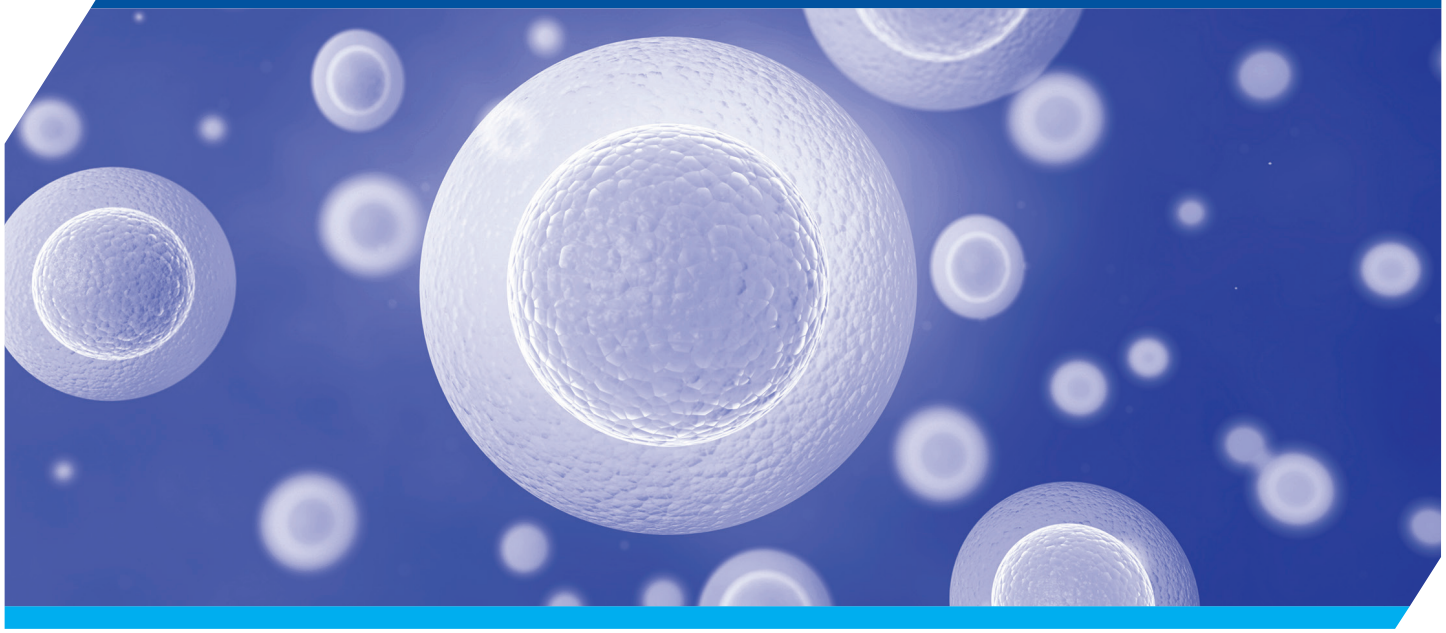
The Fertility Society of Australia

Pre-Conception Health Special Interest Group



The role of traditional and complementary medicine to improve fertility and emotional well-being

Traditional and Complementary Medicine (T&CM) is a broad set of healthcare practices that sit outside conventional medicine in many countries [1]. They are described by users as preventative and holistic, aimed to treat illness, promote health and well-being and used due to personal beliefs, preferences and resonance with traditions and cultural practices [2]. Common therapies include acupuncture, naturopathy and physical and manual therapies such as yoga, and massage [3]. Complementary medicines sold in pharmacies and health-food shops including herbs, vitamins, minerals and nutritional supplements are regulated under the Therapeutic Goods Act 1989. Few high-quality studies of the effect of T&CM on fertility have been undertaken. Of the published studies, most have focused on female fertility. Existing evidence of the effects of T&CM on subfertility and infertility-related distress is reviewed.

Your fertility

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Evidence review

Acupuncture and female subfertility and ART outcomes
Acupuncture is a Chinese medical treatment that involves insertion of fine sterile metal needles into prespecified areas of the body or acupuncture points. Auricular acupuncture is an acupuncture variant, where needles are inserted into acupuncture points on the outer ear. Another related treatment is acupressure, where sustained pressure is applied to acupuncture points [4].

A systematic review and meta-analysis of eight randomised controlled trials (RCTs) including 1,546 women with anovulatory infertility due to polycystic ovary syndrome (PCOS) was published in 2019 [5]. It found that acupuncture may improve restoration of regular menstrual periods. However, the overall quality of the evidence was low or very low and the authors concluded that there is currently insufficient evidence to support the use of acupuncture for treatment of ovulation disorders in women with PCOS.

An overview of 11 systematic reviews (SRs) (210 RCTs and 44,619 women undergoing IVF) found that despite increased clinical pregnancy rates (RR 1.12 95% CI 1.08 to 1.16, 7 SRs), there was no evidence that acupuncture had any effect on rates of live birth, ongoing pregnancy, or miscarriage regardless of whether acupuncture was performed around the time of oocyte retrieval or around the day of embryo transfer [6].

A subsequent systematic review included subgroup analyses that compared results from RCTs of acupuncture against no adjunctive treatment, against trials using sham controls [7]. There was evidence of increased chance of pregnancy when acupuncture was compared to no adjunctive treatment (RR 1.32, 95% CI 1.07–1.62, 12 trials, 2230 women). This positive effect was also seen with ongoing pregnancies (RR 1.42, 95% CI 1.17–1.73, 6 trials, 1144 women) and live births (RR 1.30, 95% 1.00–1.68, 9 trials, 1,980 women). No evidence of clinical benefit was found for acupuncture when it was compared to sham controls. This was also the case in a recent RCT of 848 women undergoing IVF where administration of acupuncture vs sham acupuncture at the time of ovarian stimulation and embryo transfer resulted in no significant difference in live birth rates [8].

Adverse effects of acupuncture were reported in six trials and included nausea, dizziness, tiredness, drowsiness, headache, chest pain, pain/itching at needle site [7].

Acupuncture to improve wellbeing in subfertile women
There is low quality evidence for the effect of acupuncture in reducing anxiety in women with infertility. A systematic review of four RCTs involving 595 infertile women [9] found a statistically significant reduction in anxiety for acupuncture compared to no treatment in two studies.

Acupuncture and male subfertility
Acupuncture may improve sperm quality and fertilisation rates in ICSI although effects on pregnancy and live birth rates have not been demonstrated. A systematic review and meta-analysis of four RCTs including 500 men with oligozoospermia or asthenozoospermia examined the effect of acupuncture on sperm quality. Men receiving acupuncture between 27 days and three months had significantly higher sperm concentration (mean difference (MD) 6.42 x 106 per ml, 95% CI 4.91 – 7.92) and rapid sperm motility (MD 6.35%, 95% CI 4.38 – 8.32, 3 RCTs, n=278) compared to controls, however this did not translate into increased clinical pregnancy rates [10]. None of the studies reported any adverse events; however, it was unclear whether data on adverse events were collected or reporting was inadequate.

There is very low-quality evidence of a small but consistent positive effect of acupuncture on sperm parameters in subfertile men. In a summary of six prospective studies [11], acupuncture for 10 days to 12 weeks was found to improve sperm viability [12, 13], concentration [12] motility [14, 15], percentage of normal morphology [16, 17], and possibly improve pregnancy rates [12]. The mechanism by which acupuncture may improve sperm quality remains unknown.

Acupuncture for improved wellbeing in subfertile men
Infertility can have a negative impact on men's psychological wellbeing and sexual function. A systematic review reported a higher prevalence of depression and anxiety in men with infertility compared to fertile men, and a higher incidence of erectile dysfunction and premature ejaculation [18]. Whilst there is very limited evidence for any interventions to improve the sexual health and wellbeing of infertile men, evidence from a meta-analysis of two RCTs (59 men) found no difference between acupuncture and sham acupuncture in improved erectile function (RR 2.73, 95% CI 0.42 to 17.78, p = 0.29, two RCTs n= 59) [19].

Chinese herbal medicine and female subfertility
Traditional Chinese herbal medicine (CHM) has a history of being used for female infertility in south-east Asian countries. CHMs are often polyherbal formulations containing a large number of herbal, mineral, or animal derived ingredients, with most formulas averaging between 10 and 15 components [20]. These formulas are usually tailored to traditional Chinese medicine diagnosis. A Delphi study reached consensus on proposed clinical practice guidelines for best CHM practice in the treatment of infertility due to PCOS in a Western healthcare context [21]. CHM formulas are often taken for three to six months pre-conceptually to improve fertility.

A meta-analysis of systematic reviews of CHM for women with infertility as a result of anovulation, PCOS, endometriosis, fallopian tube blockage or unexplained infertility included 40 RCTs and 4,247 women [22]. Compared to Western pharmaceutical treatments, CHM increased pregnancy rates (OR 3.14, 95% CI 2.72-3.62), decreased the risk of miscarriage and improved cervical mucous scores, biphasic temperatures and endometrial thickness. No significant side effects of CHM were reported. The quality of the included studies was assessed as low due to variation in the formulations of CHM, treatment protocols and due to variable comparators.

A systematic review of CHM treatments to improve outcomes for women with endometriosis included two RCTs (n=158) [23]. In one trial, no difference in pregnancy rates between CHM alone and gestrinone (antiprogesterone) subsequent to laparoscopic surgery, was found (RR 1.18, 95% CI 0.87-1.59). In the second trial, CHM administered orally and in combination with a herbal enema was compared with danazol (an androgen). Women taking CHM and those taking CHM in combination with a herbal enema were more likely to experience symptom relief than women taking danazol (RR 5.06, 95% CI 1.28-20.05 and RR 5.63, 95% CI 1.47-21.54, respectively).

A systematic review of CHM for women with anovulatory infertility due to PCOS included five trials (n=441 women) [24]. In three of these trials (n=300 women), increased pregnancy rates were found for CHM plus clomiphene, compared with clomiphene alone (OR 2.62, 95% CI 1.65-4.14). In the other two trials there were no statistically significant differences in pregnancy rates between CHM and clomiphene, or between CHM plus

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laparoscopic ovarian drilling (LOD) and LOD alone. Studies were of low quality as live birth rates were not reported and only one study assessed adverse effects.

Naturopathy and female subfertility

Women planning to conceive are more likely than women who are not, to consult a naturopath (OR 1.30, 95% CI 1.03-1.64) [3] with the aim to enhance their fertility, reduce PMS and maintain wellbeing [3, 25]. Naturopathy is a form of medicine recognized by the World Health Organization [26, 27] that is codified by holistic philosophy and principles of practice.

A systematic review of naturopathy included one small RCT investigating reproductive outcomes in a group of overweight women with PCOS (n=122) [28]. Increased pregnancy rates were found for two herbal medicine supplements containing extracts of *Glycyrrhiza glabra*, *Paeonia lactiflora*, *Cinnamomum verum*, *Hypericum perforatum* and *Tribulus terrestris* plus lifestyle coaching compared to lifestyle coaching alone in the subgroup of women wanting to conceive (RR 3.9, 95% CI 1.1 to 13.1, p=0.01). The was no evidence of improved live birth rates compared to lifestyle coaching alone and adverse effects, although few (three per cent), included dysfunctional menstrual bleeding and flu-like symptoms [29]. Caution interpreting these results is advised due to the small sub-sample of women and due to the absence of evidence for safety in pregnancy. One of the extracts used in the study was *Hypericum perforatum* (St Johns wort) which can interact negatively with hormone medicines [30] and other pharmaceuticals.

An RCT compared the effects of a complex supplement containing similar herbs (extracts of *Glycyrrhiza sp.*, *Dioscerea villosa*, *Camellia sinensis* and *Turnera diffusa*) plus nutrients (Folic acid, vitamin E, selenium and omega 3) against folic acid alone, taken for 28 to 56 days before hormone stimulation for IVF/ICSI on embryo quality (fragmentation and number of cells) and pregnancy rates in women undergoing IVF/ICSI (n=100) [31]. Slightly improved embryo quality at three days was found for the herbal nutrient complex (RR 1.6, 95% CI 1.01-2.60) however this did not translate to an increased pregnancy rate.

A third RCT evaluated Fertility Blend, a proprietary combination of herbal medicines (Vitex agnus castus and green tea extracts) and nutrients (L-arginine; vitamins E, B6, and B12; folate; iron; magnesium; zinc; and selenium) compared with a placebo [32]. Ninety-three women who had been trying to conceive for 6 to 36 months completed the study. After three months, the pregnancy rate was significantly higher in the herbal/nutritional group (26 per cent vs. 10 per cent, p = 0.01).

There is very low-quality evidence for the benefits of herbal and nutritional antioxidant supplements for women with subfertility [33]. A systematic review of 50 RCTs found a mild treatment effect for antioxidants compared to placebo, no treatment or usual care. Live birth rates were improved in eight RCTs including 651 women (OR 2.13, 95% CI 1.45 to 3.12, p< 0.001) and for spontaneous and ART conceived pregnancies in 26 RCTs including 4,271 women (OR 1.52, 95% CI 1.31 to 1.76, p< 0.001). Adverse effects including miscarriage and gastrointestinal disturbances were no more common in women who took antioxidant supplements than in controls (OR 0.79, 95% CI 0.58 to 1.08, p= 0.14, 18 RCTs, 2,834 women and OR 1.55, 95% CI 0.47 to 5.10, p=0.47, 3 RCTs, 343 women respectively).

Naturopathy and male subfertility

There is limited low-quality evidence for benefits of naturopathic (combined herbal nutrient) antioxidant supplements including carnitine, coenzyme Q10 200mg, vitamin D plus calcium, vitamin E 3-600mg, zinc and an antioxidant formulation (Menevit® Bayer Australia Ltd) for infertile men [34]. In a systematic review of 61 RCTs including 6264 men with infertility due to low sperm concentration and/or low motility or abnormally shaped sperm (morphology), significantly increased spontaneous clinical pregnancy rates (OR 2.97, 95% CI 1.91 to 4.63, p< 0.0001, 11 RCTs, 786 men) and live birth rates (OR 1.79, 95% CI 1.20 to 2.67, p= 0.005, 7 RCTs, 750 men) were observed for antioxidant supplements compared to placebo or no treatment. However, there was no evidence of reduced risk of miscarriage (OR 1.74, 95% CI 0.40 to 7.60, p= 0.46, 3 RCTs, 247 men).

No evidence of a positive effect on sperm concentration, motility, morphology or spontaneous pregnancies for antioxidant supplements was reported in another systematic review [35]. Two RCTs compared vitamin C (1000mg/day) alternating with E (800mg/day) and vitamin E (600mg) alone against placebo controls over six to eight weeks [36, 37]. No differences were found between groups.

There is some evidence that selenium, Co-enzyme Q10 (CoQ10) and carnitine supplements may improve sperm quality and increase pregnancy rates for subfertile men. A meta-analysis of seven placebo controlled RCTs including 644 infertile men, observed improved sperm concentration for Selenium (1-200mcgs per day for 12-26 weeks) (SMD 0.64%, 95% CI 0.38 to 0.90, two trials, 245 men) and CoQ10 (2-300mg per day for 12-26 weeks) (SMD 0.95%, 95% CI 0.72 to 1.19, three trials, 314 men) (35). Naturally conceived pregnancy rates were increased for men taking selenium (200mcg for 26 weeks) [38], for CoQ10 (200 mg per day for 26 weeks) [39] and for carnitine [40, 4]) compared to placebo controls.

The usefulness of these results is limited due to the very low methodological quality of studies [35]. Only two trials investigated effects of naturopathy on pregnancy rates, and none investigated its effects on live birth rates or assessed adverse effects.

Herbal medicine and female subfertility

Two systematic reviews of RCTs examining the effects on fertility of herbal medicine reported very low-level evidence of benefit for a European herbal proprietary preparation (Klimadynon®), containing *Actea racemosa* (black cohosh), as adjunct therapy to ovulation induction using clomiphene [42, 43]. One of the reviews (24 RCTs and 1,406 women) found higher pregnancy rates for women taking adjunct Klimadynon®, compared to no adjunct controls (OR 2.78 95% CI 1.83-4.23, 1 study, 196 women) [43]. When compared with adjunct Ethinyl oestradiol, women taking black cohosh had significantly higher oestradiol levels, thicker endometrium and fewer days to follicular maturation, although these clinical improvements did not translate to significantly improved pregnancy rates [42].

A more recent RCT, found similar clinical improvements for adjunct black cohosh in women with anovulatory infertility undergoing clomiphene induction compared to no adjunct controls (n=100) [44]. Significantly increased endometrial thickness, and improved hormone profiles (FSH to LH ratio and higher mid luteal progesterone) were found after one cycle in women who took the black cohosh. However, there was no statistically significant improvement in pregnancy rates. There is concern about the safety of black cohosh during pregnancy, especially in the first trimester, due to possible hormonal effects [45].

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Herbal medicine for male subfertility
There is very low-quality evidence from RCTs of two herbal medicines improving sperm characteristics, and no evidence that herbal medicine improves pregnancy or live birth rates for subfertile men. An RCT investigated *Nigella sativa* (black carraway seeds) taken over eight weeks against placebo in 64 subfertile men [46]. Men taking the black seed extract had significantly more sperm and higher percentages of motile and normal shaped sperm compared to controls. A second RCT investigated *Withania somnifera* (ashwaganda) against placebo in 46 men with oligospermia [47]. After 90 days, men taking ashwaganda had 167 per cent more sperm, 57 per cent improved motility and 53 per cent higher semen volume than controls. Another RCT recruited 260 infertile men with idiopathic infertility in an investigation of *Crocus sativus* (saffron) taken for 26 weeks against placebo [48]. No improvements in sperm density, morphology or motility were found for saffron. The evidence from these studies is limited by the absence of reporting of adverse effects.

Manual therapies and female fertility
There is little evidence of benefit on fertility from manual therapies. In one RCT reflexology versus sham reflexology was administered to 48 anovulatory women attending a fertility clinic [49]. Women received eight sessions over 10 weeks of either foot reflexology or sham reflexology with gentle massage. There were no differences between the reflexology and control groups in rates of ovulation (42 per cent vs 46 per cent) or pregnancy (15 per cent vs 9 per cent).

Yoga to improve wellbeing of subfertile women
There is some low-quality evidence from two observational studies for yoga reducing stress associated with infertility. In a non-randomised study of women waiting to do IVF, the effects on emotional health of a three-month yoga program, compared with no yoga, were investigated [50]. No improvements in scores on standardised measures of emotional wellbeing were observed for women doing yoga compared to those who were not. Another observational study investigated Hatha yoga over six weeks for stress associated with infertility among 49 women waiting for IVF [51]. Yoga was found to improve infertility-related quality of life and to reduce negative feelings and thoughts associated with infertility.

Mind-body therapies to improve wellbeing of subfertile women
Potential benefits on emotional wellbeing of art therapy, and other creative therapies have not been systematically assessed. Small low-quality studies report benefits including stress reduction, validation of feelings, and fostering self-awareness.

Summary

There is some evidence of benefit from acupuncture, Chinese herbal medicine and naturopathy in improving fertility outcomes for women with specific clinical infertility diagnoses and of acupuncture and antioxidant supplements in improving sperm quality in infertile men. Acupuncture, yoga and art therapy may reduce infertility-related distress.

An observational study of women using CAM during 12 months of ART treatment found a lower live birth rate among those using CAM compared with non-users (52). These observations were not associated with a specific CAM modality and may have been due to CAM users having a poorer fertility prognosis.

Recommendations

There is insufficient evidence to advise individuals of a clear benefit to fertility outcomes from many T&CMs. Data from systematic reviews and clinical trials provide no evidence of adverse effects of T&CMs but individuals who use T&CMs in the peri-conceptual period should be encouraged to discuss this with their general practitioner or fertility specialist to avoid potential risks and improve continuity of care.

For more information about pre-conception health visit

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Written by Caroline Smith in 2015 and updated by Susan Arentz in 2021 on behalf of PCHSIG s.arentz@westernsydney.edu.au

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References

1. Wieland LS, Manheimer E, Berman BM. Development and classification of an operational definition of complementary and alternative medicine for the Cochrane collaboration. Alternative Therapies in Health and Medicine. 2011;17(2):50.
2. Ried K, Alfred A. Quality of life, coping strategies and support needs of women seeking Traditional Chinese Medicine for infertility and viable pregnancy in Australia: a mixed methods approach. BMC Women's Health. 2013;13(1):17.
3. Steel A, Adams J, Sibbritt D. The characteristics of women who use complementary medicine while attempting to conceive: results from a nationally representative sample of 13,224 Australian women. Women's Health Issues. 2017;27(1):67-74.
4. Smith C, Armour M, Ee C, editors. Complementary Therapies and Medicines and Reproductive Medicine. Seminars in Reproductive Medicine; 2016.
5. Lim CED, Ng RWC, Cheng NCL, Zhang GS, Chen H. Acupuncture for polycystic ovarian syndrome. Cochrane Database of Systematic Reviews. 2019(7).
6. Xi J, Chen H, Peng Z-h, Tang Z-x, Song X, Xia Y-b. Effects of acupuncture on the outcomes of assisted reproductive technology: an overview of systematic reviews. Evidence-Based Complementary and Alternative Medicine. 2018;2018.
7. Smith CA, Armour M, Shewamene Z, Tan HY, Norman RJ, Johnson NP. Acupuncture performed around the time of embryo transfer: a systematic review and meta-analysis. Reproductive Biomedicine Online. 2019.
8. Smith CA, de Lacey S, Chapman M, Ratcliffe J, Norman RJ, Johnson NP, et al. Effect of acupuncture vs sham acupuncture on live births among women undergoing in vitro fertilization: a randomized clinical trial. JAMA. 2018;319(19):1990-8.
9. Hassanzadeh Bashtian M, Latifnejad Roudsari R, Sadeghi R. Effects of acupuncture on anxiety in infertile women: a systematic review of the literature. Journal of Midwifery and Reproductive Health. 2017;5(1):842-8.
10. Jerng UM, Jo J-Y, Lee S, Lee J-M, Kwon O. The effectiveness and safety of acupuncture for poor semen quality in infertile males: a systematic review and meta-analysis. Asian Journal of Andrology. 2014;16(6):884.
11. Ng EHY, So WS, Gao J, Wong YY, Ho PC. The role of acupuncture in the management of subfertility. Fertility and Sterility. 2008;90(1):1-13.
12. Siterman S, Eltes F, Wolfson V, Lederman H, Bartoov B. Does acupuncture treatment affect sperm density in males with very low sperm count? A pilot study. Andrologia. 2000;32(1):31-9.
13. Siterman S, Eltes F, Wolfson V, Zabludovsky N, Bartoov B. Effect of acupuncture on sperm parameters of males suffering from subfertility related to low sperm quality. Archives of Andrology. 1997;39(2):155-61.
14. Gerhard I, Jung I, Postneek F. Effects of acupuncture on semen parameters/hormone profile in infertile men. Molecular Andrology. 1992;4:9-24.
15. Zhang M, Huang G, Lu F, Paulus W, Sterzik K. Influence of acupuncture on idiopathic male infertility in assisted reproductive technology. Journal of Huazhong University of Science and Technology Medical sciences. 2002;22(3):228-30.
16. Pei J, Strehler E, Noss U, Abt M, Piomboni P, Baccetti B, et al. Quantitative evaluation of spermatozoa ultrastructure after acupuncture treatment for idiopathic male infertility. Fertility and Sterility. 2005;84(1):141-7.
17. Gurfinkel E, Cedenho AP, Yamamura Y, Srougi M. Effects of acupuncture and moxa treatment in patients with semen abnormalities. Asian Journal of Andrology. 2003;5(4):345-8.
18. Luk BH-K, Loke AY. The impact of infertility on the psychological well-being, marital relationships, sexual relationships, and quality of life of couples: a systematic review. Journal of Sex & Marital Therapy. 2015;41(6):610-25.
19. Lee MS, Shin BC, Ernst E. Acupuncture for treating erectile dysfunction: a systematic review. Brittish Journal of Urology International. 2009;104(3):366-70.
20. De Lacey S, Smith CA, Paterson C. Building resilience: a preliminary exploration of women's perceptions of the use of acupuncture as an adjunct to In Vitro Fertilisation. BMC Complementary and Alternative Medicine. 2009;9(1):50.
20. De Lacey S, Smith CA, Paterson C. Building resilience: a preliminary exploration of women's perceptions of the use of acupuncture as an adjunct to In Vitro Fertilisation. BMC Complementary and Alternative Medicine. 2009;9(1):50.
21. Lai L, Flower A, Moore M, Lewith G. Developing clinical practice guidelines for Chinese herbal treatment of polycystic ovary syndrome: a mixed-methods modified Delphi study. Complementary Therapies in Medicine. 2015;23(3):430-8.
22. Ried K. Chinese herbal medicine for female infertility: an updated meta-analysis. Complementary Therapies in Medicine. 2015;23(1):116-28.
23. Flower A, Liu JP, Lewith G, Little P, Li Q. Chinese herbal medicine for endometriosis. Cochrane Database of Systematic Reviews. 2012(5).
24. Zhou K, Zhang J, Xu L, Wu T, Lim CED. Chinese herbal medicine for subfertile women with polycystic ovarian syndrome. Cochrane Database of Systematic Reviews. 2016(10).
25. Rayner J-A, McLachlan HL, Forster DA, Cramer R. Australian women's use of complementary and alternative medicines to enhance fertility: exploring the experiences of women and practitioners. BMC Complementary and Alternative Medicine. 2009;9(1):52
26. WHO. Benchmarks for training in traditional/complementary and alternative medicine: Benchmarks for training in naturopathy (WB 935). In: Organization WH, editor. Retrieved 26/08/2019 from: http://wwwwhoint/medicines/areas/traditional/BenchmarksforTraininginNaturopathypdf: WHO Press, World Health Organization, Switzerland 2010.
27. Lloyd I, Wardle J. World Naturopathic Federation: The Central Role of Research in the Growth of the Global Naturopathic Profession. The Journal of Alternative and Complementary Medicine. 2019;25(2):129-32.

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References

28. Myers SP, Vigar V. The state of the evidence for whole-system, multi-modality naturopathic medicine: a systematic scoping review. Journal of Alternative & Complementary Medicine. 2019;25(2):141.

29. Arentz S, Smith CA, Abbott J, Fahey P, Cheema BS, Bensoussan A. Combined lifestyle and herbal medicine in overweight women with polycystic ovary syndrome (PCOS): A randomized controlled trial. Phytotherapy Research. 2017;31(9):1330-40.

30. Hall SD, Wang Z, Huang SM, Hamman MA, Vasavada N, Adigun AQ, et al. The interaction between St John's wort and an oral contraceptive. Clinical Pharmacology & Therapeutics. 2003;74(6):525-35.

31. Nouri K, Walch K, Weghofer A, Imhof M, Egarter C, Ott J. The impact of a standardized oral multinutrient supplementation on embryo quality in in vitro fertilization/intracytoplasmic sperm injection: a prospective randomized trial. Gynecologic and Obstetric Investigation. 2017;82(1):8-14.

32. Westphal LM, Polan ML, Trant AS, Mooney S. A nutritional supplement for improving fertility in women. Journal Reproductive Medicine. 2004;49(4):289-93.

33. Showell MG, Mackenzie-Proctor R, Jordan V, Hart RJ. Antioxidants for female subfertility. Cochrane Database of Systematic Reviews. 2017(7).

34. Smits RM, Mackenzie-Proctor R, Yazdani A, Stankiewicz MT, Jordan V, Showell MG. Antioxidants for male subfertility. Cochrane Database of Systematic Reviews. 2019(3).

35. Buhling KJ, Schumacher A, zu Eulenburg C, Laakmann E. Influence of oral vitamin and mineral supplementation on male infertility: a meta-analysis and systematic review. Reproductive Biomedicine online. 2019.

36. Rolf C, Cooper T, Yeung C, Nieschlag E. Antioxidant treatment of patients with asthenozoospermia or moderate oligoasthenozoospermia with high-dose vitamin C and vitamin E: a randomized, placebo-controlled, double-blind study. Human Reproduction. 1999;14(4):1028-33.

37. Kessopoulou E, Powers HJ, Sharma KK, Pearson MJ, Russell JM, Cooke ID, Barratt, CLR. A double-blind randomized placebo cross-over controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated male infertility. Fertility and Sterility. 1995;64(4):825-31.

38. Scott R, MacPherson A, Yates R, Hussain B, Dixon J. The effect of oral selenium supplementation on human sperm motility. British Journal of Urology. 1998;82(1):76-80.

39. Balercia G, Buldreghini E, Vignini A, Tiano L, Paggi F, Amoroso S, Ricciardo-Lamonica G, Boscaro M, Lenzi A, Littarru, GP. Coenzyme Q10 treatment in infertile men with idiopathic asthenozoospermia: a placebo-controlled, double-blind randomized trial. Fertility and Sterility. 2009;91(5):1785-92.

40. Balercia G, Regoli F, Armeni T, Koverech A, Mantero F, Boscaro M. Placebo-controlled double-blind randomized trial on the use of L-carnitine, L-acetylcarnitine, or combined L-carnitine and L-acetylcarnitine in men with idiopathic asthenozoospermia. Fertility and Sterility. 2005;84(3):662-71.

41. Lenzi A, Sgro P, Salacone P, Paoli D, Gilio B, Lombardo F, Santulli M, Agarwal A, Gandini L. A placebo-controlled double-blind randomized trial of the use of combined l-carnitine and l-acetyl-carnitine treatment in men with asthenozoospermia. Fertility and Sterility. 2004;81(6):1578-84.

42. Clark N, Will M, Moravek M, Fisseha S. A systematic review of the evidence for complementary and alternative medicine in infertility. International Journal of Gynecology & Obstetrics. 2013;122(3):202-6.

43. Arentz S, Smith CA, Abbott J, Bensoussan A. Nutritional supplements and herbal medicines for women with polycystic ovary syndrome; a systematic review and meta-analysis. BMC Complementary and Alternative Medicine. 2017;17(1):500.

44. Kamel HH. Role of phyto-oestrogens in ovulation induction in women with polycystic ovarian syndrome. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2013;168(1):60-3.

45. Dugoua J-J, Seely D, Perri D, Koren GK, Mills E. Safety and efficacy of black cohosh (Cimicifuga racemosa) during pregnancy and lactation. Journal of Population Therapeutics and Clinical Pharmacology. 2006;13(3).

46. Kolahdooz M, Nasri S, Modarres SZ, Kianbakht S, Huseini HF. Effects of *Nigella sativa* L. seed oil on abnormal semen quality in infertile men: a randomized, double-blind, placebo-controlled clinical trial. Phytomedicine. 2014;21(6):901-5.

47. Ambiye VR, Langade D, Dongre S, Aptikar P, Kulkarni M, Dongre A. Clinical evaluation of the spermatogenic activity of the root extract of Ashwagandha (*Withania somnifera*) in oligospermic males: a pilot study. Evidence-Based Complementary and Alternative Medicine. 2013;2013.

48. Safarinejad MR, Shafiei N, Safarinejad S. A prospective double-blind randomized placebo-controlled study of the effect of saffron (*Crocus sativus* Linn.) on semen parameters and seminal plasma antioxidant capacity in infertile men with idiopathic oligoasthenoteratozoospermia. Phytotherapy Research. 2011;4(25):508-16.

49. Holt J, Lord J, Acharya U, White A, O'Neill N, Shaw S, Barton, A. The effectiveness of foot reflexology in inducing ovulation: a sham-controlled randomized trial. Fertility and Sterility. 2009;91(6):2514-9.

50. Valoriani V, Lotti F, Vanni C, Noci M-C, Fontanarosa N, Ferrari G, Cozzi C, Noci I,. Hatha-yoga as a psychological adjuvant for women undergoing IVF: a pilot study. European Journal of Obstetrics and Gynecology. 2014(176):158-62.

51. Oron G, Allnutt E, Lackman T, Sokal-Arnon T, Holzer H, Takefman J. A prospective study using Hatha Yoga for stress reduction among women waiting for IVF treatment. Reproductive Biomedicine online. 2015;30(5):542-8.

52. Boivin J, Schmidt L. Use of complementary and alternative medicines associated with a 30% lower ongoing pregnancy/live birth rate during 12 months of fertility treatment. Human Reproduction. 2009;24(7):1626-31.