treat</td>
<td>Ongoing pregnancy</td>
</tr>
<tr>
<td>van Dooren 2004</td>
<td>Block randomisation (computerized tables) Adequate concealment by sealed envelopes</td>
<td>Double blind</td>
<td>Intention to treat</td>
<td>Ongoing pregnancy</td>
</tr>
<tr>
<td>Moini 2007</td>
<td>Block randomization, method not given Allocation of concealment not given</td>
<td>Double blind</td>
<td>Intention to treat</td>
<td>Clinical pregnancy</td>
</tr>
<tr>
<td>Duvan 2006</td>
<td>Envelopes generated by lottery randomization Adequate concealment by sealed envelopes</td>
<td>Double blind</td>
<td>Per Protocol</td>
<td>Ongoing pregnancy</td>
</tr>
<tr>
<td>Lentini 2003</td>
<td>Method of randomisation not given Allocation of concealment not given</td>
<td>Not blinded</td>
<td>Unreported</td>
<td>Ongoing pregnancy</td>
</tr>
<tr>
<td>Bordes 2003</td>
<td>Computerized tables Adequate concealment by third party</td>
<td>Double blind</td>
<td>Intention to treat</td>
<td>Ongoing pregnancy</td>
</tr>
<tr>
<td>Urman 2000</td>
<td>Computerized randomization Adequate concealment by third party</td>
<td>Double blind</td>
<td>Intention to treat</td>
<td>Clinical pregnancy</td>
</tr>
<tr>
<td>Rubinstein 1999</td>
<td>Method of randomisation not given Allocation of concealment by sealed envelopes</td>
<td>Double blind</td>
<td>Intention to treat</td>
<td>Clinical pregnancy</td>
</tr>
</tbody>
</table>

*Studies providing the IPD on hypertensive pregnancy complications*
### TABLE II  Overview of study characteristics of the original clinical trials providing IPD

<table>
<thead>
<tr>
<th>Author</th>
<th>Original study design</th>
<th>Aspirin treatment</th>
<th>No of patients aspirin/placebo in original trial</th>
<th>No of ongoing pregnant patients (%) aspirin/placebo</th>
<th>Patients’ criteria</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lambers et al (2009a)</td>
<td>RCT</td>
<td>Starting together with oral contraceptive pill (prior to stimulation) until day of pregnancy test/12 weeks gestation</td>
<td>84 / 85</td>
<td>26 [31.0] / 28 [32.9]</td>
<td>Age &lt;39, at least one previous IVF / ICSI with failed conception and &gt;4 oocytes at oocyte retrieval</td>
<td>Aspirin 100mg / daily versus placebo</td>
</tr>
</tbody>
</table>

*A Because the authors continued recruitment of patients after publication of the original trial, the number of patients reported in this table is higher than reported in the original article.*
### TABLE III Patient and pregnancy characteristics of the four included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years) mean (SD)</th>
<th>No. of trans-ferred embryos mean (SD)</th>
<th>Duration of infertility mean (SD)</th>
<th>Nulliparous n (%)</th>
<th>Gestational age at delivery weeks (SD)</th>
<th>Caesarean section n (%)</th>
<th>Birth weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lambers et al. (2009a) [N=54]</td>
<td>32.7 [3.1]</td>
<td>1.9 [0.32]</td>
<td>3.3 [1.9]</td>
<td>54 (100)</td>
<td>38.1 [2.7]</td>
<td>24 [47.1]</td>
<td>3.3 [0.66]</td>
</tr>
<tr>
<td>Dirckx et al. (2009) [N=53]</td>
<td>30.7 [3.9]</td>
<td>1.4 [0.49]</td>
<td>NA</td>
<td>44 (83)</td>
<td>37.8 [2.3]</td>
<td>6 [15.4]</td>
<td>3.1 [0.70]</td>
</tr>
<tr>
<td>Pakkila et al. (2005) [N=107]</td>
<td>31.3 [3.8]</td>
<td>1.7 [0.58]</td>
<td>4.0 [2.2]</td>
<td>83 [77.6]</td>
<td>38.4 [2.6]</td>
<td>21 [28]</td>
<td>3.4 [0.56]</td>
</tr>
</tbody>
</table>

### TABLE IV Number of patients with hypertensive pregnancy complications and preterm delivery in different studies

<table>
<thead>
<tr>
<th>Study (total no.of patients in the study)</th>
<th>Hypertensive pregnancy complications</th>
<th>Preterm delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin N/n (%)</td>
<td>Placebo N/n (%)</td>
</tr>
<tr>
<td>Lambers et al. [2009a] [n=54]</td>
<td>1/24 (4.2)</td>
<td>7/26 (26.9)</td>
</tr>
<tr>
<td>van Dooren et al. [2004] [n=54]</td>
<td>3/24 (12.5)</td>
<td>0/27 (0)</td>
</tr>
<tr>
<td>Dirckx et al. [2009] [n=53]</td>
<td>1/20 (5.0)</td>
<td>1/25 (4.0)</td>
</tr>
<tr>
<td>Pakkila et al. [2005] [n=107]</td>
<td>8/52 (15.4)</td>
<td>10/55 (18.2)</td>
</tr>
<tr>
<td>Total [n=268]</td>
<td>13/120 (10.8)</td>
<td>18/133 (13.5)</td>
</tr>
</tbody>
</table>

A Some data were missing therefore n values for percentage calculations were lower
Singleton pregnancies

Data on hypertensive pregnancy complications were available for 187 [96 aspirin and 91 placebo] pregnancies and data for preterm delivery were available for 180 [96 aspirin and 84 placebo] pregnancies (TABLE V). In total, seven patients in the aspirin group had hypertensive pregnancy complications (7.3%), compared with 10 in the placebo group (11.0%) (OR 0.62, 95% CI 0.22–1.7, P = 0.35). In the aspirin group five patients had preterm delivery (5.2%), compared with nine in the placebo group (10.7%) (OR 0.52, 95% CI 0.16–1.7, P = 0.27).

Twin pregnancies

Data on hypertensive pregnancy complications were available for 65 patients (24 aspirin and 41 placebo) and data on preterm delivery were available for 61 (21 aspirin and 40 placebo) patients (TABLE VI). Six (25.0%) patients in the aspirin group had hypertensive pregnancy complications, compared with eight (19.5%) in the placebo group (OR 1.2, 95% CI 0.35–4.4, P = 0.74). Fourteen (66.7%) patients in the aspirin group had preterm delivery compared with 21 (52.5%) in the placebo group (OR 1.6, 95% CI 0.51–5.0, P = 0.42).

TABLE V  Pregnancy outcome for singleton pregnancies

<table>
<thead>
<tr>
<th>Study (total no. of patients in the study)</th>
<th>Hypertensive pregnancy complications</th>
<th>Preterm delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin N/n (%)</td>
<td>Placebo N/n (%)</td>
</tr>
<tr>
<td>Lambers et al. [2009a] (n=38)</td>
<td>1/20 [5.0]</td>
<td>4/16 [25]</td>
</tr>
<tr>
<td>Dirckx et al. [2009] (n=47)</td>
<td>1/19 [5.3]</td>
<td>1/21 [4.7]</td>
</tr>
<tr>
<td>van Dooren et al. [2004] (n=30)</td>
<td>1/16 [6.3]</td>
<td>0/14 [0]</td>
</tr>
<tr>
<td>Total (n=196)</td>
<td>7/96 [7.3]</td>
<td>10/91 [11.0]</td>
</tr>
<tr>
<td>Pooled OR (95%CI)</td>
<td>OR 0.62 (0.22–1.7)</td>
<td>OR 0.52 (0.16–1.7)</td>
</tr>
</tbody>
</table>

A Some data were missing
B Pooled OR adjusted for trial
C Pooled OR adjusted for trial and hypertensive pregnancy complications

OR, odds ratio; 95% CI, 95% confidence interval
### TABLE VI Pregnancy outcome for twin pregnancies

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypertensive pregnancy complications</th>
<th>Preterm delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin N/n (%)</td>
<td>Placebo N/n (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin N/n (%)</td>
</tr>
<tr>
<td>Haapsamo et al (n=26)</td>
<td>4/11 [36.4]</td>
<td>5/15 [33.3]</td>
</tr>
<tr>
<td></td>
<td>0/4 [0]</td>
<td>3/9 [33.3]</td>
</tr>
<tr>
<td>Lambers et al (n=13)</td>
<td>0/1 [0]</td>
<td>0/4 [0]</td>
</tr>
<tr>
<td>Dirckx et al (n=6)</td>
<td>2/8 [25.0]</td>
<td>0/13 [0]</td>
</tr>
<tr>
<td>van Dooren et al (n=21)</td>
<td>6/24 [25.0]</td>
<td>8/41 [19.5]</td>
</tr>
<tr>
<td>Total (n=66)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Pooled OR (95%CI)      | OR 1.2 [0.35-4.4]                     | OR 1.6 [0.51-5.0] |

A some data were missing

B pooled OR adjusted for trial

C pooled OR adjusted for trial and hypertensive pregnancy complications
DISCUSSION

This IPD-MA demonstrates that low-dose aspirin treatment, started preconceptionally and continued throughout the first trimester of pregnancy, does not reduce the incidence of hypertensive pregnancy complications or preterm delivery in patients undergoing IVF treatment.

We focused on IVF patients, because these patients have a higher a priori risk to develop hypertensive pregnancy complications and preterm delivery. In IVF it is known precisely when embryo implantation takes place, and this makes the IVF population of women ideal for studying the exact timing for low-dose aspirin treatment. By performing IPD analysis we were able to discover unpublished data on hypertensive pregnancy complications in IVF.

Impaired physiological transformation of the uterine spiral arteries, an indicator of abnormal placentation, has been found both in women with PE and women with preterm delivery. Deficient trophoblast invasion of the spiral arteries results in an increased production of thromboxane A2 by the trophoblast cells, stimulating vasoconstriction and platelet aggregation. It has been hypothesized that low-dose aspirin treatment in this early stage of placentation could inhibit thromboxane A2 production by suppressing COX-1 and therefore restricting vasoconstriction. When started preconceptionally, low-dose aspirin could therefore theoretically provide more optimal conditions for invasion of the uterine spiral arterioles, improved placental blood flow and, consequently, could reduce chances of developing PIH, PE or preterm delivery.

In women prone to develop PE, low-dose aspirin is known to produce moderate, but consistent reductions in the disease. These results are supported by a meta-analysis of Bujold et al., who found a significant reduction in PE, especially in a subgroup of women that had started low-dose aspirin treatment before 16 weeks of gestational age. Besides a reduction in PE, Bujold et al. also reported a significant reduction in preterm delivery in the group treated with low-dose aspirin (OR 0.22, 95% CI 0.10–0.49). These results suggest that the administration of low-dose aspirin may be beneficial in the first period of trophoblast invasion.

Based on the current meta-analysis with IPD we found no confirmation for the hypothesis that preconceptionally started low-dose aspirin reduces the incidence of hypertensive pregnancy complications or preterm delivery. Subgroup analyses for the estimation of the possible preventive effect of aspirin treatment in both singletons and twins also did not reveal any beneficial effect of low-dose aspirin. The estimated effect of aspirin resembles the treatment effect of
Bujold et al. 7, but lacks significance. By collecting IPD we tried to improve the power and to confirm the hypothesis of Lambers et al. 7. We have to realize, however, that IPD derived from studies that were not powered for hypertensive pregnancy complications and preterm delivery and, even combining them, did not yield enough power to make our results significant. Therefore, we could not confirm the previous finding of lower incidence of hypertensive pregnancy complications in patients treated with low-dose aspirin in the follow-up data of our placebo-controlled randomized trial 7.

From one of the original aspirin in IVF trials we learned that low-dose aspirin treatment in IVF patients has no effect on the changes of the pulsatility index (PI) of the uterine arteries through time 27. Deurloo et al. 34 demonstrated that the PI of the uterine arteries is an accurate reflection of the peripheral resistance of the spiral arteries. Therefore, it seems reasonable to assume that since low-dose aspirin does not affect the PI of the uterine arteries, it also does not affect the spiral arteries and therefore leaves the placental blood flow unaffected. From this perspective it seems unlikely for low-dose aspirin to affect the incidence of PE and preterm delivery, even after early administration.

Although we found no significant heterogeneity between the studies, we have to bear in mind that some of the included studies were small and showed high variation in the effect of low-dose aspirin (with large CIs). Furthermore, we have to realize that, although it has been suggested that low-dose aspirin exerts its effect during early trophoblast invasion before 12 weeks of gestational age 6, one of the participating studies continued low-dose aspirin treatment for the entire pregnancy, which could have altered the treatment effect in this study 16. Unfortunately, because of the low number of studies investigating the effect of aspirin on pregnancy complications, we were not able to differentiate between studies continuing low-dose aspirin for the entire pregnancy or just in the first period of trophoblast invasion. The degree of hypertensive disorders could also vary between the studies, which may affect the prophylactic effect of aspirin. The variation in the degree of the disease could be related to different proportions of nulliparae in the studies. Nulliparae are known to have a higher risk to develop severe hypertensive complications and PE. Unfortunately, in this IPD we could not investigate the effect of aspirin on the degree of hypertension.

The preventive effect of low-dose aspirin on hypertensive pregnancy complications found in the study of Lambers et al. 7 is most probably a result of the higher proportion of twins in the group treated with placebo. Since hypertensive pregnancy complications are more common in twin pregnancies, the high proportion of twin pregnancies in the placebo group may have acted as a confounder, resulting in an overestimated effect of low-dose aspirin. Increasing the statistical power by means of IPD-MA enabled us to substantiate the remarkable observation of more twin pregnancies in the placebo group, indicating a negative effect of low-dose aspirin on embryo implantation. Recent meta-analyses 30,35-37 already demonstrated that the previous assumption of a beneficial effect on embryo implantation was false. From previous RCTs 21-22,28-29
we learned that low-dose aspirin treatment does not affect embryo quality. It must therefore affect endometrial quality resulting in an impaired environment for (multiple) embryo implantation. As a non-selective inhibitor of the COX enzyme, low-dose aspirin could exert a negative effect on the endometrium by suppressing COX-2 expression, critical to implantation during the attachment reaction. This is supported by a study of Achache et al. demonstrating lower levels of COX-2 in the secretory endometrium of IVF patients with recurrent implantation failure.

In summary, available data do not support the use of preconceptionally started low-dose aspirin treatment for the prevention of hypertensive pregnancy complications and preterm delivery. Aspirin has already been proved not to increase pregnancy rates. The significant lower incidence of twin pregnancies may even indicate a negative effect of aspirin on embryo implantation that will hopefully be further elucidated in studies investigating the interaction of aspirin with implantation factors.

Supplementary data

Acknowledgements
The authors would like to thank Hans C.F.K. Ket, VU University Medical Centre, Amsterdam, The Netherlands, for his assistance with performing the literature search.


