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## INVITED REVIEW

Male Fertility

# Male infertility: lifestyle factors and holistic, complementary, and alternative therapies

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While we may be comfortable with an allopathic approach to male infertility, we are also responsible for knowledge about lifestyle modifications and holistic, complementary, and alternative therapies that are used by many of our patients. This paper provides an evidence-based review separating fact from fiction for several of these therapies. There is sufficient literature to support weight reduction by diet and exercise, smoking cessation, and alcohol moderation. Supplements that have demonstrated positive effects on male fertility on small randomized controlled trial (RCT) include aescin, coenzyme Q<sub>10</sub>, glutathione, Korean red ginseng, L-carnitine, nigella sativa, omega-3, selenium, a combination of zinc and folate, and the Menevit antioxidant. There is no support for the use of Vitamin C, Vitamin E, or saffron. The data for Chinese herbal medications, acupuncture, mind-body practice, scrotal cooling, and faith-based healing are sparse or inconclusive.

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**Keywords:** alcohol; antioxidants; caffeine; faith-based healing; male infertility; obesity; scrotal cooling; sperm; tobacco; traditional Chinese medicine

## INTRODUCTION

There is a growing interest in the United States and worldwide for modification of lifestyle factors, as well as holistic, complementary, and alternative approaches to treat male infertility. As practitioners of allopathic medicine, it is our duty to not only be aware of what our patients are trying outside of our office, but to be proactive in guiding couples through which holistic, complementary, and alternative therapies are valid and which are worthless. Obesity, tobacco use, and excessive alcohol intake have all been associated with subfertility, but how much is too much? Will weight loss, smoking cessation, and alcohol moderation improve fertility in the subfertile man? Is caffeine good or bad for male fertility? Nutritional supplements, herbal medications, acupuncture, mind-body practice, scrotal cooling, and faith-based treatments are increasingly utilized in addition to, or instead of, conventional allopathic approaches. Do any of these approaches truly improve male infertility? This paper provides an evidence-based review of lifestyle factors, holistic, complementary, and alternative therapies as they relate to male infertility.

## MATERIALS AND METHODS

A preliminary search of the MEDLINE and Cochrane databases was performed using the following keywords: “complementary medicine,” “alternative medicine,” “obesity,” “smoking,” “alcohol,” “caffeine,” “supplements,” “herbal medicine,” “Traditional Chinese Medicine,” “acupuncture,” “acupressure,” “yoga,” “tai chi,” “qigong,” “chiropractic,” “body work,” “scrotal cooling,” “scrotal hypothermia,” “prayer,” “faith healing,” and “spiritualism” cross-referenced with “male infertility” and “sperm.” Nonhuman studies were excluded. The results and their bibliographies were analyzed and used to develop a more extensive

search of the MEDLINE database. These search results were examined for articles involving obesity and weight loss, smoking and smoking cessation, alcohol and alcohol moderation or abstinence, caffeine intake and caffeine supplementation to cryopreserved sperm, herbs and supplements, Traditional Chinese Medicine, acupuncture, mind-body practice, scrotal cooling, spiritualism, and their therapeutic use or effects in male infertility. Randomized clinical trials (RCTs) were included based on the use of objective measures, articles written in the English language, and the inclusion of clear published clinical outcomes. Observational and quasi-experimental studies and reviews were included when RCTs were not identified for the specific therapeutic modality.

## RESULTS

### *Modifiable lifestyle factors*

#### Obesity

Obesity is associated with lower serum testosterone and LH,<sup>1</sup> elevated rates of oligospermia or azoospermia,<sup>2</sup> and decreased ejaculate volume, sperm concentration, and total sperm count.<sup>3</sup> The relationship between obesity and male infertility is likely multifactorial. Hypothalamic gonadotropin-releasing hormone (GnRH) pulses that regulate the hypothalamus-pituitary-gonadal (HPG) axis depend on appropriate caloric and nutritional intake. When there is an energy imbalance, whether inadequate or excessive, disruption in GnRH pulses causes impairments in semen quality. Excess adipose tissue also results in increased conversion of testosterone to estradiol, which may lead to secondary hypogonadism through HPG axis suppression.<sup>4</sup> Obesity may also increase endorphins that blunt the GnRH pulse.<sup>5</sup> Additionally, excess scrotal fat has been hypothesized to elevate scrotal temperatures resulting in impaired sperm quality.<sup>6</sup>

Two case series investigated if bariatric surgery would improve semen parameters in obese men. In a case series of two patients who underwent bariatric surgery, one patient experienced increased sperm aneuploidy with a decline in sperm concentration, motility, and morphology, while the other became azoospermic.<sup>7</sup> In a case series of three patients who underwent bariatric surgery, all developed extreme oligoasthenoteratospermia.<sup>8</sup> This seemingly paradoxical worsening of semen quality with surgical weight loss may be explained by nutritional deficiencies from sudden weight loss disrupting normal pulsatile GnRH secretion.<sup>4</sup> In a cohort study of 43 men with BMI >33, BMI was inversely associated with sperm concentration, morphology, motility, and testosterone. Weight loss through a 14-week residential weight loss program was associated with an increase in total sperm count, semen volume, and testosterone.<sup>9</sup> While both case series of bariatric surgery demonstrated impairment of sperm production with rapid weight loss and sudden decrease in caloric intake, a lifestyle-based program with gradual weight loss through exercise and a progressive decrease in caloric intake led to improvement in sperm parameters.

There is no RCT to assess the effect of obesity or weight loss in obese men on male infertility. However, evidence suggests obesity may lower sperm parameters and testosterone. These effects may be reversible with gradual weight loss through diet and exercise, but not with bariatric surgery. Using diet and exercise to achieve and maintain normal BMI is recommended for obese men with male factor infertility.

### Tobacco

A systematic review of male smokers identified no consistent effect on sperm quality in 21 of 21 studies and no effect on chemical pregnancy or live birth rate in 4 of 4 studies.<sup>10</sup> However, since this review was published nearly 20 years ago, multiple recent studies have demonstrated contradictory findings. Smoking has been associated with lower sperm concentration,<sup>11</sup> impaired sperm motility and morphology,<sup>12</sup> and increased frequencies of sperm aneuploidy.<sup>13</sup> Use of chewing tobacco also has a dose-dependent negative effect on sperm count, motility, morphology, and viability.<sup>14</sup> The Ontario Farm Family Health Study, a retrospective cohort study on 2607 planned pregnancies, identified that male smoking reduced fecundability (fecundability ratio 0.8, 95% CI: 0.81–0.95).<sup>15</sup> Smoking appears to increase levels of spermatotoxic benzo(a)pyrene and cause oxidative injury to sperm DNA. Benzo(a)pyrene is a highly mutagenic carcinogen. Compared to nonsmokers, the sperm of smokers show high levels of benzo(a)pyrene binding to DNA in sperm.<sup>16</sup> Cigarette consumption also lowers serum antioxidant activity (superoxide dismutase,  $P = 0.01$ ) in a dose-dependent manner.<sup>17</sup>

Although there are no RCTs demonstrating a negative impact on male fertility, The American Society of Reproductive Medicine (ASRM) prudently discourages smoking and exposure to tobacco smoke in both men and women attempting to conceive.<sup>18</sup>

### Alcohol

Two studies suggest that moderate alcohol consumption does not impair semen parameters.<sup>15,19</sup> Several other studies indicate alcohol consumption is associated with deterioration of sperm parameters and testicular pathology in a dose-dependent fashion.<sup>12,20–22</sup> One study suggests that even one alcoholic drink a day may negatively impact miscarriage rates and live birth rates associated with *in vitro* fertilization (IVF).<sup>23</sup>

A case report demonstrated progressive alcohol-induced sperm alterations during heavy chronic alcohol intoxication (165 g alcohol daily for 10 years). The initial finding was teratospermia (August 2002), followed by oligoasthenoteratospermia (March 2005), cryptozoospermia (June 2007) and ultimately azoospermia (November

2007). A testicular biopsy (December 2007) revealed maturation arrest of the germinal cells at the pachytene stage with no mature sperm cells. Once alcohol withdrawal was achieved (January 2008), normospermia occurred within 3 months (April 2008).<sup>24</sup>

The effect of alcohol and alcohol sobriety on male infertility has not been assessed with a RCT. From the available literature, evidence suggests a dose- and duration-dependent effect of alcohol on male infertility. While an adverse effect on sperm parameters was not detectable in men with limited alcohol use, progressive deterioration in semen quality was demonstrated in several studies. Habitual alcohol abuse is also associated with hypogonadism which may arise from both primary testicular failure and an inhibition of gonadotropins. The deleterious effects of alcohol on male fertility may be reversible with alcohol abstinence. Even when semen parameters are not affected, alcohol use is associated with higher miscarriages and lower birth rates with IVF. The evidence is sufficient to recommend minimizing alcohol consumption for men.

### Caffeine

The effect of caffeine on male fertility has been studied both as dietary intake and as an *in vitro* supplement to sperm. High caffeine consumption (>6 cups coffee daily) was associated with increased sperm motility in one study,<sup>25</sup> while three other studies demonstrated no effect of caffeine on sperm parameters, including a study that compared low ( $\leq 100$  mg caffeine daily) to very high caffeine intake (>800 mg caffeine daily).<sup>26–28</sup> In a prospective IVF study, caffeine intake did not affect oocyte fertilization, pregnancy, miscarriage, or live birth. However, the odds of multiple gestations increased by 3.0 for each 100 mg per day of caffeine intake by men during the week of the initial clinic visit or during the week before sperm collection.<sup>27</sup>

In a number of studies, the addition of caffeine to medium increased the motility of both fresh<sup>29</sup> and cryopreserved sperm.<sup>30–34</sup> The effect of *in vitro* caffeine supplementation on other sperm parameters and fertility outcomes were inconsistent. Caffeine caused injury to the sperm head in one study,<sup>35</sup> yet another study identified no morphological changes.<sup>36</sup> A decrease in fertilization and embryonic development was noted at high concentrations of caffeine in the culture medium,<sup>34</sup> while other studies showed improvement in cervical mucus penetration<sup>30</sup> and pregnancy rates with IUI (intrauterine insemination) for subfertile men from the addition of caffeine.<sup>36</sup> An assessment of Sertoli cells cultured with increasing doses of caffeine found that low doses of caffeine ( $5 \mu\text{mol l}^{-1}$ ) stimulated lactate production which can promote germ cell survival. Moderate doses ( $50 \mu\text{mol l}^{-1}$ ) increased expression of glucose transporters. However, the antioxidant capacity of Sertoli cells decreased in a dose-dependent manner with caffeine. Sertoli cells exposed to high doses ( $500 \mu\text{mol l}^{-1}$ ) demonstrated a pro-oxidant potential with an increase of oxidative damage.<sup>37</sup>

While there is no RCT evaluating the effect of caffeine on male fertility and the existing studies on caffeine are inconsistent, moderate consumption of caffeine appears to be safe for male reproductive health. There is insufficient evidence to recommend for or against *in vitro* caffeine supplementation.

### Nonprescription medications and supplements

While the Food and Drug Administration does not regulate nutritional supplements, these have become a mainstay of infertility treatment. The following section reviews the literature on nonprescription medications and supplements. Given the vast number of supplements marketed for male infertility, this section is limited to supplements that have been investigated with a RCT. A summary of these supplementations is provided in **Table 1**.

**Table 1: Outcomes and conclusions from nonprescription medications and supplements**

Agent	Study	Population	Results (sperm quality)	Results (other)	Mechanism	Conclusion
Aescin	Fang, 2010	Subfertile men with varicocele ( $n=219$ )	Improvement in sperm concentration (defined as $\geq 30\%$ increase) occurred in 57.5% of men	Varicocele diameter decreased	Antioxidant Anti-inflammatory	+ Improved sperm concentration Decreased varicocele diameter
Ascorbic acid (Vitamin C) with alpha-tocopherol (Vitamin E)	Rolf, 1999	Asthenospermia ( $n=31$ )	No improvement in sperm parameters or 24-h sperm survival rate		ROS scavenger Antioxidant	-
Coenzyme Q <sub>10</sub>	Balercia, 2009 Safarinejad, 2009 Safarinejad, 2012	Asthenospermia ( $n=55$ ) Oligospermia, asthenospermia, or teratospermia ( $n=403$ )	Improvement of sperm concentration ( $P<0.05$ ), motility ( $P<0.05$ ), and morphology ( $P<0.05$ )	Serum FSH ( $P<0.05$ ) and LH ( $P<0.05$ ) improved No difference in serum testosterone	Antioxidant Functions in the mitochondrial electron transport chain	+ Improved sperm concentration, motility, and morphology Improved gonadotropin levels
<i>Crocus sativus</i> Linn. (saffron)	Safarinejad, 2011	Abnormal semen parameters ( $n=230$ )	No improvement in sperm parameters or antioxidant capacity		Antioxidant	-
Glutathione	Lenzi, 1993	Abnormal sperm parameters associated with unilateral varicocele ( $n=10$ ) or germ-free genital tract inflammation ( $n=10$ ) Cross-over trial	Improvement of sperm motility (38.5% vs 26.0%) and morphology (atypical forms 48.1% vs 62.5%)		Antioxidant	+ Improved sperm motility and morphology
Korean red ginseng	Park, 2015	Subfertile men with varicocele ( $n=80$ )	Improvement of sperm concentration (difference $+3.2 \times 10^6$ vs $+1.3 \times 10^6$ ml <sup>-1</sup> ), motility (difference $+11.8\%$ vs $-0.1\%$ ), morphology (difference $+1.2\%$ vs $-0.1\%$ ), and viability (difference $+8.8\%$ vs $-1.0\%$ )		Antioxidant	+ Improved sperm concentration, motility, morphology, and viability
L-carnitine	Lenzi, 2003	Asthenospermia ( $n=86$ )	Improvement of sperm concentration (difference $+9.0 \times 10^6$ vs $+5.3 \times 10^6$ ml <sup>-1</sup> ) and motility (difference $+11.0\%$ vs $+8.8\%$ )		Antioxidant Functions in fatty acid metabolism	+ Improved sperm concentration and motility
<i>Nigella sativa</i> (black cumin)	Kolahdooz, 2014	Abnormal sperm parameters ( $n=68$ )	Improvement of sperm count ( $60.2 \times 10^6$ vs $42.9 \times 10^6$ ml <sup>-1</sup> ), motility (69.7% vs 61.7%), morphology (49.1% vs 37.2%), and semen volume (4.2 vs 3.1 ml)		Antioxidant	+ Improved sperm count, motility, morphology, and semen volume
Omega-3	Safarinejad, 2011	Abnormal sperm parameters ( $n=211$ )	Improvement of sperm concentration ( $28.7 \times 10^6$ vs $16.2 \times 10^6$ ml <sup>-1</sup> ), motility (27.4 vs 18.6%), and morphology (2.8 vs 7.5%)		Antioxidant	+ Improved sperm concentration, motility, and morphology
Selenium $\pm$ NAC	Scott, 1998 Safarinejad, 2009	Asthenospermia ( $n=64$ ) Selenium only Abnormal sperm parameters ( $n=209$ ) Selenium $\pm$ NAC	Improvement of sperm concentration, motility, morphology, and seminal volume ( $P<0.05$ )	Serum testosterone increased LH and FSH decreased	Component of the antioxidant selenium-dependent glutathione peroxidase system	+ Improved sperm concentration, motility, morphology, and seminal volume Improved serum testosterone and gonadotropin levels
Zinc $\pm$ folate	Wong, 2002 Hunt, 1992	Subfertile men ( $n=94$ ) Zinc and folate Healthy young men ( $n=11$ ) Zinc depletion Crossover trial	Zinc and folate supplementation resulted in improvement of sperm concentration ( $12 \times 10^6$ vs $7.5 \times 10^6$ ml <sup>-1</sup> ), though zinc or folate supplementation alone did not improve any sperm parameters Zinc depletion resulted in reduced semen volume (2.24 vs 3.30 ml)	Zinc depletion decreased serum testosterone (21.9 vs 26.9 nmol l <sup>-1</sup> , $P=0.03$ )	Antioxidant Anti-apoptotic Cofactor of metalloenzymes involved in DNA transcription and protein synthesis	+ Zinc and folate supplementation increased sperm concentration, though zinc or folate supplementation alone did not improve any sperm parameters Zinc depletion resulted in reduced semen volume and decreased serum testosterone

Contd...



Table 1: Contd...

Agent	Study	Population	Results (sperm quality)	Results (other)	Mechanism	Conclusion
FertilAid for men	Clifton, 2009	Abnormal semen parameters ( $n=14$ )	Improved total normal motile sperm ( $P=0.05$ ), with no improvement in sperm count, motility, or morphology		Antioxidant	-
Menevit	Tremellen, 2007	Couples with isolated male infertility undergoing IVF-ICSI treatment. All men exhibited both sperm oxidative stress and DNA fragmentation ( $n=60$ )	Improvement of viable pregnancy rate (38.5% vs 16%) There was no significant change in oocyte fertilization rate or embryo quality		Antioxidant	+ Improved viable pregnancy rate with IVF-ICSI

+: positive effect; -: negative or no effect; ROS: reactive oxygen species; FSH: follicle-stimulating hormone; LH: luteinizing hormone; NAC: N-acetyl-cysteine; IVF-ICSI: *in vitro* fertilization-intracytoplasmic sperm injection

### Individual nonprescription medications and supplements

Aescin (horse chestnut seed extract) is a mixture of saponins with antioxidant, anti-edematous, and anti-inflammatory properties.<sup>38-40</sup> In a study of 219 men with varicocele-associated infertility, a 2-month course of aescin (30 mg twice a day) was compared with a control of Vitamin E, pentoxifylline, and clomiphene. Improvement in sperm concentration (defined as  $\geq 30\%$  increase) was more common in the aescin group (57.5% vs 38.5%,  $P < 0.05$ ). Varicocele size also decreased with aescin, though the effective rate was more pronounced in mild (41.7%,  $P > 0.05$ ) and moderate (64.4%,  $P < 0.05$ ) varicoceles than severe varicoceles (20%).<sup>41</sup>

Ascorbic acid (Vitamin C) is a reactive oxygen species (ROS) scavenger that may protect sperm against oxidative DNA damage.<sup>42</sup> Alpha-tocopherol (Vitamin E) is also an antioxidant. Levels of Vitamin E in sperm have been positively correlated with sperm motility ( $P < 0.001$ ).<sup>43</sup> In a study of 31 infertile men with asthenospermia, an 8-week course of high dose Vitamins C (1000 mg daily) and E (800 mg daily) was compared to placebo. Combined high dose Vitamins C and E did not improve semen parameters or the 24 h sperm survival rate.<sup>44</sup>

Coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) is an antioxidant that may also contribute to sperm production and quality through its function in the mitochondrial electron transport chain.<sup>45</sup> In a study of 55 men with asthenospermia, a 6-month course of CoQ<sub>10</sub> (200 mg daily) improved sperm motility (39% vs 33%,  $P < 0.0001$ ) compared with placebo. Motility returned to baseline after stopping CoQ<sub>10</sub> for 3 months.<sup>46</sup> Another study assessed the effects of a 6-month course of CoQ<sub>10</sub> (200 mg daily) on 191 men with oligospermia, asthenospermia, or teratospermia. Those given CoQ<sub>10</sub> had increased sperm concentration ( $28.7 \times 10^6$  vs  $16.8 \times 10^6$  ml<sup>-1</sup>,  $P = 0.005$ ), motility (35.8% vs 25.4%,  $P = 0.008$ ), and morphology (17.6% vs 14.8%,  $P = 0.01$ ), compared to placebo. Serum FSH (9.6 vs 16.4 IU l<sup>-1</sup>,  $P = 0.02$ ) and LH (8.2 vs 13.1 IU l<sup>-1</sup>,  $P = 0.03$ ) decreased. There was no significant difference in serum testosterone.<sup>47</sup> Twenty-six weeks of a higher dose of CoQ<sub>10</sub> (300 mg daily) in a different group of 212 men with oligospermia, asthenospermia, or teratospermia, similarly improved sperm concentration ( $26.4 \times 10^6$  vs  $20.8 \times 10^6$  ml<sup>-1</sup>,  $P = 0.01$ ), motility (27.6% vs 23.1%,  $P = 0.04$ ), and morphology (9.6% vs 7.8%,  $P = 0.04$ ), while serum FSH (10.7 vs 16.8 IU l<sup>-1</sup>,  $P = 0.03$ ) and LH (8.8 vs 12.6 IU l<sup>-1</sup>,  $P = 0.03$ ) decreased.<sup>48</sup>

*Crocus sativus* Linn. (saffron) is a spice containing antioxidant rich carotenoids that scavenge free radicals. A study of 230 infertile men with abnormal semen parameters demonstrated no improvement in sperm concentration, motility, or morphology after 26 weeks of saffron (60 mg daily) compared to placebo. Additionally, saffron failed to improve seminal plasma antioxidant capacity.<sup>49</sup>

Glutathione is an intracellular antioxidant found in every cell of the human body.<sup>50</sup> Glutathione therapy (600 mg IM every other day) for 2 months was assessed in a cross-over trial of 20 infertile men with

abnormal sperm parameters associated with unilateral varicocele ( $n = 10$ ) or germ-free genital tract inflammation ( $n = 10$ ). Glutathione supplementation improved sperm motility (38.5% vs 26.0%,  $P < 0.01$ ) and morphology (atypical forms 48.1% vs 62.5%,  $P < 0.001$ ) after 1 month of treatment. The benefits did not persist when the glutathione was stopped.<sup>51</sup>

Korean red ginseng (KRG) is composed of multiple ginsenosides, a class of natural product steroid glycosides and triterpene saponins, some of which have antioxidant properties.<sup>52</sup> A total of 80 infertile men with varicocele were randomized to placebo, KRG (1.5 g daily), varicocelectomy with placebo, or varicocelectomy with KRG. Semen analysis was obtained in each treatment arm after 12 weeks. Compared to placebo, treatment with KRG improved sperm concentration (difference  $+3.2 \times 10^6$  vs  $+1.3 \times 10^6$  ml<sup>-1</sup>,  $P < 0.05$ ), motility (difference  $+11.8\%$  vs  $-0.1\%$ ,  $P < 0.01$ ), morphology (difference  $+1.2\%$  vs  $-0.1\%$ ,  $P < 0.01$ ), and viability (difference  $+8.8\%$  vs  $-1.0\%$ ,  $P < 0.05$ ).<sup>53</sup>

L-carnitine is a quaternary ammonium compound required for fatty acid metabolism that also has antioxidant effects.<sup>54,55</sup> In a randomized trial of 86 infertile men with asthenospermia, a 2-month supplementation with L-carnitine (2 g daily) improved sperm motility (difference  $+11.0\%$  vs  $+8.8\%$ ,  $P = 0.04$ ) and concentration (difference  $+9.0 \times 10^6$  vs  $+5.3 \times 10^6$  ml<sup>-1</sup>,  $P = 0.01$ ) compared to placebo.<sup>56</sup>

*Nigella sativa* (black cumin) is a medicinal plant with antioxidant properties. In a study of 68 infertile men with abnormal semen parameters, a 2-month course of black cumin oil (2.5 ml twice a day) improved sperm count ( $60.2 \times 10^6$  vs  $42.9 \times 10^6$  ml<sup>-1</sup>,  $P = 0.01$ ), motility (69.7% vs 61.7%,  $P = 0.02$ ), morphology (49.1% vs 37.2%,  $P < 0.01$ ), and semen volume (4.2 vs 3.1 ml,  $P < 0.01$ ) compared to placebo.<sup>57</sup>

Omega-3 fatty acids (DHA, EPA and ALA) are essential to normal human physiology. They may act as antioxidants. Sperm from asthenospermic males have lower levels of DHA in the sperm membrane compared to those from fertile men.<sup>58</sup> Seminal plasma EPA and DHA concentrations were positively correlated with seminal plasma superoxide dismutase (SOD) and catalase-like activity ( $P = 0.001$ ), both markers of anti-oxidant activity.<sup>59</sup> In a study of 211 infertile men with abnormal semen parameters, omega-3 supplementation (515.2 mg EPA and 331.2 mg DHA daily) for 28 weeks improved sperm concentration ( $28.7 \times 10^6$  vs  $16.2 \times 10^6$  ml<sup>-1</sup>,  $P = 0.001$ ), motility (27.4% vs 18.6%,  $P = 0.002$ ), and morphology (12.8% vs 7.5%,  $P = 0.002$ ).

Selenium is a mineral that could provide beneficial effects to sperm as a component of the selenium-dependent glutathione peroxidase system.<sup>60</sup> In a study of 64 asthenospermic men, selenium supplementation to normal amounts (100  $\mu$ g daily) for 3 months improved sperm motility (28.2% vs 20.1%,  $P = 0.04$ ) compared to placebo.<sup>61</sup> Twenty-six weeks of high dose selenium supplementation (200  $\mu$ g daily) in 105 subfertile men with abnormal sperm parameters improved sperm concentration ( $27.6 \times 10^6$  vs  $22.4 \times 10^6$  ml<sup>-1</sup>,  $P = 0.03$ ),



motility (26.1% vs 22.1%,  $P = 0.03$ ), morphology (9.2% vs 7.2%,  $P = 0.03$ ), and seminal volume (3.2 vs 2.7 ml,  $P = 0.02$ ). The addition of N-acetyl-cysteine (600 mg daily), a free radical scavenger, to high dose selenium (200 µg daily) resulted in similar beneficial effects in sperm concentration ( $32.1 \times 10^6$  vs  $21.6 \times 10^6$  ml<sup>-1</sup>,  $P = 0.01$ ), motility (29.2% vs 22.8%,  $P = 0.02$ ), morphology (9.3% vs 7.2%,  $P = 0.03$ ), and ejaculate volume (3.4 vs 2.7 ml,  $P = 0.03$ ) in a separate cohort of 104 subfertile men. In both selenium and selenium + N-acetyl-cysteine (NAC) supplementation cohorts, serum testosterone (20.1 vs 17.4 nmol l<sup>-1</sup>,  $P = 0.04$ ; 20.9 vs 17.8 nmol l<sup>-1</sup>,  $P = 0.03$ ) rose, while LH (3.6 vs 4.1 IU l<sup>-1</sup>,  $P = 0.04$ ; 3.7 vs 4.4 IU l<sup>-1</sup>,  $P = 0.04$ ) and FSH (2.1 vs 2.8 IU l<sup>-1</sup>,  $P = 0.04$ ; 1.8 vs 2.6 IU l<sup>-1</sup>,  $P = 0.03$ ) fell, compared to placebo. Following cessation of selenium ± NAC supplementation, all semen parameters and serum hormone levels returned to pretreatment levels after two spermatogenesis cycles (26 weeks).<sup>62</sup>

Zinc is a micronutrient that may also promote sperm quality through its antioxidant and anti-apoptotic properties.<sup>63,64</sup> Zinc acts as a cofactor of metalloenzymes involved in DNA transcription and protein synthesis critical to spermatogenesis.<sup>65</sup> In a crossover dietary study of 11 healthy young male volunteers (mean age 28 years), severe zinc depletion resulted in reduced semen volume (2.24 vs 3.30 ml,  $P = 0.03$ ) and decreased serum testosterone (21.9 vs 26.9 nmol l<sup>-1</sup>,  $P = 0.03$ ), compared to normal zinc consumption.<sup>66</sup> In another study of 94 subfertile men, the combination of zinc and folate supplementation increased sperm concentration ( $12 \times 10^6$  vs  $7.5 \times 10^6$  ml<sup>-1</sup>,  $P < 0.05$ ), though zinc or folate supplementation alone did not improve any sperm parameters compared to placebo.<sup>67</sup>

Oxidative stress can occur as a consequence of excessive reactive oxygen species (ROS) or impaired antioxidant defense mechanisms. Although low amounts of ROS are required for critical aspects of sperm function, excessive levels of ROS can negatively impact sperm quality, function, and viability.<sup>68,69</sup> Excessive ROS damages sperm nuclear DNA and sperm plasma membrane and has also been associated with decreases in testosterone concentration.<sup>69,70</sup> All of the nonprescription medications and supplements reviewed in this section demonstrate antioxidant activity. There is at least some evidence for coenzyme Q<sub>10</sub>, glutathione, L-carnitine, black cumin, omega-3, selenium ± NAC, and zinc + folate, for the improvement of semen parameters. Aescin and Korean red ginseng may benefit subfertile men with varicocele.

A Cochrane review evaluated the effectiveness and safety of oral supplementation with antioxidants for subfertile male partners in couples seeking fertility assistance. There was low quality evidence that antioxidant supplementation may improve clinical pregnancy rates (OR = 3.43,  $P < 0.0001$ ) and live birth rates (OR = 4.21,  $P < 0.0001$ ). There was no evidence of increased risk of miscarriage, but this was uncertain as the evidence was of very low quality. Data were lacking on other adverse effects. There were insufficient data to draw any conclusions from antioxidant versus antioxidant comparison.<sup>71</sup>

#### **Combination nonprescription medications and supplements**

There are two combination male fertility supplements evaluated with a RCT. FertilAid for Men is a combination of antioxidants containing L-carnitine, grape seed extract, Vitamin A, Vitamin C, Vitamin E, selenium, maca root, Asian ginseng, and zinc. Fourteen men with abnormal semen parameters were randomized to either 90-day of FertilAid ( $n = 8$ ) or placebo ( $n = 6$ ). In the FertilAid group, total normal motile sperm improved ( $P = 0.05$ ), with no improvement in sperm count, motility, or morphology.<sup>72</sup> Given the small number of men in this study, and the limited impact on sperm parameters, it is difficult to recommend this supplement.

The Menevit antioxidant contains lycopene, Vitamin E, Vitamin C, zinc, selenium, folate, and garlic. The hypothesis that

Menevit would reduce oxidative sperm damage resulting in an improvement in embryo quality and pregnancy rates during *in vitro* fertilization-intracytoplasmic sperm injection (IVF-ICSI) treatment was tested in 60 couples with isolated male infertility. All men exhibited both sperm oxidative stress (poor sperm morphology, motility, or low membrane integrity) and DNA fragmentation (>25% TUNEL positive). Treatment with Menevit for 3 months before their partner's IVF cycle improved viable pregnancy rate (38.5% vs 16%,  $P = 0.046$ ), defined as a viable fetus at 13 weeks gestation, compared to placebo. There was no significant change in oocyte fertilization rate or embryo quality.<sup>73</sup> The Menevit antioxidant showed an improved viable pregnancy rate, but the study was limited to couples undergoing IVF-ICSI, so benefits can not be extrapolated to couples undergoing timed intercourse or IUI.

#### **Traditional Chinese medicine**

Traditional Chinese Medicine (TCM) has been used for hundreds of years to treat infertility. The goal of therapy is a balance between reproductive energy (qi), blood, and the yin and yang of internal organs. The kidney and spleen are considered especially important organs for male fertility. The kidney regulates the quality of sperm and the spleen transports nutrients required for sperm production and maturation. TCM employs herbal supplements, acupuncture and mind-body practices to improve fertility parameters.

#### **Chinese herbal medications**

Herbal medications are a foundation of TCM for male infertility. Other than ginseng, which was previously described, no RCT was identified for individual herbs or decoctions.

Herbs commonly used in TCM for male infertility have been investigated for endocrine and antioxidant activity. A total of seven herbal decoctions and 37 individual herbs, including all the herbs used in the seven decoctions, were screened *in vitro* for endocrine and antioxidant activity. The seven decoctions tested exhibited strong (5 decoctions) and weak (two decoctions) anti-estrogenic responses (1.14–13.23 mg and 0.22–0.26 mg tamoxifen equivalents per gram of dried herbs respectively), but not estrogenic, androgenic, or anti-androgenic activities. With regard to antioxidant activity, strong (three decoctions), intermediate (three decoctions), and weak (one decoction) responses were identified (1.02–1.2, 0.72–0.76, 0.44 µg ascorbic acid equivalent per mg dried herbs respectively). None of the 37 individual herbs tested showed androgenic properties while seven showed strong and three showed a weak anti-androgenic response (1.54–66.78 mg and 0.17–0.32 mg flutamide equivalents per gram of dried herb, respectively). Estrogenic responses were present in two herbs (85.3–550 µg estradiol equivalents per gram of dried herb), while 20 showed strong and 10 weak anti-estrogenic activity (1.18–1280.66 mg and 0.06–0.98 mg tamoxifen equivalent per gram of dried herb, respectively). Of the 37 herbs, strong (15 herbs), intermediate (seven herbs), and weak/no (15 herbs) antioxidant activity was detected (ranging 0.91–1.26, 0.6–0.88, 0–0.47 µg ascorbic acid equivalent per mg dried herb, respectively). Herbs exhibiting strong antioxidant activity were Radix Paeoniae Rubrae, Cortex Phellodendri, Cortex Moudan Radicis, Rehmannia Glutinosa Libosch, Fructus Corni Officinalis, Semen Cuscutae, Rhizoma Anemarrhenae Asphodeloidis, Fructus Rubi, Fructus Schisandrae Chinensis, Aurantii Fructus, Acori Graminei Rhizome, Nelumbinis Embryo, Rhizoma Cimicifugae, Pericarpium Citri Reticulate Blanco, and Flos Lonicerae Japonicae.<sup>74</sup> Because these are *in vitro* studies, these findings can not be extrapolated as *in vivo* data.

Human studies do exist for two popular decoctions: Wuzi Yanzong Wan (Pills for Reproduction) and Sheng Jing Zhong Zi Tang (Decoction

for Generating Sperm). A 3-month course of Wuzi Yanzong Wan in 35 infertile men with either asthenospermia or oligospermia improved sperm concentration ( $27.1 \times 10^6$  vs  $14.9 \times 10^6$  ml<sup>-1</sup>,  $P < 0.01$ ) and motility (50.6% vs 24.6%,  $P < 0.01$ ) compared to pretreatment sperm parameters. A 3-month course of Sheng Jing Zhong Zi Tang in a separate cohort of 35 infertile men with either asthenospermia or oligospermia, improved sperm concentration ( $33.4 \times 10^6$  vs  $14.8 \times 10^6$  ml<sup>-1</sup>,  $P < 0.01$ ) and motility (56.7% vs 25.3%,  $P < 0.01$ ) compared to pretreatment sperm parameters. The improvement in sperm concentration ( $P < 0.01$ ) and motility ( $P < 0.01$ ) was superior with Sheng Jing Zhong Zi Tang compared to Wuzi Yanzong Wan.<sup>75</sup>

A different formulation of Sheng Jing Zhong Zi Tang was assessed for an effect on antisperm antibodies. Ninety married men from couples with isolated male infertility related to either a positive sperm immobilization test (SIT) and/or gelatin agglutination test (GIT) were randomized to 60 days of either Sheng Jing Zhong Zi Tang ( $n = 60$ ) or control of prednisone 5 mg and clomiphene 50 mg ( $n = 30$ ). Men with a persistently positive SIT or GIT after 60 days of treatment were extended another 60 days of the same treatment. Men with persistently positive SIT or GIT after 120 days of treatment were extended another 60 days of treatment up to a maximum of 180 days of treatment. Treatment with 2 months of Sheng Jing Zhong Zi Tang decreased IgA, IgG, and IgM ( $P < 0.01$ ). Treatment with 4 months of prednisone and clomiphene also decreased IgA, IgG, and IgM ( $P < 0.01$ ), but the improvement was less when compared to 4 months of Sheng Jing Zhong Zi Tang (statistical analysis not published). Pregnancy within 1 year of completing treatment was 83% (50 of 60) for the wives of the men treated with Sheng Jing Zhong Zi Tang, compared to 56.6% (17 of 30) for the wives of men on prednisone and clomiphene.<sup>76</sup>

The clinical data on Chinese herbal medications for male infertility are intriguing. The nonstandardization of herbal decoctions, however, makes studies difficult to perform. RCTs and standardization of the herbal decoctions are needed to assess the clinical relevance of this treatment.

### Acupuncture

Acupuncture is a key component in TCM fertility therapy. Acupuncture is often an adjunctive therapy, used with or without electrical stimulation, and in combination with herbal medicines for male infertility. Two RCTs assessing the effect of acupuncture on male infertility are reviewed.

A study of 57 men with severe oligoasthenospermia underwent either true or placebo acupuncture. Those who underwent true acupuncture experienced improvement in total motile sperm counts (33.8% vs 24.4% motility A-C,  $P = 0.035$ ) but lower semen volume (3.7 vs 4.2 ml,  $P = 0.041$ ).<sup>77</sup> In a physiologic study of 80 healthy men 30–35 years of age, Doppler ultrasound flowmetry was used to assess differences in testicular blood flow before and after abdominal electroacupuncture. Men who received acupuncture at points correlating to genital problems (ST-29 or guilai) with electrical stimulation (10 Hz) demonstrated improvements in testicular blood flow ( $P < 0.005$ ). Electroacupuncture using a lower stimulation (2 Hz or 10 Hz) or at a different location (ST-25 or tianshu) showed no change in testicular blood flow.<sup>78</sup>

The results of acupuncture on sperm parameters are mixed with one study demonstrating improvement in total motile sperm count, but no improvement in sperm concentration, motility, or morphology, and decline of semen volume. The second study showed a testicular artery response to abdominal electroacupuncture but did not assess if this has clinical relevance for male infertility. An RCT on acupuncture with pregnancy or live birth rate as an outcome is needed before a conclusion can be made about clinical efficacy.

### Mind-body practice

Tai chi and qigong are mind-body practices that originated in China that combine meditation with exercise to improve the flow of qi throughout the body. Tai chi originated as a martial art that has evolved to an exercise promoted for general health. Qigong is a form of exercise that is recognized as a standard medical technique in China. The difference between the two lies in the complexity of movements, with qigong being a simpler form utilizing repetitive body movements and breathing techniques. The role of both tai chi and qigong in male infertility is to integrate body, breath, and mind, to achieve mental clarity, body homeostasis, and heightened sexual energy and libido. A literature review of RCTs for tai chi and qigong suggests improvements in bone density, stress management, and immune response, and a reduction in falls,<sup>79</sup> but no study assessed specific parameters of male infertility.

Yoga is a physical, mental, and spiritual discipline that originated in India. Yoga focuses on gentle stretching, exercises for breath control, and meditation. The role of yoga in male infertility focuses on reducing anxiety and optimizing erectile function.<sup>80</sup>

There were no clinical studies that directly evaluated sperm quality, pregnancy rate, or live birth rate, in relationship to tai chi, qigong, or yoga. Further studies are needed to assess if mind-body practices improve male fertility.

### Support therapies

#### Scrotal cooling

The idea of scrotal cooling to benefit male fertility is based on the negative relationship of scrotal heat and spermatogenesis. The scrotal temperature of infertile men is 0.4–0.5°C higher than in fertile men.<sup>81</sup> Further, a rise of 1°C in median scrotal temperature results in a 40% drop in sperm concentration.<sup>82</sup> These findings contribute to the common belief that “boxers are better than briefs,” though this has never been proven.

There is no RCT study on the effect of scrotal cooling and male infertility. Several small observational studies evaluated the effect of scrotal cooling on male infertility. The first study was published nearly 50 years ago. Seven oligospermic men used scrotal cooling for 14 consecutive days. Sperm count increased, but this effect did not persist beyond 2 weeks.<sup>83</sup> A series of observational studies on scrotal cooling was conducted in the 1980s for infertile men with abnormal semen parameters and elevated testis temperatures. Men were treated with scrotal cooling for 8–20 weeks. Sperm parameters improved in 64%–83% of men and pregnancy was achieved in 14%–50% of couples.<sup>84–87</sup> Discontinuation of hypothermia resulted in a return to pretreatment semen parameters.<sup>85</sup> The percentage of improved semen parameters was the same whether or not a varicocele was present.<sup>87</sup>

There are two prospective controlled studies on scrotal cooling. In both studies, scrotal cooling was done for 12 weeks. In one study of 40 infertile men with oligoasthenoteratospermia, scrotal cooling to decrease the scrotal temperature by 1°C improved sperm concentration ( $P < 0.0001$ ), motility ( $P < 0.05$ ) and morphology ( $P < 0.05$ ) after 8 and 12 weeks of treatment, compared to baseline sperm parameters.<sup>88</sup> In a separate study of 40 infertile men with oligospermia and testicular maldescent, scrotal cooling to decrease the scrotal temperature by 0.8°C improved sperm concentration ( $P < 0.01$ ) at 8 and 12 weeks of treatment compared to baseline sperm parameters, but there were no improvements in sperm motility or morphology. Pregnancy rate during the 12-week treatment period was 20% (4 of 20 men), but no information about pregnancy was provided about the matched control group.<sup>89</sup> There was no difference in testosterone and FSH in both studies. LH was increased with scrotal cooling in oligoasthenoteratospermic men but not in men with oligospermia and testicular maldescent.

**Table 2: Outcomes and conclusions from all therapeutic modalities for male infertility**

Therapy	Study	Population	Results	Mechanism	Conclusion
Bariatric surgery	Lazaros, 2012 Sermondade, 2012 Case series	Obese men ( $n=5$ )	Oligoasthenoteratospermia in 4 men Azoospermia in 1 man	Nutritional deficiencies causing disruption of GnRH secretion	– Bariatric surgery resulted in worsening of sperm parameters
Weight reduction by lifestyle modification	Håkonsen, 2011 Cohort study	Obese men ( $n=43$ )	Weight loss through a 14-week residential weight loss program increased total sperm count and testosterone	Increased testosterone Decreased aromatization Equilibration of GnRH pulse Reduction of scrotal fat	+ Gradual weight loss by diet and exercise improved total sperm count and testosterone
Tobacco cessation	None	N/A	Tobacco use associated with decreased sperm counts, motility, morphology, and increased sperm aneuploidy	Oxidative damage to sperm DNA	+ Inconclusive data but expert recommendation for tobacco cessation
Alcohol moderation	Sermondade, 2010 Case report	Alcoholic man ( $n=1$ )	Heavy alcohol use induced progressive spermatotoxicity, ultimately leading to azoospermia	Primary testicular failure Inhibition of gonadotropins	+ High dose alcohol spermatotoxic. Moderate alcohol consumption likely neutral
Caffeine intake	Sobreiro, 2005 Klonoff-Cohen, 2002 Jensen, 2010 Vine, 1997	Fertile men ( $n=500$ ) Fertile and subfertile men seen in IVF clinic ( $n=221$ ) Young healthy men from general population ( $n=2640$ )	May increase sperm motility	Stimulates lactate production and increases expression of glucose transporters in Sertoli cells High doses reduce the antioxidant capacity of Sertoli cells	– Moderation appears safe
Nonprescription medication and supplements	Balercia, 2009 Clifton, 2009 Fang, 2010 Hunt, 1992 Kolahdooz, 2014 Lenzi, 1993 Lenzi, 2003 Park, 2015 Rolf, 1999 Safarinejad, 2009 Safarinejad, 2009 Safarinejad, 2011 Safarinejad, 2011 Safarinejad, 2012 Scott, 1998 Showell, 2014 Tremellen, 2007 Wong, 2002	Healthy young men ( $n=11$ ) Abnormal semen parameters ( $n=1371$ ) Abnormal sperm parameters associated with germ-free genital tract inflammation ( $n=10$ ) Subfertile men ( $n=94$ ) Subfertile men with varicocele ( $n=309$ ) Couples with isolated male infertility undergoing IVF-ICSI treatment ( $n=60$ )	Improvement of sperm concentration, motility, and morphology Increased seminal volume Improvement of testosterone, LH, and FSH Decreased varicocele diameter Higher pregnancy rate with IVF-ICSI	Antioxidant Anti-apoptotic Anti-edematous Anti-inflammatory	+ Aescin, coenzyme Q <sub>10</sub> , glutathione, Korean red ginseng, L-carnitine, nigella sativa, omega-3, selenium±NAC, zinc + folate, and Menevit improved seminal parameters, improved gonadotropins and testosterone, decreased varicocele size, and/or increased pregnancy rate with IVF-ICSI
Chinese herbal medication	Yang, 2011 Yang, 2002	Asthenospermia or oligospermia ( $n=70$ ) Isolated male infertility associated with antisperm antibodies ( $n=90$ )	Wuzi Yanzong Wan and Sheng Jing Zhong Zi Tang improved sperm concentration and motility Sheng Jing Zhong Zi Tang improved pregnancy rates by men with antisperm antibodies compared to prednisone and clomiphene	Anti-estrogenic Antioxidant	– No RCT to judge true efficacy
Acupuncture	Dieterle, 2009 Cakbak, 2008	Severe oligoasthenospermia ( $n=57$ ) Healthy men ( $n=80$ )	Improved total motile counts. Volume decreased Acupuncture increased testicular blood flow	Guide the flow of energy (qi) throughout the body	– Mixed results. May have positive benefits
Mind-body practice	None	N/A	Improved stress management. No known direct sperm effects	Integrate mind, body, and breath to improve clarity and sexual energy	– Insufficient data
Scrotal cooling	Robinson, 1968 Zorgniotti, 1980 Zorgniotti, 1982 Zorgniotti, 1986 Mulcahy, 1984 Jung, 2001 Jung, 2005	Abnormal semen parameters ( $n=218$ ) Oligospermia with testicular maldescent ( $n=40$ )	Transient improvement in count, motility, and morphology Improved counts only in men with oligospermia or testicular maldescent	Decrease heat stress to sperm and testicles	– Cumbersome intervention with some positive data
Faith healing	None	N/A	No trials to assess	N/A	– Insufficient data

+: positive effect; – : negative or no effect; N/A: not available; GnRH: gonadotropin-releasing hormone; NAC: N-acetyl-cysteine; IVF-ICSI: *in vitro* fertilization-intracytoplasmic sperm injection; RCT: randomized controlled trial

The evidence for the beneficial effect of scrotal cooling on male fertility is based on small observational studies without matched control

groups and two prospective controlled trials. Some improvements in sperm count began following 2 weeks of scrotal cooling, but the most



robust increase in sperm count occurred at 8 weeks. Achievement of pregnancy following scrotal cooling was not adequately assessed as pregnancy was never a primary outcome in any of the studies.<sup>90</sup> Scrotal cooling does not harm and may improve sperm parameters. However, there is no ideal device for scrotal cooling on the market. A randomized controlled trial on scrotal cooling using a hydrogel pad containing I-menthol, FertilMate<sup>®</sup>, is in the initial recruitment phase.<sup>91</sup>

### Faith based treatment

Faith healing, including spiritual or prayer therapy, for infertility, is practiced by different cultures all over the world.

Several studies assessed the use of faith healing in the Middle East and Africa. On a survey of 1021 patients attending an infertility clinic in Jordan, of which 25% were male, 45% utilized complementary and alternative medicine (CAM). Of people reporting to use CAM for infertility, 44% employed religious healing.<sup>92</sup> In a Lebanese cross-sectional study of 213 consecutive patients, 41% reported using a CAM modality for their infertility. Of the men using CAM modalities, 32% used faith healing.<sup>93</sup> A survey of rural ingenuous healers in South Africa found that 91% of these healers treat infertility on a regular basis.<sup>94</sup>

Faith healing for fertility is also a part of the Western world. Several Christian websites such as [www.whatchristianswanttoknow.com](http://www.whatchristianswanttoknow.com), [www.catholicinfertility.org](http://www.catholicinfertility.org), and [www.stronginfaith.org](http://www.stronginfaith.org), describe prayer as a remedy for infertility, though the focus is primarily on women. The role of spiritual therapy for male infertility in the Christian community is not a method of achieving pregnancy *per se*, but rather a focus on hope, strength of will, and preservation of a domestic relationship through love and support. The website [www.lidsinfertility.org](http://www.lidsinfertility.org) invokes the stories of Abraham and Isaac for inspiration. Suggestions for infertile men is to do as Abraham who “exercised remarkable faith, had abiding hope, and remained faithful to the Lord” or to act as Isaac “to plead righteously” and make “a deeply sincere and determined request of the Lord.”

Faith healing is a component of male infertility treatment across cultures. As there is no study on clinical effectiveness in terms of sperm parameters, pregnancy rates, and live birth rates, no recommendation can be made regarding faith healing.

### CONCLUSIONS

Whether it is as a supplement to or instead of conventional allopathic therapy, men are increasingly using lifestyle modifications and following holistic, complementary, and alternative therapies for the management of male infertility. A summary of outcomes and conclusions from several of these therapeutic modalities is provided in **Table 2**. Valid strategies include weight reduction by diet and exercise, smoking cessation, and alcohol moderation. Supplements assessed with a RCT to have positive effects on male fertility include aescin, coenzyme Q<sub>10</sub>, glutathione, Korean red ginseng, L-carnitine, nigella sativa, omega-3, selenium, combination of zinc and folate, and the Menevit antioxidant. There are some studies suggesting benefit from Chinese herbal medications, acupuncture, and scrotal cooling, but the data are currently insufficient to make recommendations. While clinical evidence for mind-body practice and faith based healing is sparse, a familiarity to these complementary approaches allows us to be better practitioners for the many patients who value these therapies.

### COMPETING INTERESTS

The authors have no competing interests to declare.

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