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Review Article

Acupuncture and herbal medicine for female infertility: an overview of systematic reviews

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ABSTRACT

Background: Acupuncture and herbal medicine have been used as additional treatments for infertility or as an adjuvant treatment of assisted reproductive technology (ART) in infertility. Many systematic reviews (SRs) and meta-analyses (MA) have been published. This paper reviews the SRs and MA of acupuncture and herbal medicine on infertility to provide evidence for clinical decision making.

Methods: A comprehensive literature search of SRs and MA for the effects of acupuncture and herbal medicine on infertility was conducted using nine databases. Two independent reviewers extracted the data of the selected SR and MA and evaluated their methodological quality using the 'Assessment of multiple systematic reviews 2 (AMSTAR2)'.

Results: Twenty-one studies were included in this analysis. Eight studies were published in China, and three studies each were published in the USA, UK, and Australia. Conflicting evidence on the efficacy of acupuncture for infertile women has been reported. Herbal medicine for infertile women undergoing ART, women with anovulation, and women with polycystic ovary syndrome helped improve the clinical pregnancy rate. The methodological quality of SRs and MAs evaluated by AMSTAR 2 was low or very low because the protocol or list of excluded studies were omitted.

Conclusion: Herbal medicine tended to be effective in infertility, but acupuncture had low evidence of an effect on infertility. The methodological quality of the published SRs and MAs was underestimated because AMSTAR2 is a more rigorous assessment tool than the previous version.

1. Introduction

The WHO (World Health Organization) defines infertility as a disease of the reproductive system that manifests as a failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.[1] The worldwide age-standardized prevalence of infertility has increased by 0.291% ~ 0.370% per year. The age-standardized disability-adjusted life-years (DALYs) of infertility have also increased by 0.293% to 0.396% per year. In addition, women in countries with a higher socio-demographic index had the highest prevalence and DALYs growth rate.[2]

Conventional treatments for female infertility involve assisted reproductive techniques, including in vitro fertilization and artificial insemination, and drug treatments, including clomiphene and gonadotropin-releasing hormone analogs.[3] Assisted reproductive technology (ART) helps women who are unable to conceive for reasons, such as polycystic ovary syndrome (PCOS), endometriosis, and male infertility, to become pregnant. On the other hand, the live birth rate decreases as the maternal age increases or the blast cycle increases.[4] In addition, ART has the following adverse effects. Ante-partum hemorrhage, congenital anomalies, hypertensive disorders of pregnancy, preterm rupture of the membranes, Caesarean section, low birth weight, perinatal mortality, preterm delivery, and gestational diabetes.[5] More infertility couples are using complementary therapies due to problems, such as low live birth rates, adverse effects, stress, and cost.[6]

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Complementary therapies, such as acupuncture and herbal medicine, are treatment methods used in conjunction with or instead of mainstream health systems or conventional drugs. These therapies are classified into three main groups: natural products, mental and physical practice, and other complementary health approaches.[7]

Korea,[7] New Zealand,[8] Australia,[9] and the UK[10] reported the use of complementary therapies for infertile women. A study in Australia reported that women used complementary therapies to improve welfare or overcome the adverse effects of ART and because they will try anything to achieve pregnancy.[9] Similar results have been reported in studies conducted in Korea. Approximately 63.5% of infertile women reported using complementary therapies, and more women who experienced adverse effects of ART reported using complementary therapies.[7] On the other hand, both physicians and medical users have questioned the evidence of complementary therapies. They argued that there is a need for evidence of the effectiveness of complementary therapies on infertility.[10] In addition, studies on the effects of complementary therapies on infertility reported a range of results. An analysis of the effects of acupuncture, a complementary therapy, on more than 800 infertile women in Australia and New Zealand reported no significant clinical difference between acupuncture and sham acupuncture.[11] In contrast, a systematic review, which analyzed the effects of herbal medicine, another type of complementary therapy, reported a significant clinical result of herbal medicine on infertility.[12]

Therefore, we aimed to provide an overview of systematic reviews (SRs) of evidences of acupuncture and herbal medicine for female infertility.

2. Methods

2.1. Protocol and registration

This protocol of this review was registered on the Research Registry (Review Registry Unique Identifying Number: reviewregistry769, https://www.researchregistry.com/browse-the-registry#registryofsystematicreviewsmeta-analyses/registryofsystematicreviewsmeta-analysesdetails/5dd38fd3bc99bd0015e1fa3b/) and was published.[13]

2.2. Research question

The research question was to determine the current status, effectiveness, and methodological quality of SRs and MAs publications on acupuncture and herbal medicine for infertile women. The PICO can be described as follows: (1) type of participant, women diagnosed with infertility regardless of the cause; (2) types of interventions, acupuncture treatment inserted into the skin, and all kinds of herbal medicine, including single herb or herbal formulas; (3) type of main outcomes, clinical pregnancy rate (CPR), ongoing pregnancy rate (OPR) and live birth rate (LBR); (4) type of secondary outcomes, anxiety level, pain level, and adverse events; (4) study design, SR with or without meta-analysis on a randomized clinical trial (RCT).

The following provides a detailed definition of outcome indicators. CPR is defined as the presence of at least one gestational sac with or without a fetal pole and fetal heartbeat confirmed by ultrasound. OPR is defined as a pregnancy of more than 10–12 weeks of gestation and fetal heart activity confirmed by ultrasound. LBR is defined as the delivery of a live baby after 24 weeks of gestation.

2.3. Search strategy

This study searched the following databases with language restrictions for English and Korean: PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Google scholar Koreamed (www.koreamed.org), KMBASE (kmbase.medric.or.kr), NDSL (www.ndsl.kr), KCI (www.kci.go.kr), RISS (www.riss.kr), and OASIS (oasis.kiom.re.kr) from their inception until June 2019. The search strategies were adapted to each database using variations of the words “infertility”, “female”, and “acupuncture and herbal medicine”, using wildcard symbols and Boolean operators to combine the terms. The search results are presented in Appendix 1.

2.4. Data selection and extraction

After completing the search, two reviewers checked the titles and abstracts of the included articles independently to select potential eligible articles. The full texts of the chosen articles were screened according to the inclusion and exclusion criteria; any disagreements were checked and adjudicated by a third reviewer. Data extraction was performed independently by two reviewers, and the following information was collected: author name, year of publication, RCT included in each study, participants’ characteristics, interventions, comparator, and outcome measurements, included primary and secondary outcomes.

2.5. Methodological quality assessment

The quality assessment was conducted by two reviewers independently based on the ‘assessment of multiple systematic reviews 2′ (AMSTAR2), which is a 16-item validated measurement tool for assessing the methodological quality of systematic reviews.[14] The AMSTAR2 items were evaluated as ‘Yes’, ‘Partial Yes’, and ‘No’. The overall confidence of the review results was rated as high, moderate, low, and critically low based on the number of critical or noncritical flaws.[14,15]

3. Result

3.1. Search result

Fig. 1 shows the process of selecting studies for inclusion in the overview of SRs. Among the 1181 studies, 622 were duplicates and 584 were excluded. Seventeen studies were excluded for various reasons, such as not meeting the study design criteria; the reasons for exclusion are listed in Appendix 2. Finally, twenty-one studies were identified.[11,12,16-34]. Fig. 1 presents a flowchart of PRISMA for the literature studies on SRs.

3.2. Characteristics of included studies

Table 1 lists the main characteristics of the studies. Twenty SRs performed meta-analysis (MA),[11,12,16-29,31-34] and one SR did not conduct MA.[30] The SRs included were published between 2008 and 2019. Eight studies were conducted by researchers in China,[11,21-24,27,28,32] three studies in the USA,[18,19,26] three studies in the UK,[16,17,25] three studies in Australia,[12,20,34] two studies in the Republic of Korea,[29,31] one study in Iran,[30] and one study in Chile.[33] Twenty SRs were published in English,[11,12,16-28,30-34] and one in Korean.[29] Fourteen SRs analyzed the effects of acupuncture on infertile women undergoing in vitro fertilization (IVF).[11,16-19,21,23,25-27,30,32-34] Two SRs analyzed the effects of herbal medicine on infertility.[12,20] One SR analyzed the effects of acupuncture on infertile women with PCOS undergoing IVF.[31] One SR analyzed the effects of herbal medicine on infertile women undergoing IVF.[24] Two SRs analyzed the effects of herbal medicine on infertile women with PCOS.[28,29] One SR analyzed the effects of herbal medicine on infertile women with anovulation.[22] Appendix 3 provides a comparison list of the RCTs in SRs and MAs included in this study (Table 2).

Table 1
Characteristics of the systematic reviews of acupuncture and herbal medicine for infertile women (Please add the references).

Author (year) Ref	Country	Number of RCT(Total population)	Infertile women	Intervention	Comparator	Outcome measure			
						CPR	OPR	LBR	Others
Acupuncture for infertility women undergoing IVF									
Cheong (2008)[16]	UK	13 (*N*=2959)	undergoing ART	AT	No treatment Placebo Sham AT	√	√	√	
El-Toukhy (2008)[17]	UK	13 (*N*=2522)	undergoing IVF	AT	No treatment Placebo Sham AT	√		√	
Manheimer (2008)[18]	USA	7 (*N*=1521)	no regstriction???	AT	No treatment Sham AT	√	√	√	
Drake (2011)[19]	USA	4 (*N*=1312)	Reproductive-age undergoing IVF	AT	No treatment Placebo Sham AT		√	√	
Qu (2012)[21]	China	17 (*N*=3744)	undergoing IVF	AT	No treatment Placebo Sham AT	√	√	√	miscarriage, BPR, IR
Zheng (2012)[23]	China	24 (*N*=5737)	undergoing IVF	AT	No treatment Placebo Sham AT	√	√	√	BPR, IR, miscarriage, adverse effect
Cheong (2013)[25]	UK	20 (*N*=5342)	undergoing ART	AT	No treatment Placebo Sham AT			√	
Manheimer (2013)[26]	USA	16 (*N*=4038)	no regstriction???	AT	No treatment Sham AT	√	√	√	
Shen (2015)[27]	China	21 (*N*=5526)	undergoing IVF	AT	No treatment Placebo Sham AT	√			
Hassanzadeh (2017)[30]	Iran	4 (*N*=595)	no regstriction	AT	Placebo Sham AT				STAI, 20-item STAI, HAS, Chinese version of STAI
Qian (2017)[32]	China	30 (*N*=6599)	undergoing IVF	AT	No treatment Placebo Sham AT	√	√	√	BPR
Schwarze (2018)[33]	Chile	6 (*N*=1653)	undergoing IVF	AT	No treatment Sham AT	√	√	√	
Zhang (2018)[11]	China	17 (*N*=6265)	Infertile women	AT	No treatment Sham AT	√	√	√	BPR, IR, miscarriage
Smith (2019)[34]	Australia	20 (*N*=5610)	Infertile women undergoing IVF	AT	No treatment Sham AT	√			
Acupuncture for infertile women with PCOS									
Jo (2017)[31]	Korea	4 (*N*=430)	PCOS undergoing IVF	AT	No treatment Placebo	√		√	
Herbal medicine for infertility women									
Ried (2011)[20]	Australia	7 (*N*=588)	Reproductive-age	HM only HM+AT HM +WM	WM	√			
Ried (2015)[12]	Australia	40 (*N*=4255)	Reproductive-age	HM	WM	√			
Herbal medicine for infertile women undergoing IVF									
Cao (2013)[24]	China	20 (*N*=1724)	undergoing IVF	HM +IVF	IVF	√	√	√	
Herbal medicine for infertile women with PCOS									
Zhou (2016)[28]	China	5 (*N*=414)	PCOS	HM	No treatment Placebo WM Laparoscopic surgery	√			ovulation rate, adverse effect
Bae (2017)[29]	Korea	8 (*N*=525)	PCOS	Herbal medicine	No treatment	√		√	

(*continued on next page*)

Table 1 (*continued*)

Author (year) Ref	Country	Number of RCT(Total population)	Infertile women	Intervention	Comparator	Outcome measure			
						CPR	OPR	LBR	Others
Herbal medicine for infertile women with anovulation									
Tan (2012)[22]	China	15 (*N*=1659)	Anovulation	HM	No treatment Placebo WM Laparoscopic surgery	✓		✓	ovulation rate

ART, assisted reproductive technology; AT: acupuncture; BPR, biological pregnancy rate; CPR, clinical pregnancy rate; HM: herbal medicine; IR, implantation rate; IVF, in vitro fertilization; LBR, live birth rate; OPR, ongoing pregnancy rate; PCOS, polycystic ovary syndrome; WM, western medicine pharmacological treatment.

3.3. Acupuncture for infertility

Thirteen SRs reported pooled the results of acupuncture versus sham acupuncture, placebo, and no adjuvant treatment to infertile women undergoing IVF.[11,16-19,21,23,25-27,32-34] In most studies, CPR, OPR, LBR, and miscarriage were reported as the result outcomes, but the effects of acupuncture on infertility were arguable. Six SRs reported no significant difference between the acupuncture and control groups.[17,19,21,25,26,33] One review even reported that the controls showed a significantly higher CPR than the acupuncture group (RR 0.87, 95% CI 0.77–0.98).[33] In 2008, an SR conducted by Manheimer et al. compared acupuncture versus sham acupuncture, or no adjuvant treatment and reported that acupuncture had significant effects on the CPR (RR 1.65, 95% CI 1.27–2.14), OPR (RR 1.87, 95% CI 1.40–2.49), and LBR (RR 1.91, 95% CI 1.39–2.64).[18] On the other hand, Manheimer et al. conducted an SR comparing acupuncture with sham acupuncture or no adjuvant treatment in 2013. They reported no significant differences among the CPR (RR 1.12, 95% CI 0.96–1.31), OPR (RR 1.22, 95% CI 0.98–1.52), and LBR (RR 1.14, CI 0.92–1.42).[26] Cheong et al. reported a similar result in an SR. In 2008, an SR conducted by Cheong et al. reported that acupuncture on the day of ET (embryo transfer) was more effective on the LBR than no adjuvant treatment (OR 1.86, 95% CI 1.27–2.73).[16] In contrast, an SR conducted by Cheong et al. in 2013 reported that acupuncture on the day of ET had no added effects on the LBR compared to no adjuvant treatment (OR 1.22, 95% CI 0.87–1.70).[25] The other five studies concluded that acupuncture was an effective treatment or partially helped improve the CPR, OPR, or LBR for women with infertility.[11,23,27,32,34] In addition, acupuncture during IVF could improve IVF outcomes. On the other hand, most studies concluded that current research evidence was insufficient to draw a definitive conclusion.

One SR reported that acupuncture was effective in controlling the anxiety of infertile women.[30] This SR summarized the results of the four RCTs, with three RCTs reporting that acupuncture reduced anxiety.[35-37] One RCT reported that the mean Hamilton Anxiety Scale (HAS) was significantly lower in the acupuncture group,[37] and two RCTs reported that the anxiety level was significantly lower in the acupuncture group.[35,36]

3.3.1. Acupuncture for infertile women with PCOS

One SR reported the effects of acupuncture on infertile women with PCOS consisting of four RCTs.[31] The efficacy of the acupuncture and placebo treatment or no adjuvant treatment was compared. Meta-analysis showed that acupuncture had significant effects on the CPR (RR 1.33, 95% CI 1.03–1.71) and OPR (RR 2.03, 95% CI 1.08–3.81).

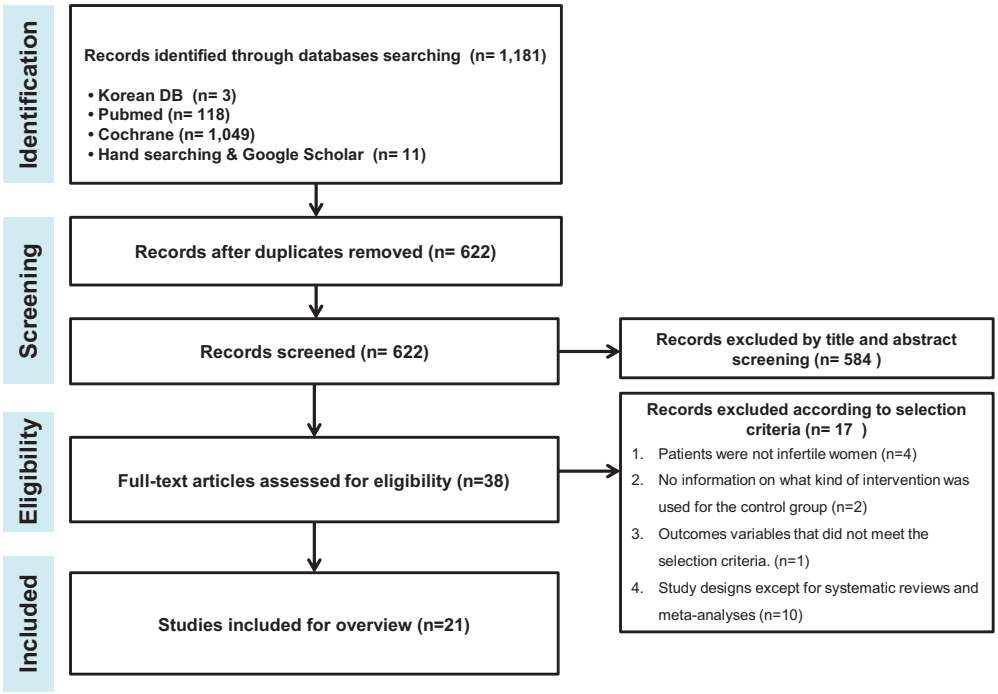

Fig. 1. Flow-chart of literature search and study selection.

Table 2
The results of meta-analysis of the included systematic reviews for each outcome related with infertility.

Author (year) ref	Intervention	Comparisons	Statistical Model	Pooled effect [95% CI] (I^2)
Acupuncture for infertility women undergoing IVF				
Clinical Pregnancy Rate				
Cheong (2008)[16]	Acupuncture on the day of ET (*n*=566)	No acupuncture (*n*=550)	RE	1.26 [0.85–1.88] (59%)
Cheong (2008)[16]	Repeated acupuncture (*n*=207)	No acupuncture (*n*=196)	FE	2.23 [1.41–3.51] (0%)
Cheong (2008)[16]	Acupuncture around the time of OR (*n*=448)	No acupuncture (*n*=420)	RE	1.14 [0.76–1.72] (48%)
El-Toukhy (2008)[17]	Acupuncture around the time of TVOR (*n*=455)	Control (*n*=422)	RE	1.06 [0.82–1.37] (44.5%)
El-Toukhy (2008)[17]	Acupuncture around the time of ET (*n*=844)	Control (*n*=779)	RE	1.23 [0.96–1.58] (68.2%)
Manheimer (2008)[18]	Acupuncture (*n*=740)	Control (*n*=626)	RE	1.65 [1.27–2.14] (16%)
Drake (2011)[19]	Acupuncture	Lying	NR	NR
Drake (2011)[19]	Acupuncture	Streitberger placebo needling	NR	NR
Drake (2011)[19]	Acupuncture	Non-qi needling	NR	NR
Qu (2012)[21]	Acupuncture (*n*=1908)	Control (*n*=1805)	RE	1.09 [0.94–1.26] (62.2%)
Zheng (2012)[23]	Acupuncture (*n*=2762)	Control (*n*=2837)	RE	1.22 [1.01–1.47] (58%)
Manheimer (2013)[26]	Acupuncture (*n*=2035)	Control (*n*=1995)	RE	1.12 [0.96–1.31] (68%)
Zheng (2012)[23]	Acupuncture (*n*=1940)	Control except Streitberger control (*n*=2000)	RE	1.34 [1.08–1.67] (52%)
Shen (2015)[27]	Acupuncture (*n*=1215)	No intervention control (*n*=1011)	RE	1.24 [1.02–1.50] (64%)
Shen (2015)[27]	Acupuncture (*n*=1010)	Sham acupuncture (*n*=1000)	RE	1.03 [0.87–1.22] (59%)
Qian (2017)[32]	Acupuncture (*n*=3264)	Control (*n*=3080)	RE	1.26 [1.06–1.50] (55%)
Schwarze (2018)[33]	Acupuncture on the day of ET (*n*=663)	Control (*n*=648)	FE	0.87 [0.77- 0.98] (19%)
Zhang (2018)[11]	Acupuncture (NR)	Control (NR)	RE	1.19 [1.06–1.34] (63.4%)
Smith (2019)[34]	Acupuncture (*n*=1447)	Sham control (*n*=1454)	RE	1.07 [0.88–1.30] (67%)
Smith (2019)[34]	Acupuncture (*n*=1129)	No treatment (*n*=1101)	RE	1.32 [1.07–1.62] (61%)
Ongoing Pregnancy Rate				
Cheong (2008)[16]	Acupuncture on the day of ET (*n*=432)	Control (*n*=431)	RE	1.38 [0.78–2.44] (71%)
Cheong (2008)[16]	Repeated acupuncture (*n*=207)	Control (*n*=196)	RE	1.79 [0.93–3.44] (45%)
Cheong (2008)[16]	Acupuncture around the time of OR (*n*=229)	Control (*n*=235)	FE	0.86 [0.58–1.26] (0%)
Manheimer (2008)[18]	Acupuncture (*n*=606)	Control (*n*=507)	RE	1.87 [1.40–2.49] (0%)
Manheimer (2013)[26]	Acupuncture (*n*=1514)	Control (*n*=1491)	RE	1.22 [0.98–1.52] (69%)
Qian (2017)[32]	Acupuncture (*n*=1803)	Control (*n*=1799)	RE	1.14 [0.87–1.48] (63%)
Zhang (2018)[11]	Acupuncture (NR)	Control (NR)	RE	1.21 [0.95–1.55] (67.1%)
Smith (2019)[34]	Acupuncture (*n*=938)	Sham control (*n*=946)	FE	0.98 [0.86–1.13] (72%)
Smith (2019)[34]	Acupuncture (*n*=585)	No treatment (*n*=559)	FE	1.42 [1.17–1.73] (0%)
Live Birth Rate				
Cheong (2008)[16]	Acupuncture on the day of ET (*n*=275)	Control (*n*=267)	FE	1.86 [1.27–2.73] (0%)
Cheong (2008)[16]	Repeated acupuncture (*n*=207)	Control (*n*=196)	RE	1.79 [0.93–3.44] (45%)
Cheong (2008)[16]	Acupuncture around the time of OR (*n*=229)	Control (*n*=235)	FE	0.87 [0.59–1.29] (0%)
Manheimer (2008)[18]	Acupuncture (*n*=496)	Control (*n*=389)	RE	1.91 [1.39–2.64] (0%)
Drake (2011)[19]	Acupuncture	Strietberger placebo needling	NR	NR
Qu (2012)[21]	Acupuncture (*n*=995)	Control (*n*=995)	RE	1.42 [0.92–2.20] (86.5%)
Zheng (2012)[23]	Acupuncture (*n*=929)	Control (*n*=934)	FE	1.09 [0.74–1.60] (69%)
Zheng (2012)[23]	Acupuncture (*n*=317)	Control except Streitberger control (*n*=315)	FE	1.63 [1.16–2.30] (22%)
Cheong (2013)[25]	Acupuncture around the time of OR (*n*=229)	Control (*n*=235)	FE	0.87 [0.59–1.29] (0%)
Cheong (2013)[25]	Acupuncture around the day of ET (*n*=1302)	Control (*n*=1203)	RE	1.22 [0.87–1.70] (69%)
Manheimer (2013)[26]	Acupuncture (*n*=1552)	Control (*n*=1523)	RE	1.14 [0.92–1.42] (68%)
Qian (2017)[32]	Acupuncture (*n*=1219)	Control (*n*=1112)	RE	1.17 [0.80–1.72] (74%)
Zhang (2018)[11]	Acupuncture (NR)	Control (NR)	RE	1.36 [1.09–1.69] (70.1%)
Smith (2019)[34]	Acupuncture (*n*=1233)	Sham control (*n*=1232)	RE	1.01 [0.80–1.28] (64%)
Smith (2019)[34]	Acupuncture (*n*=1005)	No treatment (*n*=975)	RE	1.30 [1.00–1.68] (63%)
Miscarriage				
Cheong (2008)[16]	Acupuncture on the day of ET (*n*=204)	Control (*n*=205)	FE	0.88 [0.35–2.22] (0%)
Cheong (2008)[16]	Repeated acupuncture (*n*=207)	Control (*n*=196)	FE	1.68 [0.90–3.12] (0%)
Cheong (2008)[16]	Acupuncture around the time of OR (*n*=191)	Control (*n*=187)	FE	0.81 [0.46–1.46] (0%)
Qu (2012)[21]	Acupuncture (*n*=191)	Control (*n*=182)	RE	0.95 [0.68–1.35] (0%)
Cheong (2013)[25]	Acupuncture around the time of OR (*n*=142)	Control (*n*=120)	FE	0.79 [0.42–1.47] (17%)
Cheong (2013)[25]	Acupuncture around the day of ET (*n*=340)	Control (*n*=276)	FE	1.10 [0.73–1.67] (0%)
Manheimer (2013)[26]	Acupuncture (*n*=563)	Control (*n*=507)	RE	1.09 [0.85–1.40] (0%)
Zhang (2018)[11]	Acupuncture (NR)	Control (NR)	RE	0.89 [0.67–1.20] (0%)
Smith (2019)[34]	Acupuncture (*n*=1346)	Sham control (*n*=1352)	RE	1.15 [0.78–1.67] (28%)
Smith (2019)[34]	Acupuncture (*n*=1036)	No treatment (*n*=1006)	RE	1.43 [1.03–1.98] (0%)
Biological Pregnancy Rate				
Qu (2012)[21]	Acupuncture (*n*=1233)	Control (*n*=1155)	RE	1.01 [0.84–1.20] (73.7%)
Qian (2017)[32]	Acupuncture (*n*=2164)	Control (*n*=2202)	RE	1.06 [0.82–1.37] (69%)
Implantation Rate				
Qu (2012)[21]	Acupuncture (*n*=1535)	Control (*n*=1329)	RE	1.22 [0.93–1.62] (69.8%)
Zhang (2018)[11]	Acupuncture (NR)	Control (NR)	RE	1.31 [1.08–1.59] (68.5%)
Acupuncture for infertile women with PCOS				
Clinical Pregnancy Rate				
Jo (2017)[31]	Acupuncture (*n*=200)	Control (*n*=230)	RE	1.33 [1.03–1.71] (0%)
Ongoing Pregnancy Rate				
Jo (2017)[31]	Acupuncture (*n*=64)	Control (*n*=100)	RE	2.03 [1.08–3.81] (0%)
Herbal medicine for infertility women				
Clinical Pregnancy Rate				
Ried (2011)[20]	Herbal medicine (*n*=379)	WM fertility medication (*n*=112)	RE	3.50 [2.34–5.24] (42%)
Ried (2015)[12]	Herbal medicine (*n*=2520)	Control (*n*=1727)	RE	1.74 [1.56–1.94] (50%)

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Table 2 (*continued*)

Author (year) ref	Intervention	Comparisons	Statistical Model	Pooled effect [95% CI] (I^2)
Acupuncture for infertility women undergoing IVF				
Herbal medicine for infertile women undergoing IVF				
Clinical Pregnancy Rate				
Cao (2013)[24]	Herbal medicine (NR)	Control (NR)	RE	2.04 [1.67–2.49] (0%)
Ongoing Pregnancy Rate				
Cao (2013)[24]	Herbal medicine (NR)	Control (NR)	RE	1.91 [1.17–3.10] (0%)
Implantation Rate				
Cao (2013)[24]	Herbal medicine (NR)	Control (NR)	RE	1.64 [1.33–2.01] (0%)
Adverse effects				
Cao (2013)[24]	Herbal medicine (NR)	Control (NR)	RE	0.39 [0.14–1.11] (0%)
Herbal medicine for infertile women with PCOS				
Clinical Pregnancy Rate				
Zhou (2016)[28]	Herbal medicine +clomiphene	clomiphene	FE	2.62 [1.65–4.14] (0%)
Bae (2017)[29]	Herbal medicine +WM (n=230)	WM (n=217)	RE	2.33 [1.53–3.54] (0%)
Herbal medicine for infertile women with anovulation				
Clinical Pregnancy Rate				
Tan (2012)[22]	Herbal medicine (n=918)	Clomiphene (n=627)	FE	3.12 [2.50–3.88] (12%)
Tan (2012)[22]	Herbal medicine (n=64)	Clomiphene combination therapy (n=50)	FE	2.12 [0.98–4.57] (0%)

Abbreviations: ET, embryo transfer; FE, fixed effect; IVF, in vitro fertilization; NR, not report; OR, oocyte retrieval; PCOS, polycystic ovary syndrome; RE, random effect; TVOR, time of transvaginal oocyte retrieval; WM, western medicine.

3.4. Herbal medicine for infertility

An SR of the effects of herbal medicine on infertility conducted by the same author was carried out in 2011 and 2015.[12,20] The SR published in 2015 contained the results of the 2011 publication. This review compared herbal medicine and pharmacological treatment, such as clomiphene, gestrinone, prednisolone, tamoxifen, danazol, laparoscopic drilling, and human choriontropic gonadotropin. The SR performed in 2015 showed that CPR (RR 1.74, 95% CI 1.56–1.94) reported better results in herbal medicine, but more heterogeneity (I^2=50%).[12]

3.4.1. Herbal medicine for infertile women undergoing IVF

Cao reported the effects of herbal medicine on infertile women undergoing IVF.[24] Infertile women undergoing IVF were compared with those who took herbal medicine and those who did not take herbal medicine. The result of MA revealed significant effects of herbal medicine on the CPR (OR 2.04, 95% CI 1.67–2.49) and OPR (OR 1.91, 95% CI 1.17–3.10).

3.4.2. Herbal medicine for infertile women with PCOS

Two SRs compared the effects of herbal medicine on infertile women with PCOS.[28,29] Zhou reported no significant effects compared to herbal medicine and clomiphene. On the other hand, when clomiphene and herbal medicine were combined, there was a significant difference in the CPR (OR 2.62, 95% CI 1.65–4.14) compared to that with clomiphene alone, but the quality of evidence was very low.[28] Bae compared herbal medicine and biomedical drugs, such as clomiphene, letrozole, and progesterone, and reported significant differences in the CPR (OR 2.33, 95% CI 1.53–3.54), but the authors reported that the risk of bias of the RCT included was unclear.[29]

3.4.3. Herbal medicine for infertile women with anovulation

One SR compared the effects of herbal medicine on infertile women with anovulation.[22] Tan compared herbal medicine and biomedicine pharmacology, which included clomiphene, diethylstilbestrol, medroxyprogesterone, and human chorionic gonadotropin. Meta-analysis comparing herbal medicine and clomiphene showed a significant difference in the CPR (OR 3.12, 95% CI 2.50–3.88), but the jadad scores of the included RCTs were 1 or 2, indicating poor methodological quality.

3.5. Methodological quality of SR

Fifteen, six, and only one SR were rated as “Critically low”, “Low”, and “moderate”, respectively. No review of the AMSTAR2 assessment was rated ‘high’ because the critical items of AMSTAR2 (item 2, the authors did not state that they had a written protocol or guide; item 7, the authors did not provide a list of excluded studies.) were affected. Appendices 4 and 5 present the result of the AMSTAR2 assessment of each SR.

3.6. Results on adverse effects

3.6.1. Acupuncture for infertility

No significant adverse effects were reported. The other SR compared ‘Nausea’, ‘Dizziness’, ‘Fainting’, ‘Tiredness’, ‘drowsiness’, ‘Headache’, ‘Chest pain’, ‘Itching/pain’, ‘Relaxation’, ‘Calm’, ‘Energized’, and ‘Bruising’ in the acupuncture and control group. A significant difference in ‘Itching/pain’ was observed between the acupuncture and control groups (RR 1.51, 95% CI 1.14–2.00). The other side effects were similar in the acupuncture and control groups.[34]

3.6.2. Herbal medicine for infertility

SRs reported adverse effects, such as ovarian hyperstimulation syndrome, luteinized unruptured follicle syndrome, and multiple pregnancy. On the other hand, there was no difference in adverse effects between the experimental and control groups, and no clinically significant harm was reported.

4. Discussion

4.1. Summary of main results

Twenty-one SRs and Mas were reviewed. The SRs that showed the effects of infertility on herbal medicine reported their effectiveness on CPR and OPR for infertile women. In addition, systematic reviews of the effects of acupuncture on infertility showed that acupuncture had significant effects on the improvement of CPR, OPR, and LBR. In contrast, other systematic reviews reported that acupuncture did not induce significant improvements in CPR compared to sham acupuncture or no treatment.

4.2. Overall completeness of the evidence

The SRs of infertility treatments are increasing every year, and the SRs of acupuncture and herbal medicine for infertility are in-

creasing steadily. On the other hand, an evaluation of the effects of acupuncture and herbal medicine on infertility is controversial. Therefore, this paper reviewed the effects of acupuncture and herbal medicine on infertility. This study included 21 SRs published from 2008 to 2019, with each SR containing four to 40 RCTs and 414 to 6599 participants. In most studies, acupuncture was compared with sham acupuncture or no adjuvant treatment. A mixture of SRs showed that acupuncture was effective on infertility, whereas some SRs showed that acupuncture was not useful in infertility. One SR reported that acupuncture was effective in controlling anxiety. Most SRs that reviewed the effects of herbal medicine on infertility reported positive effects.

The concurrent use of herbal medicine and clomiphene has been reported to have a greater effect on IVF than the biomedicine drug and IVF alone. Some SRs reported that herbal medicine had a significant positive effect compared to biomedicines, such as clomiphene, whereas others reported no significant difference between herbal medicine and clomiphene. According to the SR that reported the adverse effects of acupuncture on the day of ET, it is unclear which mechanism caused these adverse effects.[33] Acupuncture has a positive effect on CPR, implantation, and LBR when combined with IVF/intracytoplasmic sperm injection (ICSI). On the other hand, further study will be needed to determine if acupuncture has positive effects on IVF or ICSI. An SR of the effects of herbal medicine on infertility reported a 60% pregnancy rate. In addition, the probability of a clinical pregnancy was doubled when combined with herbal medicine in IVF. Herbal medicine improved the quality of the embryos and endometrium, which may have helped the pregnancy rates.[12]

4.3. Methodological quality of included systematic reviews

This overview provides evidence to assist in making decisions regarding the use of acupuncture and herbal medicine for infertility for physicians and decision-makers. In most SRs, the methodological quality was very low because there were defects in the critical items of AMSTAR2, Q2 and Q7. Item Q2 assesses whether the protocol in the explicit statement specifies the purpose of the SR, review methods, and risk of bias criteria, as well as if there is a significant deviation from the protocol. No protocols or guide statements were reported except for four SRs. The protocol was the best way to ensure that the SR was transparent, robust, and free from bias. In addition, the key to a high-quality SR is the proper implementation of the protocol's main objectives, study designs, and planning analysis. Therefore, the protocols helped make SRs transparent, reproducible, and prevent bias.[38] In addition, studies showed that the SR that published the actual protocol was more sophisticated and of higher quality than the SR that did not.[39] In addition, Q7 asks whether an exclusion list was provided. Only five SRs reported an exclusion list from this overview. An exclusion list is recommended because the authors can exclude RCTs arbitrarily that differ from their desired results.[40] Nevertheless, as AMSTAR2 is a more rigorous assessment tool than the previous version, the evaluation results should be interpreted by considering that the methodological quality of the published SRs and MAs was underestimated.

4.4. Limitations

This overview had some limitations. First, the quality of the studies included may have been evaluated by the latest rigorous AMSTAR 2, which may have indicated that the quality of the included studies was low overall. Future SR and MA should carefully check the items of AMSTRA 2. Second, it was difficult to conclude that acupuncture and herbal medicine are effective in infertility because the type of acupuncture and herbal medicine and the timing of the intervention of the RCT included in each SR varied. Third, all types of sham acupuncture were included: blunt end, non-penetrating the skin, penetrating non-qi lines, and penetrating qi lines unrelated to infertility. Touching the skin causes physiological reactions, and penetrating non-qi lines can also cause physiological reactions. In addition, it is unclear if the qi lines that are unrelated to infertility have no effects on infertility. Therefore, the effectiveness of sham acupuncture is still unclear, and the results from such comparisons should be interpreted with caution.[41]

4.5. Conclusion

Twenty-one SRs and MAs were published from 2008 to 2019, with each SR containing four to 40 RCTs and 414 to 6599 participants. A review of the CPR, OPR, and LBR showed that acupuncture required more evidence to determine its effects on female fertility. In contrast, herbal medicine was more effective on infertility when combined with biomedicine than with biomedicine alone. On the other hand, when evaluated with the stricter methodological tool, AMSTAR2, the methodological quality of SR and MA was low because the protocol was omitted, and the study list was excluded. When performing an SR and MA in the future, care should be taken to avoid underestimating the methodological quality because of the rigorous evaluation criteria of the relatively new evaluation tool, AMSTAR2.

Author contributions

Jang Won Lee: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. Min Kyung Hyun: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. Hye Jin Kim: Formal analysis, Writing - review & editing. Dong-Il Kim: Conceptualization, Formal analysis, Writing - review & editing.

Conflict of interest

The authors have no conflict of interest to declare.

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Ethical statement

Not applicable.

Data availability

Not applicable.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2020.100694.

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