Should empiric therapies be used for male factor infertility?

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Disclaimer: Authors for "fertile battles" are chosen to represent the full breadth of opinions. Individual authors, even within one side of the debate, do not necessarily agree with all viewpoints expressed.

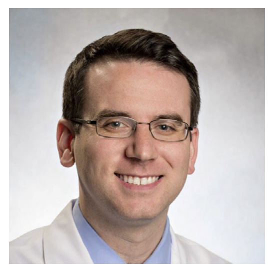
PRO: Empiric therapies should be used for male factor infertility

Pro 1. Sarah C. Vij, M.D.

Empiric Medical Therapy

Idiopathic male infertility is defined as abnormal semen parameters without an underlying cause. The primary treatment option used in this patient population is empiric medical therapy (EMT). Hormone treatment, particularly antiestrogens, is the most widely used method of EMT for idiopathic male infertility. Specifically, clomiphene citrate (CC), anastrozole, and human chorionic gonadotropin (hCG) are the most commonly prescribed (1). For idiopathic male infertility EMT is a moderately effective treatment option with regards to improvement in semen parameters and pregnancy rate, but no clear predictors have been identified to determine which patients will respond optimally.

Clomiphene citrate is the most studied medication in the treatment of idiopathic male infertility. Ghanem et al. (2) randomly assigned men with oligoasthenozoospermia (OAT) to CC (25 mg/day) plus vitamin E (400 mg/day) versus placebo and found an increase in sperm count, motility, and pregnancy rate in the treatment arm. Similarly, a retrospective analysis of 77 male patients treated with 25 mg of CC daily for idiopathic male infertility and/or hypogonadism demonstrated an improvement in sperm concentration (mean 14 million/mL to



CON: Empiric therapies should not be used for male factor infertility

Con 1. Martin Kathrins, M.D.

Empiric Medical Therapy

We often have little to offer men with idiopathic infertility. Options for such patients are precious few—including nutraceuticals. Our inclination has long been to offer empiric prescribed medical therapies, but this approach simply lacks high-quality evidence, despite our best wishes.

Clomiphene citrate holds a special place in this area. A 2012 survey found that two-thirds of responding urologists in the United States used CC for empiric therapy (1). However, of the numerous CC trials conducted—many of which were randomized and double blind—only one identified improved pregnancy rates. This sole study included a vitamin E antioxidant in the treatment arm (2), and no information was provided on baseline serum testosterone levels, so it is impossible to know which of the men who benefited were treated in a "targeted" fashion to correct an underlying endocrinopathy. Systematic analysis and Cochrane review results also have failed to support the use of CC for empiric medical therapy, specifically for men with oligoasthenoteratozoospermia (69, 70). Publications on the empiric use of CC date back to the mid-1960s, and there is a reason no consensus has been reached on its efficacy: it simply does not work (71).

In contradistinction to the poor evidence for scattershot empiric therapy with CC, targeted therapy with anastrozole,

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21 million/mL) and total motile sperm count (mean 13 million to 28 million) (3). A meta-analysis of 11 randomized controlled trials by Chua et al. (4) examined the evidence to support the treatment of idiopathic male infertility with estrogen antagonists. Their data revealed a statistically significant improvement in pregnancy rate, sperm concentration, and sperm motility. A series of 307 men treated with CC for idiopathic OAT showed an improvement in sperm concentration (8.5 million to 15.4 million), which was more evident in young patients with a normal body mass index and short duration of infertility (5).

Men with a low testosterone (T) to estradiol (E_2) ratio are often treated with anastrozole. Although this treatment is less studied than CC in idiopathic male infertility, there is evidence that anastrozole improves semen parameters in some patients. Shoshany et al. (6) reported an improvement in sperm concentration and total motile sperm counts in 85% of patients with oligospermia and low T to E_2 ratio.

In addition to anastrozole and CC, follicle-stimulating hormone (FSH) has been used to treat idiopathic male infertility. Attia et al. (7) performed a systematic review of six randomized controlled trials involving over 450 male patients who were prescribed FSH for idiopathic infertility. The pregnancy rate (odds ratio [OR] 4.94) and live-birth rate (OR 9.31) were statistically significantly higher in the FSH group as compared with the nontreatment group (7).

There is a paucity of recent data suggesting that treatment with hCG improves semen parameters or pregnancy rate in idiopathic male infertility. The primary patient population treated with this medication is men with hypogonadotropic hypogonadism.

The primary treatment option for male patients with idiopathic infertility is EMT, ahead of referral for assisted reproductive techniques (ART), which are costly and are burdensome for the female partner. The data to support using EMT are moderate for CC but sparse for the other agents discussed. The quality of the data to support using CC in this population is weak, but the risk profile of the medication is minimal. Given the long-term safety profile of CC, a trial of therapy certainly seems warranted before referring a couple for ART, particularly in the absence of female factor infertility (8).

Pro 2. Kai J. Buhling, M.D.

Nutraceuticals and Vitamins

Thirty percent of all cases of infertility might be based on a male factor, such as a restriction in sperm quality, quantity, or motility (9). Studies have shown that environmental factors—including smoking, stress, or alcohol consumption—

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an aromatase inhibitor, does offer benefits. Several retrospective and prospective trials have reliably demonstrated an improvement in semen parameters among men with a suboptimal ratio of serum T to E_2 (72, 73). It is interesting that empiric therapy with anastrozole in the absence of an underlying endocrinopathy has not proven to be efficacious (74).

Gonadotropin therapy, generally in the form of FSH supplementation, has also been studied. A Cochrane review indicated that FSH supplementation among men with idiopathic infertility may improve spontaneous pregnancy rates, the quality of the evidence to support that conclusion was only moderate (7). A closer evaluation of the cited studies in the Cochrane review revealed that they were infrequently applied to men in a truly empiric fashion. The studies often did not include baseline T status or only enrolled—and saw a benefit among—men with an inappropriately normal-range baseline FSH, the latter qualifying more as “targeted” than empiric therapy (75–77). As is so often the case, even the higher quality studies were underpowered and lacked blinding or placebo control (78). Furthermore, the significant protocol heterogeneity across the studies was such that the pooled meta-analysis results for this question are of dubious value, which should dissuade us from using this expensive therapy for our patients purely as empiric therapy. Beyond these concerns, there are essentially no reliable data on live-birth rates with FSH supplementation.

We need to rely on the highest quality medical evidence possible when advising our patients, particularly when the infertility is idiopathic. The provision of purely empiric therapy relies more on wishful thinking in the clouds than the *terra firma* of controlled clinical trials. There are simply far too many scenarios where a prescription medication will not help, and we owe it to our male patients with idiopathic infertility to advise them of this truth.

Con 2. Marian Showell, M.P.H., M.L.I.S.

Nutraceuticals and Vitamins

Subfertility is believed to affect from 48.5 million to 186 million people worldwide (79–81). It affects 10% to 15% of

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can have a negative impact on sperm quality (10). Spermiogenesis is a very complex process that needs several micronutrients and metals, including antioxidants and zinc (11). Several studies also have found a correlation between the blood concentrations of micronutrients and sperm quality, showing a positive effect for vitamin A, folic acid, vitamin B_{12}, ascorbic acid, vitamin D, vitamin E, iodine, zinc, and copper (12–17).

Despite the difficulties in implementing studies on dietary supplements, there have been a number of higher quality studies on various micronutrients that were able to demonstrate a statistically significant positive effect on spermatogenesis. The best outcome criterion would be the pregnancy rate. But this in turn also depends on many other factors such as egg quality and timing of sexual intercourse. Thus, sperm quality is the most easily measurable quality factor, but sperm quality also can vary over time, as shown in the World Health Organization (WHO) guidelines (1). Several prospective placebo-controlled studies have been published (Table 1); owing to the production time of sperm, the studies have spanned 3 to 6 months. Only two prospective studies have measured pregnancy rate as an end point (Table 1).

Taking into account that the nutrients with a positive effect do not have any negative health impact, specific supplementation seems to be justified. The minimum recommendation should be the consumption of 1 teaspoon (~5 mL) of tomato paste a day.

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couples trying to conceive (82), and 50% of these couples are thought to have male partner subfertility (83, 84). So men are carrying an equal burden in the struggle for these couples to have a baby. Sperm is very susceptible to oxidative stress, which occurs during the natural process of the cells using oxygen. These toxins, known as free radicals or reactive oxygen species (ROS), are the by-products of this function; ROS are known to damage sperm and thus to limit the chances of conception (85).

The nutraceuticals and vitamins predominantly used in male subfertility therapy are vitamin E, vitamin C, carotenoids, carnitines, coenzyme Q10 (ubiquinol), cysteine, and the micronutrients folate, selenium, and zinc (86, 87). These antioxidants are capable of reducing the production of free radicals, slowing or preventing the oxidation and repairing cell damage (88). So does it logically follow that the consumption of unregulated, easily accessible, relatively cheap, over-the-counter antioxidant supplements will increase a couple's likelihood of having a baby? The simple answer is *no*—the evidence shows that this is not the case.

The most important outcomes for a couple trying to conceive are a live birth, clinical pregnancy, or miscarriage, with live birth rated as the most important (89). The 2019 Cochrane review indicated that there may be an increase in live-birth rate for those couples taking antioxidants, but the quality of this evidence was deemed to be low. There were biases within the trials, and the result was based on only a total of 750 men from a small number of studies. Only two of seven trials compared the same antioxidant, resulting in trials with conflicting results; in fact only two small studies of the seven in the placebo/no-treatment groups in this analysis reported a statistically significant effect on live birth, and the remaining five were showed no statistical significance (90). Importantly, since the publication of this review the data have been made available from two new, good-quality, large randomized controlled trials, both of which have shown that taking antioxidants has absolutely no effect on live birth. These trials—the Folic Acid and Zinc Supplementation Trial (FAZST) (91) and the Males, Antioxidants, and Infertility (MOXI) trial (92) (combination antioxidant)—added an additional 2,544 men to the Cochrane review. When the live-birth data for these trials are added to the meta-analysis, the live-birth rate for men taking antioxidants becomes statistically nonsignificant (Peto OR 1.01; 95% confidence interval [CI], 0.86–1.17). So antioxidants do not increase a couple's chances of having a baby.

Until all trials in this area report on clinically important outcomes, the evidence for the use of antioxidants will remain problematic. The majority of trials in this area only ever intend to report on sperm parameters. It is well known that both fertile and infertile men can have similar semen profiles, so it follows that sperm parameters cannot act as surrogate outcomes for the possibility of a live birth (93). Of the 61 included studies in the current Cochrane review of this topic, only 12 studies reported clinically relevant outcomes, and 44 did not (90).

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The harms from antioxidant consumption are relatively unknown as adverse events are very poorly reported across the male fertility trials. Only three trials included in the Cochrane review reported on miscarriage, with very low-quality evidence. Gastrointestinal upset was more apparent in the treatment groups (between 2% and 9%) as opposed to only 2% of the nontreatment group (90). The FAZST trial also found that abdominal discomfort, nausea, and vomiting were more common in the treatment groups (91).

The nutraceutical global market is huge, estimated to be worth more U.S. $278 billion by 2024 (94). It is driven by powerful advertising and social media influencers that promote and sell unregulated products to vulnerable subfertile couples. These couples might be tempted by these over-the-counter antioxidants, but there is no regulatory body overseeing quality, so there is no guarantee that they are receiving correct dosages. It has been shown that large doses may cause a “rebound effect” that can cause oxidation and be damaging to the sperm (95, 96).

In conclusion, we see that the evidence shows that there is no effect of antioxidants on live birth, the evidence regarding harm is sparse, and the most common outcomes studied do not reflect the important outcomes for infertile couples. We do not know which antioxidants may have an effect or not, and there is no guarantee that supplements are delivering the appropriate therapeutic dosages. So, *no*, we should not be encouraging subfertile men to take antioxidants, prescribed or otherwise.

Pro 3. Peter Chan, M.D.

Lifestyle Changes

Lifestyle modifications are often ignored because the evidence for their benefits lies mainly in improvement in semen parameters rather than pregnancy and live-birth rates. The absence of evidence, however, is not evidence of absence. Many reproductive outcomes depend heavily on factors beyond semen quality (e.g., a woman’s fertility status is unmodifiable by a man’s lifestyle changes), so there has been little interest in supporting long-term, sizable studies to evaluate the impact of various lifestyle modifications beyond semen quality. A profertility lifestyle may at best improve a couple’s odds of success or at least minimize their fertility status worsening with time.

Con 3. Mark Sigman M.D.

Lifestyle Changes

A variety of lifestyle interventions are often thrown at male partners of couples trying to conceive. It is important to keep in mind that although some interventions are associated with semen parameter changes, this may do little more than create false hopes and increased anxiety for the patient unless live-birth rates are increased. For many years, men have been told to avoid tight underwear (briefs). The rationale is that testes are cooler than the core body temperature, so when the testes temperature is experimentally elevated, spermatogenesis decreases. Does the type of underwear actually affect the chance of a couple conceiving? A number of small observational

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TABLE 1

Selection of prospective studies on micronutrients and sperm quality.

Micronutrient	Dose	Effect
Folic acid	5,000 μg folic acid + 66 mg zinc vs. placebo	Increase of sperm count 74% (18)
Ascorbic acid	200 mg ascorbic acid vs. 1,000 mg ascorbic acid vs. placebo	Increase sperm count, increase sperm morphology, increase sperm motility (19)
Ascorbic acid	1,000 mg ascorbic acid vs. 1,000 mg vitamin E vs. placebo	Reduction of DNA-fragmented spermatozoa (20)
Vitamin D	83 μg vitamin D vs. placebo in obese individuals	Increase of testosterone levels (21)
Vitamin E	300 mg vitamin E vs. placebo	Pregnancy rate 21% vs. 0 (22)[a]
Selenium	100 μg selenium vs. 100 μg selenium + 1,000 mg vitamin A + 10 mg ascorbic acid + 15 mg vitamin E	Increase sperm motility (23)
Zinc	400 mg zinc vs. 400 mg zinc + 20 mg vitamin E vs. 400 mg zinc + 20 mg vitamin E + 10 mg ascorbic acid vs. placebo	Reduction of asthenozoospermia with zinc (24)
Ubichinon Compositum	300 mg Ubichinon Compositum vs. placebo	Increase sperm count Increase sperm morphology Increase sperm motility (25)
L-Carnitine	2,000 mg L-carnitine + 1,000 mg L-acetyl-carnitine vs. placebo	Pregnancy rate 21.8% vs. 1.7% (26)[a]
N-Acetylcysteine	200 μg selenium vs. 600 mg N-acetyl-cysteine vs. 200 μg selenium + 600 mg *N*-acetyl-cysteine	Increase sperm count Increase sperm morphology Increase sperm motility (27)
Lycopene	14 mg LactoLycopene vs. placebo	Increase of sperm morphology Increase of sperm motility (28)

[a] Study measuring an effect on pregnancy rate as an end point.

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Although high-heat exposure to the scrotum can impair semen parameters, the recommendation that healthy men optimize their fertility status by reducing heat exposure (e.g., by avoiding saunas and hot baths) is unsupported (29). However, the question remains as to whether infertile men

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studies have addressed this; some reported lower semen parameters in men who wore briefs compared with those who wore boxers (30, 97–99). The clear knowledge gap has been evidence of a change in fecundity, which was recently answered by a study of 501 couples from the Longitudinal Investigation of Fertility and the Environment (LIFE) Study who were attempting to conceive (32). The type of underwear worn was correlated with fecundity, and the bottom line was that there was no effect on semen parameters, time to pregnancy, conception delay, or infertility. In fact, some of the semen parameter changes in men wearing briefs were suggestive of better sperm function rather than worse. The data clearly showed we should let men wear whatever underwear they choose.

With the widespread use of personal technology, our suspicious eyes have turned toward cell phones and laptop computers. Both emit electromagnetic radiation (EMR), but laptops may also raise the testes temperature when supported on the user's lap. Cell phone frequencies are 0.9–2.45 GHz, which is considered nonionizing radiation—it does not directly result in effects on DNA, unlike ionizing radiation. What is the biologic basis for concerns about cell phones? We really do not have a clear biologic mechanism beyond hypotheses, such as it may increase oxidative stress leading to a cascade of adverse effects. More importantly, there are no data linking cell phone use to lower fecundity. What cell phone use does to rodents exposed for 18 hours a day is interesting but inadequate to extrapolate to lower chances of human conception with normal cell phone use (100). Some users do keep cell phones in trouser pockets, but that is not equivalent to storing them against the scrotum. In addition, the increase in temperature from cell phone radiation is inadequate to significantly raise the temperature of the testes (101). Although observational studies have correlated the amount of cell phone use to semen parameters, those studies did not account for multiple other confounders such as obesity—which is related to scrotal temperature (102). We may suggest that men not store or use their cell phones directly against their scrotums, but that does not reflect how men actually store or use them. The data are clearly insufficient to recommend changes to current usage patterns.

The data for laptop use extremely weak, and unfortunately the studies have been few. Assessing in vitro changes in sperm placed under a laptop computer is not fecundity data. Although laptop use of computers is common, most men place them on their thighs, not over their genitals. We clearly need more data to be able to make intelligent recommendations for changes in usage patterns.

Heat exposure from saunas and hot tubs also has been cited as a potential cause of infertility. A widely cited study reported that discontinuation of hot tub use resulted in an improvement in total motile count, which was not statistically significant with a sample size of 11 patients

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could improve their fertility by avoiding excessive heat. Men also often wonder if wearing boxer-type underwear is beneficial. Although studies have shown that better sperm quantity among men attending a fertility clinic is usually correlated with wearing boxer-style underwear (30, 31), improvement in time-to-pregnancy remains to be established (32).

The adverse effects of using mobile cell phones, laptop computers, and Wi-Fi on sperm parameters have mainly been studied (33–39) in animals, in vitro, or among small numbers of men with very short-term observational data that did not measure reproductive outcomes. We are in need of good evidence to demonstrate long-term negative affects of electromagnetic waves and to support the efficacy of reducing their exposure for improving the relevant reproductive outcomes.

The deleterious effects of smoking on semen quality have been clearly shown (40, 41), but moderate consumption of caffeine and alcohol have little impact. The results in ART outcomes are less consistent; some studies have shown lower fertilization (42), pregnancy, and live-birth rates (43–45) with alcohol and tobacco consumption, and have found a beneficial effect of smoking cessation of the male partner (4% reduction of treatment failure/year of cessation) (46). Infertile men should reduce alcohol and stop tobacco consumption for better odds of natural conception. If ART is needed, reducing usage of these products may help, but there is no need to "overdelay" ART.

Obesity can lead to erectile dysfunction, increased scrotal temperatures, and reduced semen parameters and function. Adverse reproductive outcomes—including impaired blastocyst development, reduced pregnancy outcomes, or increased miscarriage with ART (47–54)—have been linked to paternal obesity. Though controversies exist, weight normalization in obese men through lifestyle modification (55, 56) and bariatric surgery (57–59) can improve semen parameters including sperm DNA integrity (60).

With regards to diet, high intake of *trans* fatty acids (found in industrially processed food) and saturated fats (mainly from meat, poultry, dairy products, and palm/coconut oil) has been consistently related to poor semen quality (61–64). By contrast, men attending a fertility clinic showed better sperm morphology with a higher intake of omega-3 polyunsaturated fatty acids (Ω-3 PUFAs) (62). Oily fish (e.g., salmon, herring, mackerel, sardines, and anchovies) are sources of Ω-3 PUFAs. Indeed, among men in subfertile couples, higher fish intake has been linked to better sperm parameters (65). In a randomized trial, infertile men with idiopathic OAT taking Ω-3 PUFAs supplementation (1.84 g/day for 32 weeks) showed statistically significant improvement in semen parameters (66). Even plant-based sources of Ω-3 PUFAs such as walnuts (75 g/day, about $^3/_4$ of a cup) have been shown in a randomized trial to improve sperm parameters in young healthy men consuming a typical Western-style diet (67). A prospective cohort study of over 500 couples planning preg-

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(103). Dry heat exposure through Finnish sauna use was found to lower sperm count and motility ($P<.001$) although the semen parameters remained in the fertile reference range (104). It is important to note that sauna temperatures are typically 176–194°F, while jacuzzi and hot tubs are significantly cooler at 100–104°F, which suggests that general avoidance of all heat may not be appropriate. Most importantly there are no fecundity data to indicate that this type of exposure actually leads to infertility, which makes general recommendations for all heat exposure problematic at best.

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nancy showed that consumption of more than eight seafood servings per cycle improved fecundity (68).

Clinicians can offer evidence-based, sensible counseling on lifestyle modification for infertile men. This advice—which is generally in line with recommendations beneficial to cardiovascular, metabolic, and sexual health—is backed by evidence on improving semen parameters and, to a lesser extent, the more relevant outcomes of pregnancy or live-birth rates. Optimizing weight, moderately increasing the consumption of fish and reducing the consumption of meat (especially processed meat products), stopping smoking, and reducing of alcohol consumption are all sound recommendations. However, the male partner should not defer a fertility evaluation or delay implementation of various treatment options, including medical and surgical interventions and ART. Realistically, these men often need more than just turning off their mobile phones or getting a new style of undies.

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REFERENCES

1. Ko EY, Siddiqi K, Brannigan RE, Sabanegh ES. Empirical medical therapy for idiopathic male infertility: a survey of the American urological association. J Urol 2012;187:973–8.
2. Ghanem H, Shaeer O, El-Segini A. Combination clomiphene citrate and antioxidant therapy for idiopathic male infertility: a randomized controlled trial. Fertil Steril 2010;93:2232–5.
3. Sharma D, Zillioux J, Khourdaji I, Reines K, Wheeler K, Costabile R, et al. Improvements in semen parameters in men treated with clomiphene citrate—a retrospective analysis. Andrologia 2019;51:e13257.
4. Chua ME, Escusa KG, Luna S, Tapia LC, Dofitas B, Morales M. Revisiting oestrogen antagonists (clomiphene or tamoxifen) as medical empiric therapy for idiopathic male infertility: a meta-analysis. Andrology 2013;1:749–57.
5. Boeri L, Serino A, Ventimiglia E, La Croce G, Capogrosso P, Paciotti M, et al. Who is the most suitable candidate for clomiphene treatment? Findings of an observational survery in a cohort of primary infertile men. J Urol 2015;193:e946–7.
6. Shoshany O, Abhyankar N, Mufarreh N, Daniel G, Niederberger C. Outcomes of anastrozole in oligozoospermic hypoandrogenic subfertile men. Fertil Steril 2017;107:589–94.
7. Attia AM, Abou-Setta AM, Al-Inany HG. Gonadotrophins for idiopathic male factor subfertility. Cochrane Database Syst Rev 2013;8:CD005071.
8. Krzastek SC, Sharma D, Abdullah N, Sultan M, Machen GL, Wenzel JL, et al. Long-term safety and efficacy of clomiphene citrate for the treatment of hypogonadism. J Urol 2019;202:1029–35.
9. World Health Organization. Laboratory manual for the examination and processing of human semen. 5th ed. Geneva: WHO; 2010.
10. Buhling KJ, Laakmann E. The effect of micronutrient supplements on male fertility. Curr Opin Obstet Gynecol 2014;26:199–209.
11. Fallah A, Mohammad-Hasani A, Hosseinzadeh Colagar A. Zinc is an essential element for male fertility: a review of Zn roles in men's health, germination, sperm quality, and fertilization. J Reprod Infertil 2018;19:69–81.
12. Al-Azemi MK, Omu AE, Fatinikun T, Mannazhath N, Abraham S. Factors contributing to gender differences in serum retinol and alpha-tocopherol in infertile couples. Reprod Biomed Online 2009;19:583–90.
13. Boxmeer JC, Smit M, Utomo E. Low folate in seminal plasma is associated with increased sperm DNA damage. Fertil Steril 2009;92:548–56.
14. Hammoud AO, Meikle AW, Peterson CM, Stanford J, Gibson M, Carrell DT. Association of 25-hydroxy-vitamin D levels with semen and hormonal parameters. Asian J Androl 2012;14:855–9.
15. Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev 2010;31:702–55.
16. Colagar AH, Marzony ET, Chaichi MJ. Zinc levels in seminal plasma are associated with sperm quality in fertile and infertile men. Nutr Res 2009;29:82–8.
17. Li P, Zhong Y, Jiang X, Wang C, Zuo Z, Shaet A. Seminal plasma metals concentration with respect to semen quality. Biol Trace Elem Res 2012;148:1–6.
18. Wong WY, Merkus HM, Thomas CM, Menkveld R, Zielhuis GA, Steegers-Theunissen RP. Effects of folic acid and zinc sulfate on male factor subfertility: a double-blind, randomized, placebo-controlled trial. Fertil Steril 2002;77:491–8.
19. Dawson EB, Harris WA, Teter MC, Powell LC. Effect of ascorbic acid supplementation on the sperms quality of smokers. Fertil Steril 1992;58:1034–9.
20. Greco E, Iacobelli M, Rienzi L, Ubaldi F, Ferrero S, Tesarik J. Reduction of the incidence of sperm DNA fragmentation by oral antioxidant treatment. J Androl 2005;26:349–53.
21. Pilz S, Frisch S, Koertke H, Kuhn J, Dreier J, Obermayer-Pietsch B, et al. Effect of vitamin D supplementation on testosterone levels in men. Horm Metab Res 2011;43:223–5.
22. Suleiman SA, Ali ME, Zaki ZMS, el-Malik EM, Nasret MA, et al. Lipid peroxidation and human sperm motility: protective role of vitamin E. J Androl 1996;17:530–7.
23. Scott R, MacPherson A, Yates RW, Hussain B, Dixon J. The effect of oral selenium supplementation on human sperm motility. Br J Urol 1998;82:76–80.
24. Omu AE, Al-Azemi MK, Kehinde EO, Anim JT, Oriowo MA, Mathew TC. Indications of the mechanisms involved in improved sperm parameters by zinc therapy. Med Princ Pract 2008;17:108–16.
25. Safarinejad MR. Efficacy of coenzyme Q10 on semen parameters, sperm function and reproductive hormones in infertile men. J Urol 2009;182:237–48.
26. Cavallini G, Ferraretti AP, Gianaroli L, Biagiotti G, Vitali G. Cinnoxicam and L-carnitine/acetyl-L-carnitine treatment for idiopathic and varicocele-associated oligoasthenospermia. J Androl 2004;25:761–70.
27. Safarinejad MR, Safarinejad S. Efficacy of selenium and/or N-acetyl-cysteine for improving semen parameters in infertile men: a double-blind, placebo controlled, randomized study. J Urol 2009;181:741–51.
28. Williams EA, Parker M, Robinson A, Pitt S, Pacey AA. A randomized placebo-controlled trial to investigate the effect of lactolycopene on semen quality in healthy males. Eur J Nut 2020;59:825–33.
29. Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society for Reproductive Endocrinology and Infertility. Optimizing natural fertility: a committee opinion. Fertil Steril 2017;107:52–8.
30. Mínguez-Alarcón L, Gaskins AJ, Chiu YH, Messerlian C, Williams PL, Ford JB, et al. Type of underwear worn and markers of testicular function among men attending a fertility center. Hum Reprod 2018;33:1749–56.
31. Jurewicz J, Radwan M, Sobala W, Radwan P, Jakubowski L, Hawuła W, et al. Lifestyle factors and sperm aneuploidy. Reprod Biol 2014;14:190–9.
32. Sapra KJ, Eisenberg ML, Kim S, Chen Z, Buck Louis GM. Choice of underwear and male fecundity in a preconception cohort of couples. Andrology 2016;4:500–8.
33. Jaffar FHF, Osman K, Ismail NH, Chin KY, Ibrahim SF. Adverse effects of Wi-Fi radiation on male reproductive system: a systematic review. Tohoku J Exp Med 2019;248:169–79.
34. Avendaño C, Mata A, Sanchez Sarmiento CA, Doncel GF. Use of laptop computers connected to internet through Wi-Fi decreases human sperm motility and increases sperm DNA fragmentation. Fertil Steril 2012;97:39–45.e2.
35. Gorpinchenko I, Nikitin O, Banyra O, Shulyak A. The influence of direct mobile phone radiation on sperm quality. Cent European J Urol 2014;67:65–71.
36. Yildirim ME, Kaynar M, Badem H, Cavis M, Karatas OF, Cimentepe E. What is harmful for male fertility: cell phone or the wireless Internet? Kaohsiung J Med Sci 2015;31:480–4.
37. Kamali K, Atarod M, Sarhadi S, Nikbakht J, Emami M, Maghsoudi R, et al. Effects of electromagnetic waves emitted from 3G+ Wi-Fi modems on human semen analysis. Urologia 2017;84:209–14.
38. Mortazavi S, Parsanezhad M, Kazempour M, Ghahramani P, Mortazavi A, Davari M. Male reproductive health under threat: short term exposure to radiofrequency radiations emitted by common mobile jammers. J Hum Reprod Sci 2013;6:124–8.
39. Mortazavi SA, Taeb S, Mortazavi SM, Zarei S, Haghani M, Habibzadeh P, Shojaei-Fard MB. The fundamental reasons why laptop computers should not be used on your lap. J Biomed Phys Eng 2016;6:279–84.
40. Li Y, Lin H, Li Y, Cao J. Association between socio-psycho-behavioral factors and male semen quality: systematic review and meta-analyses. Fertil Steril 2011;95:116–23.
41. Sharma R, Harlev A, Agarwal A, Esteves SC. Cigarette smoking and semen quality: a new meta-analysis examining the effect of the 2010 World Health Organization laboratory methods for the examination of human semen. Eur Urol 2016;70:635–45.
42. Braga DP, Halpern G, Figueira Rde C, Setti AS, Iaconelli A Jr, Borges E Jr. Food intake and social habits in male patients and its relationship to intracytoplasmic sperm injection outcomes. Fertil Steril 2012;97:53–9.
43. Klonoff-Cohen H, Natarajan L, Marrs R, Yee B. Effects of female and male smoking on success rates of IVF and gamete intra-fallopian transfer. Hum Reprod 2001;16:1382–90.
44. Klonoff-Cohen H, Bleha J, Lam-Kruglick PA. Prospective study of the effects of female and male caffeine consumption on the reproductive end points of IVF and gamete intra-fallopian transfer. Hum Reprod 2002;17:1746–54.

45. Klonoff-Cohen H, Lam-Kruglick P, Gonzalez C. Effects of maternal and paternal alcohol consumption on the success rates of in vitro fertilization and gamete intrafallopian transfer. Fertil Steril 2003;79:330–9.
46. Vanegas JC, Chavarro JE, Williams PL, Ford JB, Toth TL, Hauser R, et al. Discrete survival model analysis of a couple's smoking pattern and outcomes of assisted reproduction. Fertil Res Pract 2017;3:5.
47. Bakos HW, Henshaw RC, Mitchell M, Lane M. Paternal body mass index is associated with decreased blastocyst development and reduced live birth rates following assisted reproductive technology. Fertil Steril 2011;95:1700–4.
48. Umul M, Kose SA, Bilen E, Altuncu AG, Oksay T, Guney M. Effect of increasing paternal body mass index on pregnancy and live birth rates in couples undergoing intracytoplasmic sperm injection. Andrologia 2015;47:360–4.
49. Thomsen L, Humaidan P, Bungum L, Bungum M. The impact of male overweight on semen quality and outcome of assisted reproduction. Asian J Androl 2014;16:1–6.
50. Keltz J, Zapantis A, Jindal SK, Lieman HJ, Santoro N, Polotsky AJ. Overweight men: clinical pregnancy after ART is decreased in IVF but not in ICSI cycles. J Assist Reprod Genet 2010;27:539–44.
51. Palmer NO, Bakos HW, Fullston T, Lane M. Impact of obesity on male fertility, sperm function and molecular composition. Spermatogenesis 2012;2:253–63.
52. Colaci DS, Afeiche M, Gaskins AJ, Wright DL, Toth TL, Tanrikut C, et al. Men's body mass index in relation to embryo quality and clinical outcomes in couples undergoing in vitro fertilization. Fertil Steril 2012;98:1193–9.e1.
53. Merhi ZO, Keltz J, Zapantis A, Younger J, Berger D, Lieman HJ, et al. Male adiposity impairs clinical pregnancy rate by in vitro fertilization without affecting day 3 embryo quality. Obesity (Silver Spring) 2013;21:1608–12.
54. Ramasamy R, Bryson C, Reifsnyder JE, Neri Q, Palermo GD, Schlegel PN. Overweight men with nonobstructive azoospermia have worse pregnancy outcomes after microdissection testicular sperm extraction. Fertil Steril 2013;99:372–6.
55. Håkonsen LB, Thulstrup AM, Aggerholm AS, Olsen J, Bonde JP, Andersen CY, et al. Does weight loss improve semen quality and reproductive hormones? Results from a cohort of severely obese men. Reprod Health 2011;8:24.
56. Jaffar M. Does weight loss improve fertility with respect to semen parameters? Results from a large cohort study. Int J Infertil Fetal Med 2016;7:94–9.
57. Samavat J, Cantini G, Lotti F, Di Franco A, Tamburrino L, Degl'Innocenti S, et al. Massive weight loss obtained by bariatric surgery affects semen quality in morbid male obesity: a preliminary prospective double-armed study. Obes Surg 2018;28:69–76.
58. El Bardisi H, Majzoub A, Arafa M, AlMalki A, Al Said S, Khalafalla K, et al. Effect of bariatric surgery on semen parameters and sex hormone concentrations: a prospective study. Reprod Biomed Online 2016;33:606–11.
59. Lee Y, Dang JT, Switzer N, Yu J, Tian C, Birch DW, Karmali S. Impact of bariatric surgery on male sex hormones and sperm quality: a systematic review and meta-analysis. Obes Surg 2019;29:334–46.
60. Mir J, Franken D, Andrabi SW, Ashraf M, Rao K. Impact of weight loss on sperm DNA integrity in obese men. Andrologia 2018;50:e12957.
61. Chavarro JE, Furtado J, Toth TL, Ford J, Keller M, Campos H, Hauser R. Trans-fatty acid levels in sperm are associated with sperm concentration among men from an infertility clinic. Fertil Steril 2011;95:1794–7.
62. Attaman JA, Toth TL, Furtado J, Campos H, Hauser R, Chavarro JE. Dietary fat and semen quality among men attending a fertility clinic: dietary fat and semen quality among men attending a fertility clinic. Hum Reprod 2012;27:1466–74.
63. Jensen TK, Heitmann BL, Blomberg Jensen M, Halldorsson TI, Andersson AM, Skakkebæk NE, et al. High dietary intake of saturated fat is associated with reduced semen quality among 701 young Danish men from the general population. Am J Clin Nutr 2013;97:411–8.
64. Chavarro JE, Mínguez-Alarcón L, Mendiola J, Cutillas-Tolín A, López-Espín JJ, Torres-Cantero AM. Trans fatty acid intake is inversely related to total sperm count in young healthy men. Hum Reprod 2014;29:429–40.
65. Afeiche MC, Gaskins AJ, Williams PL, Toth TL, Wright DL, Tanrikut C, et al. Processed meat intake is unfavorably and fish intake favorably associated with semen quality indicators among men attending a fertility clinic. J Nutr 2014;144:1091–8.
66. Safarinejad MR. Effect of omega-3 polyunsaturated fatty acid supplementation on semen profile and enzymatic anti-oxidant capacity of seminal plasma in infertile men with idiopathic oligoasthenoteratospermia: a double-blind, placebo-controlled, randomised study. Andrologia 2011;43:38–47.
67. Robbins WA, Xun L, FitzGerald LZ, Esguerra S, Henning SM, Carpenter CL. Walnuts improve semen quality in men consuming a Western-style diet: randomized control dietary intervention trial. Biol Reprod 2012;87:101.
68. Gaskins AJ, Sundaram R, Buck Louis GM, Chavarro JE. Seafood intake, sexual activity, and time to pregnancy. J Clin Endocrinol Metab 2018;103:2680–8.
69. Willets AE, Corbo JM, Brown JN. Clomiphene for the treatment of male infertility. Reprod Sci 2013;20:739–44.
70. Vandekerckhove P, Lilford R, Vail A, Hughes E. WITHDRAWN: Clomiphene or tamoxifen for idiopathic oligo/asthenospermia. Cochrane Database Syst Rev 1997;4:CD000151.
71. Jungck EC, Roy S, Greenblatt RB, Mahesh VB. Effect of clomiphene citrate on spermatogenesis in the human. Fertil Steril 2016;15:40–3.
72. Cavallini G, Biagiotti G, Bolzon E. Multivariate analysis to predict letrozole efficacy in improving sperm count of non-obstructive azoospermic and cryptozoospermic patients: a pilot study. Asian J Androl 2013;15:806–11.
73. Pavlovich C, Kind P, Goldstein M, Schlegel P. Evidence of a treatable endocrinopathy in infertile men. J Urol 2001;165:837–41.
74. Helo S, Ellen J, Mechlin C, Feustel P, Grossman M, Ditkoff E, McCullough A. A randomized prospective double-blind comparison trial of clomiphene citrate and anastrozole in raising testosterone in hypogonadal infertile men. J Sex Med 2015;12:1761–9.
75. Kamischke A, Behre HM, Bergmann M, Simoni M, Schäfer T, Nieschlag E. Recombinant human follicle stimulating hormone for treatment of male idiopathic infertility: a randomized, double-blind, placebo-controlled, clinical trial. Hum Reprod 1998;13:596–603.
76. Matorras R, Pérez C, Corcóstegui B, Pijoan JI, Ramón O, Delgado P, Rodríguez-Escudero FJ. Treatment of the male with follicle-stimulating hormone in intrauterine insemination with husband's spermatozoa: a randomized study. Hum Reprod 1997;12:24–8.
77. Foresta C, Bettella A, Garolla A, Ambrosini G, Ferlin A. Treatment of male idiopathic infertility with recombinant human follicle-stimulating hormone: a prospective, controlled, randomized clinical study. Fertil Steril 2005;84:654–61.
78. Paradisi R, Natali F, Fabbri R, Battaglia C, Seracchioli R, Venturoli S. Evidence for a stimulatory role of high doses of recombinant human follicle-stimulating hormone in the treatment of male-factor infertility. Andrologia 2014;46:1067–72.
79. Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Hum Reprod 2007;22:1506–12.
80. Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. Hum Reprod Update 2015;21:411–46.
81. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med 2012;9:e1001356.
82. Evers JL. Female subfertility. Lancet 2002;360:151–9.
83. Irvine DS. Epidemiology and aetiology of male infertility. Hum Reprod 1998;13(Suppl 1):33–44.
84. Winters BR, Walsh TJ. The epidemiology of male infertility. Urol Clin N Am 2014;41:195–204.
85. Agarwal A, Parekh N, Selvam MKP, Henkel R, Shah R, Homa ST, et al. Male oxidative stress infertility (MOSI): proposed terminology and clinical practice guidelines for management of idiopathic male infertility. T World J Mens Health 2019;37:296–312.

86. Eskanazi B, Kidd SA, Marks AR, Sloter E, Block G, Wyrobek AJ. Antioxidant intake is associated with semen quality in healthy men. Hum Reprod 2005;20:1006–12.
87. Majzoub A, Agarwal A. Systematic review of antioxidant types and doses in male infertility: benefits on semen parameters, advanced sperm function, assisted reproduction and live-birth rate. Arab J Urol 2018;16:113–24.
88. Mirończuk-Chodakowska I, Witkowska AM, Zujko ME. Endogenous non-enzymatic antioxidants in the human body. Adv Med Sci 2018;63:68–78.
89. Martins da Silva SJ. Male infertility and antioxidants: one small step for man, no giant leap for andrology? Reprod Biomed Online 2019;39:879–83.
90. Smits RM, Mackenzie-Proctor R, Yazdani A, Stankiewicz MT, Jordan V, Showell MG. Antioxidants for male subfertility. Cochrane Database Syst Rev 2019;3:CD007411.
91. Schisterman EF, Sjaarda LA, Clemons T, Carrell DT, Perkins NJ, Johnstone E, et al. Effect of folic acid and zinc supplementation in men on semen quality and live birth among couples undergoing infertility treatment: a randomized clinical trial. JAMA 2020;323:35–48.
92. Steiner AZ, Hansen KR, Barnhart KT, Cedars MI, Legro RS, Diamond MP, et al. The effect of antioxidants on male factor infertility: the Males, Antioxidants, and Infertility (MOXI) randomized clinical trial. Fertil Steril 2020;113:552–60.e3.
93. Harbin Consensus Conference Workshop Group. Improving the Reporting of Clinical Trials of Infertility Treatments (IMPRINT): modifying the CONSORT statement. Fertil Steril 2014;102:952–9.
94. Grand View Research. Dietary supplements market size, share & trends analysis report by ingredient (vitamins, minerals), by form, by application, by end user, by distribution channel, by region, and segment forecasts, 2020–2027. Available at: https://www.grandviewresearch.com/industry-analysis/dietary-supplements-market.
95. Dattilo M, Giuseppe D, Ettore C, Ménézo Y. Improvement of gamete quality by stimulating and feeding the endogenous antioxidant system: mechanisms, clinical results, insights on gene-environment interactions and the role of diet. J Assist Reprod Genet 2016;33:1633–48.
96. Ghyczy M, Boros M. Electrophilic methyl groups present in the diet ameliorate pathological states induced by reductive and oxidative stress: a hypothesis. Br J Nutr 2001;85:409–14.
97. Parazzini F, Marchini M, Luchini L, Tozzi L, Mezzopane R, Fedele L. Tight underpants and trousers and risk of dyspermia. Int J Androl 1995;18:137–40.
98. Munkelwitz R, Gilbert BR. Are boxer shorts really better? A critical analysis of the role of underwear type in male subfertility. J Urol 1998;160:1329–33.
99. Jung A, Leonhardt F, Schill W-B, Schuppe H-C. Influence of the type of undertrousers and physical activity on scrotal temperature. Hum Reprod 2005;20:1022–7.
100. Oh JJ, Byun SS, Lee SE, Choe G3, Hong SK. Effect of electromagnetic waves from mobile phones on spermatogenesis in the era of 4G-LTE. Biomed Res Int 2018;2018:1801798.
101. El-Hamd MA, Aboeldahab S. Cell phone and male infertility: an update. J Integr Nephrol Androl 2018;5:1–5.
102. Agarwal A, Deepinder F, Sharma RK, Ranga G, Li J. Effect of cell phone usage on semen analysis in men attending infertility clinic: an observational study. Fertil Steril 2008;89:124–8.
103. Shefi S, Tarapore PE, Walsh TJ, Croughan M, Turek PJ. Wet heat exposure: a potentially reversible cause of low semen quality in infertile men. Int Braz J Urol 2007;33:50–6.
104. Garolla A, Torino M, Sartini B, Cosci I, Patassini C, Carraro U, Foresta C. Seminal and molecular evidence that sauna exposure affects human spermatogenesis. Int Braz J Urol 2007;33:50–7.