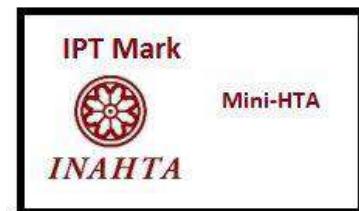




TECHNOLOGY REVIEW (MINI-HTA)

ACUPUNCTURE AS AN ADJUNCT TREATMENT FOR SUBFERTILITY

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
006/2023



DISCLAIMER

This technology review (mini-HTA) is prepared to assist health care decision-makers and health care professionals in making well-informed decisions related to the use of health technology in health care system, which draws on restricted review from analysis of best pertinent literature available at the time of development. This technology review has been subjected to an external review process. While effort has been made to do so, this document may not fully reflect all scientific research available. Other relevant scientific findings may have been reported since the completion of this technology review. MaHTAS is not responsible for any errors, injury, loss or damage arising or relating to the use (or misuse) of any information, statement or content of this document or any of the source materials.

Please contact htamalaysia@moh.gov.my if further information is required.

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590, Putrajaya
Tel: 603 8883 1229

Available online via the official Ministry of Health Malaysia website: <http://www.moh.gov.my>

eISSN:

SUGGESTED CITATION: Maharita AR and Izzuna MMG. Acupuncture As An Adjunct Treatment For Subfertility. Technology Review. Ministry of Health Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2023. 27p. Report No.: 006/2023

DISCLOSURE: The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

Prepared by

Puan Maharita Ab Rahman
Pharmacist
Senior Principal Assistant Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Reviewed by

Dr. Izzuna Mudla Mohamed Ghazali
Public Health Physician
Deputy Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

External reviewer(s)

Dr. Haris Tham Seong Wai
Senior Consultant
O&G and Fertility Specialist
Hospital Raja Permaisuri Bainun, Ipoh

Assoc. Prof. Dr. Kim Yun Jin
School of Traditional Chinese Medicine
Xiamen University Malaysia

EXECUTIVE SUMMARY

BACKGROUND

According to the World Health Organisation (WHO), infertility is a disease of reproductive system defined as failure to achieve clinical pregnancy after 12 months or more regular unprotected sexual intercourse (without other reason, either breastfeeding or postpartum amenorrhoea). As for subfertility, it is the form of reduced fertility characterised by the prolonged time of unwanted non-conception. Women with infertile problem was affected with psychological problem.

Although, there are numerous conditions can cause subfertility and infertility, many effective treatments are available to increase the chances for conception in the patients. The treatments included drugs, hormone, surgery, intra-uterine insemination (IUI), controlled ovarian hyperstimulation (COH), assisted reproductive technology (ART), in vitro fertilisation (IVF), gamete intra-fallopian transfer (GIFT) and in traditional and complementary treatment including herbal medicine and acupuncture.

The T&CM Division of Ministry of Health Malaysia (MOH) is looking forward to offer the acupuncture services in subfertility management as the demand among public is increasing. Currently, acupuncture services offered in the T&CM Division as a complementary treatment to the allopathic medicine of post-stroke management, chronic pain management and chemotherapy-induced nausea and vomiting. Thus to expand the services for this indication as well as to cope with the demand, the Director of T&CM Division requested for further assessment on acupuncture as an adjunct treatment for subfertility.

OBJECTIVE/ AIM

To assess the efficacy/effectiveness, safety and cost-effectiveness of acupuncture as an adjunct treatment for subfertility.

RESULTS:

Search results

A total of **243** records were identified through the Ovid interface and PubMed. After removal of duplicates and irrelevant titles, **55** titles were found to be potentially relevant and were screened using the inclusion and exclusion criteria. Of these, **16** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria, **5** studies were included while the other **11** studies were excluded since the studies either already included in the selected studies or narrative review. **Five** full text articles finally selected for this review comprised of three overviews of SRs, one SR with Meta-analysis (MA) and one randomised controlled trial (RCT). The studies were conducted mainly in China, United State of America, United Kingdom, Australia, Republic of Korea, Iran and Chile.

CONCLUSIONS

Based on the review, acupuncture showed a potential to improve clinical pregnancy rate among subfertile women who were undergoing IVF procedure. However, the findings were supported with low to moderate quality of scientific evidence. For ongoing pregnancy rate, biochemical pregnancy rate, live birth rate and miscarriage, the findings varied. On the other hand, there were studies reported that patients who underwent IVF either with or without PCOS showed no significant difference in CPR, OPR, LBR, and miscarriage when compared to control group. In terms of safety, those with acupuncture experience significant mild adverse events such as local pain, itching and pain.

METHODS

Literature search was conducted by an *Information Specialist* who searched for published articles on nasojejunal feeding tube. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® 1946 to Jun 2023. Parallel searches were run in PubMed, US FDA and INAHTA database as well as CADTH. Some limitations applied during search (animal study). Additional articles were identified from reviewing the references of retrieved articles. The last search was performed on 30 Jun 2023

TABLE OF CONTENTS

Disclaimer and Disclosure	i
Authors	ii
External reviewers	ii
Executive summary	iii
Abbreviations	vi
1.0 BACKGROUND	1
2.0 OBJECTIVE/ AIM	2
3.0 TECHNICAL FEATURES	2
4.0 METHODS	5
5.0 RESULTS	7
5.1 – EFFICACY/EFFECTIVENESS	9
5.2 - SAFETY	17
5.3 - ORGANISATIONAL ISSUES	18
5.4 - ECONOMIC IMPLICATION	18
5.5 - LIMITATION	18
6.0 CONCLUSION	18
7.0 REFERENCES	19
8.0 APPENDICES	
Appendix 1 - Literature search strategy	21
Appendix 2 – CASP Checklist	22
Appendix 3 - Evidence table	23

ABBREVIATIONS

ART	Assisted Reproductive Technology
BPR	Biochemical Pregnancy Rate
COH	Controlled Ovarian Hyperstimulation
CPR	Clinical Pregnancy Rate
GIFT	Gamete Intra-Fallopian Transfer
IUI	Intra-Uterine Insemination
IVF	In-Vitro Fertilisation
MA	Meta-analysis
MR	Miscarriage
LBR	Live Birth Rate
OPR	Ongoing Pregnancy Rate
OR	Odd Ratio
PCOS	Polycystic ovary syndrome
RR	Relative Risk
SR	Systematic Review
TCM	Traditional Chinese Medicine
T&CM	Tradition & Complementary Medicine

1.0 BACKGROUND

Subfertility and infertility are two different conditions encountered in couples trying to conceive baby. According to the World Health Organisation (WHO), infertility is a disease of reproductive system defined as failure to achieve clinical pregnancy after 12 months or more regular unprotected sexual intercourse (without other reason, either breastfeeding or postpartum amenorrhoea). As for subfertility, it is the form of reduced fertility characterised by the prolonged time of unwanted non-conception.¹

According to national statistic, Malaysia fertility rate showed decreasing trend from 2019-2023. In 2020 the fertility rate was 1.976 births per women but the rate was 1.924 in 2023.² The National Population and Family Board (LPPKN) reported that 6% to 9% of Malaysia couples experienced infertility in 2014, and the number was doubled to between 10% to 15% in 2020.³ An SR and MA by Nik Hazlina NH et. al. published in 2022 reported that the overall pooled prevalence of infertility was 46.25%.⁴ The authors assessed the relationship between psychological effects and infertility. The pooled meta-regression analysis showed that women with infertile problem had significantly more psychological distress and depression; odd ratio 1.63 (95% CI 1.24 to 2.13; $I^2 = 57\%$) and 1.40 (95% CI 1.11, 1.75; $I^2 = 50\%$), respectively.⁴ On the other hand, infertility affects an estimated 48-186 million people worldwide. Male factor is the sole cause of approximately one-third of all cases on infertility.⁵

A common cause for subfertility included ovulatory disorders, tubal disease, peritoneal adhesions, endometriosis, uterine abnormalities, abnormalities of sperm and advancing female age.⁶ On the other hand, infertility is unexplained after thorough evaluation in about 5-10% of cases.⁶ The most common cause of anovulation or oligo-ovulation is polycystic ovarian syndrome (PCOS), the aetiology in about 70% cases.⁵ Other common causes are hypothalamic dysfunction, hyperprolactinaemia, age-related ovulation dysfunction and premature ovarian failure.⁶ Meanwhile in male, congenital anomalies, urogenital infections and trauma, systemic disorders and varicocoele are some of the causes and factors associated with male infertility.⁵

Although, there are numerous conditions can cause fertility problems, many effective treatments are available to increase the chance for conception in subfertility/infertile patients. The treatments included drugs (clomiphene citrate, gonadotrophin therapy, dopamine agonist), hormone, surgery (tubal surgery), intra-uterine insemination (IUI), controlled ovarian hyperstimulation (COH), assisted reproductive technology (ART), in vitro fertilisation (IVF), gamete intra-fallopian transfer (GIFT) and etc.⁶

Traditional and complementary medicine (T&CM) such as herbal medicine as well as acupuncture have been opted by some patients.⁶ The T&CM Division of Ministry of Health Malaysia is looking forward to offer the acupuncture services in subfertility management as the demand among public is increasing. Currently, acupuncture services offered in the T&CM Division as a complementary treatment to the allopathic medicine of post-stroke management, chronic pain management and chemotherapy-induced nausea and vomiting. Thus, to expand the services for this indications and to cope with the demand, the Director of T&CM Division requested for further assessment on acupuncture as an adjunct treatment for subfertility.

2.0 OBJECTIVE / AIM

To assess the efficacy/effectiveness, safety and cost-effectiveness of acupuncture as an adjunct treatment for subfertility.

3.0 TECHNICAL FEATURES

3.1 Acupuncture

Acupuncture is a procedure which involves insertion and manipulation of fine filiform needles or other alternative stimulators into the acupoints to relieve pain of for therapeutic purposes. It is integral part of Traditional Chinese Medicine (TCM).⁷

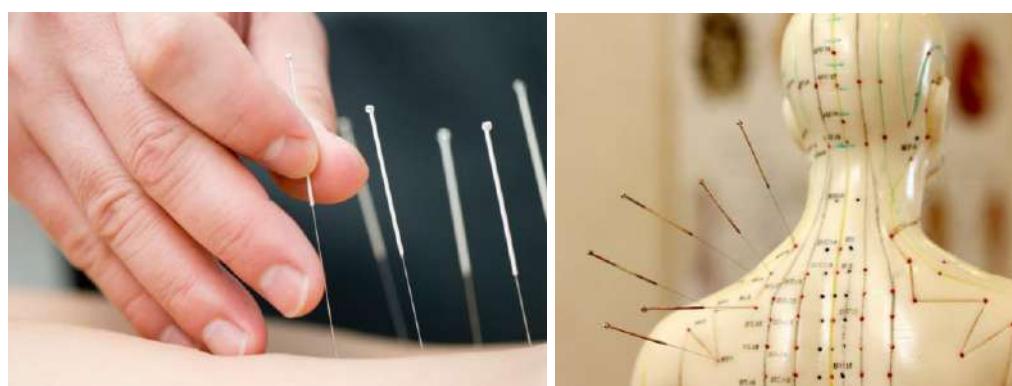
3.2 Acupuncture in pregnancy

In pregnancy, acupuncture is believed to stimulate fertility by relieving the stagnation of qi and tonifying the liver, spleen and kidneys which leads to improve blood circulation to the reproductive organs, strengthened the immune system and balanced the hormones.⁷ It was believed that the acupuncture will regulate the function of the hypothalamic-pituitary-ovarian axis by changing the concentration of central opioids, improve blood circulation to the uterus and ovaries by inhibit the uterine central sympathetic nerve activity, and reduce stress, anxiety or depression.⁸

There are various types of acupuncture which used as adjunct treatment in subfertility. Listed here are the types of acupuncture performed for infertility and subfertility of the included studies.

i. Traditional acupuncture

Traditional acupuncture involves the insertion of thin filiform needles into specific points of the body to stimulate and balance the flow of qi.⁹ It is based on the concept that disruptions or imbalances in the flow of qi can lead to various physical and emotional health issues. The primary goal of acupuncture is to restore the harmonious flow of qi through a network of channels or meridians that are believed to be connected to different organs and functions in the body. By inserting needles at specific points aim to regulate and restore the body's natural balance, alleviate pain, and promote overall health conditions.¹⁰



<https://www.mosherhealth.com/mosher-health-system/acupuncture/forms>

Figure 1: Acupoint and Acupuncture

ii. Electro-acupuncture

Electro-acupuncture is a form of acupuncture that combines traditional acupuncture techniques with the use of electrical stimulation, these needles are attached to electrodes that deliver a mild electrical current to stimulate the acupuncture points.¹¹ The charge increases local blood flow, enhanced release of Neurotransmitters, improved qi flow, and modulation of inflammatory responses.¹²

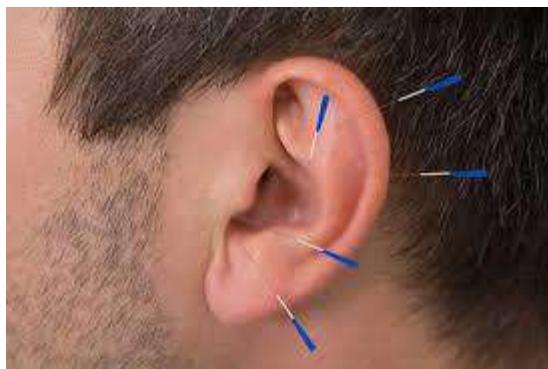


https://www.researchgate.net/figure/Electroacupuncture-at-Zusanli-ST-36-and-Sanyinjiao-SP-6_fig2_328915675

Figure 2: Electro-Acupuncture

iii. Auricular acupuncture

Auricular acupuncture is a form of acupuncture that involves stimulating specific points on the ear. It is based on the belief that the ear is a microsystem of the entire body, and by stimulating these ear points, one can influence various bodily functions and promote disease management.¹³ The auricular acupuncture may improve blood flow and microcirculation in the ear and other parts of the body, which can aid in management.¹⁴



<https://selbyacupuncture.com/wellness-blog/needles-and-ears-how-auricular-acupuncture-can-help/>

Figure 3: Auricular Acupuncture

iv. Laser acupuncture

Laser acupuncture is a one of acupuncture technique that combines the traditional acupuncture with modern laser technology.¹⁵ Laser acupuncture utilizes non-thermal, low-level laser therapy (LLLT) to target specific acupuncture points on the body. This is often considered a non-invasive and painless, as it does not involve the insertion of needles into the skin.¹⁶



<https://www.brownchiro.com/treatments/laser-acupuncture/>

Figure 4: Laser Acupuncture

3.3 Acupuncture Services in Ministry of Health, Malaysia

In 2017, T&CM Division published a 3rd edition of TCM Practice Guideline of Acupuncture. The guideline is to guide healthcare professionals in the T&CM Units of public healthcare facilities towards safe and efficient practice acupuncture. The acupuncture techniques stated in the guideline are manual acupuncture and electro-acupuncture. Currently, the acupuncture services offered at the T&CM Units of public healthcare facilities are indicated for post-stroke management, chronic pain management and chemotherapy-induced nausea and vomiting. The simplified acupuncture regimes for each problem are simplified in **Table 1-Table 3**.⁶

Table 1: Acupuncture treatment regime for post stroke patients

Severity of stroke	Minimum number of sessions	Frequency of treatment	Assessment	Maximum number of sessions
Mild	10	Once in 3 days	Every 10 th session	20 sessions
Moderate	20	Once in 2 days	Every 10 th session	30 sessions
Severe	30	Once in 2 days	Every 10 th session	40 sessions

**The above recommended regime may be modified based on either the practitioner's assessment on the patient's response to the prescribed treatment or the point that the patient's condition has shown improvement.*

Table 2: Acupuncture treatment regime for chronic pain patients

Diagnosis	Minimum number of sessions	Frequency of treatment	Assessment	Maximum number of sessions
Chronic pain	5	Every day or alternate days	5 th session	10 sessions

*The above recommended regime may be modified based on either the practitioner's assessment on the patient's response to the prescribed treatment or the point that the patient's condition has shown improvement.

Table 3: Acupuncture treatment regime for chemotherapy-induced nausea and vomiting

Minimum number of sessions	<ul style="list-style-type: none"> One session or according to the chemotherapy regime
Breakdown of sessions	<ul style="list-style-type: none"> Acupuncture treatment is given 20 minutes to two hours PRIOR to chemotherapy. Electro-acupuncture on bilateral PC6 (Nei Guan) and ST36 (Zu San Li)
Assessment	<ul style="list-style-type: none"> Assessment done at day one and day five post chemotherapy using the Multinational Association of Supporting Care in Cancer (MASCC) Antiemesis Tool (MAT)
Maximum number of sessions	<ul style="list-style-type: none"> No maximum number of sessions. Acupuncture can be given at the beginning until the completion of planned chemotherapy cycles

*The above recommended regime may be modified based on either the practitioner's assessment on the patient's response to the prescribed treatment or the point that the patient's condition has shown improvement.

4.0 METHODS

4.1 SEARCHING

Literature search was conducted by the author and an *Information Specialist* who searched for full text articles pertaining to acupuncture in subfertility and infertility.

The following electronic databases were searched through the Ovid interface:

- MEDLINE® In-Process and Other Non-Indexed Citations and Ovid MEDLINE® 1946 to Jun 2023

Other databases:

- PubMed
- Other websites: US FDA, INAHTA, CADTH

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. **Appendix 1** showed the detailed search strategies. The last search was conducted on 29 September 2023.

4.2 SELECTION

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria. Relevant articles were then critically appraised using *Critical Appraisal Skills Programme (CASP) checklist* and graded according to *US/Canadian Preventive Services Task Force (Appendix 2)*. ROB 2 assessment also used for the selected RCT and ROBIS for SR. Data were extracted and summarised in evidence table as in **Appendix 3**.

The inclusion and exclusion criteria were:

Inclusion criteria:

a.	Population	People with subfertility and infertility
b.	Intervention	Acupuncture
c.	Comparator	i. No comparator ii. Others subfertility / infertility intervention.
d.	Outcomes	i. Efficacy and effectiveness ii. Safety
e.	Study design	SR, RCT, Control Trial, Cohort study
f.	Full text articles	

Exclusion criteria:

a.	Study design	Animal study
b.		Non full text articles

5.0 RESULTS**Search results**

An overview of the search is illustrated in **Figure 2**. A total of **253** records were identified through the Ovid interface, PubMed and 10 were identified through the other sources such as academician. After removal of duplicates and irrelevant titles, **55** titles were found to be potentially relevant and were screened using the inclusion and exclusion criteria. Of these, **16** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria, **six** studies were included while the other **10** studies were excluded since the studies either already included in the selected studies or narrative review. **Six** full text articles finally selected for this review comprised of three overviews of SRs, two SRs with MA and one randomised controlled trial (RCT). The studies were conducted mainly in China, United State of America, United Kingdom, Australia, Republic of Korea, Iran and Chile.

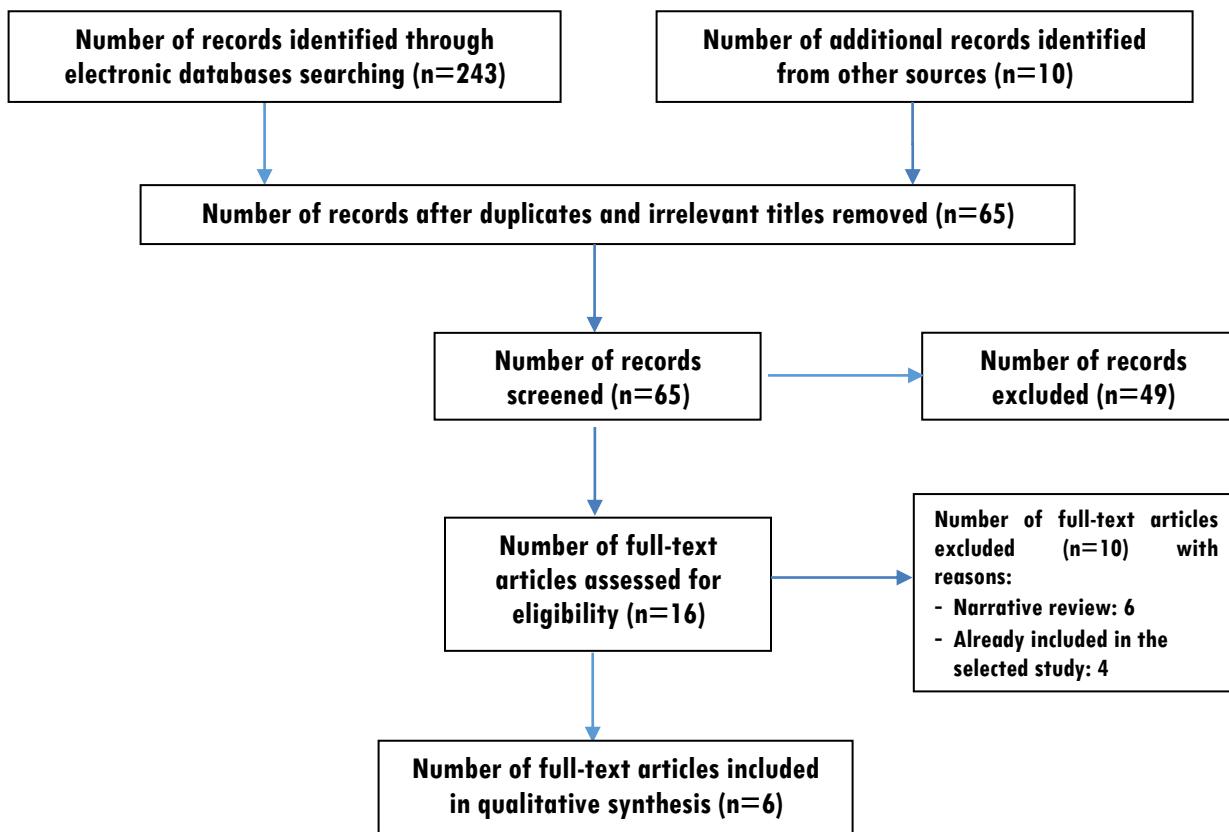


Figure 2: Flow chart of retrieval of articles used in the results

Quality assessment of the studies

The risk of bias in the included studies were assessed using domain-based evaluation. This is achieved by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

- X High
- Unclear
- + Low
- ? No information

The risk of bias for the overview of SRs and the SRs was considered 'unclear bias' following the uncertainty of the included primary studies especially on the characteristics of the included studies. The risk of bias assessment for the included primary studies varied either low risk, unclear risk and high risk. Meanwhile for the RCT, although the ROB2 assessment was considered low, the sample size was small, involving 79 patients and might not represent population of interest. The results of risk of bias of included studies are summarised in **Figure 3.1 and 3.2**

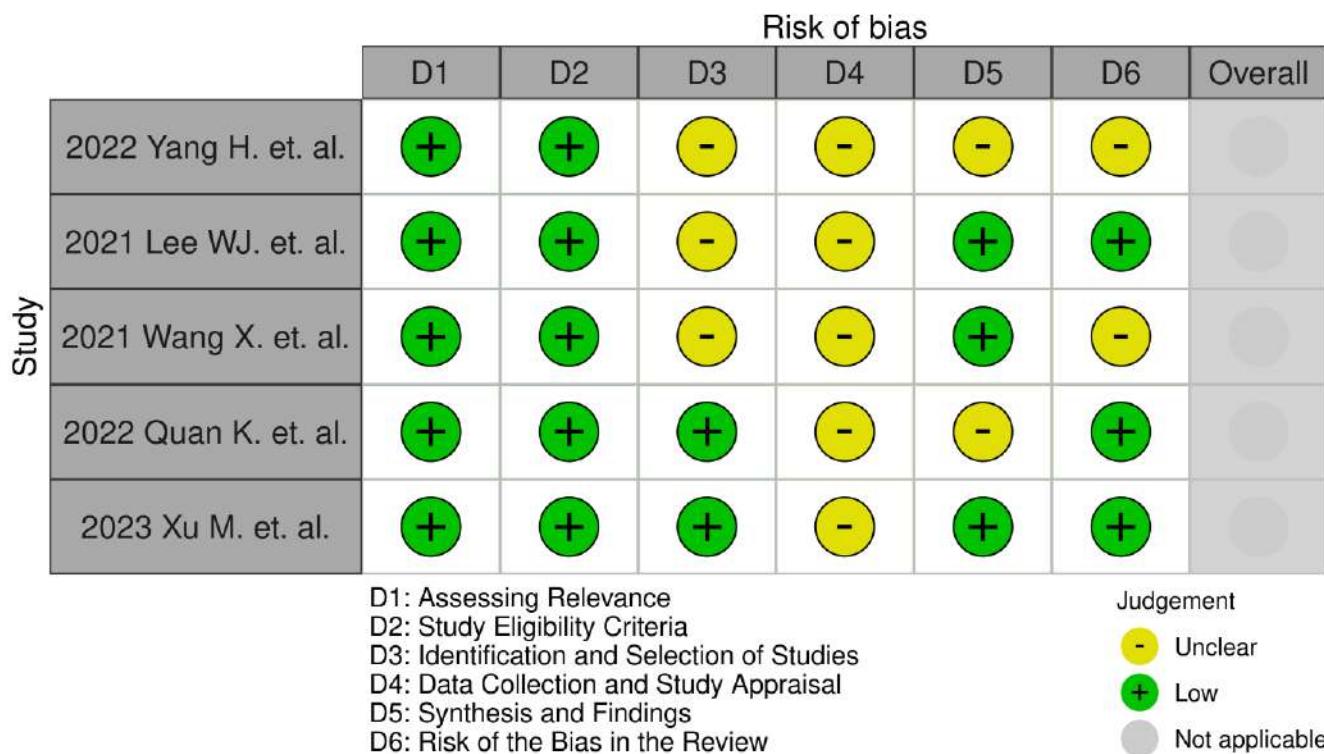


Figure 3.1: Risk of Bias of Overview of Reviews and Systematic Reviews

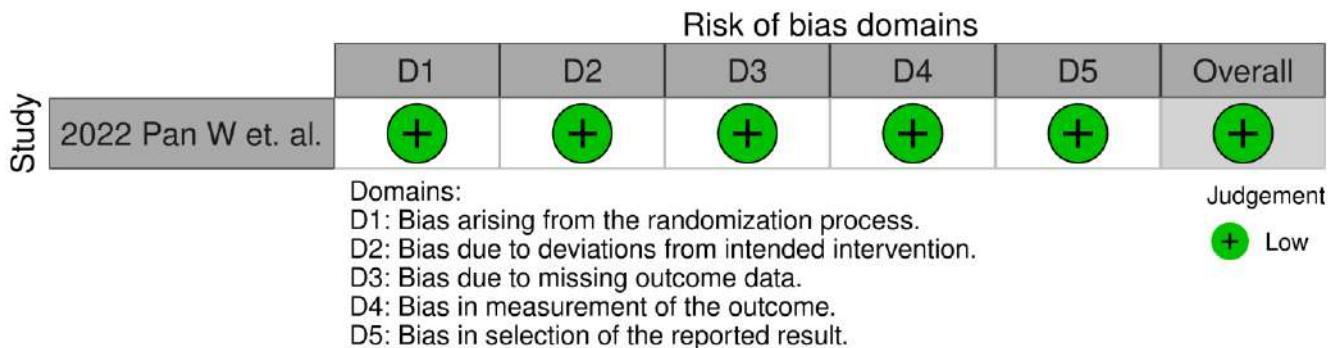


Figure 3.2: Risk of Bias of Randomised Control Trial

5.1 EFFICACY / EFFECTIVENESS

Yang H. et. al. conducted an overviews of SRs to summarise and evaluate the current evidence on the efficacy and safety of acupuncture for polycystic ovary syndrome. The authors also want to assess the quality and risks of bias of the available SRs. The overviews included eleven SRs of RCTs published between 2014 to 2022. The included studies compared between acupuncture alone or in combination with other treatment and control group. The acupuncture included either traditional/manual acupuncture, electro-puncture, warm acupuncture, abdominal acupuncture, needle-pricking, transcutaneous electrical acupoint stimulation, moxibustion, acupoint catgut embedding and acupuncture combined with medicines, with lifestyle interventions and with in vitro fertilisation (IVF). Meanwhile control groups either used western medicine, herbal medicine, conventional treatment, placebo, sham acupuncture, lifestyle intervention, physical intervention, relaxation or no treatment. The outcomes measures included fertility outcomes (clinical pregnancy rate [CPR], live birth rate [LBR], ongoing pregnancy rate [OPR], miscarriage [MPR], ovulation rate and recovery of menstrual cycle), endocrine outcome (luteinizing hormone/follicle-stimulating hormone [LH/FSH] ratio, testosterone and Ferriman-Gallwey score), glycaemia and antropometric outcomes (fasting insulin, fasting plasma glucose, homeostasis model assessment of insulin resistance [HOMA-IR], body mass index [BMI] and waist hip rate [WHR]) and safety outcomes (ovarian hyper-stimulation syndrome [OHSS] and adverse events). The quality of the included SRs was assessed with AMSTAR2 (for methodology), ROBIS, PRISMA-A and publication bias. Descriptive analyses were conducted and no quantitative synthesis was considered. According to the descriptive analyses, combination of acupuncture with other medicines were reported as effective in improving CPR, ovulation rate and menstrual cycle. The combination also reduced the luteinizing hormone/follicle-stimulating hormone [LH/FSH] ratio, homeostasis model assessment of insulin resistance, and BMI. When compared with medicine alone, acupuncture alone also can improve CPR as well as improved menstrual cycle of PCOS patients. In study that involved IVF/ICSI procedure, acupuncture with IVF/ICSI improved CPR and OPR when compared with IVF/ICSI alone. Although the findings favoured acupuncture in certain outcomes, the results were supported with low quality of SRs.^{17, level 1} The summary of the outcomes was shown in Table 4, 5 and 6.

Table 4: Fertility Outcomes among PCOS

Outcomes	Intervention versus Control				
	Acupuncture versus Sham Acupuncture	Acupuncture versus treatment no	Acupuncture versus Medicine	Acupuncture with medicine versus medicine alone	Acupuncture with IVF/ICSI versus IVF/ICSI alone
Clinical Pregnancy Rate (CPR)	<ul style="list-style-type: none"> No significant difference in improving CPR Reported in 3 SRs (low and very-low quality) 	(no information)	<ul style="list-style-type: none"> Acupuncture improved CPR Reported in 1 moderate quality SR 	<ul style="list-style-type: none"> Acupuncture with medicine improved CPR Reported in 3 SRs (high, low and very-low quality) 	<ul style="list-style-type: none"> Acupuncture with IVF/ICSI improved CPR Reported in 1 low quality SR
Ongoing Pregnancy Rate (OPR)	(no information)	(no information)	(no information)	(no information)	<ul style="list-style-type: none"> Acupuncture with IVF/ICSI had significant effect on OPR Reported in 1 very-low quality SR
Miscarriage Rate (MR)	(no information)	(no information)	(no information)	<ul style="list-style-type: none"> One moderate-quality of SR reported no significant difference between group One low-quality SR reported that acupuncture with medicine resulted in lower MR than medicine alone 	(no information)
Ovulation Rate (OR)	<ul style="list-style-type: none"> No significant difference reported in 2 very-low quality SRs 	(no information)	(no information)	<ul style="list-style-type: none"> Acupuncture with medicine could improve ovulation rate compared to medicine alone Reported in 4 moderate-quality SRs 	(no information)
Menstrual Cycle	(no information)	<ul style="list-style-type: none"> Acupuncture had better effect to improve menstrual cycle of PCOS compared to no treatment Reported in 1 moderate-quality SR 	<ul style="list-style-type: none"> Acupuncture was better than medicine Reported in 1 low-quality medicine 	<ul style="list-style-type: none"> Acupuncture with medicine could promote recovery of menstrual cycle compared to medicine alone Reported in 1 low-quality SR 	(no information)

Adapted from Yang H. et. al.¹⁷

Table 5: Endocrine Outcomes among PCOS

Outcomes	Intervention versus Control					
	Acupuncture versus Sham Acupuncture	Acupuncture versus no treatment	Acupuncture versus Medicine	Acupuncture with medicine versus medicine alone	Acupuncture with medicine versus sham acupuncture	Acupuncture versus mixed control
Luteinizing hormone/follicle-stimulating hormone (LH/FSH) Ratio	<ul style="list-style-type: none"> No significant difference in reducing LH/FSH in both groups Reported in 1 low-quality SR 	<ul style="list-style-type: none"> No significant difference in reduction of LH/FSH in both groups Reported in 2 low-quality studies 	<ul style="list-style-type: none"> Acupuncture had better effect than medicine was reported in 1 low-quality SR No significant difference was reported in 2 low-quality evidence 	<ul style="list-style-type: none"> Acupuncture with medicine could reduce LH/FSH was reported in 2 moderate- and low-quality SRs No significant difference was reported in 1 very-low quality SR 	<ul style="list-style-type: none"> Acupuncture with medicine had better outcome than sham acupuncture was reported in 1 SR 	(no information)
Testosterone	<ul style="list-style-type: none"> No significant difference reports in 1 low-quality SR 	<ul style="list-style-type: none"> Testosterone reduction was higher in acupuncture group than in no intervention was reported in 1 low-quality SR 	<ul style="list-style-type: none"> No significant difference was reported in 3 SRs Acupuncture was better than sham acupuncture was reported in 1 SR 	<ul style="list-style-type: none"> Acupuncture with medicine showed better reduction of testosterone level compared to medicine alone which was reported in 5 low-quality SRs 	<ul style="list-style-type: none"> No significant difference when both groups also received medicine Reported in 1 low-quality SR 	(no information)
Ferriman-Gallaway Score	(no information)	(no information)	(no information)	(no information)	(no information)	<ul style="list-style-type: none"> No significant difference between both group was reported in 1 low-quality SR

Adapted from Yang H. et. al.¹⁷

Table 6: Glycaemia and anthropometric outcomes among PCOS

Outcomes	Intervention versus Control				
	Acupuncture as adjuvants	Acupuncture versus no treatment	Acupuncture versus Medicine	Acupuncture with medicine versus medicine alone	Acupuncture versus mixed controls
Fasting insulin	(no information)	<ul style="list-style-type: none"> No significant difference in reducing insulin level Reported in 1 low-quality SR 	<ul style="list-style-type: none"> No significant difference in reducing insulin level Reported in 1 low-quality SR 	<ul style="list-style-type: none"> Acupuncture with medicine had better treatment effect than medicine alone Reported in 2 low-quality SRs and 1 very-low quality SR 	<ul style="list-style-type: none"> No significant difference between groups Reported in 1 very-low quality SR
Fasting plasma glucose	(no information)	<ul style="list-style-type: none"> No significant difference Reported in 1 low-quality SR 	(no information)	(no information)	<ul style="list-style-type: none"> Acupuncture reducing fasting plasma glucose slightly better than a mixed control Reported in 1 very-low SR
HOMA-IR	(no information)	(no information)	(no information)	<ul style="list-style-type: none"> Acupuncture with medicine had better effect on HOMA-IR when compared with medicine alone Reported in 1 moderate-quality SR 	<ul style="list-style-type: none"> Acupuncture reduced HOMA-IR more than mixed controls Reported in 1 very-low quality SR
BMI	<ul style="list-style-type: none"> As adjuvant, acupuncture improved the BMI reduction Reported in 2 moderate- and low-quality SRs 	<ul style="list-style-type: none"> Acupuncture showed better reduction effect on BMI Reported in 1 moderate-quality SR 	<ul style="list-style-type: none"> Acupuncture was slightly better to reduce BMI compared to medicine Reported in 1 low-quality SR 	(no information)	<ul style="list-style-type: none"> Acupuncture significantly reduced BMI better than controls Reported in 1 very-low quality SR
Waist hip rate	(no information)	(no information)	(no information)	(no information)	<ul style="list-style-type: none"> Acupuncture was better than mixed controls Reported in 1 very-low quality SR

*HOMA-IR: Homeostasis model assessment of insulin resistant; BMI: Body mass index; WHR: Waist hip rate

Wang X. et. al. (2021) conducted an overview of SRs to summarise the evidences of essential outcomes of acupuncture in in vitro fertilization and embryo transfer (IVF-ET) and evaluate the SRs methodological quality. Sixteen SRs on acupuncture for infertile women undergoing IVF-ET with or without intracytoplasmic sperm injection (ICSI) were included. The causes of the infertility were male-infertility, tubal factors, endometriosis, PCOS and unclear causes. The acupuncture included traditional acupuncture, electro-acupuncture, manual acupuncture, auricular acupuncture and transcutaneous electrical acupoint stimulation (TEAS) or laser acupuncture. The controls were either sham acupuncture, Western medicine, Chinese herb, or no adjunctive treatment. The primary outcomes assessed were CPR, LBR, biochemical pregnancy rate (BPR), OPR and MR. The secondary outcome was adverse events. For quality assessment, the authors followed AMSTAR-2, GRADE and ROBIS

assessment. Overall, the authors reported that methodology assessment of the 16 SRs were low, where seven of them had high-risk of bias. The authors performed a re-meta analyses of the primary outcomes to assess the combined effects of the included reviews. The analysis suggested that, when compared with sham acupuncture, the acupuncture was superior in improving CPR of IVF-ET with substantial heterogeneity (risk ratio (RR) = 1.31, 95% CI: 1.13 to 1.52, $p = 0.0004$, $I^2 = 66\%$). However, the other outcomes showed no statistical difference in improving LBR, or OPR, and reducing BPR or MR between acupuncture and sham acupuncture (RR = 0.92, 95% CI: 0.83 to 1.00, $p = 0.06$; RR = 1.13, 95% CI: 0.90 to 1.41, $p = 0.30$; RR = 1.08, 95% CI: 0.87 to 1.32; and OR = 1.20, 95% CI: 0.87 to 1.65, $p = 0.28$; respectively). When compared with no adjunctive treatment groups, the acupuncture improved CPR (RR = 1.25, 95% CI: 1.11 to 1.42, $p = 0.0003$) and OPR (RR = 1.38, 95% CI: 1.04 to 1.83, $p = 0.03$). Acupuncture also more superior than no adjunctive treatment in reducing MR (OR = 1.42, 95% CI: 1.03 to 1.95, $p = 0.03$) and BPR (RR = 1.19, 95% CI: 1.02 to 1.37, $p = 0.02$). Although the analysis showed that acupuncture seems to be beneficial in increasing the pregnancy rate in patients undergoing IVF-ET, there was high heterogeneity and methodological quality defects of the included studies.^{7, level 1}

Another overview of SRs conducted by Lee JW et. al. (2021) to provide evidences of acupuncture and herbal medicine among infertile women. The overview included 21 SRs published between 2008 and 2019. The quality assessment of the included SRs was based on AMSTAR2 where 15 SRs were categorised as critically low quality, 6 SRs low quality and 1 SR as moderate. For the effects of acupuncture in infertile women, out of 21 SRs, 14 SRs analysed the effects of acupuncture on infertile women undergoing IVF, and 1 SR analysed the effects of acupuncture on infertile women with PCOS undergoing IVF. Meanwhile, the another six SRs were assessing the effects of herbal medicine in infertile women. Thirteen SRs reported on pooled results of acupuncture versus sham acupuncture, placebo and no adjuvant treatment among infertile women undergoing IVF. The primary outcomes reported in most studies were CPR, OPR, LBR and miscarriage. Six SRs reported that there were no significant differences between acupuncture and control groups. However, one SR reported that control group was significantly had higher CPR than acupuncture group (RR = 0.87, 95% CI 0.77 to 0.98). Another SR reported that when compared between acupuncture and sham/no adjuvant treatment, acupuncture had significant effects on CPR, OPR and LBR (RR 1.65, 95% CI 1.27 to 2.14; RR 1.87, 95% CI 1.40 to 2.49 and 1.91, 95% CI 1.39 to 2.64, respectively). However, similar authors reported on their next study that no significant difference on CPR, OPR and LBR when compared with sham acupuncture or no adjuvant treatment. Another authors also reported that although their previous study showed acupuncture on the day of embryo transfer was more effective on LBR than no adjuvant, the repeated study reported no effects on the LBR. According to the authors, the differences assumed to be affected with the quality of the new included studies. During IVF procedure, 5 studies reported that acupuncture was effective treatment or partially helped to improve CPR, OPR and LBR than no adjuvant treatment during IVF procedure. In infertile women with

PCOS, pooled result showed that acupuncture had significant effects on CPR and OPR; RR 1.33, (95% CI 1.03 to 1.71) and RR 2.03 (95% CI 1.08 to 3.81), respectively.^{18, level 1}

Xu M. et. al. conducted an SR with MA to evaluate the effects of acupuncture on IVF-ET outcomes. The SR included 25 RCTs (a total of 4,757 participants) that evaluated the effects of acupuncture on IVF outcomes in women undergoing IVF with or without ICSI. The intervention measures of acupuncture reported were either manual acupuncture, electrical acupuncture or transcutaneous acupoint electrical stimulation (TEAS). The control groups consisted of blank acupuncture and placebo acupuncture. The major outcomes assessed were CPR and LBR. Other outcomes were BPR, OPR, implantation rate and miscarriage. The authors subdivide the analysis according to four conditions which were different types of control, different types of interventional acupuncture methods, different types of acupuncture time and different acupuncture courses. First, for different types of control, the included RCTs compared the interventional acupuncture with blank acupuncture groups and placebo acupuncture. Overall, comparison between interventional acupuncture and control reported that only miscarriage showed no significant difference (RR = 1.06, 95% CI 0.64 – 1.75, P = 0.83). Meanwhile, the other outcomes IR, BPR, CPR, OPR and LBR showed significant improvement in interventional acupuncture. The full results were shown in Table 7. Second, based on different acupuncture methods, either with manual acupuncture, electrical acupuncture or TEAS, the authors found that pooled CPR and LBR were significantly higher than all control groups. Meanwhile, pooled MR showed no difference between manual acupuncture or electrical acupuncture when compared with control groups. The summary of the findings was tabulated in Table 8. Next for different types of acupuncture time, there was two which were before or during the time of controlled ovarian hyper-stimulation (COH) and around the time of embryo transfer (ET). Before or during the time of COH, the pooled implantation rate, CPR and LBR were significantly higher in interventional acupuncture than all control groups. Then, around the time of ET, the pooled implantation rate, BPR, CPR, OPR and LBR were significantly higher in interventional acupuncture groups than all control groups. The summary of the findings was in Table 9. Lastly for different acupuncture courses, the courses assessed were either four sessions and less than four sessions. In at least four session course, the pooled implantation rate, BPR, CPR and LBR were significantly higher in interventional acupuncture than control groups. In less than four sessions, the pooled implantation rate, BPR, CPR, OPR and LBR were significantly higher in interventional group than control groups. Meanwhile, no significant difference in miscarriage reported. The overall results were shown in Table 10.^{22, level 1}

Table 7: Different controls (Interventional Acupuncture vs Controls)

Outcomes					
Clinical Pregnancy Rate (CPR)	Biochemical Pregnancy Rate (BPR)	Live Birth Rate (LBR)	Ongoing Pregnancy Rate (OPR)	Implantation rate (IR)	Miscarriage (MR)
RR=1.33, 95% CI 1.23–1.43, P<0.00001	RR=1.51, 95% CI 1.32–1.74, P<0.00001	RR = 1.33, 95% CI 1.19– 1.49, P<0.00001	RR=1.65, 95% CI 1.32–2.05, P<0.00001	RR=1.28, 95% CI: 1.15–1.42, P<0.00001	RR=1.06, 95% CI 0.64– 1.75, P=0.83

*RR = risk ratio

Table 8: Different acupuncture methods (Interventional Acupuncture vs Controls)

Interventional Acupuncture	Outcomes					
	Clinical Pregnancy Rate (CPR)	Biochemical Pregnancy Rate (BPR)	Live Birth Rate (LBR)	Ongoing Pregnancy Rate (OPR)	Implantation rate (IR)	Miscarriage (MR)
Manual Acupuncture (MA)	RR: 1.33, 95% CI 1.20–1.47, P<0.00001	RR=1.53, 95% CI 1.30–1.80, P<0.00001	RR: 1.24, 95% CI 1.05– 1.46, P=0.01	RR: 1.64, 95% CI 1.29–2.08, P<0.0001	RR: 1.15, 95% CI 0.96–1.37, P=0.12	RR: 1.05, 95% CI 0.57– 1.96, P=0.87
Electrical Acupuncture (EA)	RR: 1.41, 95% CI 1.16–1.71, P=0.0004	RR: 1.58, 95% CI 1.04–2.39, P=0.03	RR: 1.80, 95% CI 1.11– 2.92, P=0.02	RR: 1.69, 95% CI 0.96– 2.96, P=0.07	RR: 1.12, 95% CI 0.49–2.56, P=0.79	nil
Transcutaneous Acupoint Electrical Stimulation (TEAS)	RR: 1.32, 95% CI 1.11–1.57, P=0.001	nil	RR: 1.50, 95% CI 1.20– 1.86, P=0.0003	nil	RR: 1.45, 95% CI 1.20–1.75, P=0.0001	nil

*RR = risk ratio

Table 9: Different acupuncture time (Interventional Acupuncture vs Controls)

Acupuncture Time	Outcomes					
	Clinical Pregnancy Rate (CPR)	Biochemical Pregnancy Rate (BPR)	Live Birth Rate (LBR)	Ongoing Pregnancy Rate (OPR)	Implantation rate (IR)	Miscarriage (MR)
Before or during the time of controlled ovarian hyper-stimulation (COH)	RR: 1.42, 95% CI 1.23–1.64, P<0.00001	nil	RR: 1.96, 95% CI 1.40–2.74, P<0.0001	nil	RR: 2.05, 95% CI 1.32–3.19, P=0.001	nil
Around the time of embryo transfer (ET)	RR: 1.27, 95% CI 1.16–1.40, P<0.00001	RR: 1.44, 95% CI 1.21–1.72, P<0.0001	RR: 1.28, 95% CI 1.12–1.46, P=0.0003	RR: 1.54, 95% CI 1.19–2.00, P=0.001	RR: 1.26, 95% CI 1.12–1.43, P=0.0002	RR: 1.02, 95% CI 0.53–1.96, P=0.15

Table 10: Different acupuncture course (Interventional Acupuncture vs Controls)

Acupuncture course	Outcomes					
	Clinical Pregnancy Rate (CPR)	Biochemical Pregnancy Rate (BPR)	Live Birth Rate (LBR)	Ongoing Pregnancy Rate (OPR)	Implantation rate (IR)	Miscarriage (MR)
At least 4 sessions	RR: 1.43, 95% CI 1.23–1.65, P<0.00001	RR: 1.45, 95% CI 1.10–1.91, P=0.009	RR: 1.96, 95% CI 1.40–2.74, P<0.0001	nil	RR: 2.05, 95% CI 1.32–3.19, P=0.001	nil
Less than 4 sessions	RR: 1.30, 95% CI 1.19–1.41, P<0.00001	RR: 1.53, 95% CI 1.31–1.78, P<0.00001	RR: 1.25, 95% CI 1.11–1.41, P=0.0002	RR: 1.65, 95% CI 1.32–2.07, P<0.0001	RR: 1.24, 95% CI 1.11–1.38, P=0.0002	RR: 1.02, 95% CI 0.61–1.70, P=0.95

Quan K. et. al. (2022) conducted an SR with MA to evaluate the efficacy and safety of acupuncture for female with infertility who underwent ovulation induction, IVF or intracytoplasmic sperm injection. From systematic search, 25 RCTs with total of 7,676 patients were included. All the included studies compared between acupuncture (intervention group) and control which consisted of either no acupuncture or sham (placebo) acupuncture. There were four primary outcomes observed which were CPR, LBR, BPR, and OPR. Meanwhile the secondary outcomes were implantation rate, number of oocytes retrieved, good-quality embryo rate, miscarriages, ectopic pregnancy rate and adverse events. According to the authors, most of the included trials in the SR were high quality except one study were considered low quality because the trial was not providing an adequate control. For the primary outcomes, the study showed that acupuncture was significantly better when compared to control groups in LBR, CPR and BPR; 32.1% versus 27.9% (OR = 1.34 95% CI 1.07 to 1.67; P < 0.05), 40.4% versus 33.9% (RR = 1.43; 95% CI 1.21 to 1.69; P < 0.05), and 40.4% versus 36.4% (RR = 1.42; 95% CI 1.05, 1.9); P < 0.05), respectively. On the other hand, for OPR, both acupuncture and control group had no significant difference; (29.2% versus 28.5%; OR 1.25; 95% CI 0.88 to 1.79; P = 0.21). For secondary outcome, only implantation rate was significantly higher in acupuncture group compared to control group; 28.1% versus 25.6% (OR 1.19; 95% CI 1.07 to 1.33); P = 0.002). Whereas the other outcomes had no significant difference between groups.^{19, level 1}

Pan W. et. al. conducted an RCT to evaluate the efficacy of acupuncture combined with herbal medicine on ovulation and pregnancy rates and the levels of hormone associated with infertility in women with PCOS. The study involved 79 women between age of 20 and 40-years old which were considered eligible under 2003 Rotterdam criteria.²⁰ According to 2003 Rotterdam criteria, PCOS is a syndrome of ovarian dysfunction along with the cardinal features hyperandrogenism and polycystic ovary (PCO) morphology.²¹ All patients were randomised either to receive acupuncture (41 patients) or sham acupuncture (38 patients). Both groups also received herbal medicine. The participants will be assessed for couples of time; at baseline, at each menstrual cycle, after three menstrual cycles of treatment and 24-week followed-up after completion of the treatment. The primary outcome was pregnancy rate during study which was determined with B-ultrasound or HCG positivity in blood or urine.

The secondary outcomes were ovulation rate, change from baseline in PCOS and TCM syndrome scores and change from baseline of the serum sex hormone levels included estradiol (E₂), testosterone (T), progesterone (P), LH and FSH. The insulin resistance index (HOMA-IR) was also assessed at baseline and after treatment of 3 menstrual cycle. During treatment, the trial reported that 15 participants were successfully conceived where 10 (24.39%) of them were in acupuncture group with herbal medicine. After six months of followed-up, another 11 subjects were pregnant where nine (29.03%) of them were in acupuncture group with herbal medicine. Overall, the pregnancy rate in acupuncture with herbal medicine group was 46.34% (19/41) which was significantly higher compared to sham acupuncture with herbal medicine group (18.42%); $p = 0.008$. On the other, after three menstrual cycle the ovulation rate was also significantly higher in acupuncture group with herbal medicine than sham acupuncture with herbal medicine group; 58.14% versus 45.74%; $p = 0.046$. Other than that, the PCOS score and testosterone level in acupuncture group with herbal medicine also improved than sham acupuncture group with herbal medicine. After completion of treatment, compared with baseline, patients in acupuncture group had statistically significant improvement in PCOS score, TCM score E₂, T, P, LH levels and the ratio of LH/FSH but no significant improvement in FSH level or HOMA-IR. Meanwhile in sham acupuncture group, when compared to baseline, the patients showed statistically significant improvements only in PCOS and TCM score as well as progesterone levels but no significant variations in the levels of other hormones.^{20, level II-1}

5.2 SAFETY

The overview of SRs by Yang H. et. al. reported that acupuncture group had better effect to reduce the risk of ovarian-hyper stimulating syndrome (OHSS) in patients underwent IVF/ICSI. However, the evidence was supported with low-quality SRs. In terms of adverse events, when compared to sham acupuncture and medicine alone, acupuncture group showed more adverse events such as local pain and bruise. On the other hand, no significant difference in rates of adverse events between acupuncture and physical exercise, and between acupuncture and medicine. In one high-quality SR, more adverse events occurred in the group receiving acupuncture with medicine than in the group receiving medicine alone.¹⁷

Quan K. et. al. reported that adverse events was significantly higher in acupuncture group compared to control group (RR = 1.65; 95% CI (1.15, 2.36); $P < 0.05$). The adverse events listed were local pain, bleeding, bruising and pruritus.¹⁹

Wang X. et. al. reported that only mild adverse events occurred such as mild allergy, nausea, drowsiness, headache, chest pain, dizziness and fatigue in patient who underwent acupuncture.⁷

Lee JW et. al. (2021) reported that there was no significant adverse reaction between acupuncture and control group for nausea, dizziness and fainting, tiredness, drowsiness headache, chest pain and bruising. However, there was significant difference in itching/pain between acupuncture and control group.¹⁸

The RCT by Pan W. et. al. reported that neither acupuncture group with herbal medicine nor sham acupuncture with herbal medicine group reported any noticeable side effects during the study period.²¹

5.3 ORGANISATIONAL ISSUES

Traditional Chinese medicine (TCM) practitioners and academicians reported that, acupuncture usually offered for indications of ovarian dysfunction and polycystic ovarian syndrome (PCOS) among sub-fertile women. The treatment is typically given before IVF or embryo transfer procedures. Additionally, herbal medicine may also be given concurrently with acupuncture therapy. Besides that, the acupuncturist must be certified and registered Traditional Chinese Medicine (TCM) practitioners with qualifications and experience related to the field of TCM Obstetrics and Gynaecology.

5.4 ECONOMIC IMPLICATION

There was no retrievable evidence retrieved on used of acupuncture as an adjunct treatment for subfertility. However, according to T&CM Division acupuncture service, in private practice acupuncture treatment for subfertility was offered around RM100 per session. Usually each patient requires about 10 treatment sessions.

5.5 LIMITATIONS

We acknowledge some limitations in our review and these should be considered when interpreting the results. Although there is no limitation in language, at the end only English full text articles were included. Regarding the included studies, the interventional acupunctures assessed were varied either manual acupuncture, electrical acupuncture, auricular acupuncture, TEAS acupuncture and etc. On the other hand, the causes of the infertile/subfertility were not specified in few studies which might also affect the overall analysis. Other limitations were involving the methodology of the primary studies included in the overview of SRs and the SRs itself.

6.0 CONCLUSION

Based on the review, acupuncture showed a potential to improve clinical pregnancy rate among subfertile women who were undergoing IVF procedure. However, the findings were supported with low to moderate quality of scientific evidence. For ongoing pregnancy rate, biochemical pregnancy rate, live birth rate and miscarriage, the findings varied. On the other hand, there were studies reported that patients who underwent IVF either with or without PCOS showed no significant difference in CPR, OPR, LBR, and miscarriage when compared to control group. In terms of safety, those with acupuncture experience significant mild adverse events such as local pain, itching and pain.

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8.0 APPENDIX

APPENDIX 1: LITERATURE SEARCH STRATEGY

Database: **Ovid MEDLINE(R) ALL <1946 to September 27, 2023>**

1. ACUPUNCTURE/
2. acupuncture.tw.
3. pharmacopuncture.tw.
4. INFERTILITY/
5. infertility.tw.
6. (sterility adj1 reproductive).tw.
7. sub-fertility.tw.
8. subfertility.tw.
9. FERTILITY/
10. determinant*, fertility.tw.
11. (fertility adj1 differential).tw.
12. fertility determinant*.tw.
13. fertility incentive*.tw.
14. (fertility adj2 (marital or natural)).tw.
15. (fertility adj1 preference*).tw.
16. (world fertility adj1 survey*).tw.
17. (fertility adj1 below replacement).tw.
18. subfecundity.tw.
19. fecundability.tw.
20. fecundity.tw.
21. fertility.tw.

Other Databases

EBM Reviews - Health Technology Assessment

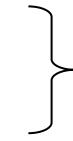
EBM Reviews - Cochrane database of systematic reviews

EBM Reviews - Cochrane Central Registered of Controlled Trials

EBM Reviews - Database of Abstracts of Review of Effects

EBM Reviews - NHS economic evaluation database

PubMed
INAHTA
US FDA



Same MeSH, keywords, limits used as per MEDLINE search



Same MeSH and keywords as per MEDLINE search

APPENDIX 2: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-I Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
- III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 3: EVIDENCE TABLE

(Available upon request)