SOUTH BAYLO UNIVERSITY

Infertility & IVF with Adjunct Acupuncture: A Systematic Review & Meta-analysis

By

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RESEARCH PAPER

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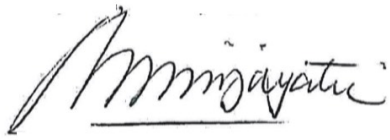

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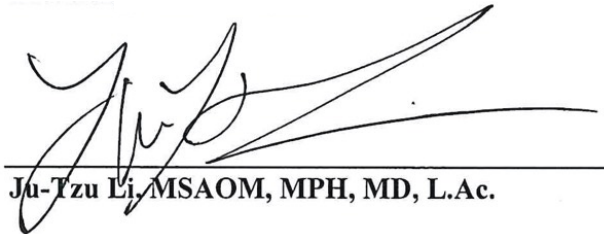

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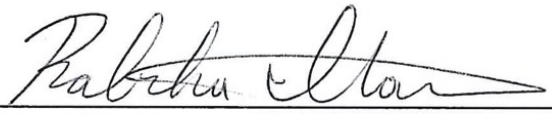

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Note

This systematic review follows the Cochrane guidelines for Systematic Reviews (SR) as specified in its Handbook (Higgins & Green, 2011), which is the gold standard for SR in the EBM community. The format of this research paper is APA 6, as per the 7/5/2019 agreement.

Evidence Based Medicine (EBM)

EBM has a relatively short history. In the 1970s, against the background of an uncertain economic climate and growing public expenditure on biomedical interventions, writers questioned the efficacy of biomedicine, arguing that modern medicine resulted in clinical, social and cultural iatrogenesis, and refuting any central role for biomedicine in the decline of infectious disease in the 20th century. Others went further and questioned whether many clinical interventions, despite being used for many years, were either effective or efficient, insisting that treatment should not be based on 'medical opinion' but on 'scientific fact'. This recommendation has been formalized into a hierarchy of evidence graded according to how 'compelling' or influential such evidence is. Thus Level 1 evidence, considered the most compelling, is that accruing from 'one or more systematic reviews of high quality RCTs', whilst Level 5 comprises expert opinions, case studies or reports and is said to be the least compelling. EBM has been defined as "the use of current best evidence". The rise of EBM has placed the production of evidence at the heart of clinical practice, restructuring how we now approach clinical problems.

Infertility and IVF with adjunct acupuncture: Systematic Review & Meta-analysis

Adelaide Isabella D'Ambrosio-Hicks

South Baylo University at Anaheim, 2020

Research Advisor: Dr. Qiwei Zheng

Abstract

Background

Acupuncture has been introduced as an adjuvant therapy to IVF cycles in many controlled trials. There has been a debate among trials regarding the effectiveness and safety of the procedure.

Objectives

To determine the effectiveness and safety of acupuncture as an adjunct to IVF cycles for primary and secondary female infertility. In addition, to reveal any differences among countries if present.

Methods

I conducted a literature search for relevant randomized controlled trials, with no restriction in date and language, and included eight studies. The main selected outcomes included clinical pregnancy, ongoing pregnancy, and live birth rate. Other outcomes such as the rate of miscarriage and side effects were analyzed as well. Due to high heterogeneity between Chinese trials and other countries' trials, I performed a subgroup analysis according to the country to investigate the results of different controlled trials.

Results

The analysis – which reviews 2172 patients, 1091 of which were allocated to the acupuncture group, while the other 1081 patients underwent sham acupuncture - revealed that in China, acupuncture leads to lower clinical (RR = 0.80, 95% CI [0.66, 0.97], p=0.02) and ongoing (RR=0.78, 95% CI [0.63, 0.97], p=0.03) pregnancy rates. While outside China, acupuncture increases clinical pregnancy rates (RR = 1.32, 95% CI [0.99, 1.77], p=0.01) and ongoing pregnancy rates (RR=1.41, 95% CI [0.89, 2.23], p=0.14). Rates of miscarriage did not differ between both arms (RR=1.04, 95% CI [0.72, 1.50], P=0.83). Regarding side effects, acupuncture leads to increased incidence of headache and puncture site itching (RR=3.0, P=0.03, and RR=1.5, P=0.007 respectively).

Conclusion

Although it is agreed that acupuncture is a very safe procedure with minimal or no side effects, published randomized control trials do not provide sufficient evidence to prove the efficacy of acupuncture throughout the world; subgroup results indicate good results outside China and less efficacy among Chinese trials. I believe this to be the consequence of the design and structure of these trials, especially those considering sham acupuncture an acceptable placebo.

Background

Infertility is the failure of a couple to become pregnant after 12 months of attempts with unprotected sex according to the World Health Organization (WHO). In 2010, a systematic analysis of health surveys worldwide revealed that 48.5 million couples suffer from infertility (Mascarenhas, Flaxman, Boerma, Vanderpoel, & Stevens, 2012). The global incidence of infertility ranges from 9% to 18% (Aghajanova, Hoffman, Mok-Lin, & Herndon, 2017), with secondary infertility being the more common than primary infertility (Nachtigall, 2006). As an etiology, several factors may induce infertility in females such as maternal age during gestation, psychological factors, and auto-immune disorders. However, diseases of the genital tract are generally the main causes (Vander Borght & Wyns, 2018). Polycystic ovarian syndrome, tuberculosis, endometriosis, and pelvic inflammatory disease (PID) are at the top of the list (Kowalcek, Wihstutz, Buhrow, & Diedrich, 2001). In 15%-20% of infertile females, the cause cannot be explained and no disease is found (Pandian, Gibreel, & Bhattacharya, 2015).

Increasingly, couples are turning to assisted reproductive technology (ART) for help with conceiving and ultimately giving birth to a healthy live baby of their own. One of the most commonly used options is in vitro fertilization (IVF). The process is comprised of different procedures: it starts with drugs to stimulate follicular production and ends with the harvest of mature eggs after about two weeks. It is thus called a ‘cycle ’(National Institute for Health and Care Excellence, 2013). The process is lengthy, stressful and - in the US - quite expensive, costing over $41,000 (Katz et al., 2011).

Because of the increased popularity of TCM in the western world, many couples have turned to this form of Complementary Alternative Medicine as adjuvant to their IVF attempts.

Due to the high cost of IVF in developed countries, demand for acupuncture treatment has grown steadily worldwide since the late 20th century. In the US, a 2006 survey by the National Institute of Health (NIH) found that 1.1% of the American population – about 2.13 million – reported using acupuncture with high perceived benefit, with infertility later found to be one of the most common reasons to seek acupuncture treatment (Cheong, Hung Yu Ng, & Ledger, 2008; Cochrane, Smith, Possamai-Inesedy, & Bensoussan, 2014).

In Chinese medicine, acupuncture represents a well-known therapeutic approach. It has been proved scientifically that acupuncture may increase blood flow to the female reproductive organs through the application of acupuncture in the lower limbs and lower parts of the abdomen. Therefore, increasing and enriching the lining of the uterus (Napadow et al., 2008; Stener-Victorin, Waldenström, Andersson, & Wikland, 1996).

Many countries have adopted the technique such as the United States (Wang et al., 2018), and used acupuncture in various medical conditions including treatment of infertility in women (Cheong, Dix, Hung Yu Ng, Ledger, & Farquhar, 2013). Anderson et al. proposed that acupuncture can be used as an adjuvant therapy to treat infertility through the following four mechanisms: 1) acupuncture may mediate the release of neurotransmitters, including ß-endorphin and serotonin, resulting in the release of gonadotropin-releasing hormone (GnRH) and thereby influencing pituitary gonadotropin secretion, ovarian follicular growth and finally ovulation. 2) acupuncture can induce ovulation through the mediation of the hypothalamic-pituitary ovarian axis; 3) acupuncture may inhibit uterine central sympathetic nerve activity and lower uterine arteries impedance, thus increasing blood flow to the uterus; 4) acupuncture may stimulate the production of endogenous opioids, thus reducing the stress response (Anderson, Haimovici, Ginsburg, Schust, & Wayne, 2007).

Acupuncture has gained quite a reputation in the recent century. Many trials have been performed to assess the role of acupuncture as an adjuvant therapeutic approach to IVF in increasing pregnancy outcomes and live birth rates.

Objectives

Infertility is still a prevalent issue, notwithstanding all the technological advances in the field of ART. IVF in particular, because of the high cost and the significant stress associated with each cycle, would benefit from any optimization, especially if it were low-cost and free of major side effects. Currently an IVF cycle has a large financial, social, and psychological impact on patients, and carries the risk of multiple pregnancies, miscarriages, and even ovarian cancer.

For this reason, the use of acupuncture in IVF has recently increased. However, there is a demand for evidence of proven effectiveness.

Within the new paradigm of EBM, the value of acupuncture intervention is measured on the basis of quantifiable and provable results, and the amount of evidence that can be relied upon to justify its use. This means that it is extremely important – for the wide acceptance of this intervention - to be able to point to enough evidence supporting claims of 'effectiveness'.

While several studies have reported positive synergistic effects of adding acupuncture treatments at different times in the IVF cycle, and especially at the time of embryo transfer, many other studies, and especially currently available systematic reviews, have concluded – to the contrary – that adding acupuncture treatment during the IVF cycle does not enhance the cycle success rate, or even has negative effects.

This systematic review aims to assess the efficacy of acupuncture as an adjunct to IVF cycles regarding clinical pregnancy, ongoing pregnancy, and live birth rate among patients with primary and secondary infertility and in addition, the rates of miscarriage and different side effects associated with the procedure. It will also analyze existing studies to individuate and understand the discrepancies in results and thus provide critical understanding of the factors that affect the results in current studies.

Methods

This systematic review and meta-analysis follows the PRISMA statement (Moher et al., 2009). All steps are performed in strict accordance with the Cochrane's handbook of systematic reviews of interventions (Higgins & Green, 2011).

Search criteria (PICO)

Randomized Control Trials (RCT) only.

Participants:

Women with primary or secondary infertility.

Intervention:

IVF + Acupuncture.

Comparison:

No intervention or sham acupuncture.

Outcomes

Primary: clinical pregnancy, i.e., evidence of a gestational sac with fetal heartbeat at 7-8 weeks, confirmed by ultrasound.

Secondary: a) ongoing pregnancy, i.e., evidence of a gestational sac with fetal heartbeat at over 12 weeks, confirmed with ultrasound; b) live birth; c) adverse events including miscarriage, ectopic pregnancy, fetal abnormalities, side effects, ovarian hyperstimulation syndrome (OHSS), and infection.

Eligibility criteria

Retrieved studies are marked as included if they meet the following inclusion criteria: 1) studies that are randomized controlled trials, 2) population: women with primary and secondary infertility, 3) intervention: acupuncture as an adjuvant to IVF, 4) comparator: placebo

acupuncture or sham acupuncture, and 5) primary outcome: clinical pregnancy, secondary outcomes: ongoing pregnancy, live birth, rate of miscarriage, and side effects. The following studies were excluded: 1) non-randomized controlled trials, 2) women receiving acupressure, laser acupuncture, or other types of acupuncture that do not include needle penetration of the skin, 3) other comparator arms than placebo or sham acupuncture and 4) studies with no accessible data, conference abstracts, and animal studies.

Literature search

The following databases were searched for published articles from inception to February 10, 2020: EBSCO, PubMed, EMBASE, COCHRANE, MEDLINE, the Menstrual Disorders and Subfertility Group (MDSG, Specialized Register), and Clinical Trial registers CENTRAL, clinicaltrial.gov, and the WHO International Clinical Trials Registry Platform (ICTRP). Also, opengrey.eu for gray literature, and Google Scholar for additional sources only, especially of gray literature, as its search algorithm is unknown and cannot be controlled. Its searches are adapted to the user and thus cannot probably be replicated. No language restrictions were applied.

I used a combination of Medical Subject Headings (MeSH) and text words to include: a) acupuncture studies: ‘acupuncture’, ‘moxibustion’, ‘TCM’, ‘traditional Chinese medicine’, electroacupuncture’, ‘electro-acupuncture’; and b) the intervention: ‘IVF’, ‘in vitro fertilization’, ‘in-vitro fertilization’, ‘assisted reproduction technologies’, ‘ART’, ‘embryo transfer’, ‘ET’. These terms were combined in Boolean searches to generate subsets of publications relevant to the topic. I developed the following search strategy for all databases: (acupuncture OR moxibustion OR "traditional Chinese medicine" OR electroacupuncture OR "electro-acupuncture") AND (IVF OR "in vitro fertilization" OR "assisted reproduction technologies" OR

"embryo transfer"). The resulting number of hits per database is shown in the Appendix Table A.1.

Data collection and analysis

Screening of results

Following the literature search of all included databases, eligible studies and relevant controlled trials were exported and screened in two steps. The first step was title and abstract screening to exclude other study designs and animal trials. The second step was full-text screening to ensure that the controlled trials met the inclusion criteria. After screening and reading the full text of the included papers, I performed an additional step through searching the references of the studies for possible missed trials. I conducted a quick re-search of the databases to ensure no missed study. The complete screening yielded a total of 8 studies. Note that these studies are from the US, Australia, China, and different countries in Europe. The search also produced a few titles from Korea which had to be excluded as they were all Randomized Comparative Trials rather than Controlled.

Figure 1 shows the PRISMA flow chart for the literature search. Appendix Table A.2 lists the 8 studies that made the cut.

Data extraction

After a thorough reading of included trials, I used Microsoft excel for the extraction of data. Extracted data included three main groups: 1) baseline characteristics of participants, 2) data for outcomes to be entered in the analysis, 3) data for assessment of the risk of bias among trials. Demographic data included patients' age, infertility duration, sample size, country, number of retrieved oocytes, percentage of patients with primary infertility, and body-mass index.

Outcomes for analysis included clinical pregnancy as the primary outcome, and other secondary outcomes as: ongoing pregnancy, live birth, rate of miscarriage, and side effects.

Quality assessment and Risk of bias analysis

The methodological quality of the trials passing the above selection and thus the quality assessment of this review was performed in agreement with the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE). The GRADE process elucidated in its manual is considered the standard in medical research evaluation and is recommended for use in Cochrane Systematic Reviews. Only randomized controlled trials were included to ensure high-quality evidence. I used the Cochrane's risk of bias tool (Green et al., 2011) for assessment of the risk of bias. This tool assesses the risk of bias through the following domains: 1) proper randomization of patients, 2) the blinding of allocation of patients into the intended treatment arms (Allocation concealment), 3) Blinding of patients only (termed single blinding), or blinding of both personnel and participants (double-blinding), 4) Attrition bias, 5) whether the outcomes mentioned in the protocol are all reported or not (Selection bias), 6) blinding of outcome assessors to prevent over- and/or under-estimation of outcome values, and 7) other bias.

Data synthesis

Establishing clinical pregnancy as primary outcome instead of live birth allowed for more data, as only few RCTs report live births. Most of the participants do not follow up regularly after pregnancy is achieved, so most of those data would be lost.

Continuous data were pooled as mean differences (MD) and relative confidence intervals, while dichotomous data were pooled as risk ratio (RR) and confidence intervals. I used Review Manager Software version 5.3, 2014 for data analysis ("RevMan 5 | Cochrane Community," n.d.). I used the inverse variance method for analysis of continuous outcomes and the Mantel–

Haenszel method for analysis of dichotomous outcomes. Two main tests indicate inconsistency among studies (Higgins, Thompson, Deeks, & Altman, 2003), the I-square test (I^2) and the P-value of the Chi-square test. Values of $I^2>50\%$ and $P<0.1$ are considered significant identifiers of heterogeneity according to the Cochrane Handbook (Higgins & Green, 2011). I performed the analysis of homogeneous data under a fixed-effects model, while heterogeneous data were analyzed under the random-effects model, as suggested and standard in Cochrane systematic reviews with meta-analysis. I performed a subgroup analysis according to the country in which each trial was conducted and included two main groups, China group, and outside China group.

I used Review Manager to perform other steps as well: the program offers the option to create a summary of the risk of bias among studies in a simple figure, in addition to a graph that summarizes low and high-risk studies in different domains. All figures were also created using RevMan 5.3

Results

Summary of included studies

This review presents the analysis of 2172 patients, 1091 of which are allocated to the acupuncture group, and 1081 to sham acupuncture. Table 1 shows a summary of baseline characteristics of participants, the mean age of patients in the acupuncture groups was 34.3 years, and 34.5 in the control groups. A total of 990 patients (489 in the intervention arm, and 501 in the control group) did not experience any IVF cycles before, and an average of 10.3 oocytes was retrieved from the patients. Table 2 illustrates previous IVF/ICSI cycles and different causes of infertility of patients. Brief summary of the included trials, in chronological order:

1. Paulus et al. (Paulus, Zhang, Strehler, El-Danasouri, & Sterzik, 2002) were the first to conduct a randomized controlled trial comparing acupuncture with placebo in women receiving IVF cycles. The study included 160 patients and found acupuncture to be effective in increasing pregnancy rates ($p<0.01$). acupuncture treatment was performed 30 minutes before and after embryo transfer (ET).The following points were chosen for needle insertions before embryo transfer: PC6 (*Neiguan*), SP8 (*Diji*), LV3 (*Taichong*), DU20 (*Baihui*), and ST29 (*Guilai*), plus Auricular points Shenmen and Uterus (*Zhigong*) on the Right ear, and Endocrine (*Neifenmi*), and Brain stem (*Naodian*) on the Left ear. All needles were left in place for 25 minutes. After embryo transfer, the following points were selected: ST36 (*Zusanli*), SP6 (*Sanyinjiao*), SP10 (*Xuehai*), LI4 (*Hegu*) plus Auricular points Shenmen and Uterus (*Zhigong*) now on the Left ear, and Endocrine (*Neifenmi*), and Brain stem/Subcortex (*Naodian*) now on the Right ear. Patients in the control group had no acupuncture, but remained lying still for the same amount of time before and after ET.

2. Dieterle et al. (Dieterle, Ying, Hatzmann, & Neuer, 2006) included 116 patients in the acupuncture group, and 109 in the control group, and found that acupuncture increases clinical pregnancy rates ($p<0.01$). The acupuncture treatment in the 'real' acupuncture group was performed on the day of ET, only 30 minutes after embryo transfer (ET), and used the following points: Ren4 (*Guanyuan)*, Ren6 (*Qihai),* ST29 *(Guilai),* PC6 (*Neiguan)*, SP10 (*Xuehai*, and SP8 (*Diji)*. Ear seeds (vaccaria hispanica, of family carophyllaceae) were placed on ear points: Shenmen, Uterus (*Zhigong*), Endocrine (*Neifenmi*), and Subcortex/Brain stem (*Pízhìxià*) and left for two days, with the instruction to rub and press them twice daily for 10 minutes. Three day after ET, the patients in this group received a second acupuncture treatment on points: LI4 (*Hegu*), SP6 (*Sanyinjiao*), ST36 (*Zusanli*), KI3 (*Taixi*), and LV3 (*Taichong*). Ear seeds were put on the same points, on the opposite ear and again pressed twice a day for 10 minutes, for the following two days. The control group received acupuncture on points: SJ9 (*Sidu*), SJ12 (*Xiaoluo*), GB31 (*Fengshi*), GB32 (*Zhongdu*), and GB34 (Yanglingqua). In addition, ears seeds on 4 random points. This treatment for the control group 2 was designed to have no effect on fertility and took place also after ET on the day, and 3 days later.

3. During the same year, Smith et al. (Smith, Coyle, & Norman, 2006) performed a similar trial in Australia, loosely based on the same points as Paulus et al. except LV4 (sic in the paper, we believe this to be LV3, as LV4 is NOT in Paulus) and DU20 which were excluded. The paper is not clear about the exact points used and when the different treatments occurred, one of which was several days before ET, seemingly with other points based on the pattern identification diagnosed by the principal acupuncturist investigator. Two acupuncturists administered 3 treatments, the first during the stimulating injection period, the second immediately before ET, and the third immediately after ET. The control group received placebo acupuncture on the same

days and points, with the Streitberger needle.

This study found no significant differences between both groups (p=0.08).

4. Westergaard et al. (Westergaard et al., 2006) conducted a trial in Denmark and found that acupuncture leads to more pregnancy rates (p=0.038), using the same acupuncture points as Paulus et al., though this trial includes three groups: group 1 used the same protocol as Paulus et al, but with no auricular acupuncture protocol, group 2 again the same protocol, but with an additional treatment two days after ET with points: DU20, Ren3, ST29, SP10, SP6, ST36, and LI 4. Group 3, the control, received no acupuncture treatment. In this study all treatments were performed by nurses, trained by an acupuncturist.

5. Later studies initiated by Domar et al. (Domar, Meshay, Kelliher, Alper, & Powers, 2009) and 6. Andersen et al. (Andersen et al., 2010) found no significant effect of acupuncture. They both used the same points as Paulus et al., with no ear acupuncture. Differences in Andersen: a) DU20 added to the treatment after ET, b) having a control group using placebo acupuncture on the same points, but with the Streitberber needle (where the blunted shaft retreats into the handle and there is no penetration), and c) nurses performing the acupuncture treatment, after a 'thorough training' period (in Andersen).

7. - 8. Two Chinese studies by So et al.(So et al., 2009; Wing Sze So, Ng, Yeuk Wong, Shu Biu Domar et alYeung, & Chung Ho, 2010), were initiated in China by Wing Sze So and colleagues. The 2009 trial again used the points from Paulus et al., but without ear acupuncture, after classifying the patients according to a pattern diagnosis – or a combination of - KI Yang/Yin Xu, LV Qi stagnation with Blood stasis, SP Qi Xu with Phlegm, with apparently no other implication as to points used; treatments were performed by a certified acupuncturist with two years of experience. The placebo acupuncture was performed by the same acupuncturist with

Streitberger's placebo needles on the same points the 2010 study had the intervention group receiving acupuncture on ET day, but only after ET, using the same points as Paulus, but without ear acupuncture. The control group again had placebo acupuncture with the Streitberger needle on the same pointss. These studies found that real acupuncture has no effect on increasing clinical pregnancy, while sham acupuncture did result in a significant improvement in pregnancy rates ($p=0.038$).

Table 3 summarizes the points used by all studies, organized in alphabetical order.

Results of risk of bias assessment

The risk of bias assessment revealed an overall low risk of bias. All included trials reported adequate randomization of patients and allocation concealment. Regarding the blinding of participants and personnel, two studies (Domar et al., 2009; Smith et al., 2006) were single-blind, therefore they were classified as high risk of bias. Three studies (Dieterle et al., 2006; Paulus et al., 2002; Westergaard et al., 2006) did not report enough evidence to ensure double-blinding, therefore were put to "unclear" risk. The remaining three studies (Andersen et al., 2010; So et al., 2009; Wing Sze So et al., 2010) were double-blind studies. All studies reported proper blinding of outcome assessment, except three studies (Dieterle et al., 2006; Paulus et al., 2002; Westergaard et al., 2006) which did not report enough evidence. All studies were at low risk of bias regarding other domains, and no other bias was found as well. Figure 2 shows a risk of bias graph and a summary of the risk of bias assessment among included studies.

Analysis of efficacy endpoints

Clinical Pregnancy

The overall risk ratio (RR) did not reveal any significant results between both groups (RR = 1.14, 95% CI [0.90, 1.45], p=0.28). Pooled results were highly inconsistent (I^2=73%, P=0.0005). Therefore, subgroup analysis according to the country was conducted.

In China, the results significantly favor the control group over the acupuncture arm (RR = 0.80, 95% CI [0.66, 0.97], p=0.02). Pooled data were homogeneous (I^2=0%, P=0.86).

The combined risk ratio of trials conducted outside china revealed that there is no significant difference between both groups (RR = 1.32, 95% CI [0.99, 1.77], p=0.06). There was marked inconsistency among studies (I^2=68%, P=0.008), figure 3a. According to Cochrane's leave-one-out method, inconsistency is best solved by excluding Andersen et al. Homogeneous results favor the acupuncture group significantly (RR = 1.46, 95% CI [1.12, 1.91], p=0.005), figure 3b.

Ongoing Pregnancy

The ongoing pregnancy outcome was reported by six studies (Andersen et al., 2010; Dieterle et al., 2006; Smith et al., 2006; So et al., 2009; Westergaard et al., 2006; Wing Sze So et al., 2010). The combined effect estimate showed no significant difference between both arms (RR = 1.12, 95% CI [0.82, 1.52], p=0.47). Results were markedly heterogeneous (I^2=76%, P<0.001). Subgroup analysis showed that in China, the control group is significantly associated with more ongoing pregnancies than the acupuncture group (RR=0.78, 95% CI [0.63, 0.97], p=0.03). Data were homogeneous (I^2=0%, P=0.94). While outside China, ongoing pregnancies were the same in both groups (RR=1.41, 95% CI [0.89, 2.23], p=0.14), pooled results were inconsistent (I^2=79%, P=0.003), figure 4a. Heterogeneity was best solved after excluding Andersen et al. Homogeneous results favored the acupuncture group (RR=1.73, 95% CI [1.29, 2.31], p<0.001), figure 4b.

Live birth

Three studies (Andersen et al., 2010; So et al., 2009; Wing Sze So et al., 2010) reported live birth outcome. The overall risk ratio showed that the control group is significantly associated with a more live birth rate than the acupuncture group (RR= 0.82, 95% CI [0.69, 0.97], P=0.02). The analysis shows no inconsistency among studies (I^2=0%, P=0.9), figure 5.

Miscarriage

Miscarriage was reported by four studies (Andersen et al., 2010; Smith et al., 2006; So et al., 2009; Wing Sze So et al., 2010). No statistically significant difference was found between the acupuncture and placebo groups (RR=1.04, 95% CI [0.72, 1.50], P=0.83). No heterogeneity was found (I^2=0%, P=0.6), figure 6.

Analysis of side effects

Two studies (So et al., 2009; Wing Sze So et al., 2010) reported intervention-related side effects. The results show that the acupuncture group is associated with a significantly increased incidence of headache and puncture site itching (RR=3.0, P=0.03, and RR=1.5, P=0.007 respectively). While there was no statistically significant difference between both groups regarding nausea (P=1.00), dizziness (P=0.15), fainting (P=0.07), tiredness (P=0.56), drowsiness (P=0.31), and chest pain (P=0.68). Figure 7 summarizes the side effects with relative risk ratios and confidence intervals.

Discussion

The results of this research suggest that outside China, acupuncture is an effective adjuvant approach that leads to increased rates of clinical and ongoing pregnancies, while contrary results are revealed for studies conducted within the great country, in which acupuncture actually leads to lower clinical and ongoing pregnancy rates. Other secondary outcomes, such as live birth, were significantly lower in the acupuncture groups as well. Regarding side effects, acupuncture increases the incidence of headache and puncture site itching, while there was no difference between both groups regarding the incidence of miscarriage, nausea, dizziness, fainting, tiredness, drowsiness, and chest pain.

The results of the subgroup analyses are consistent with other studies in the literature. A clinical trial (So et al., 2009) conducted in China found that the placebo acupuncture group is associated with more overall pregnancy rates that the real acupuncture group. Another trial conducted a year later, found that patients who received placebo acupuncture intervention had more ongoing pregnancy and implantation rates than those who discontinued the trial (Wing Sze So et al., 2010). The exact explanation of why acupuncture decreases pregnancy rates among Chinese patients while increasing them among other populations remains unclear. However, there is increasing evidence that supports the effect of placebo acupuncture. A study by Birch (Birch, 2006) has shown that placebo acupuncture may induce a clinical response and is not an inert control. Vincent and Lewith (Vincent & Lewith, 1995) found the same results. Lund et al. (Lund, Näslund, & Lundeberg, 2009) found that sham acupuncture is not an inactive control. A large controlled trial pain (Haake et al., 2007) studied the effect of acupuncture in reducing chronic back pain. The study included three arms: real acupuncture, a placebo acupuncture

group, and a control group receiving conventional care. The study found that both real and placebo acupuncture have the same efficacy superior to conventional care methods.

Contrary results were found in controlled trials performed outside China. Three controlled trials (Dieterle et al., 2006; Paulus et al., 2002; Westergaard et al., 2006) reported that acupuncture leads to increased clinical and ongoing pregnancy rates, while another three trials found no significant difference between both groups (Andersen et al., 2010; Domar et al., 2009; Smith et al., 2006). A previous meta-analysis found that acupuncture increases pregnancy rates in patients undergoing IVF (Ng, So, Gao, Wong, & Ho, 2008). Another meta-analysis (Manheimer et al., 2008) found more live birth and pregnancy rates in the real acupuncture group. Although the exact pathogenesis of how acupuncture increases pregnancy rates remain unknown, these studies relied on the evidence that acupuncture has been suggested to stimulate the release of several neurotransmitters (including serotonin and endorphins). These transmitters enhance the production of Gonadotropin-releasing hormones from the hypothalamus, which in turn increases the production of follicular-stimulating hormone (FSH) that leads to stimulating and improving female ovulation (Chang, Chung, & Rosenwaks, 2002; Ferin & Vande Wiele, 1984; Petraglia et al., 1987).

There are no reported serious adverse events for acupuncture. However, trials have shown that many patients may experience mild to moderate side effects of nausea and headache (So et al., 2009; Wing Sze So et al., 2010). Other trials have reported that acupuncture leads to positive side effects such as the feeling of relaxation, calm and peace (Smith et al., 2006). Acupuncture is therefore considered a safe therapeutic approach.

In the present systematic review and meta-analysis, only randomized controlled trials were included. This gives the review some strength. The risk of bias assessment revealed an overall low risk of bias which further supports the results of this study. However, several limitations need to be taken into consideration. The results of the analysis, though it is correct, may not represent the "true effect" of acupuncture. This may be primarily due to the low number of included studies in the China group (two studies). More controlled trials are needed with a larger sample size to provide solid evidence that solves this debate. Moreover, double blinding may play a critical role in affecting the results. This is supported by the fact that sham acupuncture has been effective in increasing pregnancy rates in double-blind studies only (So et al., 2009; Wing Sze So et al., 2010). Other trials included in this analysis are either single-blind (Domar et al., 2009; Smith et al., 2006) or did not report data about blinding (Dieterle et al., 2006; Paulus et al., 2002; Westergaard et al., 2006). Heterogeneity is the most important limitation; a pooled homogeneous analysis of all trials was not possible.

Conclusion

As a conclusion, acupuncture reduces clinical and ongoing pregnancy rates among Chinese patients, while increases them among patients outside china. The overall analysis of live birth outcome showed that placebo acupuncture increases live births more than real acupuncture. As for the side effects, no side effects were found to be associated with the procedure, except for headache and puncture site itching. It is important to notice the discussion currently going on about the use of sham acupuncture as placebo. Many articles have been published on this topic, and many comments regarding the likelihood that considering sham acupuncture an inert placebo invalidates many of the RCTs currently available. Another topic of discussion is the definition of double blinding in acupuncture trials, as something not really possible to achieve. It is my opinion – formed after a few years of practice experience – that OM (both acupuncture and herbal medicine) has a tremendous impact on the resolution of seemingly hard cases of infertility. And yet, this factual experience common to many acupuncturists, is not represented in published systematic reviews. This seems to indicate that the study design currently deemed ‘correct’, may not be the right one for studying this type of interventions.

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Appendix

Appendix Tables: Table A.1. shows results from each database, while Table A.2. lists the studies (8) that were found to satisfy all the eligibility requirements.

Table A.1

Hits per DB searched.

Database	Results
Pubmed	234
Cochrane	195
EMBASE	318
Menstrual Disorders and Subfertility Group. clinicaltrial.gov. WHO International Clinical Trials Registry Platform (ICTRP)). opengrey.eu Google Scholar CENTRAL	178

Table A.2.

List of included studies

#	Title	Reference	Country of study	Journal
1	Acupuncture on the day of embryo transfer: a randomized controlled trial of 635 patients	(Andersen et al., 2010)	Denmark	Reproductive Biomedicine Online
2	Effect of acupuncture on the outcome of in vitro fertilization and intracytoplasmic sperm injection: a randomized, prospective, controlled clinical study	(Dieterle, Ying, Hatznann, & Neuer, 2006)	Germany	Fertility and Sterility
3	The impact of acupuncture on in vitro fertilization outcome	(Domar, Meshay, Kelliher, Alper, & Powers, 2009)	USA	Fertility and Sterility
4	Influence of acupuncture on the pregnancy rate in patients who undergo assisted reproduction therapy	(Paulus, Zhang, Strehler, El-Danasouri, & Sterzik, 2002)	Germany	Fertility and Sterility
5	Influence of acupuncture stimulation on pregnancy rates for women undergoing embryo transfer	(Smith, Coyle, & Noeman, 2008)	Australia	Fertility and Sterility
6	A randomized double-blind comparison of real and placebo acupuncture in IVF treatment	(So et al., 2009)	China	Human Reproduction
7	Acupuncture for frozen-thawed embryo transfer cycles: a double-blind randomized controlled trial	(So et al.; 2010)	China	Reproductive Biomedicine Online
8	Acupuncture on the day of embryo transfer significantly improves the reproductive outcome in infertile women: a prospective, randomized trial	(Westergaard et al., 2006)	Denmark	Fertility and Sterility

Figures

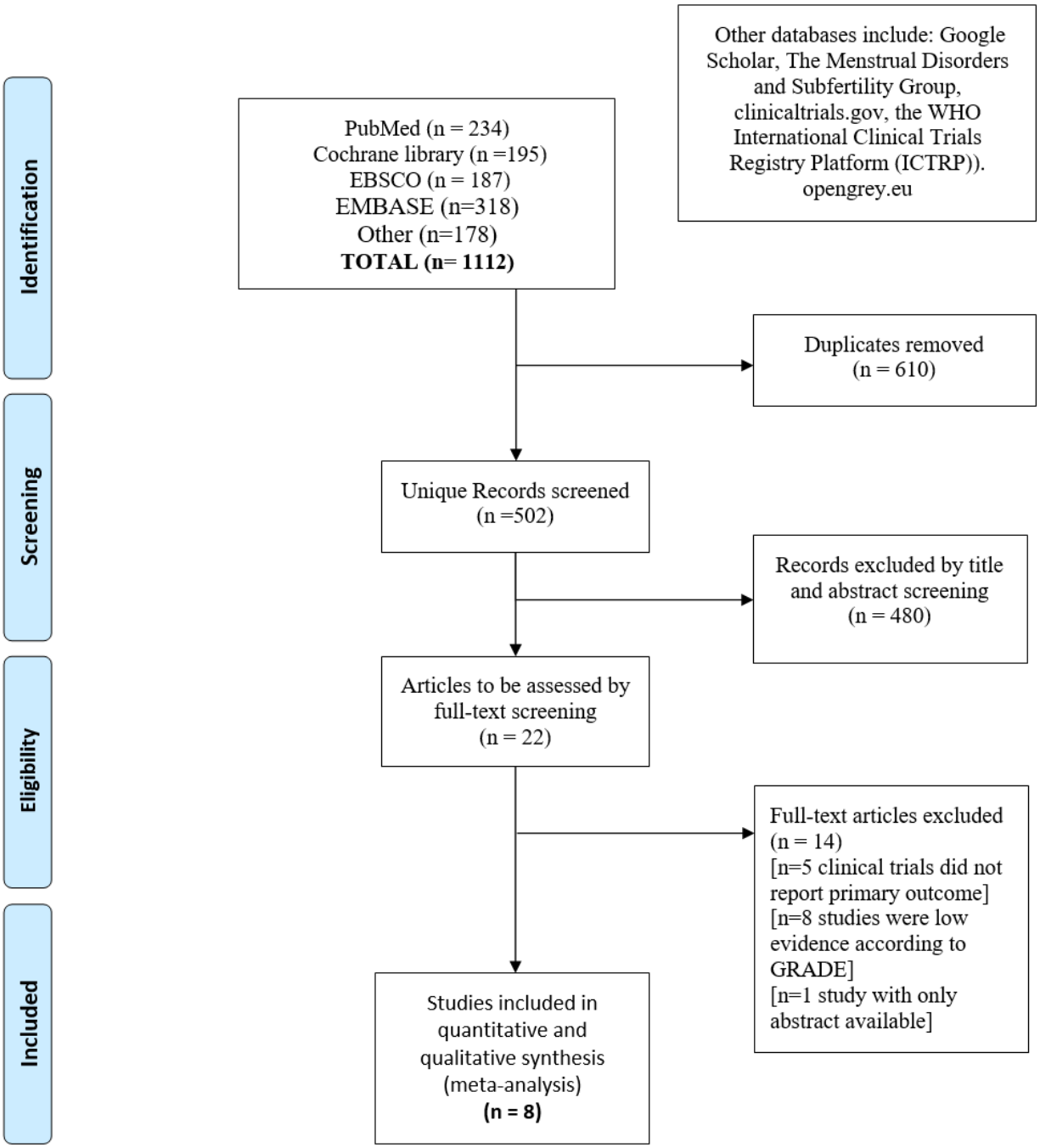

Figure 1. PRISMA-modified literature flowchart

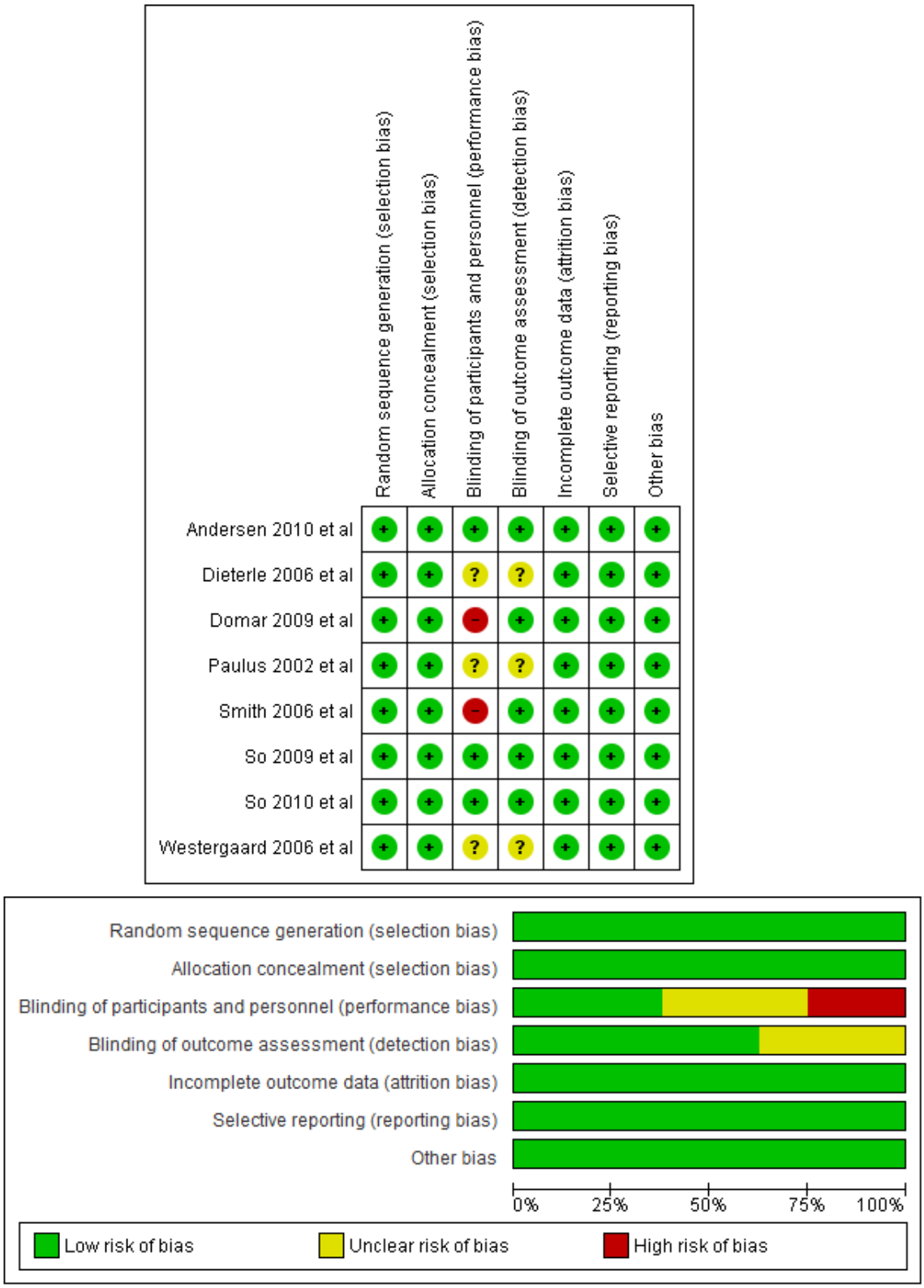

Figure 2. Detailed risk of bias assessment and risk of bias graph of included trials. Created with RevMan 5.3.

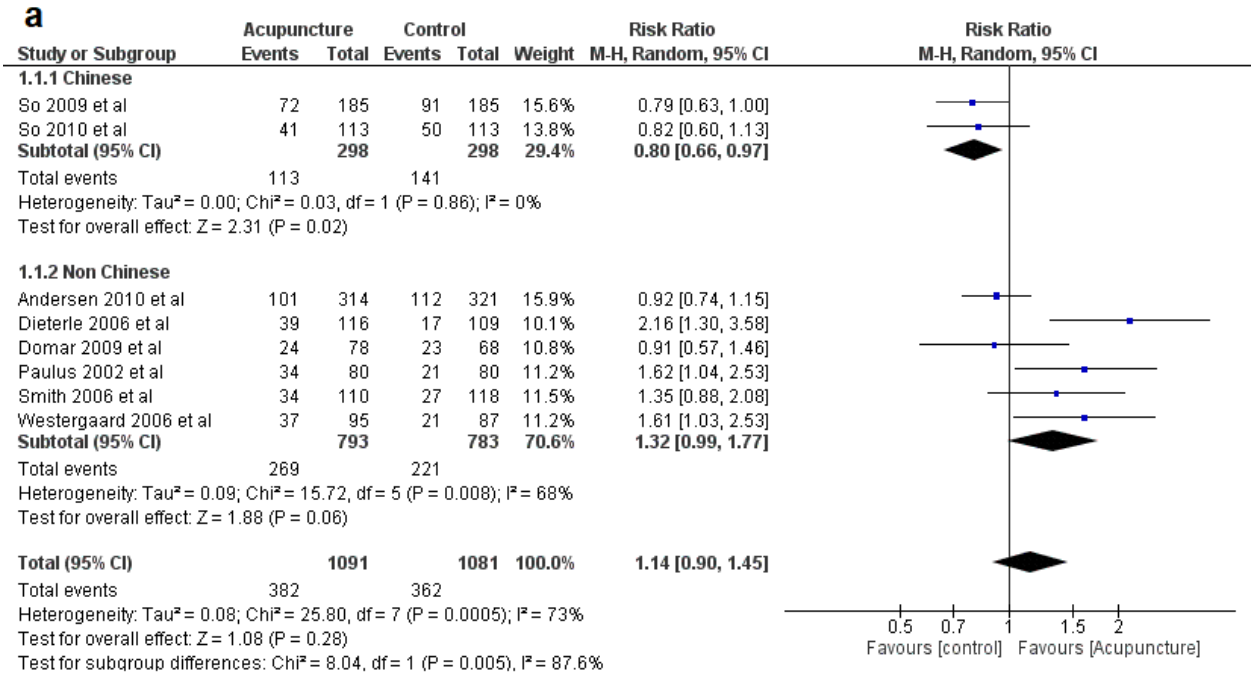

Figure 3. Forest plot for the analysis of the clinical pregnancy outcome, a) results before leave-one-out analysis, b) after leave-one-out. Created with RevMan 5.3

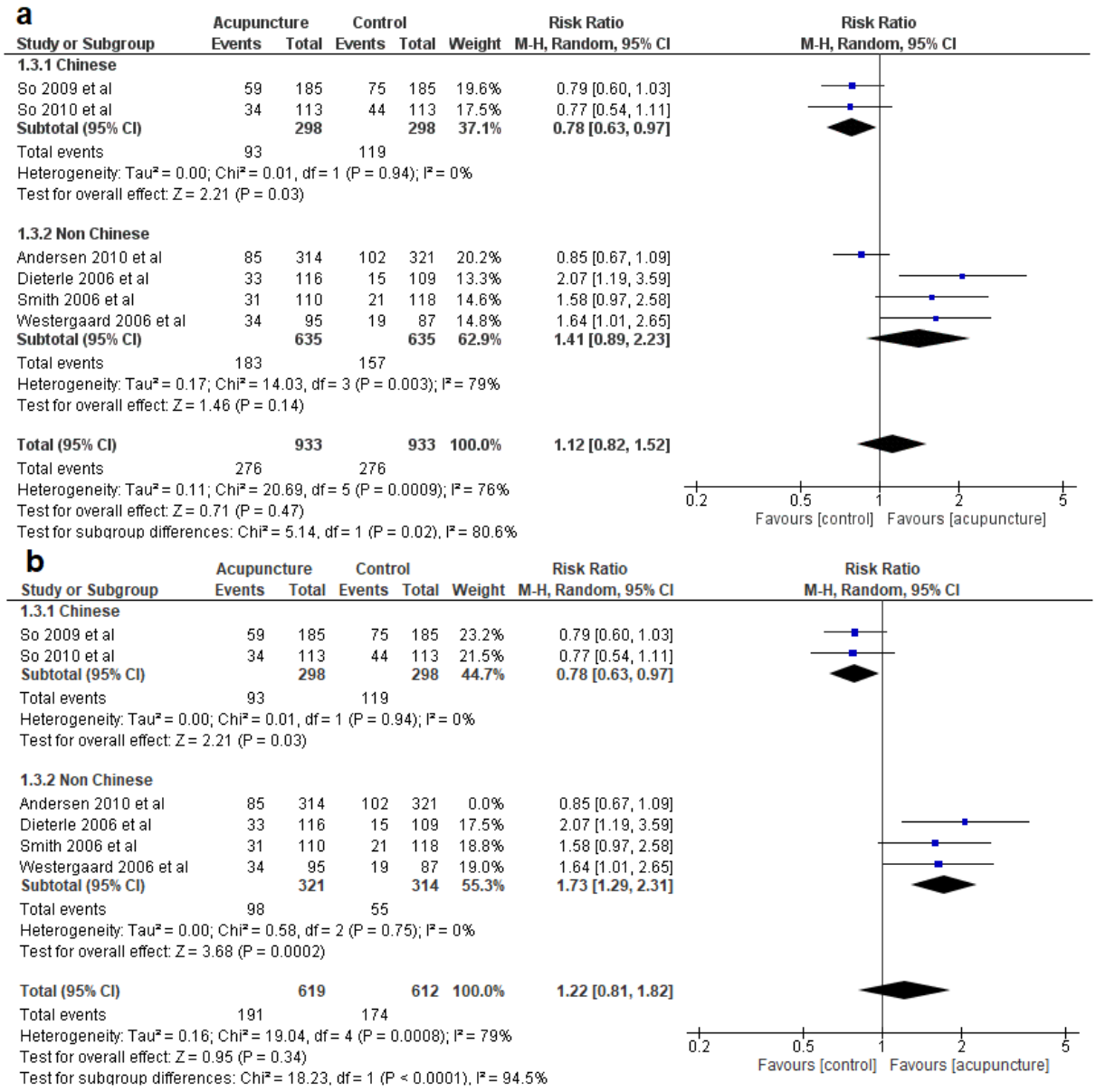

Figure 4. Forest plot for the analysis of ongoing pregnancy outcome, a) before leave-one-out, and b) after exclusion of Andersen et al. Created with RevMan 5.3

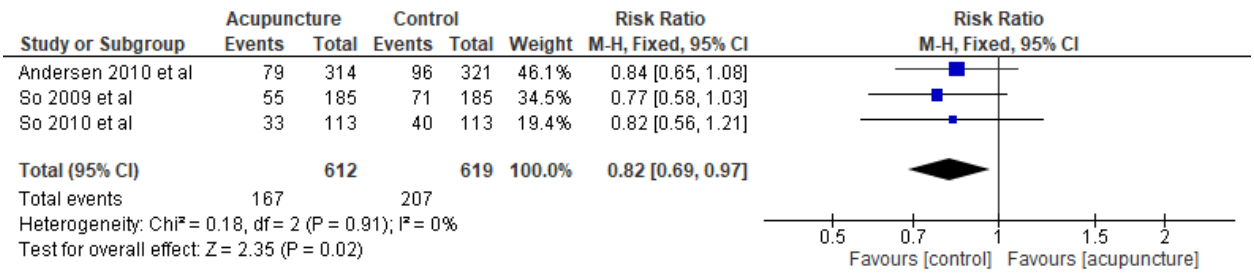

Figure 5. Forest plot for the analysis of the live birth outcome. Created with RevMan 5.3.

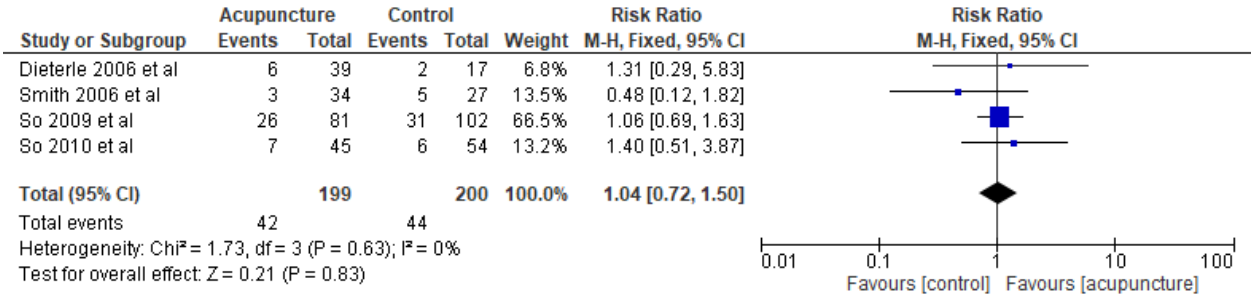

Figure 6. Forest plot for the analysis of the miscarriage outcome. Created with RevMan 5.3.

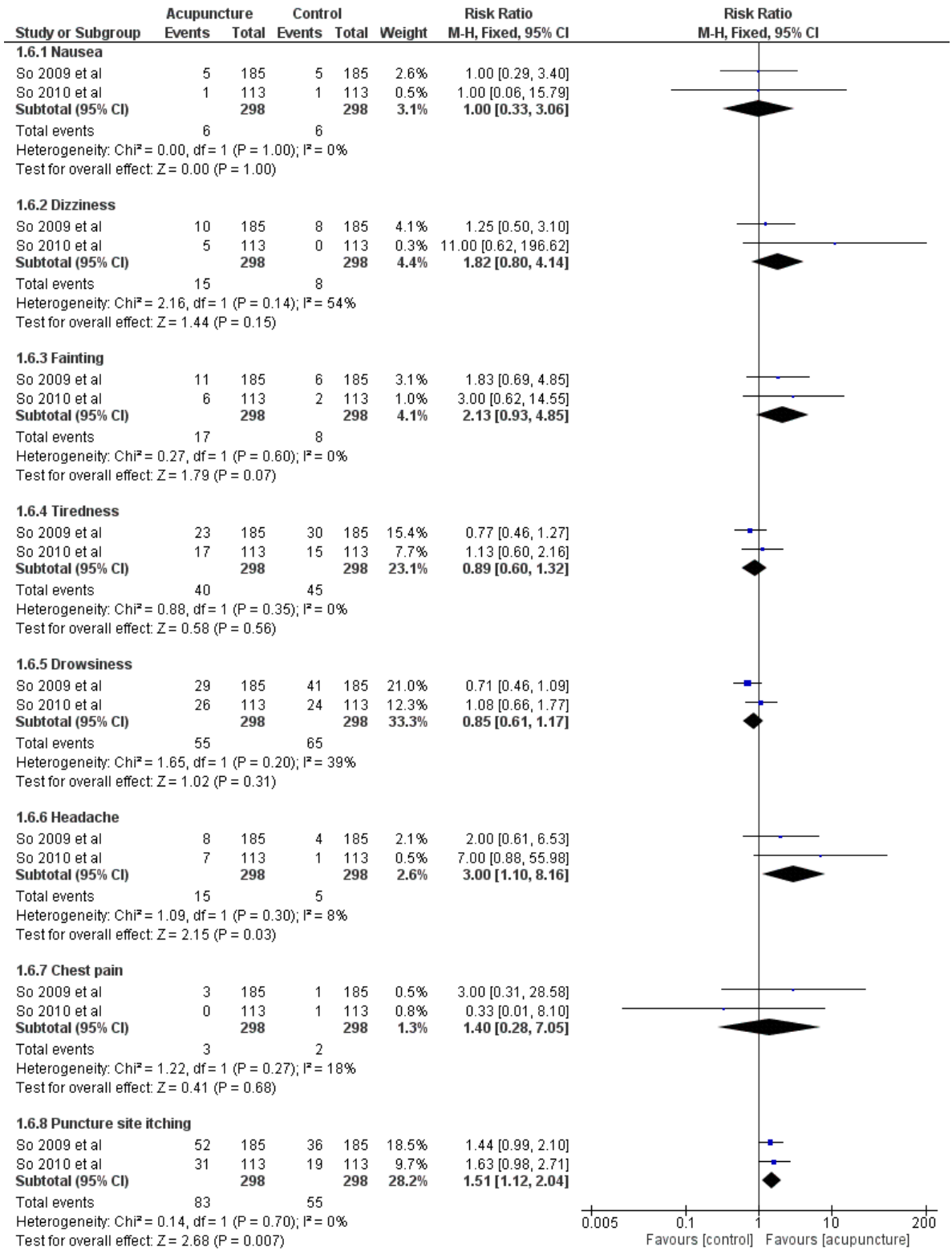

Figure 7. Forest plot of the analysis of intervention-related side effects including nausea, dizziness, fainting, tiredness, drowsiness, headache, chest pain, and puncture site itching. Created with RevMan 5.3.

Tables

Table 1

Summary of baseline characteristics of included participants.

Study	Year	Sample Size		Age, years		BMI		Infertility duration, years		Primary infertility		Follicles aspirated		Country
		ACP	Control	ACP	Control	ACP	Control	ACP	Control	ACP	Control	ACP	Control	
Anderson et al [1]	2010	314	321	31 (26-37)	31 (26-36)	22.5 (19-31)	22.5 (19-33)	2.5 (1.0-6.0)	2.5 (1.0-5.0)	215 (68)	233 (73)	10 (3-20)	10 (4-22)	Denmark
Dieterle et al	2006	116	109	35.1 ± 3.8	34.7 ± 4	24.5 ± 5.1	24.1 ± 4.7	5.4 ± 3.4	5.3 ± 3.1	93 (80.2)	86 (78.9)	11.2 ± 7.2	12.7 ± 9.4	Germany
Domar et al	2009	78	68	36.1 ± NR	36.1 ± NR	NR	NR	NR	NR	NR	NR	9.08 ± NR	10.94 ± NR	United States
Paulus et al	2002	80	80	32.8 ± 4.1	32.1 ± 3.9	NR	NR	NR	NR	NR	NR	NR	NR	Germany
Smith et al	2006	110	118	35.9 ± 4.7	36.1 ± 4.8	25.4 ± 4.2	26 ± 5.6	NR	NR	NR	NR	NR	NR	Australia
So et al	2009	185	185	35.7 ± 3.7	36 ± 3	21.6 ±2.1	21.7 ± 2.7	4 ± 3	4.5 ± 3.3	118 (64)	109 (59)	8.3 ± 5.2	7.7 ± 4.4	China
So et al	2010	113	113	35.3 ± 3.7	35.8 ± 1.1	21.6 ± 2.3	21.9 ± 2.6	5 ± 3	5 ± 3	42 (37.2)	44 (38.9)	12.9 ± 5.7	11.8 ± 5.8	China
Westergaard et al	2006	95	87	35.8 ± 5.25	36.5 ± 4.5	25.5 ± 6	24 ± 3.5	4 ± 2	4.5 ± 2	44 (46)	37 (43)	10.4 ± 0.3	10.6 ± 0.7	Denmark

Data are reported as mean ± SD and n (%) unless otherwise specified. NR: Not reported, BMI: Body-mass index, ACP: Acupuncture group.

[1] Data are reported as median (5^{th} centile – 95^{th} centile)

Table 2

Previous IVF/ICSI cycles and causes of infertility for included patients.

Study	Year	IVF History				Infertility diagnosis							
		First IVF/ICSI cycle		Repeated (≥1) Cycles		Male factor		Tubal factor		Endometriosis		Unexplained	
		ACP	Control	ACP	Control	ACP	Control	ACP	Control	ACP	Control	ACP	Control
Anderson et al	2010	174 (55)	192 (60)	140 (45)	129 (40)	125 (40)	131 (41)	54 (17)	45 (14)	19 (6)	18 (6)	53 (17)	55 (17)
Dieterle et al	2006	19 (16)	18 (17)	97 (84)	91 (83)	58 (50)	60 (55)	38 (33)	35 (32)	18 (16)	11 (10)	NR	NR
Domar et al	2009	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Paulus et al	2002	NR	NR	NR	NR	47 (59)	46 (58)	22 (28)	21 (26)	NR	NR	9 (11)	11 (14)
Smith et al	2006	55 (50)	54 (45)	55 (50)	64 (54)	45 (40)	60 (51)	51 (46)	38 (32)	26 (23.6)	28 (23.6)	29 (26)	22 (18)
So et al	2009	129 (70)	128 (69)	56 (30)	57 (31)	96 (52)	98 (53)	33 (18)	26 (14)	22 (12)	16 (9)	15 (8)	18 (10)
So et al	2010	75 (66.4)	73 (64.6)	38 (33.6)	40 (35.4)	53 (46.9)	58 (51.3)	19 (16.8)	22 (19.5)	13 (11.5)	12 (10.6)	11 (9.7)	9 (8)
Westergaard et al	2006	37 (39)	36 (31)	67 (71)	64 (74)	24 (25)	20 (23)	15 (16)	19 (22)	1 (1)	0 (0)	30 (32)	26 (30)

Data are n (%) unless otherwise specified. NR: Not reported, IVF: In vitro fertilization, ICSI: Intra-cytoplasmic sperm injection, ACP: Acupuncture group.

Table 3

Study points

Study	Year	Intervention group points		Control group points	Comments
		Before ET	After ET		
Anderson et al.	2010	Same as Paulus, without ear points	Same as Paulus, without ear points., + DU20	Placebo on same points with Streitberger needle	$p > 0.05$ all Tx's by nurses
Dieterle et al.	2006		Right after: Ren4, Ren6, ST29, PC6, SP8, SP10 Ear seeds: Shenmen, Uterus, Endocrine, Subcortex 3 days after: ST36, SP6, LI4, KI3, LV3 + same ear seeds	SJ9, SJ12, GB31, GB32, GB34 + 4 different ear seeds, all designed for no effect on fertility, both on ET day and 3 days later	$p < 0.01$
Domar et al.	2009	Same as Paulus, without ear points	Same as Paulus, without ear points	No acupuncture	$p > 0.05$ all Tx's by nurses
Paulus et al.	2002	PC6, SP8, LV3, DU20, ST29 Auricular: Shenmen, Uterus (R), Endocrine, Brain stem/Subcortex (L)	ST36, SP6, SP10, LI4 Auricular: Shenmen, Uterus (L), Endocrine, Brain stem/Subcortex (R)	No acupuncture	$p < 0.01$
Smith et al.	2006	First Tx with Pattern ID points several days before, then on ET day: PC6, SP8, LV3, ST29	ST36, SP6, SP10	Placebo on same points with Streitberger needle	$p > 0.05$
So et al.	2009	Same as Paulus, but no ear points	Same as Paulus but no ear points	Placebo on same points with Streitberger needle	$p < 0.05$ favoring control
So et al. (frozen embryo)	2010	None	Same as Paulus, but no ear points	Placebo on same points with Streitberger needle	$p < 0.05$ favoring conrol
Westergaard et al.	2006	Same as Paulus, without ear points	Same as Paulus, without ear points	No acupuncture	$p = 0.038$ by nurses