Systematic Review and Meta-Analysis

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Efficacy evaluation of low-dose aspirin in IVF/ICSI patients evidence from 13 RCTs

A systematic review and meta-analysis

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Abstract

Background: We conducted a systematic review and meta-analysis of existing literature to evaluate the different outcomes of low-dose aspirin on patients undergoing in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI), including clinical pregnancy rate, implantation rate, live birth rate, miscarriage rate, fertilization rate, number of oocytes retrieved, and so forth.

Methods: Electronic databases including PubMed, MEDLINE, and Embase were searched between 1997 and March 2016 to identity eligible studies. The following comparisons between treatment groups were included: aspirin versus placebo; aspirin versus control group; aspirin versus aspirin + prednisolone + control.

Results: Thirteen randomized controlled trials which included 3104 participants were selected. There were no significant differences in implantation rate (RR = 1.15; 95% CI = 0.78–1.70), live birth rate (RR = 1.06; 95% CI = 0.93–1.21), miscarriage rate (RR = 1.28; 95% CI = 0.93–1.77), fertilization rate (RR = 0.91; 95% CI = 0.75–1.11), and endometrial thickness (WMD = 0.15; 95% CI = −0.38–0.67). But the research showed that aspirin treatment may improve the clinical pregnancy rate (RR = 1.16; 95% CI = 1.04–1.28) compared to placebo or no treatment, and reduce the number of oocytes retrieved (WMD = −0.68; 95% CI = −0.91–0.46).

Conclusions: Our findings suggest that low-dose aspirin may improve the pregnancy rate in IVF/ICSI, with the recommended clinical use dose of 100 mg/day. Considering the limitation of included studies, further well-designed large-scaled RCTs are necessary to clarify whether aspirin may improve assisted reproduction outcomes in IVF/ICSI patients.

Abbreviations: ART = assisted reproductive techniques, HCG = human chorionic gonadotropin, ICSI = intracytoplasmic sperm injection, IVF = in vitro fertilization, RCT = randomized controlled trials.

Keywords: aspirin, assisted reproductive techniques, clinical pregnancy rate, in vitro fertility, systematic review

1. Introduction

Assisted reproductive technology (ART) development, which has had more than 30 years of history, has been utilized all over the world, as millions of "test-tube babies" have been born. ART has become a common way of reliable and effective treatment of infertility, and many infertile couples have benefited from the progress and development of the ART. Although the ART has made a certain progress, the implantation rate and clinical pregnancy rate is still low.[1] How to further improve the clinical pregnancy rate is a constant challenge in reproductive medicine. Researchers test many auxiliary drug interventions for adjuvant therapy, with one of the most clinical effective being aspirin.[2,3]

Aspirin also called acetylsalicylic acid and has many clinical applications, including as an antipyretic and analgesic, inhibition, prevent thrombosis and improve microcirculation. It is widely used in clinical fields, including the treatment of cardiovascular diseases, gynecological diseases, and so on. With the development of medical science, more and more experiments have established that aspirin play an important role in infertility and ART. However, there remains uncertainty about, but its effectiveness and the dose-dependent effectiveness. This paper aims to explore the effect of low-dose aspirin in assisted reproductive outcomes through meta-analysis of 13 randomized controlled trials (RCT) articles.

2. Materials and methods

2.1. Data source and search strategy

This meta-analysis do not involve patients, and thus do not require institutional review board approval. Electronic databases including PubMed, MEDLINE, and Embase were searched between 1997 and March 2016 to identity eligible studies, using

Editor: Daryle Wane.

Funding: This study was funded by the National Natural Science Foundation of China (Grant Nos. 81100421, 81601343), Top Six Talent Peaks Program of Jiangsu (2014-WSW-080), the National Science Foundation of Yangzhou (YZ2014050, YZ2016110).

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:37(e7720)

Received: 7 December 2016 / Received in final form: 28 June 2017 / Accepted: 13 July 2017

http://dx.doi.org/10.1097/MD.0000000000007720

the following key words: "aspirin or acetylsalicylic acid," "IVF or in vitro fertilization," "RCT or randomized controlled trials," and "ART or assisted reproductive techniques." Furthermore, the reference lists of every article were retrieved and reviews were manually searched to identify additional eligible studies.

2.2. Eligibility criteria

Studies were included if they met the following criteria: They had to be RCT; the study population included women undergoing IVF or intracytoplasmic sperm injection (ICSI); the clinical outcome of implantation, miscarriage, pregnancy, and live birth was recorded for all participants; low-dose aspirin (<120 mg) was used compared with placebo or no treatment. Review articles, case reports, letters to the editor, and editor comments were excluded.

2.3. Data collection

Eligibility evaluation and data abstraction were analyzed independently by 2 investigators (Liping Wang, Xiaman Huang) according to the meta-analysis observational studies in PRISMA guidelines, and the discrepancies were adjudicated by consensus. For each study, the following data were extracted: first author; year of publication; country; included patients (aspirin/placebo); blinding; treatment and dose; inclusion criteria; type of analysis in original article; outcome measures (clinical pregnancy rate; implantation rate; live birth rate; miscarriage rate; fertilization rate; endometrial thickness; oocytes retrieved).

2.4. Statistical analysis

All results were merged for meta-analysis with the Review Manager 5.2 (version 5.2, The Nordic Cochrane Centre, The Cochrane Collaboration, 2016). The number of women who were randomly assigned was regarded as the total number of participants in each study. Using the Mantel–Haenszel random-effects model and Fixed model dichotomous outcomes were summarized by calculating the relative risk (RR) and 95% confidence intervals (95% CIs) and Weighted mean difference (WMD). Heterogeneity between studies was assessed by the Chi-squared test and I^2 with $P<.10$ indicating significant heterogeneity. I^2 results interpretation: $I^2<25\%$: low heterogeneity; $I^2=25\%$ to 50%: moderate heterogeneity; $I^2>50\%$: a high degree of heterogeneity.

3. Results

The electronic search retrieved a total of 1129 citations. (Aspirin or acetylsalicylic acid) AND (IVF or in vitro fertilization) and (RCT or randomized controlled trials) AND (ART or assisted reproductive techniques.) Of these, 855 articles were excluded on the basis of title and abstract; 24 articles were assessed fully for eligibility. A total of 11 articles were excluded for the following reasons: the effect of aspirin after treatment had not been evaluated in terms of ART outcomes (n=2); the study was not randomized controlled trial (n=5); no control group (n=4). Therefore, 13 studies were finally included in this meta-analysis (Fig. 1). The characteristics of the included studies are listed in Table 1.[2,4–15]

The process of randomization was appropriate in 13 studies. Allocation concealment was carried out in 13 studies, which may give rise to selection bias. The researchers and participants were blinded to the intervention in 13 studies. For outcome assessment, there were drop outs in 2 studies, and the reason was reported. Results of quality assessment of the studies are shown in Fig. 2.

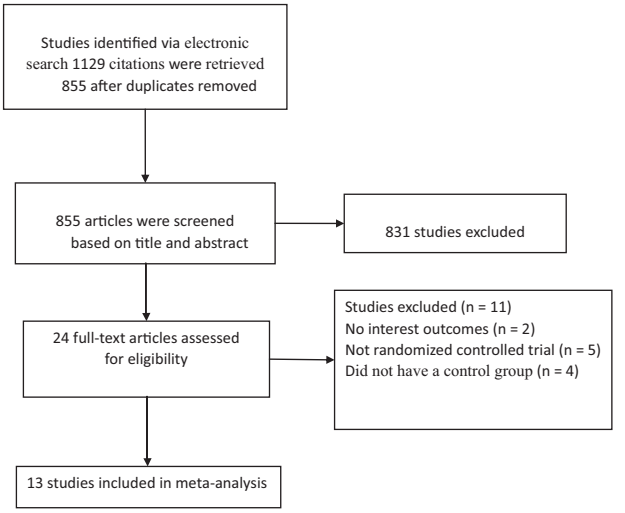

Figure 1. Flowchart of study selection.

3.1. Clinical pregnancy rate

All 13 studies (3104 participants) that reported clinical pregnancy as an outcome were included (Fig. 2A). Clinical pregnancy occurred in 531 of 1565 (33.9%) women randomized to low-dose (75–100 mg/d) aspirin and 449 of 1539 (29.1%) women randomized to placebo or no treatment. The pooled analysis using the random-effects model demonstrated that low-dose aspirin use might improve the clinical pregnancy rate compared with placebo or no treatment group (RR=1.16; 95% CI=1.04–1.28; $P=.005$). There was significant heterogeneity between studies ($I^2=19\%$).

The 4 papers studying (1743 participants) a lower dose of aspirin (75–80 mg/d) found that it may also improve the clinical pregnancy rate compared with placebo or no treatment group using the random-effects model analysis (Fig. 2B). But there was no significant heterogeneity between studies (RR=1.13; 95% CI=0.99–1.29; $P=.07$) ($I^2=19\%$).

3.2. Number of oocytes retrieved

There were 5 studies (1061 patients) which reported the number of oocytes retrieved. The random-effect model was used for the meta-analysis. The results showed that the number of oocytes retrieved of the aspirin was significantly higher than that of the placebo or no treatment groups (MD=−0.70; 95% CI=−1.52–0.12; $P=1.00$), while no significant heterogeneity was found ($I^2=0\%$) (Fig. 3A).

3.3. Implantation rate

Seven studies reported implantation rate outcomes in 1240 patients. Implantation occurred in 102 of 612 (16.7%) women randomized to low-dose aspirin and in 90 of 628 (14.3%) women randomized to placebo or no treatment. Thus, the random-effect model was used for the meta-analysis. The results showed there was no significant difference in the implantation rate between the aspirin and placebo groups (RR=1.15; 95% CI=0.78–1.70;

Table 1

The characteristics of included studies.

Study	Year	Country	Included patients (aspirin/placebo)	Blinding	Treatment (aspirin/placebo)	Inclusion criteria	Type of analysis in original article	Outcome measures
Louis et al	1997	California	15/13	No	Aspirin (81 mg/d) placebo (81 mg/d)	Endometrial thickness ≥ 8 mm	Unclear	Pregnancy rates; implantation rates; live birth rate
Mara et al	1999	USA	35/39	Yes	Aspirin (100 mg/d) placebo (100 mg/d)	≥ 35 years old	Student's *t*-test	Pregnancy rates; implantation rates; oocytes retried
Bulent et al	2000	USA	139/136	Yes	Aspirin (80 mg/d) control group (80 mg/d)	≥ 35 years old ≥ 1 implantation failure	χ^2 test and t-test	Pregnancy rates; implantation rates; oocytes retried
Bordes et al	2003	France	69/69	Yes	Aspirin (100 mg/d) placebo (100 mg/d)	Underwent controlled ovarian hyperstimulation (COH)	Unclear	Pregnancy rates; endometrial thinness; oocytes retried
Dooren et al	2004	Netherlands	85/85	Yes	Aspirin (100 mg/d) placebo (100 mg/d)	Age < 39 years	Unclear	Pregnancy rate
Ingrid et al	2004	China	30/30	Yes	Aspirin (80 mg/d) placebo (80 mg/d)	Follicles ≥ 17 mm; FSH ≥ 10 U/L;	Mann-Whitney rank-sum; χ^2 test	Pregnancy rates; implantation rates; fertilization rate; endometrial thinness; oocytes retried
Urben et al	2004	Sweden	703/677	No	Aspirin (75 mg/d) control group (75 mg/d)	Age ≤ 40 years; follicles ≥ 18 mm	χ^2 test; *t*-test	Pregnancy rates; live birth rates; miscarriage rate; fertilization rate
Pakkila et al	2005	Finland	174/175	No	Aspirin (100 mg/d) placebo (100 mg/d)	Age < 40 years; fewer than 4 previous ovarian stimulations;	χ^2 test; 2 tailed *t*-test;	Pregnancy rates; live birth rates; miscarriage rate; oocytes retried
Candan et al	2006	Turkey	41/40	Yes	Aspirin (100 mg/d) placebo (100 mg/d)	Follicles ≥ 18 mm	Student's test	Pregnancy rates; oocytes retried
Marieke et al	2008	Netherlands	84/85	Yes	Aspirin (100 mg/d) placebo (100 mg/d)	<39 years old; FSH ≤ 10 U/L;	χ^2 test and *t*-test	Pregnancy rates; implantation rates; live birth rate; Fertilization rate
Dirckx et al	2009	Belgium	97/96	Yes	Aspirin (100 mg/d) placebo (100 mg/d)	≥31 years old	χ^2 test and t-test	Pregnancy rates; live birth rate; miscarriage rate; oocytes retried
Haapsamo et al	2009	USA	57/56	Yes	Aspirin (100 mg/d) placebo (100 mg/d)	Age < 40 years; fewer than 4 previous ovarian stimulations	Mann-Whitney *U*-test; *t*-test	Pregnancy rates; implantation rates; live birth rate; miscarriage rate; endometrial thinness
Haapsamo et al	2010	Finland	227/229	Yes	Aspirin (100 mg/d) placebo (100 mg/d)	Age < 40 years; fewer than 4 previous ovarian stimulations;	Fisher's exact test	Pregnancy rates; live birth rate; miscarriage rate

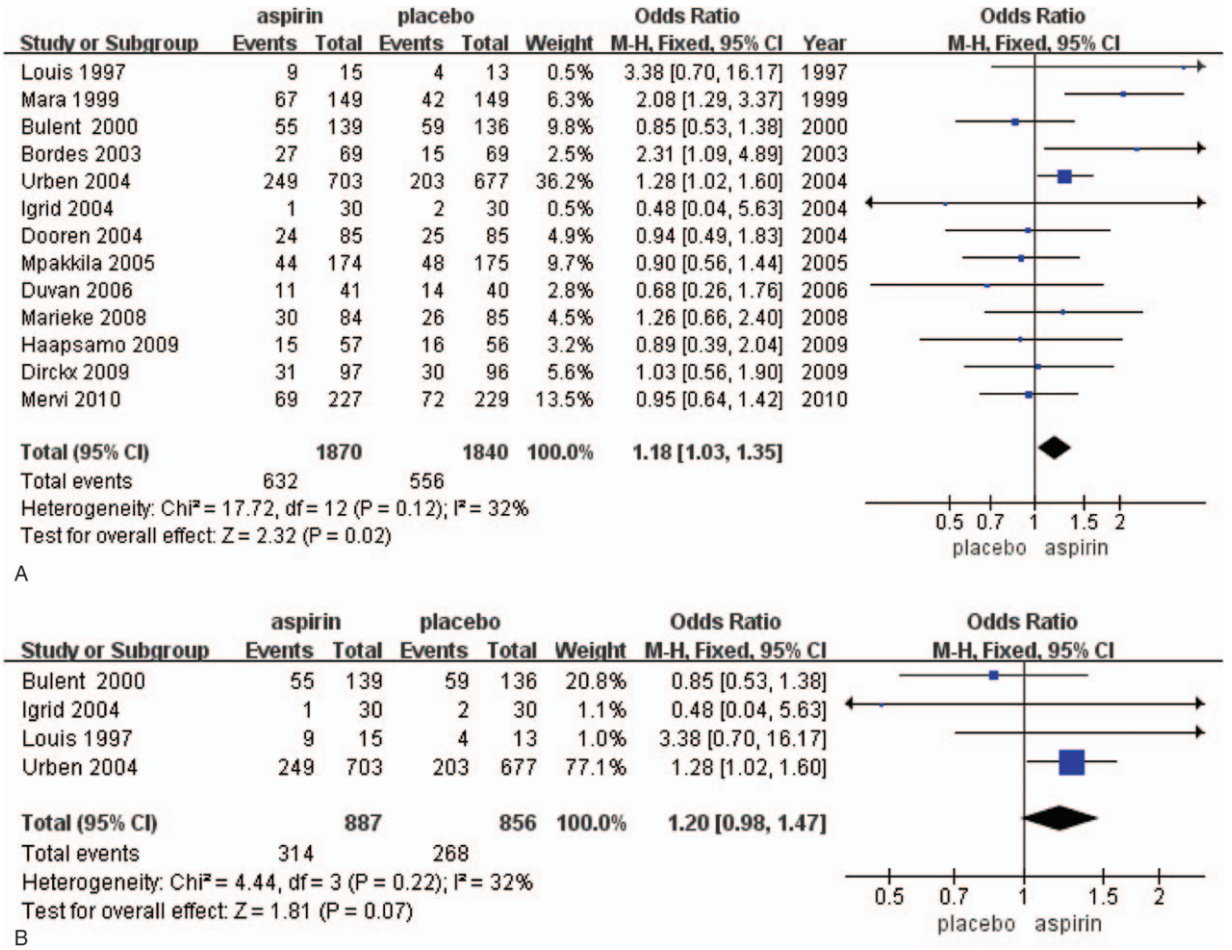

Figure 2. The Forest plots for (A) clinical pregnancy rate, (B) the improved clinical pregnancy rate.

$P=.07$). In terms of single study data, only 2 trials reported a significant increase in implantation rate (Fig. 3B).

3.4. Live birth rate

There were 7 studies (1372 aspirin patients vs 1347 placebo patients) which reported live birth rate. There was no heterogeneity among the studies ($I^2=0\%$) (Fig. 4B). The results showed that there was no significant difference in live birth rate between the aspirin and placebo groups (RR = 1.08; 95% CI = 0.93–1.21; $P=.74$). In terms of single study data, only 2 trials reported a significant increase in birth rate[2,9] (Fig. 3C).

3.5. Miscarriage rate

There were 5 studies (1850 participants) which reported on miscarriage rates (Fig. 3D). Miscarriage occurred in 78 of 936 (8.3%) women randomized to low-dose aspirin and in 60 of 914 (6.6%) women randomized to placebo or no treatment. No significant change in the rate of miscarriage was observed between aspirin and placebo or treatment groups. Considering the result from the pooled data analysis, as well as any single study (RR = 1.28; 95% CI = 0.93–1.77; $P=.53$). No significant heterogeneity was detected between studies ($I^2=0\%$).

3.6. Fertilization rate

The fertilization rate was reported in 3 studies (1609 participants). Fertilization occurred in 353 of 817 (43.2%) women randomized to low-dose aspirin and in 361 of 792 (45.6%) women randomized to placebo or no treatment. Pooling the results of 3 studies showed no significant difference between patients treated with the aspirin compared with the placebo (RR = 0.91; 95% CI = 0.75–1.11; $P=.95$). There was no heterogeneity among the studies ($I^2=0\%$) (Fig. 4A).

3.7. Endometrial thickness

There were 3 studies (311 participants) that reported on endometrial thickness (Fig. 4A). No significant change in the rate of endometrial thickness was observed between aspirin and placebo or treatment groups. This was true across the result from the pooled data analysis, as well as any single study (RR = 0.15; 95% CI = −0.38–0.67; $P=.05$) (Fig. 4B).

4. Discussions

The data of this systematic review and meta-analysis show that low-dose aspirin may improve clinical pregnancy rate in IVF/ICSI. As infertility treatment success rate remains low, the years

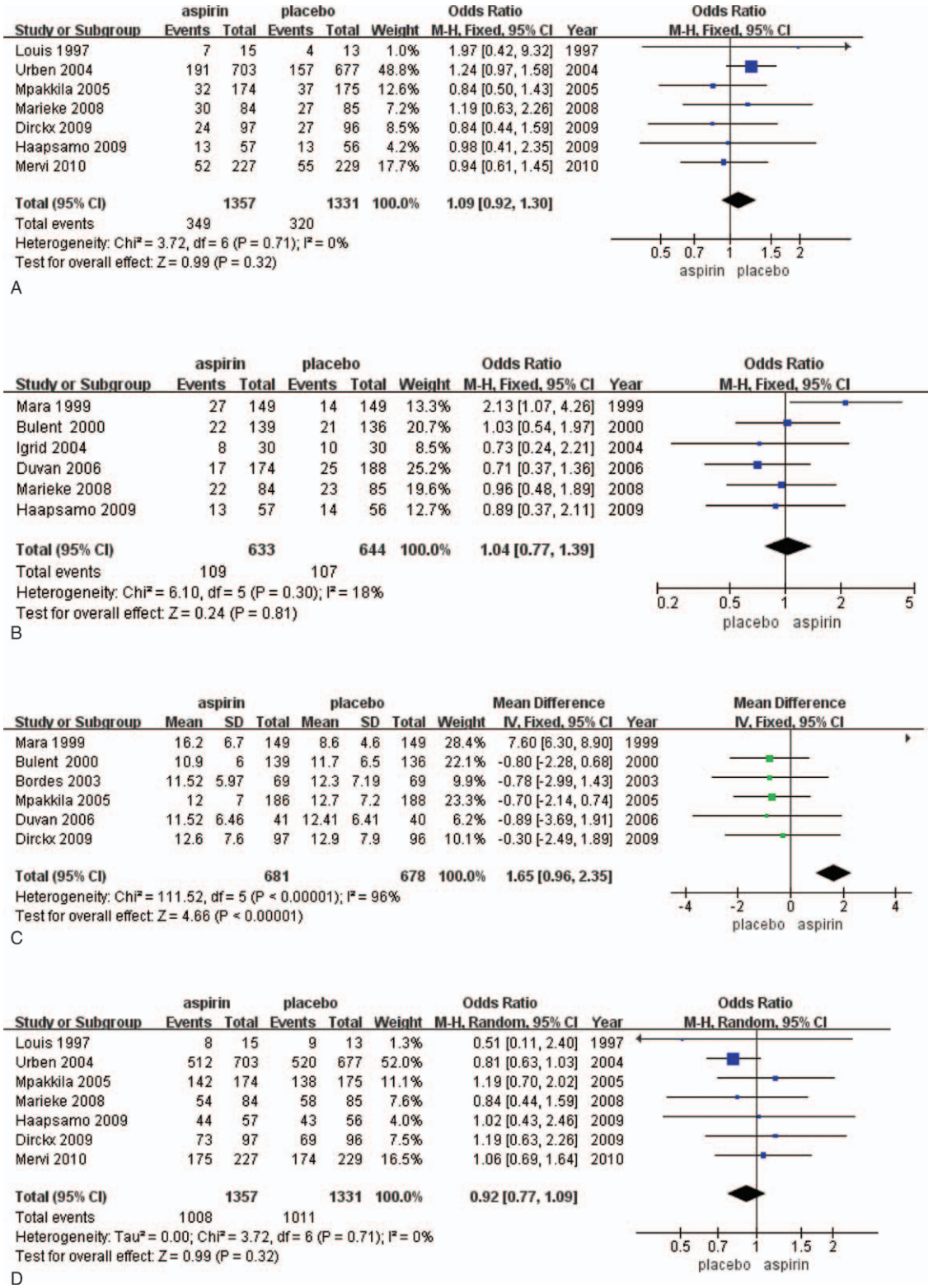

Figure 3. The Forest plots for (A) number of oocytes retrieved, (B) implantation rate, (C) live birth rate, (D) miscarriage rate.

tried various methods have been used to improve (IVF/ICSI) outcomes.[16] This research focus on aspirin effects on clinical pregnancy outcomes.

Rubinstei et al have shown that aspirin can effectively inhibit platelet aggregation. The mechanism is through selective acetylation of COX a serine hydroxyl, irreversible inhibition of the cyclooxygenase (COX) enzyme, reducing activity of thromboxane A2 (TXA2) and prostaglandin synthesis (PGs), inflammatory reaction,[4] thus inhibiting platelet activity, and preventing the formation of blood clots, as well as reducing

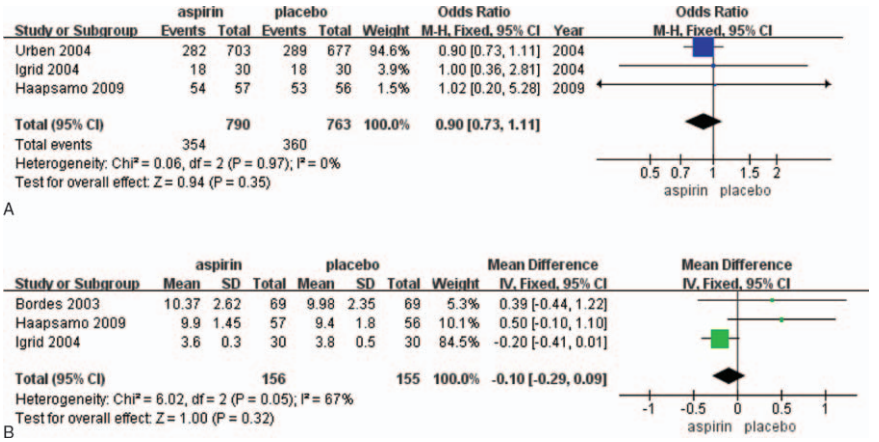

Figure 4. The Forest plots for (A) fertilization rate, (B) endometrial thickness.

resistance in the blood vessels and increasing tissue perfusion. This systemic and local environment affect the ovarian and endometrial, making it unfavorable to the embryo implantation.[17] As well as this, low-dose aspirin can treat fetal retardation[18] of severe pregnancy, high character,[19] recurrent abortion[20] and uterine ovarian perfusion.[21]

Ng et al[22] carried out clinical randomized controlled trials which found that in patients receiving low-dose aspirin therapy IVF cycle and ovary decreasing PI, increased blood flow velocity, human chorionic gonadotropin (hCG) levels, E2 levels, and the number of eggs compared with the control group. Hsieh et al[23] with 3-dimensional ultrasonic testing found that patients with endometrial blood flow in the super ovulation cycle is significantly lower than the natural cycle. Repeatedly failed IVF patients are often due to high endometrial artery blood flow resistance and low blood flow. Aspirin can improve human endometrial thickness, shape, reduce PI, resistance index (RI), increase the amount of blood flow perfusion and increase the rate of lining of 3 wire.[23]

In 1991, Testart and Gauthier[24] first use animal experiments to show that aspirin may increase clinical pregnancy rates by use increasing uterine artery blood flow. Therefore, based on animal experiments, we can assume that aspirin was a positive role in patients with low implantation and pregnancy rates. In our study pregnancy occurred in 531 of 1565 (33.9%) women randomized to low-dose aspirin and in 449 of 1539 (29.1%) women randomized to placebo. The pooled analysis using the random-effects model demonstrated that aspirin may improved the clinical pregnancy rate compared with placebo or no treatment groups (RR = 1.16; 95% CI = 1.04–1.28; $P = .25$). It showed that low-dose aspirin also can improve the clinical pregnancy rate of IVF patients, but we have not found the implantation rate to have obvious change.

Academics have found that small doses of aspirin is more effective, as it gives a better ratio of TXA2/PGI2, which results is a greater reduction vascular tone and improve tissue perfusion.[25] Literature shows that 100 mg/day can reach the best biological effect without affecting the blood coagulation time.[26] So the authors of this study choose this as the ideal dose for treatment.

Another study was suggested low doses of aspirin can significantly increase the thickness of the endometrium in patients with clinical pregnancy.[2] Therefore, further studies could be done exploring if increasing endometrial thickness (through increased blood supply promoting endometrial growth) improves endometrial receptivity and the clinical pregnancy rate.

For the first time in 2011, aspirin was studied in nonselective IVF/ICSI follicles cycle with different duration of endometrial thickness and clinical pregnancy outcome. Results showed that aspirin group compared with the control group had significant differences ($P < .05$), and the authors first suggested that it may be through the process of controlling super ovulation (COH). They suggested that aspirin effect time should be greater than 25.65 ± 2.06 days, to increase the transplant the endometrial thickness, and improve endometrial reception of embryos.[27]

On March 2016, Liu Juan et al included 50 female patients with infertility due to ovulatory dysfunction and divided them into the study group (aspirin 100 mg/d+ clomiphene) and control group (clomiphene treatment) with 25 patients in each. The results showed that low-dose aspirin therapy helps increase blood supply to the uterus, effectively promoting the development of endometrial thickness, and helping improve the clinical pregnancy rate.[28]

Before we start writing this manuscript, we have 19 articles included, now we have 13 RCT articles after eliminate 6 of them not RCT articles in our manuscript. After carefully reading our study, we had been modified the first line of Materials and Methods following with the PRISMA guidelines. In our manuscript all the pregnancy rate means clinical pregnancy rate, it is 4 weeks after transfer, the fetus heartbeat can be monitor by ultrasound. We have already modified all this parameter from pregnancy rate to clinical pregnancy rate. In our manuscript, implantation rates means the number of embryo implantation/the total number of embryos, clinical pregnancy rates means the pregnancy cycles/the number of transplantation cycle. After embryo implantation, it usually takes 14 days to check the heartbeat of the fetus. Aspirin may play a very important role in the maternal adjustment. There was no change in implantation rate, but significantly improve the clinical pregnancy rate. Further studies are required to focus on this aspect to verify that aspirin influence more to the maternal environment than the embryo quality.

In summary, low-dose aspirin is an effective treatment for IVF patients because it can improve the clinical pregnancy rate and number of oocytes retrieved. Further larger RCTs with adequate sample sizes and methodologically rigorous trials, including in various kinds of subgroups (e.g., according to age, endometrial

thickness and other outcomes, or in freezing thawing cycle) are required to determine whether there is a difference in effectiveness between low-dose aspirin and placebo.

References

[1] Edwards RG, Craft I. Development of assisted conception. Br Med Bull 1990;46:565–9.

[2] Weckstein LN, Jacobson A, Galen D, et al. Low-dose aspirin for oocyte donation recipients with a thin endometrium: prospective, randomized study. Fertil Steril 1997;68:927–30.

[3] Frattarelli JL, Miller BT, Scott RT, et al. Adjuvant therapy enhances endometrial receptivity in patients undergoing assisted reproduction. Reprod Biomed Online 2006;12:722–9.

[4] Rubinstein M, Marazzi A, de Fried EP. 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.

[5] Urman B, Mercan R, Alatas C, et al. 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.

[6] Bordes A, Damon BVA, Hadj S, et al. Does aspirin improve IVF results? Hum Reprod 2003;18:119–19.

[7] Van Dooren IM, Schoot BC, Dargel E, et al. Low-dose aspirin demonstrates no positive effect on clinical results in the first in vitro fertilization (IVF) cycle. Fertil Steril 2004;82:S18.

[8] Lok IH, Yip SK, Cheung LP, et al. 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.

[9] Waldenström 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.

[10] Päkkilä M, Räsänen J, Heinonen S, et al. 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.

[11] Duvan CI, Ozmen B, Satıroglu H, et al. 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.

[12] Dirckx K, Cabri P, Merien A, et al. Does low-dose aspirin improve pregnancy rate in IVF/ICSI? A randomized doubleblind placebo controlled trial. Hum Reprod 2009;24:856–60.

[13] 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.

[14] Lambers MJ, Hoozemans DA, Schats R, et al. 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.

[15] Haapsamo M, Martikainen H, Tinkanen H, et al. 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.

[16] Sher G, Fisch JD. Effect of vaginal sildenafil on the outcome of in vitro fertilization (IVF) after multiple IVF failures attributed to poor endometrial development. Fertil Steril 2002;78:1073–6.

[17] Antithrombotic Trialists' CollaborationCollaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324:71–86.

[18] Wallenburg HCS, Rotmans N. Prevention of recurrent idiopathic fetal growth retardation by low-dose aspirin and dipyridamole. Am J Obstet Gynecol 1987;157:1230–5.

[19] Jouppila P, Kirkinen P, Koivula A, et al. Failure of exogenous prostacyclin to change placental and fetal blood flow in preeclampsia. Am J Obstet Gynecol 1985;151:661–5.

[20] Vinatier D, Dufour P, Cosson M, et al. Antiphospholipid syndrome and recurrent miscarriages. Eur J Obstet Gynecol Reprod Biol 2001;96: 37–50.

[21] Bollwein H, Weber F, Steffen S, et al. The effect of acetylsalicylic acid and captopril on uterine and ovarian blood flow during the estrous cycle in mares. Theriogenology 2004;61:301–9.

[22] Ng EHY, Chan CCW, Tang OS, et al. Endometrial and subendometrial vascularity is higher in pregnant patients with live birth following ART than in those who suffer a miscarriage. Hum Reprod 2007;22: 1134–41.

[23] Hsieh YY, Tsai HD, Chang CC, et al. Gynecology: low-dose aspirin for infertile women with thin endometrium receiving intraeuterine insemination: a prospective, randomized study. J Assist Reprod Genet 2000; 17:174–7.

[24] Testart J, Gauthier A. The action of anti-inflammatory drugs on the fertility of female rats with intrauterine contraceptive devices. J Reprod Fertil 1981;63:257–61.

[25] Ozturk O, Greaves M, Templeton A. Aspirin dilemma remodelling the hypothesis from a fertility perspective. Hum Reprod 2002;17:1146–8.

[26] Clarke RJ, Mayo G, Price P, et al. Suppression of thromboxane A2 but not of systemic prostacyclin by controlled-release aspirin. N Engl J Med 1991;325:1137–41.

[27] Yu T. Effect of low-dose aspirin therapy in assisted reproductive technology in the application of different periods. Doctoral dissertation, China, 2011.

[28] Liu J, Wen C, Zhang W, et al. Effect of low-dose aspirin on endometrial development in ovulotropic period. Armed Poli Med 2016;27:237–9.