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REVIEW ARTICLE

A systematic review of the evidence for complementary and alternative medicine in infertility

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ABSTRACT

Background: The use of complementary and alternative medicine (CAM) by patients and physicians has increased markedly in recent years. Many case reports, case series, and uncontrolled trials of varying quality have been completed; however, there is now a slowly increasing number of randomized controlled trials (RCTs) examining the use of CAM. *Objectives:* To identify, survey, and review RCTs investigating the use of CAM for infertility treatment. *Search strategy:* The MEDLINE and Cochrane databases were electronically searched. *Selection criteria:* RCTs examining modalities for treatment or improvement of health status were reviewed. *Data collection and analysis:* RCTs were included based on use of objective measures, articles written in English, availability through the University of Michigan database, and clear published clinical outcomes. *Main results:* Thirty-seven articles assessing a variety of CAM modalities met inclusion criteria. Acupuncture, selenium supplementation, weight loss, and psychotherapeutic intervention had 3 or more studies demonstrating beneficial effect. Other interventions had been studied less and evidence for them was limited. *Conclusions:* Although there is preliminary evidence of the effectiveness of some CAM interventions among infertile patients, many of these interventions require further investigation before they can be considered for routine clinical use.

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1. Introduction

The use of complementary and alternative medicine (CAM) by both infertility patients and physicians has increased markedly over the past 3 decades [1]. Frequently, patients utilize these therapies in addition to, or in lieu of, biomedical therapy [2]. Within recent years, substantial shifts in CAM use have occurred, and studies examining the scientific basis of these therapies are mounting [1]. Subsequently, in contemporary practice, an integrated structure is emerging where biomedical treatment and CAM are blended.

The Cochrane Collaboration defines CAM as "…a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or a culture in a given historical period" [3].

Complementary and alternative medicine interventions encompass a broad range of interventions that act through a variety of measurable and immeasurable mechanisms. These modalities include, but are not limited to, homeopathic and herbal medicines, acupuncture and acupressure, energy healing, massage, specified diets, and psychosocial interventions. A huge number of case reports, case series, and uncontrolled trials of varying quality have been executed examining CAM. Fortunately, randomized controlled trials (RCTs) critically examining CAM are accumulating [1]. The aim of the present review was to provide a comprehensive overview of the evidence-based CAM therapies available for infertility treatment.

2. Materials and methods

A preliminary search of the MEDLINE and Cochrane databases was performed using the keywords "CAM," "alternative medicine," "acupuncture," "acupressure," and "herbal medicine," cross-referenced with "infertility," "IVF," and "assisted reproduction." The results and their bibliographies were analyzed and used to develop a more extensive search of the MEDLINE database on February 3, 2011, using the keywords listed in Table 1, with a secondary search completed on November 3, 2012. These search results were examined for articles involving acupuncture, herbs and supplements, diet and nutrition, and psychotherapy and their therapeutic use in infertility. The sequence and criteria for exclusion are provided in Fig. 1. RCTs were included based on use of objective measures, articles written in the English language after January 1, 1986, and inclusion of clear published clinical outcomes. Observational and quasi-experimental studies were excluded from the review. Given the huge number of studies on the use of traditional Chinese medicine and the lack of such studies

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Table 1
Search terms.

Main terms	Cross-referenced terms	
Infertility	Acupressure	Licorice root
IVF	Acupuncture	Macrobiotic
Assisted reproduction	Antioxidant supplement	Massage
	Aromatherapy	Meditation
	Ayurveda	Meridians
	Bioelectromagnetic	Milk thistle
	Biofeedback	Mind body medicine
	Black cohosh	Mindfulness
	CAM	Music therapy
	Chasteberry	Nutritional supplement
	Chinese medicine	Oral antioxidant
	Chinese yam	Phytoestrogen
	Chiropractic	Primrose oil
	Complementary and alternative medicine	Probiotic
	Diet	Psychotherapy
	Dong quai	*Qi*
	Electrophysiology	Red clover
	Essential fatty acid	Reiki
	Ethnobotanical	Shaman
	Ethnobotany	Soy
	Exercise	Spiritual healing
	False unicorn	Stress
	Guided imagery	Supplements
	Healing touch	*Tai chi*
	Herbal	TCM
	Holistic	Therapeutic touch
	Homeopathy	Traditional healing
	Hops flower	Vegan
	Hypnosis	Vegetarian
	Integrative medicine	*Viburnum opulus*
	Isoflavone	Wild yam
	Journaling	Yoga

Abbreviations: CAM, complementary and alternative medicine; TCM, traditional Chinese medicine.

published in English, this modality was excluded from the review. Owing to the large number of outcomes reported in many of the studies reviewed, not all results could be included.

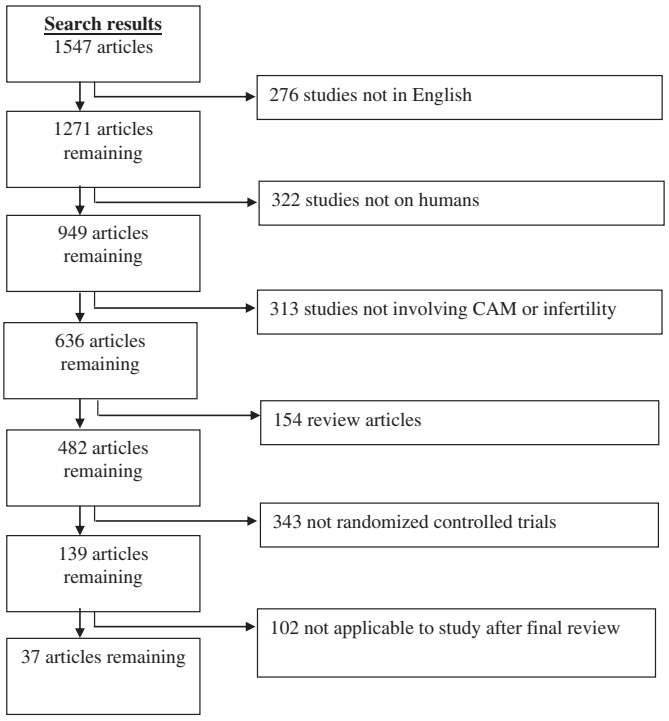

Fig. 1. Search methodology.

3. Results

Based on the inclusion criteria, 37 RCTs were included (Fig. 1). The results are presented according to therapeutic modality.

3.1. Acupuncture

In the past 15 years, several studies have sought to examine the role of acupuncture as an adjunct to infertility treatment. Acupuncture is administered in a point-specific manner along "meridians," which presumably correlate with energy flow (*qi*) throughout the body. Acupuncture can be administered with or without electrical stimulation and is occasionally combined with traditional Chinese herbal medicines. A key factor to consider in evaluating the effect of acupuncture is that, when practiced according to traditional Chinese medicine, acupoints are selected based on both diagnosis and patient-specific symptomatology. While RCTs are designed to evaluate therapeutic interventions rigorously, they do not share this individualized approach and, rather, adhere to a standardized protocol. This standardization, while essential for enabling statistical analyses, may confound the demonstrated effect of acupuncture in individual patients.

3.1.1. Male factor infertility

Acupuncture has been examined for its role in male infertility, primarily among men with abnormal semen parameters. A placebo-controlled study by Dieterle et al. [4] compared true and placebo acupuncture in 57 men with severe oligoasthenospermia. Those who had true acupuncture experienced significant improvement in total motile sperm counts but lower semen volume, and pregnancy rates were not assessed. In another physiologic study of healthy male volunteers (30–35 years of age) [5], ultrasound Doppler flowmetry was used to assess differences in testicular blood flow before and after acupuncture treatment. Improvements in blood flow were noted in patients who received acupuncture with electrical stimulation (10 Hz) and those who had stimulation administered at points correlating to genital problems (ST-29 or *guilai*) [5].

Acupuncture may have a role for couples seeking a holistic approach to improving semen quality. However, subsequent placebo-controlled studies are warranted to evaluate the precise mechanism of these interventions and whether they result in greater pregnancy rates.

3.1.2. In vitro fertilization (IVF) and assisted reproductive technology (ART) outcomes

Acupuncture as an adjunct to IVF has recently been the topic of several studies. Although the physiology is poorly understood, a small study by Ho et al. [6] demonstrated a reduced pulsatility index of uterine arteries when electro-acupuncture was performed twice weekly until the day before oocyte retrieval. A small study by Magarelli et al. [7] showed significant changes in serum cortisol and prolactin during controlled ovarian hyperstimulation among women who received acupuncture compared with those who did not, which subsequently correlated with higher pregnancy rates in the former group.

Three RCTs have reported benefits of acupuncture as an adjunct to standard analgesia and anesthesia regimens for oocyte retrieval. Stener-Victorin et al. [8] first evaluated this in 150 women undergoing IVF and compared the analgesic effects of a paracervical block in combination with either electro-acupuncture or alfentanil. No differences were noted in pain from oocyte retrieval. Sator-Katzenschlager et al. [9] additionally noted benefits of acupuncture in reducing retrieval-associated pain when added to standard analgesic regimens. However, the use of acupuncture seems to be limited as an adjunct to standard regimens; a study by Gejervall et al. [10] comparing electro-acupuncture with conventional analgesia demonstrated higher pain scores during and immediately after retrieval among women who received acupuncture.

The first RCT to evaluate acupuncture as an adjuvant therapy for improving IVF pregnancy rates was performed in Germany in 2002. Paulus et al. [11] randomized 160 infertile women (21–43 years of age) undergoing IVF to acupuncture or no acupuncture. Those in the acupuncture arm had auricular acupuncture at fertility-specific acupoints on the day of embryo transfer (ET), 25 minutes before and immediately after the procedure. The control arm underwent ET without adjunct therapy. The clinical pregnancy rate among those who received acupuncture was 42.5%, compared with 23.6% among those who did not ($P = 0.03$). This effect was re-demonstrated in 2006 by Westergaard et al. [12], who reported a clinical pregnancy rate of 39% among women who underwent acupuncture and 24% among those who did not ($P = 0.038$). Several differences in this study are important to highlight. No auricular acupuncture was performed, possibly showing less of a contribution of this particular acupoint. Additionally, a third arm examining additional acupuncture 2 days after ET showed no added benefit. A trial by Dieterle et al. [13], however, showed some benefit of luteal-phase acupuncture versus sham acupuncture, with clinical pregnancy rates of 33.6% and 15.6%, respectively.

Despite these initial studies showing a positive effect of adjuvant acupuncture on IVF, subsequent studies have yet to produce similar results. Smith et al. [14] failed to show improvement in clinical pregnancy rate (23% vs 31%) when comparing sham and true acupuncture on the day of ET. So et al. [15] conducted a similar trial comparing true acupuncture on the day of ET with placebo acupuncture using blunt needles; the authors reported higher pregnancy rates in the placebo group (55.1% vs 43.8%; $P = 0.038$). Two large infertility groups in the USA have also recently reported no benefit of adjunct acupuncture. Domar et al. [16] compared true acupuncture with no acupuncture in patients undergoing IVF and reported similar pregnancy rates (30.8% vs 33.8%). Moy et al. [17] compared true acupuncture with sham acupuncture in the IVF population and also found no difference in pregnancy rates (45.3% vs 52.7%); however, theirs was an underpowered study.

Although results are mixed with regard to the benefits of acupuncture in relation to IVF pregnancy rates, all studies were consistent in showing no increase in adverse events and several showed improvements in anxiety levels [14,16]. However, it must be remembered that acupuncture is potentially time consuming and expensive, and it is not painless; furthermore, there is still no irrefutable evidence from RCTs to prove its effect. As an IVF adjunct, acupuncture may provide an alternative approach for improving anxiety and the pain associated with the procedural aspects of IVF and it may have a positive effect on pregnancy rates; however, additional studies are warranted.

3.2. Herbs and supplements

Several dietary supplements composed of a variety of herbs and minerals are commercially available, marketed for use for infertility, and unregulated by regulatory institutions such as the Food and Drug Administration. The following is a review of the evidence for several herbs and supplements used for male and female infertility.

3.2.1. Male factor infertility

Selenium is one of the most studied supplements for male infertility, and 4 studies have examined its impact on semen parameters. In a dietary study of 11 healthy men, participants were fed a diet with varying concentrations of selenium over a 120-day period [18]. Plasma concentrations correlated with dietary supplementation, and participants fed a diet high in selenium had 18% decreased total motile sperm fraction, decreased triiodothyronine, and increased thyroid-stimulating hormone. This indicates that diets high in selenium might be associated with decreased sperm motility, potentially secondary to effects on thyroid hormone production. Safarinejad et al. [19] completed a double-blind, placebo-controlled RCT of 468 healthy men. Participants who were given selenium together with N-acetylcysteine (NAC) had increased sperm concentration, sperm motility, and percentage of morphologically normal sperm—all of which correlated with seminal concentrations of selenium and NAC. In another study, 54 men were randomized to vitamin E with selenium versus vitamin B alone, with 20 returning for follow-up [20]. Participants taking vitamin E with selenium were found to have decreased lipid peroxidation and improved sperm motility. In a study by Scott et al. [21], men treated with selenium had increased sperm motility but no change in sperm density compared with those treated with placebo.

Zinc supplementation has also been examined with regard to male factor infertility. In a dietary study, 11 male volunteers were fed a zinc-deprived diet for 28 days [22]. They were subsequently noted to have decreased serum testosterone (26.9 vs 21.9 nmol/L) and decreased seminal volumes (3.30 vs 2.24 mL). Another study of infertile men who smoked cigarettes demonstrated that, compared with placebo, zinc supplementation improved sperm quality and increased seminal interleukin-4, while reducing tumor necrosis factor-α and interferon-γ [23]. As such, it would seem that zinc is an important dietary component in the production of semen.

With regard to antioxidants, Keskes-Ammar et al. [20] found that participants taking vitamin E with selenium had decreased lipid peroxidation and improved sperm motility compared with men whose diets were supplemented with vitamin B. Whether this effect was secondary to the selenium or the vitamin E is unknown. Additionally, Kessopoulou et al. [24] demonstrated that oral vitamin E improved the in vitro function of human spermatozoa, as assessed by zona-binding test. Thus, it seems that vitamin E supplementation may have some promise in improving semen parameters; however, more evidence is needed. A proprietary antioxidant preparation, Menevit (Bayer Australia, Pymble, New South Wales, Australia), was studied by Tremellen et al. [25]. It was found to improve pregnancy rates (38.5% vs 16%; $P < 0.05$) but not oocyte fertilization rates or embryo quality among couples undergoing IVF-intracytoplasmic sperm injection. Safarinejad et al. [26] examined semen parameters in infertile men supplemented with the antioxidant coenzyme Q_{10}. Supplementation was associated with an improvement in sperm density, motility, count, and morphology, as well as an increased mean acrosome reaction. There was no effect on pregnancy rate.

Shahin et al. [27] examined the use of Indian ginseng (*Withania somnifera*; 5 g per day orally for 3 months), which is commonly used in Ayurvedic medicine for infertility. Participants were noted to have decreased levels of oxidants and improved levels of antioxidants and vitamins A, C, and E in seminal plasma. Additionally, they had increased levels of testosterone, luteinizing hormone, follicle-stimulating hormone, and prolactin ($P < 0.05$) following treatment. Thus, Indian ginseng may offer some benefit for the treatment of male factor infertility.

Overall, upon examining many supplements for male factor infertility, the breadth of possibilities and the lack of data confirming efficacy are apparent. There is at least preliminary evidence for the use of selenium, zinc, and Indian ginseng, as well as a wealth of antioxidants such as vitamin E and coenzyme Q_{10}, to improve semen parameters. How these supplements directly affect subsequent pregnancy and birth rates has yet to be determined.

3.2.2. Female factor infertility

Multiple vitamin and herbal supplements have been examined with regard to their effect on female infertility. Many herbal preparations—a large number of which contain phytoestrogens—are marketed purporting positive fertility effects. Black cohosh (*Cimicifuga racemosa*) is a phytoestrogen-containing herbaceous flowering plant native to the USA. A primary study by Shahin et al. [28] demonstrated that, in women with unexplained infertility who were undergoing clomiphene induction, those supplemented with black cohosh (120 mg per day, cycle days 1–12) had increased levels of luteinizing hormone, progesterone, and estradiol, in addition to increased endometrial thickness and

clinical pregnancy rates (36.7% vs 13.6%; $P < 0.01$) compared with controls. In a subsequent study, Shahin et al. [27] compared follicular-phase black cohosh supplementation with ethinyl estradiol supplementation; black cohosh improved endometrial thickness, follicular maturation, and estradiol levels among couples with unexplained infertility undergoing clomiphene induction. There was no statistically significant difference in clinical pregnancy rates (14.0% versus 21.1%). In a study by Unfer et al. [29], women treated with both progesterone and phytoestrogens for luteal-phase support were found to have higher rates of implantation (25.4% vs 20.2%), clinical pregnancy (39.3% vs 20.9%), and delivery (30.3% vs 16.2%) compared with controls.

A study by Westphal et al. [30] found that nutritional supplementation with FertililtyBlend (Daily Wellness, Honolulu, HI, USA)—a proprietary nutritional supplement containing chasteberry and green tea extracts, L-arginine, vitamins, and minerals—increased the average number of days in the cycle in which basal temperatures were greater than 37 °C during the luteal phase and increased pregnancy rates after 5 months of supplementation compared with controls (26% vs 10%; $P = 0.01$).

A single study on the use of intravaginal probiotics immediately after oocyte retrieval met inclusion criteria. In this RCT of vaginal probiotic supplementation versus placebo, Gilboa et al. [31] found that probiotic supplementation immediately after oocyte retrieval had no effect on vaginal colonization or pregnancy rate in IVF cycles [31]. Thus, there is limited evidence that some herbal preparations improve pregnancy rates; however, more studies must be completed to prove safety and efficacy.

3.3. Diet and nutrition

Three studies examining diet and nutrition—focusing primarily on weight loss interventions in obese infertile women—met review criteria. Weight loss as small as 5%–10% of body weight has been shown to improve reproductive function in obese patients with polycystic ovary syndrome (PCOS) [32]; however, the best methods for weight loss in these patients have not yet been determined. Additionally, fertility-enhancing medications might not be necessary for patients who can successfully restore their reproductive function through weight loss.

A primary intervention examined was the impact of low-calorie diets. Stamets et al. [33] investigated the effects of 2 different low-calorie diets in 26 obese infertile women with PCOS over 1 month. Participants were randomized to a diet high in either protein or carbohydrate, and all diets were designed to create a 1000-kcal deficit per day. Women in both groups experienced significant weight loss, without any significant differences noted between the diets. Women in both groups were also noted to have a significant decrease in testosterone, fasting insulin, insulin-to-glucose ratio, circulating leptin, total cholesterol, and low-density lipoprotein (LDL). Clinical markers of reproductive function, such as ovulation or pregnancy rates, were not reported.

Karimzadeh and Javedani [34] studied 343 overweight and infertile PCOS patients; the women were randomized to treatment with lifestyle modification (low-calorie diet and exercise), clomiphene alone, metformin alone, or clomiphene with metformin for 8 months. The authors reported no significant differences between the groups in terms of menstrual cycles or clinical pregnancy rates. There was a significantly higher rate of multiple pregnancies in the groups taking clomiphene, with or without metformin. The lifestyle intervention group also showed a significant reduction in waist circumference, insulin, and LDL compared with the other 3 groups.

Galletly et al. [35] investigated the stimulant dexfenfluramine versus placebo as an adjunct to a weight-loss program in 21 obese infertile women. Women in both groups demonstrated weight loss, improved self-esteem, and diminished anxiety and depression; however, there were no significant differences between dexfenfluramine and placebo in terms of these measures.

The combination of a healthy diet and weight loss are broadly beneficial to women's health, and the available evidence demonstrates that improved hormonal parameters from diet and exercise are at least equivalent to those from medication use. Given this array of benefits, it would be reasonable to consider lifestyle modifications aimed at weight loss in the treatment armamentarium for obese women with PCOS.

3.4. Psychotherapy

Women undergoing infertility treatment report higher levels of anxiety, depression, and emotional stress compared with those who conceive naturally [36]. Many couples undergoing infertility treatment seek counseling as a form of emotional support, and many studies have examined the effect of counseling on reducing anxiety and depression, and improving pregnancy rates. In a Chinese study [37], 4 sessions of eastern body–mind–spirit group counseling effectively reduced the anxiety level of women undergoing IVF, with a nonsignificant trend toward a higher pregnancy rate compared with controls who did not receive counseling. A study by Hosaka et al. [38] demonstrated that 5 sessions of psychiatric group intervention resulted in decreased psychological discomfort, decreased inflammation (denoted by natural killer cell activity), and higher pregnancy rate compared with controls (37.8% vs 13.5%).

In a study by Domar et al. [39], participants receiving emotion-focused psychological intervention reported less depression and more infertility-specific wellbeing compared with controls at 1 month. At 1 year, participants in the group receiving problem-focused psychological intervention were more likely to have a viable pregnancy than participants in both other groups (55% problem focused, 54% emotion focused, 20% control). Thus, it would appear that counseling might have a positive impact on pregnancy rate. However, these findings are contradicted by a study by de Klerk et al. [40] in which the pregnancy rate among couples who received 3 sessions of experimental psychosocial therapy during their first IVF cycle was not statistically different from that among controls who did not receive psychotherapy [40]. Thus, while counseling demonstrates no adverse effects and might be effective for improving psychological wellbeing among infertility patients, there is an unclear effect on improving reproductive parameters.

4. Discussion

Despite limited data and relatively few RCTs of CAM interventions for infertility, there is preliminary evidence to suggest that some of these modalities may be effective adjuncts in fertility treatment. At least 3 clinical trials with consistent results have examined the use of acupuncture, selenium supplementation, weight loss, and psychotherapy. It seems that acupuncture and psychotherapy have at least some effect on the psychological wellbeing of patients undergoing infertility treatment, and some studies show a nonsignificant trend toward increased pregnancy rates; however, additional studies must be completed to confirm these trends. Selenium supplementation may have some role in improving semen parameters, potentially through modulation of thyroid hormone, but evidence is limited and there remain conflicting results. Additionally, for obese patients with PCOS, lifestyle modifications—including low-calorie diets—aimed at weight loss could be considered. There is little evidence for dietary intervention for patients without PCOS.

While the present study reviewed the available RCTs on CAM treatment for infertility, methodological issues are remarkably pervasive in these studies, and brevity precludes their full discussion. The results discussed were selected by the present authors, and additional evidence should be examined where interest warrants. Similarly, the individualized nature of many CAM modalities prohibits a

randomized controlled study design. As such, no studies regarding meditation and mindfulness, massage, exercise, or online-based support groups met inclusion criteria. Additionally, the present review was restricted to studies published in the English language, which could have limited a full assessment of the spectrum of CAM, particularly in the areas of ethnobotany and traditional Chinese medicine.

Complementary and alternative medicine is commonly used in much of the world and is gaining in popularity in western medical practice. Often, patients' use of CAM arises from their cultural norms or their dissatisfaction with access to, effectiveness of, or cultural appropriateness of available biomedical treatments [2]. As data pertaining to the biomedical effectiveness of these modalities continue to lag behind patients' enthusiastic use of CAM, practitioners caring for infertile patients will increasingly be called upon to individually assess the safety and efficacy of CAM. Certainly, superior RCTs regarding CAM interventions are called for so that simple, precise, quantitative, and irrefutable evidence could place CAM in a scientifically earned place. As such, continued investigation into the demonstrable benefits and risks of these medicines and therapies is needed to best serve infertile patients and evaluate the use of routine clinical recommendation.

Conflict of interest

The authors have no conflicts of interest.

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