Title: Preconceptual care for couples seeking fertility treatment, an evidence-based approach.

Running title: Preconceptual care in the fertility unit

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Abstract

There is accumulating evidence demonstrating that positive lifestyle modification and the optimization of the preconceptual period can influence the reproductive potential for both men and women. However, a large percentage of couples attending fertility clinics with potential to improve preconception habits may not always receive appropriate preconceptual advice. Additionally, supplements and adjuncts that promise to increase fertility treatment success rates are marketed to infertile patients despite lack of convincing evidence supporting benefit. This review aims to identify possible associations between lifestyle factors for couples seeking fertility treatment and fertility treatment outcomes and to offer possible explanations of the biological basis of these associations. An electronic search was conducted from 1978 until July 2019 linking preconceptual behaviors for women and men with the outcome of fertility treatment. The literature search explored the importance of numerous factors including smoking, caffeine, alcohol, obesity, physical exercise, recreational drugs, stress, diet, supplements, alternative medicine, environmental factors and pollutants. Some associations were found to be more significant than others. The preconceptual period is undeniably a delicate and important window which should not be overlooked during fertility counseling. Simple lifestyle modifications could positively influence fertility treatment outcomes. Fertility teams, consisting of clinicians, fertility nurses, dieticians, psychologists, exercise advisors and others, should dedicate time to offer evidence-based preconceptual advice and targeted interventions to couples seeking fertility treatment.

Keywords: ART; fertility treatment; infertility; lifestyle; preconceptual health

Essential points

- A large percentage of couples attending fertility clinics face multiple lifestyle issues but do not always receive appropriate preconceptual advice.
- The preconceptual period is undeniably a delicate and important window which should not be overlooked during fertility counseling.
- Simple lifestyle modifications could positively influence fertility treatment outcomes.
- Fertility teams should offer tailored, evidence-based preconceptual advice and targeted interventions to couples seeking fertility treatment.
Introduction

Couples seeking fertility treatment are often highly motivated to take any steps necessary to maximize the chance of conception. However, a large percentage of couples attending fertility clinics with potential to improve preconception habits may not always receive appropriate preconceptual advice despite accumulating evidence that lifestyle factors affect the reproductive potential and fertility treatment success rates (1-3).

A number of studies have demonstrated lack of awareness regarding the effect of preconceptual lifestyle amongst couples undergoing assisted reproductive technology (ART) (4, 5). In a questionnaire-based study before fertility consultation, 65% of women endorsed for four or more of negative lifestyle factors (6). Similarly, a prospective study on more than 12,000 ART patients in the United States (US), identified multiple harmful lifestyle behaviors (3). This lack of knowledge regarding behaviors and adjuncts, which may or may not affect fertility (7, 8) often encourages fertility myths (9, 10). There is both the need and increasing demand for physician led preconceptual counseling (11). The Environment and Reproductive Health (EARTH) study investigated the impact of various factors in both women and men on fertility and pregnancy outcomes highlighting the importance of certain factors that impacted reproductive outcomes (12).

Aim

This review aims to identify and summarize associations between lifestyle factors for couples seeking fertility treatment and fertility treatment outcomes. This is not an exhaustive list to put couples on further stress around their fertility journey; on the contrary, it is an evidence-based discussion aiming to dispel fertility myths, increase awareness and provide simple directions which could enhance fertility treatment outcomes. This manuscript attempts to offer possible explanations for the biological basis of the observed associations, with implications for future research.

Methods

An electronic search was conducted in PubMed, Embase, Medline and Cochrane databases and references of relevant studies were cross-checked in order to include all relevant studies from database inception 1978 until July
2019 linking preconceptual lifestyle with the outcome of any type of fertility treatment. The following word combinations were used for the search: caffeine (coffee, tea, coke, soda, soft drinks), smoking, BMI (body mass index), weight, obesity, alcohol, recreational drugs (cannabis, marijuana, opioids), exercise, diet (vitamins A, C, D, E, multivitamin supplements, selenium, zinc, coenzyme Q10, L-arginine, folate, melatonin, carnitines, N-acetyl-cysteine, antioxidants, pentoxifylline, inositol, Mediterranean diet, dairy, meat, whole grain, phytoestrogens), acupuncture, alternative medicine, season, sunlight, environmental pollutants (perfluorinated chemicals, pesticides, mercury, lead, solvents, cell phone, laptop, phthalates, phenols, cosmetics), stress AND fertility OR IVF (in vitro fertilization) OR ART for both men and women. References from selected studies were cross-checked and meeting proceedings of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine were also searched. Studies looking into modifiable factors in relation to natural fecundity were excluded as the review focused on infertile couples.

**Lifestyle**

- **Stress**

Measuring the effect of psychological factors is challenging and often overlooked. However, stress is one of the most prominent reasons for discontinuation of fertility treatment (13). Women undergoing ART often suffer from anxiety, with more than 30% fulfilling the criteria for major depression (14-18). Stress influences female reproductive function (18-21) (table 1, supplementary material). Women seem to be affected more than men (22) but stress in the male partner has been associated with impaired sperm parameters and sperm DNA damage (23-25). There are also two studies linking paternal stress with adverse pregnancy outcomes and reduced live births (26, 27).

There are more than 60 studies for women and 15 for men looking into fertility treatment outcomes in relation to stress or following certain interventions to reduce anxiety (table 2, supplementary material). Numerous psychosocial interventions have been proposed including mind-body interventions, cognitive-behavior therapy, web-based teaching, counseling, internet community support, partnership and coping enhancement program, yoga, acupuncture, acupressure, self-administered cognitive coping and relaxation intervention (11, 28-30). The most recent systematic reviews investigating the effect of psychosocial interventions on fertility treatment outcome fail to reach a consensus since very few studies report on live birth rates (LBRs) (28, 31, 32). The development of a complex intervention has
been proposed, targeting both partners and enhancing their partnership with emphasis on the most stressful period: waiting for the pregnancy test.

Fertility teams should identify the couples most likely to benefit from stress reducing interventions and provide tailored support and advice (33). Various tools have been validated for this purpose (34). More research is needed in order to develop well-designed psychological/educational interventions. Even though their value to improve success rates has yet to be proven, successful interventions could help alleviate the psychological burden of infertility, recognize possible psychiatric conditions and create a better experience increasing conformity to current and future cycles (35).

- **BMI**

Obesity has been linked to infertility and to adverse obstetric outcomes. However, worldwide more than half of women and men of reproductive age are overweight or obese (36, 37).

In women, BMI in relation to ART has been extensively studied in more than 100 studies (tables 3, 4 supplementary material). The most recent systematic review and meta-analysis demonstrated a significantly decreased chance of live birth after ART for obese women (BMI ≥ 30 kg/m²) (38). Central obesity (waist-hip ratio above 0.85 for females) seems to have negative effect on ART success rates (39-41); for a waist-hip ratio increase of 0.1 unit, a 30% decrease in probability of conception per cycle was documented in a donor intrauterine insemination (IUI) program (39). Interestingly, waist circumference seems to be inversely related to LBR amongst women undergoing fertility treatment regardless of BMI (42). There is also, accumulating evidence of altered metabolic fingerprint for embryos from obese women, demonstrating that the environment around conception affects not only the course of fertility treatment but may also have long-term consequences for the offspring (43). Embryos from the high BMI group exhibit different metabolism patterns with decreased glucose consumption and higher endogenous triglycerides (44).

The lowest odds of live birth after IVF are documented when both partners have BMI ≥25 kg/m² according to a large cohort study (45). There is accumulating evidence demonstrating the adverse effect of male obesity on ART but further research is warranted. Confounders such as type of infertility and female BMI should be accounted for
and LBR should be the main outcome of interest (46). Obesity causes sperm DNA damage (47, 48) and seems the strongest lifestyle factor affecting spermatogenesis (49). A recent systematic review and meta-analysis concluded that raised male BMI resulted in a statistically significant decrease in CPR and LBR after IVF and ICSI (46). ICSI does not overcome the influence of obesity on sperm, suggesting that the effect is not limited to conventional semen analysis parameters. Indeed, paternal obesity affects sperm molecular composition, embryo morphokinetics (50) and blastocyst development (51). Male BMI may be more important than semen parameters for embryo quality and IVF outcomes (52). Increased weight and waist or hip circumference have also been associated with impaired semen parameters and hormonal profile (53).

There are few studies supporting various weight loss interventions for overweight women (hypocaloric diet, weight reduction programs, physical exercise, behavioral/lifestyle targeted interventions, internet-based interventions, bariatric surgery and medication such as orlistat, insulin sensitizers and acarbose) while data on lifestyle interventions in men/couples are lacking (54). Two available studies on interventions for obese men suggested beneficial effect of weight loss for sperm parameters and DNA integrity (55, 56). Weight loss as little as 10% in addition to a month of moderate weight management interventions for women had measurable positive effect on hormonal profile, menstrual cycle, spontaneous ovulation, and pregnancy rate (PR) (36). Regardless of weight loss, energy restriction itself has beneficial effect on reproduction for women with polycystic ovary syndrome (PCOS) (57). However, a randomized study did not find benefit from a six-month lifestyle program before fertility treatment for obese infertile women compared to immediate fertility treatment (58). A multicenter randomized controlled trial (RCT) yielded similar results. An intense weight loss program for obese women before IVF (12 week low calorie liquid formula diet of 880 kcal/day and weight stabilization for 2–5 weeks), resulted in considerable weight loss but no improvement of IVF LBRs eventhough spontaneous conceptions increased (59). A systematic review concluded that dropout is significant problem in lifestyle interventions programs for overweight and obese infertile women (median dropout rate of 24%) (60). Another thorough systematic review and meta-analysis looked into non-surgical weight loss options for couples seeking fertility treatment. The authors concluded that pregnancy was more likely for women on calorie restriction or aerobic exercise (54). For the extremes of high BMI, bariatric surgery reduces the intensity and length of ovarian stimulation, increases the number and quality of retrieved oocytes, resulting in more top quality embryos and higher LBRs (61, 62).
There is evidence that cannot be ignored, demonstrating a significant effect of obesity on fertility for both men and women. Also, parental obesity is linked to adverse pregnancy outcomes and to transgenerational effects for the offspring (63-65). Therefore, individualized weight loss and weight maintenance programs with dietician input should be in place for couples undergoing fertility treatment eventhough there is limited evidence on the type of proposed intervention (66). The initial fertility appointment should involve couple’s BMI calculation and waist/hip circumference measurement, Couples should be advised that it is worth optimizing their BMI (20-25kg/m²) before starting any type of fertility treatment (36). However, the age-related fertility decline should not be overlooked. Individualized counseling should take into account female age since delaying treatment in an effort to achieve the desirable weight loss could force someone out of the reproductive window (67). Besides, it has been demonstrated that cumulative LBRs after ART for older women are impacted more by age than by high BMI (68).

- Physical exercise

Studying the effect of physical exercise on ART outcomes is challenging since it is based on self-reports and depends on the intensity and type of exercise, weight loss and dietary habits (table 5, supplementary material). Accelerometer is rarely used and women tend to be less physically active at some points of treatment (69).

Physical exercise and lifestyle modification, along with weight loss for overweight women, is advised for PCOS patients since it improves lipid and hormonal profile and helps to achieve ovulation with good results on CPR (70, 71). Regular exercise before ART also improves the chances of pregnancy independently of weight loss for obese women (72). Physical exercise acts through metabolic pathways and insulin sensitization in order to benefit ovarian function (73, 74). Endometrial receptivity could also be influenced by this natural insulin sensitizer (75). Ultimately, physical activity improves the general well-being and reduces cardiovascular risks while also offering a stress-coping mechanism. Nevertheless, excessive exercise can create menstrual disturbances and anovulation (76). A recent systematic review and meta-analysis concluded that physically active women before their IVF/ICSI cycle (for more than 2.5 hours/week) have significantly increased LBR and CPR independently of age and weight loss (77). However, a study including more than 2000 IVF patients, showed a 40% reduced chance of live birth for women exercising more than four hours/week for 1-9 years before ART and 30% lower chance for women participating in cardiovascular exercise in general (78). Due to the limited number of studies reporting on LBR and the heterogeneity amongst them, results should be interpreted with caution.
Physical exercise in men, apart from weight loss, has been suggested to improve semen parameters and reduce seminal markers of inflammation and oxidative stress. A prospective cohort study found improved sperm concentration with weightlifting and outdoor activities, which did not translate to improved outcomes (79). Several RCTs by a research group in Iran have looked at moderate aerobic exercise, resistance exercise and their combination for 24 weeks for infertile men. All interventions had positive effect on sperm parameters and DNA integrity leading to significant favorable effect on PRs (80-82). On the contrary, cycling for more than 5 hours/week before first IVF cycle adversely influenced sperm concentration and total motile sperm (83). Overall, strong evidence regarding paternal exercise before fertility treatment is lacking but based on the existing literature, moderate exercise seems beneficial while cycling for >5 hours/week should be avoided.

- Smoking

Smoking is common amongst women and men of reproductive age with prevalence exceeding 30% in Europe. It is estimated that 21% of women and 22% of men of reproductive age in the US are smokers (84, 85). Smoking is one of the most well-studied lifestyle factors in relation to fertility treatment. Tobacco smoke contains more than 4800 compounds with more than 200 toxicants and 80 known or suspected carcinogens (86). Smoking affects every step of reproduction. Trying to quantify the effect of smoking is challenging and dependent on self-reports. The impact varies depending on dose and duration of exposure, presence of other toxicants, individual characteristics and sensitivity (87-91) (table 6,7 supplementary material).

It has been documented that female smoking halves the odds of a live birth and increases the risk of miscarriage by 265% (92). Another study links every extra cigarette per day for women, with increased risk of failing ART. For every year of smoking cessation for the male partner, this risk is reduced by 4% (93). Lower chance of achieving a live birth following fertility treatment is documented when either partner or both smoke (94).

The most recent meta-analysis (95) (28 studies, 5009 women), concluded that female smoking leads to impaired outcomes including significantly decreased LBR and increased MR. In utero exposure to cigarette smoking affects fetal ovarian germ cell proliferation, ovarian cell numbers and signaling pathways within the fetal ovary in humans, possibly affecting the future fertility of the female offspring (96-99).
Paternal smoking should not be overlooked. Firstly, because it is a cause of passive smoking for women, which is damaging for fertility treatment success rates (100-102) in a way comparable to active smoking (103). Secondly, because smoking affects male reproductive function (104, 105). Lastly, as preconceptual male smoking confers significant alterations in sperm DNA methylation pattern, it could lead to transgenerational effect with implications on the health of the offspring (106).

With regards to smoking the advice should be clear; couples attending a fertility unit should be advised to stop smoking entirely and smoking cessation interventions should be encouraged (107).

- Alcohol

The adverse impact of alcohol on women’s fertility has been recognized since the 1980’s, however up to 40% of women seeking fertility advice report drinking alcohol (108). The majority of studies demonstrate adverse effect on sperm parameters and/or fertility treatment outcomes, depending on dose and frequency of consumption (109). (table 8,9, supplementary material).

A prospective cohort study concluded that the consumption of four drinks/week significantly reduced ART LBRs especially if both partners had this habit (110). A 2014 review confirmed the adverse effect of alcohol intake on fertilization and PRs; this effect was independent of alcohol type and increase with the amount consumed (111). A recent review highlighted that while current female alcohol consumption adversely affects fertilization, embryo quality, and implantation, alcohol intake in the year before ART does not affect clinical outcomes (112). A large, multicenter, prospective study investigated alcohol consumption at different time points (108). One extra drink/day (12 gr of alcohol) for women during the year preceding ART led to a 13% reduction in oocyte retrieval, during the month preceding ART decreased the chance of pregnancy and during the week before ART increased the chance of miscarriage. For men, one extra alcoholic drink daily during the month before ART, resulted in an increased risk of not achieving live birth by 2.28. Eventhough the existing studies are few and heterogeneous, couples should be discouraged to consume alcohol when seeking fertility since there is no evidence that even small amounts are safe.

- Caffeine

There are few studies looking into caffeine consumption in relation to fertility treatment outcomes, with conflicting results for both women (113-119) and men (120-123) (table 10,11a,b, supplementary material), even-though coffee
and soft drinks are popular amongst couples of reproductive age. The average caffeine consumption for women before/during ART has been reported between 125-450 mg/day (average cup of coffee theoretically contains 100 mg of caffeine). However, caffeine consumption is challenging to quantify and the cut-off used varies between studies. Measurement of caffeine should take into consideration type of beverage, addition of sugar or syrup, brewing method, cup size and caffeine content. What is considered “usual” caffeine quantity varies and even though coffee is the first thing that comes to mind, soft drinks, tea and chocolate should also be considered. Caffeine is often accompanied with other habits, possible confounders, such as smoking, alcohol and stress.

A study of more than 4500 cycles, did not find a significant effect of coffee/tea/soda consumption on LBRs. Caffeine did not affect implantation rates (IRs) or number of retrieved oocytes, but correlated with significantly lower peak estradiol levels. However, high caffeine consumption for both partners (>800 mg/week for the woman and >1400 mg/week for her partner) reduced the chance of achieving live birth by 9% after adjusting for confounders, even though the result was not statistically significant (117). Two most recent studies failed to demonstrate an association between caffeine intake and ART outcomes (115, 119). A 2017 systematic review (124) showed significantly increased MR for daily intake of 300mg of caffeine. The authors did not demonstrate an association between caffeine intake and LBR post ART after analyzing the results of only two cohort studies. The current advice for pregnant women/women seeking fertility is up to 200mg of caffeine per day (European Food Safety Authority) or 300 mg/day (World Health Organization).

For men, current literature supports that moderate caffeine intake is not detrimental for success rates (116) but suggests that excess consumption could impact outcomes. The EARTH study documented a 36% decline in LBR if the male partner consumed ≥ 272mg of caffeine daily compared to intake of less than 99mg/day (125). A prospective study found increased odds of multiple gestation when the male partner increased caffeine intake by 100mg/day during the week of the initial visit to the fertility center without other observed associations (114).

- Recreational drug use

Less than 1% of women reported recreational drug use in a study assessing lifestyle habits of 12800 IVF patients in the US (3). Almost 5% of patients in an IVF program in Rome tested positive for drug use (126). Marijuana smoking for women in the year preceding fertility treatment led to a 25% reduction in retrieved oocytes and couples
had 28% reduced fertilization rate while marijuana smoking for both partners separately and combined led to lower offspring birthweight (127). A recent study suggests that marijuana effect on ART outcomes could be opposing for men and women. While female marijuana smoking at the initial appointment led into more than double adjusted probability of pregnancy loss after fertility treatment, positive marijuana status at the time of enrollment for men was associated with significantly higher adjusted probability of clinical pregnancy and live birth independently of women’s marijuana smoking status (128). Intensity of marijuana smoking was not related to treatment outcomes. In this study, sperm parameters were better for men who ever reported marijuana smoking compared to men who had never smoked marijuana. These findings were unexpected and appear conflicting to previous results (127). The authors highlighted that results should be interpreted more as lack of evidence of negative impact rather than proof of positive effect of male partner marijuana smoking to fertility treatment outcomes. Besides, the number of fertility patients reporting marijuana smoking is small and there is often heterogeneity in the methods of different studies which could partially explain conflicting results (power calculation, accounting for confounders, consideration of other lifestyle habits such as use of other drugs, adjustment of marijuana smoking status for both partners etc). In view of the legalization of marijuana in many parts of the world and its potential use as therapeutic tool, more research is needed around the association of marijuana smoking and reproductive outcomes as the existing evidence is scarce.

Negative effects of other drugs (including cocaine, ecstasy and opioids) on sperm parameters and male fertility have also been documented (85). Couples seeking fertility treatment should abstain from recreational drugs as this lifestyle may adversely affect ART outcomes and the welfare of the offspring and may have adverse transgenerational effects.

- Mediterranean diet

There are interesting studies, looking into dietary habits in relation to reproductive function for women and men (examples of the variety of dietary factors explored are summarized in table 1). However, comparisons can only be based on self-reported habits, which differ amongst cultures and are prone to report bias. There are few prospective studies/RCTs, such as PREPARE trial which explores preconceptual dietary interventions in relation to fertility treatment outcomes (129).
Mediterranean dietary pattern for couples undergoing IVF/ICSI led to a 40% increased chance of achieving pregnancy (Food, Lifestyle and Fertility Outcome project) (163). Higher ongoing PR was documented for women with a healthy diet following recommendations of the Netherlands Nutrition Centre (161). The most recent prospective study (164) demonstrated that normoweight women, younger than 35, who adhered to Mediterranean diet for six months before fertility treatment, had significantly higher CPR and LBR regardless of nutritional supplements. Similarly, for male partners in couples undergoing ART, adherence to Mediterranean diet improves sperm parameters (130, 131).

The existing evidence suggests that healthy dietary habits could enhance the couples’ reproductive potential but more research is needed, aiming to identify the optimal nutritional advice and interventions in the preconceptual period and to incorporate this information in fertility counseling. Personalized online programs offering lifestyle advice and individual coaching have also been proposed (165). However, healthy diet patterns in the modern world are often accompanied by significant pollution (pesticides, heavy metals etc.) and may have conflicted impacts on reproduction (133, 166).

**Supplements**

There is plethora of literature and a big market around nutrition supplements. Marketing logos are promising that supplements can boost fertility for men and women. Numerous studies are looking into various vitamins and antioxidants in an effort to identify interactions with human reproduction. The studies for each factor (including N-acetyl-cysteine, Vitamin C, L-arginine, melatonin, myo-inositol, phytoestrogen, folic acid, Vitamin E combinations and pentoxyfilline), and the pathophysiology behind the observed effect on reproduction can be found in supplementary material (tables 12-15).

- **Vitamin D**

A large percentage of women attending fertility clinics have vitamin D deficiency or insufficiency; the percentage reaches 98% in observational studies (167). A systematic review did not find strong evidence to support vitamin D screening and supplementation for women prior to ART but suggested that this might be cost effective (168). Patients with vitamin D values in the highest tertile, were almost four times more likely to achieve pregnancy after IVF treatment regardless of patient characteristics and number of embryos transferred (169). The two most recent
meta-analyses concluded that women replete in vitamin D have significantly higher LBRs following ART (170, 171).

For men, vitamin D may have a role in sex steroid production and semen quality (172, 173). However, an RCT comparing high dose Vitamin D and calcium administration to placebo for infertile men with serum vitamin D<50 ng/ml, did not find significant effect on semen quality although it identified significantly higher chance of live birth for oligozoospermic men (174).

Vitamin D depletion is easy to correct; supplements are widely available, cheap and are considered safe, therefore, the discussion around vitamin D in relation to fertility treatment has direct clinical implications (table 12, supplementary material). It seems reasonable to measure vitamin D and treat deficiency/insufficiency for women preparing for fertility treatment. Normal vitamin D levels may also prove beneficial during pregnancy (175-179).

Future prospective studies should be designed around a uniform vitamin D cut-off, timing of measurement and duration and dose of supplementation. Authors should report on LBR, on confounding factors and on seasonality.

- Antioxidants, nutritional supplements

Antioxidants act by neutralizing reactive oxygen species (ROS) and thus prevent oxidative stress and have been suggested to improve ART outcomes (180). Numerous substances can act as antioxidants including some well-known vitamins. Multivitamins and supplements grow into a very strong commercial field being one of the biggest selling markets especially for women. However, most studies do not report on LBRs and there is great heterogeneity in their methods, duration of administration, patient background and reason for infertility. Furthermore, several studies have examined the use of supplements with countless ingredients, some in dosages not commercially available in most countries, which does not facilitate comparisons and does not identify which micronutrient is actually of benefit. There is usually variation in the dose/duration of treatment (mostly chosen arbitrarily). At the moment, there is no strong evidence to support the use of any antioxidant for nutritionally adequate men or women before or during fertility treatment to enhance success rates.

- Combinations

A 2017 Cochrane review, 50 RCTs were included involving 6510 women attending a reproductive clinic for reasons other than male factor infertility (181). The authors concluded that very low quality evidence (from eight trials)
suggests that antioxidants may be associated with an increased LBR but based on the four trials reporting on women undergoing IVF/ICSI, antioxidants were not associated with increased LBR or CPR. A recent review on the effect of micronutrients for couples undergoing IVF included five studies. For women only two studies were found eligible (182, 183). For men, the micronutrients assessed included vitamin E, a combination of antioxidants and a fig extract. The authors suggested that despite the heterogeneity of the existing studies, micronutrient supplementation may be of value for couples undergoing fertility treatment but no clear directions could be given (184). Carnitine supplementation for infertile men has beneficial effect on sperm motility and PR according to a systematic review (185). A Cochrane review on antioxidant supplementation for male infertility concluded that antioxidants may increase the chance of live birth but the quality of evidence was low (186). Multiple supplements and dietary factors have been studied in relation to sperm parameters but it remains to be shown if these results translate into improved fertility treatment outcomes.

- Coenzyme Q10

Coenzyme Q10 supplements have been shown to work in specific groups of subfertile women such as cases of advanced maternal age, young poor responders and clomiphene citrate resistant PCOS patients (the connecting link in all these cases being possibly oxidative stress and mitochondrial dysfunction). However, there are only three RCTs (one underpowered) and none demonstrated a significant effect on LBR (187-189). For men, there are five RCTs (190-194). A meta-analysis of three relevant trials concluded that coenzyme Q10 improved sperm parameters but this did not translate into improved LBR or PR (195). The value of coenzyme Q10 in fertility treatment warrants further research. It seems to be safe for humans up to a dose of 900 mg/day for four weeks (196). The ideal dose should be established and the ideal pre-treatment period should be defined; long enough in order to exhibit favorable results in follicle recruitment and maturation but not too long to delay treatment.

**Complementary and alternative medicine**

Complementary medicine has been proposed for men and women as an adjunct during fertility treatment. However, good quality evidence is lacking. A review on the use of twelve different complementary medicine methods for men and women did not demonstrate a benefit neither in improving fertility treatment outcomes nor in improving mental health (197). The strongest evidence was noted for the use of acupuncture but the results were not conclusive.
• Acupuncture

The origins of acupuncture date back more than 3000 years and it has been widely used in ART, even though, many doubt its value or attribute the conceived value to the placebo effect (198, 199). Acupuncture has been evaluated as a form of analgesia during egg collection or embryo transfer and as an adjunct to IVF, with no conclusive results (200-203). Different forms and protocols of acupuncture have been examined (electro-acupuncture, laser acupuncture, needle acupuncture, transcutaneous electrical acupoint stimulation). Possible biological basis of its effect is summarized in supplementary data tables 16 and 17. Standardization of technique (frequency, duration, timing and placebo), is necessary in order to make sound comparisons. It would be interesting to assess if controls are inactive and if other methods of stress-relief have comparable outcomes. A 2013 Cochrane review on methods of analgesia did not dismiss the idea of acupuncture during egg collection (204). A 2017 systematic review and meta-analysis of four RCTs (205) including women with PCOS concluded that acupuncture increases CPR and ongoing PR, reduces ovarian hyperstimulation syndrome but has no effect on LBR. The most recent systematic review and meta-analysis found a beneficial effect of acupuncture as an adjunct to embryo transfer for women with poor previous ART outcomes. However, the overall effect of acupuncture was superior to no treatment but no better than the sham control (206).

For men the use of acupuncture has been examined as an adjunct to improve sperm parameters with conflicting results (207, 208). It has also been suggested to improve testicular blood flow and alleviate anxiety (197, 209). A systematic review and meta-analysis did not demonstrate a significant effect on PRs (210). Most of the existing studies do not provide evidence on LBRs and use various protocols and controls. Therefore, there is not enough evidence to support the use of acupuncture in order to improve male fertility (197).

• Massage therapy

Massage techniques have been associated with stress reduction, reduction in uterine contractions and enhancement of blood flow in the abdominal region. One study reports significantly higher ongoing PRs and birth rates (211). In this retrospective, observational study massage therapy was assessed 30 minutes prior to embryo transfer (deep relaxation massage on a vibrating device versus no intervention). More studies are needed to confirm its value.

Environmental exposures
• Seasonality

Some studies failed to demonstrate an effect of seasonality on ART (212-214), while others documented seasonal variation in various parameters (215). Higher fertilization rates and better embryo quality have been documented in spring (216) and higher CPR in summer (217). Better results were documented when the month preceding stimulation had more sunlight, higher temperatures and less rain (218). Better fertilization rates and embryo quality have also been documented with extended daylight hours (219). These results could be linked to vitamin D and melatonin levels but more research is needed to confirm these associations.

• Environmental pollutants

Environmental pollutants are extremely common in the modern world and more than half couples attending a fertility clinic are exposed to pollutants at such an extent, that environmental chemicals are detected in their serum, urine and follicular fluid with possible impact on clinical outcomes (220-222). Such substances often act as endocrine disruptors altering the follicular microenvironment and thus affecting fertilization and embryo quality (223, 224). Polybrominated diphenyl ethers, commonly found in the indoor environment, alter hormonal homeostasis and are associated with early pregnancy loss and abnormal implantation in women undergoing ART (225). A recent study found reduced IVF PRs during the period of highest urinary bisphenol A (BPA), phthalate metabolites and parabens (226). Paternal urine concentration of certain phthalates for couples undergoing IVF or IUI are associated with significantly decreased odds of implantation and live birth (227). There is sparse evidence from interesting studies looking into pesticides, BPA, phthalates and heavy metals (table 2).

• Air pollution

Air pollution has been associated with an adverse effect on various sperm parameters in the ART setting (250-252) and may even influence sperm sex ratio (253) and sperm aneuploidy (254). For women, various air pollutants adversely affect fertility treatment outcomes, including the probability of intrauterine pregnancy and live birth (255-258). The results are evident even after short-term exposure (259, 260). Traffic pollution, in particular, has been linked to impaired outcomes (261, 262). Women who live closer to major roadways, enrolled in the EARTH study (263), had significantly decreased chance of implantation and live birth following IVF after accounting for confounders, while no adverse effect was documented for male partners (264).
Electromagnetic field exposure

Exposure to electromagnetic field is rapidly increasing and its safety for reproduction needs to be explored. Rodent studies demonstrate an adverse effect on follicular development and ovarian reserve (265). In mice, cell phone related radiation affected embryo development (266). Interesting results come from in vitro studies on human and mouse sperm assessing various sources of radiation, from cell phones to microwave ovens (267) demonstrating adverse effect from every day habits such as use of Wifi-connected laptop for 4 hours (268). For men attending a fertility center, wireless internet use was adversely related to total sperm count and sperm motility (269). Cell phone use adversely affected the hormonal profile and semen quality with increasing frequency of use in observational studies (270-272) and a systematic review (273). Conversely, a cohort study on 153 men attending a fertility clinic, did not find an association between cell phone use and semen parameters (274).

Other factors

For men attending fertility clinics, several parameters have been sporadically shown to affect sperm parameters and sperm DNA integrity. These include exposure to noise and sedentary work of more than 6 hours/day (24), periodontal infections (275, 276), exposure to solvents, high temperatures, mechanical vibrations (242, 247, 277) and certain types of underwear; men wearing boxers had 25% higher sperm concentration, increased sperm count and lower FSH than those wearing tight underwear (278). Research in these fields is sparse and results should be interpreted with caution.

Discussion

This review provides an insight into the existing evidence demonstrating that lifestyle factors can affect outcomes for couples undergoing fertility treatment. As discussed, some associations are more evident than others. For many of these factors, the favorable outcomes could be attributed to the generally better well-being; a patient who is better nourished, normoweight, exercises, does not smoke or drink and has healthy habits is expected to have better ART outcome. It should be noted that this work explores associations and not clear causation. Associations can arise between variables in the presence and absence of a causal relationship (279).

Since fertility treatment involves numerous steps and processes, it is challenging to associate outcomes with a single factor. Stimulation protocols, culture media, pH and oxygen concentration, consumables such as Petri dishes,
materials and culture surfaces in the ART laboratory can affect outcomes (280-283). Besides, success rates are also related to the couple’s individual characteristics and type of infertility. Therefore, assessing for confounders and for potential bias is particularly challenging and clear causation can rarely be demonstrated. Also, the precise timing and duration required for a positive effect of lifestyle modifications on fertility treatment outcomes is currently speculated (284). Hypotheses include the “olive tree hypothesis” which advocates that toxins, such as smoking, affect mainly growing follicles and could be reversible in six months (285). Due to the nature of the question that this review attempts to answer, there are few randomized trials and most data are either retrospective, epidemiological, or based on questionnaires, prone to report and recollection bias. Furthermore, many studies do not report on LBRs, which is the most relevant outcome for clinical practice.

In the world of ART, progress is rapid; lots of new technologies are entering the laboratory at a fast pace and there is a lot of discussion and a strong market around adjuncts and supplements which promise to increase success rates (286). Going forwards with all these promising techniques is great but we should not forget the basics. Simple advice, based on the existing literature, such as weight loss, balanced diet, correction of vitamin deficiencies, smoking and alcohol cessation, stress management and avoidance of known pollutants, could make a difference in clinical outcomes (table 3). For couples seeking fertility treatment preconceptual care should not be overlooked. This also includes pre-pregnancy advice and investigations, which are essential for everyone trying to conceive (folic acid and vitamin D intake, rubella immunization and haemoglobinopathy screening, optimization of chronic conditions etc) (287).

- Preconceptual counseling

Preconceptual counseling is often not considered high priority (288, 289). Couples seem hesitant to seek lifestyle advice, mostly due to lack of awareness but also due to personal reasons (290, 291). As a result, even basic preconceptual advice such as folic acid supplementation is neglected by a significant percentage of patients (5, 292).

The need to incorporate preconceptual care in fertility programs is now recognized and clinics providing tailored fertility assessment and pro-fertility counseling for both men and women, have been successfully running (293, 294). The fertility status awareness tool (FertiSTAT) has been developed to permit women to check which are their
reproductive risk factors and seek personalized counseling (295). Online material through a fertility education website has been successful in increasing knowledge around age and fertility, as well as ART in the short term (296). The results of individualized preconceptual care programs for subfertile couples in the Netherlands also seem promising (297). The LIFESTYLE study, a multicenter RCT, is designed to assess the cost-effectiveness of a lifestyle modification program for subfertile, overweight/obese women prior to fertility care versus fertility care alone (298). Also, the FAST study described tailored preconceptual counseling and ongoing encouragement in order to promote healthy lifestyle in infertile couples with promising results (299). This consists of assessment of risk factors, discussion regarding positive changes and telephone consultation to boost encouragement every one to two weeks.

Fertility teams should individually identify and address behaviors that could affect the reproductive potential and provide evidence-based recommendations and interventions for positive lifestyle modifications before any type of fertility treatment (294). Encouragement to adhere with advice should be offered throughout treatment. Information should be provided in various forms (verbal, written, online tools, applications, reliable websites) after an honest discussion in order to identify areas that need improvement (5). Emphasis should be given on the positive effect that these changes will bring to avoid cultivating feelings of guilt and self-blame, which may increase anxiety and drop out risk. This may be better achieved through a multidisciplinary team (MDT) approach in the fertility center. These MDTs, consisting of clinicians, fertility nurses, dieticians, psychologists, exercise advisors and others, should dedicate time to offer tailored preconceptual advice and holistic management to the infertile couple instead of a universal approach to all.

Conclusion

The preconceptual period is undeniably a delicate and important window for the couple and should not be overlooked during fertility counseling. There is space for more well designed studies to deeper investigate the observed associations between lifestyle factors and fertility treatment outcomes in order to offer clear advice. Future studies should also focus on how to incorporate efficiently this information in fertility counseling in a structured way, and which lifestyle modification strategies to adopt. Fertility MDTs may lead to optimal results by offering constant support, evidence-based advice and interventions to cover the couple’s individual needs before and throughout treatment.
**Note from the authors:** Additional tables with extensive references and detailed notes on the effect of each studied lifestyle factor on reproduction are available upon request directed to the corresponding author.

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Title: Preconceptual care for couples seeking fertility treatment, an evidence-based approach.

Running title: Preconceptual care in the fertility unit

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Abstract

There is accumulating evidence demonstrating that positive lifestyle modification and the optimization of the preconceptual period can influence the reproductive potential for both men and women. However, a large percentage of couples attending fertility clinics with potential to improve preconception habits may not always receive appropriate preconceptual advice. Additionally, supplements and adjuncts that promise to increase fertility treatment success rates are marketed to infertile patients despite lack of convincing evidence supporting benefit. This review aims to identify possible associations between lifestyle factors for couples seeking fertility treatment and fertility treatment outcomes and to offer possible explanations of the biological basis of these associations. An electronic search was conducted from 1978 until July 2019 linking preconceptual behaviors for women and men with the outcome of fertility treatment. The literature search explored the importance of numerous factors including smoking, caffeine, alcohol, obesity, physical exercise, recreational drugs, stress, diet, supplements, alternative medicine, environmental factors and pollutants. Some associations were found to be more significant than others. The preconceptual period is undeniably a delicate and important window which should not be overlooked during fertility counseling. Simple lifestyle modifications could positively influence fertility treatment outcomes. Fertility teams, consisting of clinicians, fertility nurses, dieticians, psychologists, exercise advisors and others, should dedicate time to offer evidence-based preconceptual advice and targeted interventions to couples seeking fertility treatment.

Keywords: ART; fertility treatment; infertility; lifestyle; preconceptual health

Essential points

- A large percentage of couples attending fertility clinics face multiple lifestyle issues but do not always receive appropriate preconceptual advice.
- The preconceptual period is undeniably a delicate and important window which should not be overlooked during fertility counseling.
- Simple lifestyle modifications could positively influence fertility treatment outcomes.
- Fertility teams should offer tailored, evidence-based preconceptual advice and targeted interventions to couples seeking fertility treatment.
Introduction

Couples seeking fertility treatment are often highly motivated to take any steps necessary to maximize the chance of conception. However, a large percentage of couples attending fertility clinics with potential to improve preconception habits may not always receive appropriate preconceptual advice despite accumulating evidence that lifestyle factors affect the reproductive potential and fertility treatment success rates (1-3).

A number of studies have demonstrated lack of awareness regarding the effect of preconceptual lifestyle amongst couples undergoing assisted reproductive technology (ART) (4, 5). In a questionnaire-based study before fertility consultation, 65% of women endorsed for four or more of negative lifestyle factors (6). Similarly, a prospective study on more than 12,000 ART patients in the United States (US), identified multiple harmful lifestyle behaviors (3). This lack of knowledge regarding behaviors and adjuncts, which may or may not affect fertility (7, 8) often encourages fertility myths (9, 10). There is both the need and increasing demand for physician led preconceptual counseling (11). The Environment and Reproductive Health (EARTH) study investigated the impact of various factors in both women and men on fertility and pregnancy outcomes highlighting the importance of certain factors that impacted reproductive outcomes (12).

Aim

This review aims to identify and summarize associations between lifestyle factors for couples seeking fertility treatment and fertility treatment outcomes. This is not an exhaustive list to put couples on further stress around their fertility journey; on the contrary, it is an evidence-based discussion aiming to dispel fertility myths, increase awareness and provide simple directions which could enhance fertility treatment outcomes. This manuscript attempts to offer possible explanations for the biological basis of the observed associations, with implications for future research.

Methods

An electronic search was conducted in PubMed, Embase, Medline and Cochrane databases and references of relevant studies were cross-checked in order to include all relevant studies from database inception 1978 until July
2019 linking preconceptual lifestyle with the outcome of any type of fertility treatment. The following word combinations were used for the search: caffeine (coffee, tea, coke, soda, soft drinks), smoking, BMI (body mass index), weight, obesity, alcohol, recreational drugs (coca, cannabis, marijuana, opioids), exercise, diet (vitamins A, C, D, E, multivitamin supplements, selenium, zinc, coenzyme Q10, L-arginine, folate, melatonin, carnitines, N-acetyl-cysteine, antioxidants, pentoxyfilline, inositol, Mediterranean diet, dairy, meat, whole grain, phytoestrogens), acupuncture, alternative medicine, season, sunlight, environmental pollutants (perfluorinated chemicals, pesticides, mercury, lead, solvents, cell phone, laptop, phthalates, phenols, cosmetics), stress AND fertility OR IVF (in vitro fertilization) OR ART for both men and women. References from selected studies were cross-checked and meeting proceedings of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine were also searched. Studies looking into modifiable factors in relation to natural fecundity were excluded as the review focused on infertile couples.

**Lifestyle**

- **Stress**

Measuring the effect of psychological factors is challenging and often overlooked. However, stress is one of the most prominent reasons for discontinuation of fertility treatment (13). Women undergoing ART often suffer from anxiety, with more than 30% fulfilling the criteria for major depression (14-18). Stress influences female reproductive function (18-21). Women seem to be affected more than men (22) but stress in the male partner has been associated with impaired sperm parameters and sperm DNA damage (23-25). There are also two studies linking paternal stress with adverse pregnancy outcomes and reduced live births (26, 27).

There are more than 60 studies for women and 15 for men looking into fertility treatment outcomes in relation to stress or following certain interventions to reduce anxiety. Numerous psychosocial interventions have been proposed including mind-body interventions, cognitive-behavior therapy, web-based teaching, counseling, internet community support, partnership and coping enhancement program, yoga, acupuncture, acupressure, self-administered cognitive coping and relaxation intervention (11, 28-30). The most recent systematic reviews investigating the effect of psychosocial interventions on fertility treatment outcome fail to reach a consensus since very few studies report on...
live birth rates (LBRs) (28, 31, 32). The development of a complex intervention has been proposed, targeting both partners and enhancing their partnership with emphasis on the most stressful period: waiting for the pregnancy test.

Fertility teams should identify the couples most likely to benefit from stress reducing interventions and provide tailored support and advice (33). Various tools have been validated for this purpose (34). More research is needed in order to develop well-designed psychological/educational interventions. Eventhough their value to improve success rates has yet to be proven, successful interventions could help alleviate the psychological burden of infertility, recognize possible psychiatric conditions and create a better experience increasing conformity to current and future cycles (35).

- BMI

Obesity has been linked to infertility and to adverse obstetric outcomes. However, worldwide more than half of women and men of reproductive age are overweight or obese (36, 37).

In women, BMI in relation to ART has been extensively studied in more than 100 studies. The most recent systematic review and meta-analysis demonstrated a significantly decreased chance of live birth after ART for obese women (BMI ≥ 30 kg/m²) (38). Central obesity (waist-hip ratio above 0.85 for females) seems to have negative effect on ART success rates (39-41); for a waist-hip ratio increase of 0.1 unit, a 30% decrease in probability of conception per cycle was documented in a donor intrauterine insemination (IUI) program (39). Interestingly, waist circumference seems to be inversely related to LBR amongst women undergoing fertility treatment regardless of BMI (42). There is, also, accumulating evidence of altered metabolic fingerprint for embryos from obese women, demonstrating that the environment around conception affects not only the course of fertility treatment but may also have long-term consequences for the offspring (43). Embryos from the high BMI group exhibit different metabolism patterns with decreased glucose consumption and higher endogenous triglycerides (44).

The lowest odds of live birth after IVF are documented when both partners have BMI ≥25 kg/m² according to a large cohort study (45). There is accumulating evidence demonstrating the adverse effect of male obesity on ART but further research is warranted. Confounders such as type of infertility and female BMI should be accounted for and LBR should be the main outcome of interest (46). Obesity causes sperm DNA damage (47, 48) and seems the
strongest lifestyle factor affecting spermatogenesis (49). A recent systematic review and meta-analysis concluded that raised male BMI resulted in a statistically significant decrease in CPR and LBR after IVF and ICSI (46). ICSI does not overcome the influence of obesity on sperm, suggesting that the effect is not limited to conventional semen analysis parameters. Indeed, paternal obesity affects sperm molecular composition, embryo morphokinetics (50) and blastocyst development (51). Male BMI may be more important than semen parameters for embryo quality and IVF outcomes (52). Increased weight and waist or hip circumference have also been associated with impaired semen parameters and hormonal profile (53).

There are few studies supporting various weight loss interventions for overweight women (hypocaloric diet, weight reduction programs, physical exercise, behavioral/lifestyle targeted interventions, internet-based interventions, bariatric surgery and medication such as orlistat, insulin sensitizers and acarbose) while data on lifestyle interventions in men/couples are lacking (54). Two available studies on interventions for obese men suggested beneficial effect of weight loss for sperm parameters and DNA integrity (55, 56). Weight loss as little as 10% in addition to a month of moderate weight management interventions for women had measurable positive effect on hormonal profile, menstrual cycle, spontaneous ovulation, and pregnancy rate (PR) (36). Regardless of weight loss, energy restriction itself has beneficial effect on reproduction for women with polycystic ovary syndrome (PCOS) (57). However, a randomized study did not find benefit from a six-month lifestyle program before fertility treatment for obese infertile women compared to immediate fertility treatment (58). A multicenter randomized controlled trial (RCT) yielded similar results. An intense weight loss program for obese women before IVF (12week low calorie liquid formula diet of 880 kcal/day and weight stabilization for 2–5 weeks), resulted in considerable weight loss but no improvement of IVF LBRs eventhough spontaneous conceptions increased (59). A systematic review concluded than dropout is significant problem in lifestyle interventions programs for overweight and obese infertile women (median dropout rate of 24%) (60). Another thorough systematic review and meta-analysis looked into non-surgical weight loss options for couples seeking fertility treatment. The authors concluded that pregnancy was more likely for women on calorie restriction or aerobic exercise (54). For the extremes of high BMI, bariatric surgery reduces the intensity and length of ovarian stimulation, increases the number and quality of retrieved oocytes, resulting in more top quality embryos and higher LBRs (61, 62).
There is evidence that cannot be ignored, demonstrating a significant effect of obesity on fertility for both men and women. Also, parental obesity is linked to adverse pregnancy outcomes and to transgenerational effects for the offspring (63-65). Therefore, individualized weight loss and weight maintenance programs with dietician input should be in place for couples undergoing fertility treatment even though there is limited evidence on the type of proposed intervention (66). The initial fertility appointment should involve couple’s BMI calculation and waist/hip circumference measurement. Couples should be advised that it is worth optimizing their BMI (20-25kg/m²) before starting any type of fertility treatment (36). However, the age-related fertility decline should not be overlooked. Individualized counseling should take into account female age since delaying treatment in an effort to achieve the desirable weight loss could force someone out of the reproductive window (67). Besides, it has been demonstrated that cumulative LBRs after ART for older women are impacted more by age than by high BMI (68).

- Physical exercise

Studying the effect of physical exercise on ART outcomes is challenging since it is based on self-reports and depends on the intensity and type of exercise, weight loss and dietary habits. Accelerometer is rarely used and women tend to be less physically active at some points of treatment (69).

Physical exercise and lifestyle modification, along with weight loss for overweight women, is advised for PCOS patients since it improves lipid and hormonal profile and helps to achieve ovulation with good results on CPR (70, 71). Regular exercise before ART also improves the chances of pregnancy independently of weight loss for obese women (72). Physical exercise acts through metabolic pathways and insulin sensitization in order to benefit ovarian function (73, 74). Endometrial receptivity could also be influenced by this natural insulin sensitizer (75). Ultimately, physical activity improves the general well-being and reduces cardiovascular risks while also offering a stress-coping mechanism. Nevertheless, excessive exercise can create menstrual disturbances and anovulation (76). A recent systematic review and meta-analysis concluded that physically active women before their IVF/ICSI cycle (for more than 2.5 hours/week) have significantly increased LBR and CPR independently of age and weight loss (77). However, a study including more than 2000 IVF patients, showed a 40% reduced chance of live birth for women exercising more than four hours/week for 1-9 years before ART and 30% lower chance for women participating in cardiovascular exercise in general (78). Due to the limited number of studies reporting on LBR and the heterogeneity amongst them, results should be interpreted with caution.
Physical exercise in men, apart from weight loss, has been suggested to improve semen parameters and reduce seminal markers of inflammation and oxidative stress. A prospective cohort study found improved sperm concentration with weightlifting and outdoor activities, which did not translate to improved outcomes (79). Several RCTs by a research group in Iran have looked at moderate aerobic exercise, resistance exercise and their combination for 24 weeks for infertile men. All interventions had positive effect on sperm parameters and DNA integrity leading to significant favorable effect on PRs (80-82). On the contrary, cycling for more than 5 hours/week before first IVF cycle adversely influenced sperm concentration and total motile sperm (83). Overall, strong evidence regarding paternal exercise before fertility treatment is lacking but based on the existing literature, moderate exercise seems beneficial while cycling for >5 hours/week should be avoided.

- Smoking

Smoking is common amongst women and men of reproductive age with prevalence exceeding 30% in Europe. It is estimated that 21% of women and 22% of men of reproductive age in the US are smokers (84, 85). Smoking is one of the most well-studied lifestyle factors in relation to fertility treatment. Tobacco smoke contains more than 4800 compounds with more than 200 toxicants and 80 known or suspected carcinogens (86). Smoking affects every step of reproduction. Trying to quantify the effect of smoking is challenging and dependent on self-reports. The impact varies depending on dose and duration of exposure, presence of other toxicants, individual characteristics and sensitivity (87-91).

It has been documented that female smoking halves the odds of a live birth and increases the risk of miscarriage by 265% (92). Another study links every extra cigarette per day for women, with increased risk of failing ART. For every year of smoking cessation for the male partner, this risk is reduced by 4% (93). Lower chance of achieving a live birth following fertility treatment is documented when either partner or both smoke (94).

The most recent meta-analysis (95) (28 studies, 5009 women), concluded that female smoking leads to impaired outcomes including significantly decreased LBR and increased MR. In utero exposure to cigarette smoking affects fetal ovarian germ cell proliferation, ovarian cell numbers and signaling pathways within the fetal ovary in humans, possibly affecting the future fertility of the female offspring (96-99).
Paternal smoking should not be overlooked. Firstly, because it is a cause of passive smoking for women, which is damaging for fertility treatment success rates (100-102) in a way comparable to active smoking (103). Secondly, because smoking affects male reproductive function (104, 105). Lastly, as preconceptual male smoking confers significant alterations in sperm DNA methylation pattern, it could lead to transgenerational effect with implications on the health of the offspring (106).

With regards to smoking the advice should be clear; couples attending a fertility unit should be advised to stop smoking entirely and smoking cessation interventions should be encouraged (107).

- Alcohol

The adverse impact of alcohol on women’s fertility has been recognized since the 1980’s, however up to 40% of women seeking fertility advice report drinking alcohol (108). The majority of studies demonstrate adverse effect on sperm parameters and/or fertility treatment outcomes, depending on dose and frequency of consumption (109).

A prospective cohort study concluded that the consumption of four drinks/week significantly reduced ART LBRs especially if both partners had this habit (110). A 2014 review confirmed the adverse effect of alcohol intake on fertilization and PRs; this effect was independent of alcohol type and increase with the amount consumed (111). A recent review highlighted that while current female alcohol consumption adversely affects fertilization, embryo quality, and implantation, alcohol intake in the year before ART does not affect clinical outcomes (112). A large, multicenter, prospective study investigated alcohol consumption at different time points (108). One extra drink/day (12 gr of alcohol) for women during the year preceding ART led to a 13% reduction in oocyte retrieval, during the month preceding ART decreased the chance of pregnancy and during the week before ART increased the chance of miscarriage. For men, one extra alcoholic drink daily during the month before ART, resulted in an increased risk of not achieving live birth by 2.28. Eventhough the existing studies are few and heterogeneous, couples should be discouraged to consume alcohol when seeking fertility since there is no evidence that even small amounts are safe.

- Caffeine

There are few studies looking into caffeine consumption in relation to fertility treatment outcomes, with conflicting results for both women (113-119) and men (120-123), eventhough coffee and soft drinks are popular amongst couples of reproductive age. The average caffeine consumption for women before/during ART has been reported
between 125-450 mg/day (average cup of coffee theoretically contains 100 mg of caffeine). However, caffeine consumption is challenging to quantify and the cut-off used varies between studies. Measurement of caffeine should take into consideration type of beverage, addition of sugar or syrup, brewing method, cup size and caffeine content. What is considered “usual” caffeine quantity varies and even though coffee is the first thing that comes to mind, soft drinks, tea and chocolate should also be considered. Caffeine is often accompanied with other habits, possible confounders, such as smoking, alcohol and stress.

A study of more than 4500 cycles, did not find a significant effect of coffee/tea/soda consumption on LBRs. Caffeine did not affect implantation rates (IRs) or number of retrieved oocytes, but correlated with significantly lower peak estradiol levels. However, high caffeine consumption for both partners (>800 mg/week for the woman and >1400 mg/week for her partner) reduced the chance of achieving live birth by 9% after adjusting for confounders, eventhough the result was not statistically significant (117). Two most recent studies failed to demonstrate an association between caffeine intake and ART outcomes (115, 119). A 2017 systematic review (124) showed significantly increased MR for daily intake of 300mg of caffeine. The authors did not demonstrate an association between caffeine intake and LBR post ART after analyzing the results of only two cohort studies. The current advice for pregnant women/women seeking fertility is up to 200mg of caffeine per day (European Food Safety Authority) or 300 mg/day (World Health Organization).

For men, current literature supports that moderate caffeine intake is not detrimental for success rates (116) but suggests that excess consumption could impact outcomes. The EARTH study documented a 36% decline in LBR if the male partner consumed ≥ 272mg of caffeine daily compared to intake of less than 99mg/day (125). A prospective study found increased odds of multiple gestation when the male partner increased caffeine intake by 100mg/day during the week of the initial visit to the fertility center without other observed associations (114).

- Recreational drug use

Less than 1% of women reported recreational drug use in a study assessing lifestyle habits of 12800 IVF patients in the US (3). Almost 5% of patients in an IVF program in Rome tested positive for drug use (126). Marijuana smoking for women in the year preceding fertility treatment led to a 25% reduction in retrieved oocytes and couples had 28% reduced fertilization rate while marijuana smoking for both partners separately and combined led to lower
A recent study suggests that marijuana effect on ART outcomes could be opposing for men and women. While female marijuana smoking at the initial appointment led into more than double adjusted probability of pregnancy loss after fertility treatment, positive marijuana status at the time of enrollment for men was associated with significantly higher adjusted probability of clinical pregnancy and live birth independently of women’s marijuana smoking status (128). Intensity of marijuana smoking was not related to treatment outcomes. In this study, sperm parameters were better for men who ever reported marijuana smoking compared to men who had never smoked marijuana. These findings were unexpected and appear conflicting to previous results (127). The authors highlighted that results should be interpreted more as lack of evidence of negative impact rather than proof of positive effect of male partner marijuana smoking to fertility treatment outcomes. Besides, the number of fertility patients reporting marijuana smoking is small and there is often heterogeneity in the methods of different studies which could partially explain conflicting results (power calculation, accounting for confounders, consideration of other lifestyle habits such as use of other drugs, adjustment of marijuana smoking status for both partners etc). In view of the legalization of marijuana in many parts of the world and its potential use as therapeutic tool, more research is needed around the association of marijuana smoking and reproductive outcomes as the existing evidence is scarce.

Negative effects of other drugs (including cocaine, ecstasy and opioids) on sperm parameters and male fertility have also been documented (85). Couples seeking fertility treatment should abstain from recreational drugs as this lifestyle may adversely affect ART outcomes and the welfare of the offspring and may have adverse transgenerational effects.

- Mediterranean diet

There are interesting studies, looking into dietary habits in relation to reproductive function for women and men (examples of the variety of dietary factors explored are summarized in table 1). However, comparisons can only be based on self-reported habits, which differ amongst cultures and are prone to report bias. There are few prospective studies/RCTs, such as PREPARE trial which explores preconceptual dietary interventions in relation to fertility treatment outcomes (129).
Mediterranean dietary pattern for couples undergoing IVF/ICSI led to a 40% increased chance of achieving pregnancy (Food, Lifestyle and Fertility Outcome project) (163). Higher ongoing PR was documented for women with a healthy diet following recommendations of the Netherlands Nutrition Centre (161). The most recent prospective study (164) demonstrated that normoweight women, younger than 35, who adhered to Mediterranean diet for six months before fertility treatment, had significantly higher CPR and LBR regardless of nutritional supplements. Similarly, for male partners in couples undergoing ART, adherence to Mediterranean diet improves sperm parameters (130, 131).

The existing evidence suggests that healthy dietary habits could enhance the couples’ reproductive potential but more research is needed, aiming to identify the optimal nutritional advice and interventions in the preconceptual period and to incorporate this information in fertility counseling. Personalized online programs offering lifestyle advice and individual coaching have also been proposed (165). However, healthy diet patterns in the modern world are often accompanied by significant pollution (pesticides, heavy metals etc.) and may have conflicted impacts on reproduction (133, 166).

Supplements

There is plethora of literature and a big market around nutrition supplements. Marketing logos are promising that supplements can boost fertility for men and women. Numerous studies are looking into various vitamins and antioxidants in an effort to identify interactions with human reproduction (including N-acetyl-cysteine, Vitamin C, L-arginine, melatonin, myo-inositol, phytoestrogen, folic acid, Vitamin E combinations and pentoxyfilline).

- Vitamin D

A large percentage of women attending fertility clinics have vitamin D deficiency or insufficiency; the percentage reaches 98% in observational studies (167). A systematic review did not find strong evidence to support vitamin D screening and supplementation for women prior to ART but suggested that this might be cost effective (168). Patients with vitamin D values in the highest tertile, were almost four times more likely to achieve pregnancy after IVF treatment regardless of patient characteristics and number of embryos transferred (169). The two most recent meta-analyses concluded that women replete in vitamin D have significantly higher LBRs following ART (170, 171).
For men, vitamin D may have a role in sex steroid production and semen quality (172, 173). However, an RCT comparing high dose Vitamin D and calcium administration to placebo for infertile men with serum vitamin D<50 ng/ml, did not find significant effect on semen quality although it identified significantly higher chance of live birth for oligozoospermic men (174).

Vitamin D depletion is easy to correct; supplements are widely available, cheap and are considered safe, therefore, the discussion around vitamin D in relation to fertility treatment has direct clinical implications. It seems reasonable to measure vitamin D and treat deficiency/insufficiency for women preparing for fertility treatment. Normal vitamin D levels may also prove beneficial during pregnancy (175-179). Future prospective studies should be designed around a uniform vitamin D cut-off, timing of measurement and duration and dose of supplementation. Authors should report on LBR, on confounding factors and on seasonality.

- Antioxidants, nutritional supplements

Antioxidants act by neutralizing reactive oxygen species (ROS) and thus prevent oxidative stress and have been suggested to improve ART outcomes (180). Numerous substances can act as antioxidants including some well-known vitamins. Multivitamins and supplements grow into a very strong commercial field being one of the biggest selling markets especially for women. However, most studies do not report on LBRs and there is great heterogeneity in their methods, duration of administration, patient background and reason for infertility. Furthermore, several studies have examined the use of supplements with countless ingredients, some in dosages not commercially available in most countries, which does not facilitate comparisons and does not identify which micronutrient is actually of benefit. There is usually variation in the dose/duration of treatment (mostly chosen arbitrarily). At the moment, there is no strong evidence to support the use of any antioxidant for nutritionally adequate men or women before or during fertility treatment to enhance success rates.

- Combinations

A 2017 Cochrane review, 50 RCTs were included involving 6510 women attending a reproductive clinic for reasons other than male factor infertility (181). The authors concluded that very low quality evidence (from eight trials) suggests that antioxidants may be associated with an increased LBR but based on the four trials reporting on women undergoing IVF/ICSI, antioxidants were not associated with increased LBR or CPR. A recent review on the effect of
micronutrients for couples undergoing IVF included five studies. For women only two studies were found eligible (182, 183). For men, the micronutrients assessed included vitamin E, a combination of antioxidants and a fig extract. The authors suggested that despite the heterogeneity of the existing studies, micronutrient supplementation may be of value for couples undergoing fertility treatment but no clear directions could be given (184). Carnitine supplementation for infertile men has beneficial effect on sperm motility and PR according to a systematic review (185). A Cochrane review on antioxidant supplementation for male infertility concluded that antioxidants may increase the chance of live birth but the quality of evidence was low (186). Multiple supplements and dietary factors have been studied in relation to sperm parameters but it remains to be shown if these results translate into improved fertility treatment outcomes.

- **Coenzyme Q10**

Coenzyme Q10 supplements have been shown to work in specific groups of subfertile women such as cases of advanced maternal age, young poor responders and clomiphene citrate resistant PCOS patients (the connecting link in all these cases being possibly oxidative stress and mitochondrial dysfunction). However, there are only three RCTs (one underpowered) and none demonstrated a significant effect on LBR (187-189). For men, there are five RCTs(190-194). A meta-analysis of three relevant trials concluded that coenzyme Q10 improved sperm parameters but this did not translate into improved LBR or PR (195). The value of coenzyme Q10 in fertility treatment warrants further research. It seems to be safe for humans up to a dose of 900 mg/day for four weeks (196). The ideal dose should be established and the ideal pre-treatment period should be defined; long enough in order to exhibit favorable results in follicle recruitment and maturation but not too long to delay treatment.

**Complementary and alternative medicine**

Complementary medicine has been proposed for men and women as an adjunct during fertility treatment. However, good quality evidence is lacking. A review on the use of twelve different complementary medicine methods for men and women did not demonstrate a benefit neither in improving fertility treatment outcomes nor in improving mental health (197). The strongest evidence was noted for the use of acupuncture but the results were not conclusive.

- **Acupuncture**
The origins of acupuncture date back more than 3000 years and it has been widely used in ART, even though, many doubt its value or attribute the conceived value to the placebo effect (198, 199). Acupuncture has been evaluated as a form of analgesia during egg collection or embryo transfer and as an adjunct to IVF, with no conclusive results (200-203). Different forms and protocols of acupuncture have been examined (electro-acupuncture, laser acupuncture, needle acupuncture, transcutaneous electrical acupoint stimulation). Standardization of technique (frequency, duration, timing and placebo), is necessary in order to make sound comparisons. It would be interesting to assess if controls are inactive and if other methods of stress-relief have comparable outcomes. A 2013 Cochrane review on methods of analgesia did not dismiss the idea of acupuncture during egg collection (204). A 2017 systematic review and meta-analysis of four RCTs (205) including women with PCOS concluded that acupuncture increases CPR and ongoing PR, reduces ovarian hyperstimulation syndrome but has no effect on LBR. The most recent systematic review and meta-analysis found a beneficial effect of acupuncture as an adjunct to embryo transfer for women with poor previous ART outcomes. However, the overall effect of acupuncture was superior to no treatment but no better than the sham control (206).

For men the use of acupuncture has been examined as an adjunct to improve sperm parameters with conflicting results (207, 208). It has also been suggested to improve testicular blood flow and alleviate anxiety (197, 209). A systematic review and meta-analysis did not demonstrate a significant effect on PRs (210). Most of the existing studies do not provide evidence on LBRs and use various protocols and controls. Therefore, there is not enough evidence to support the use of acupuncture in order to improve male fertility (197).

- **Massage therapy**

Massage techniques have been associated with stress reduction, reduction in uterine contractions and enhancement of blood flow in the abdominal region. One study reports significantly higher ongoing PRs and birth rates (211). In this retrospective, observational study massage therapy was assessed 30 minutes prior to embryo transfer (deep relaxation massage on a vibrating device versus no intervention). More studies are needed to confirm its value.

**Environmental exposures**

- **Seasonality**
Some studies failed to demonstrate an effect of seasonality on ART (212-214), while others documented seasonal variation in various parameters (215). Higher fertilization rates and better embryo quality have been documented in spring (216) and higher CPR in summer (217). Better results were documented when the month preceding stimulation had more sunlight, higher temperatures and less rain (218). Better fertilization rates and embryo quality have also been documented with extended daylight hours (219). These results could be linked to vitamin D and melatonin levels but more research is needed to confirm these associations.

- Environmental pollutants

Environmental pollutants are extremely common in the modern world and more than half couples attending a fertility clinic are exposed to pollutants at such an extent, that environmental chemicals are detected in their serum, urine and follicular fluid with possible impact on clinical outcomes (220-222). Such substances often act as endocrine disruptors altering the follicular microenvironment and thus affecting fertilization and embryo quality (223, 224). Polybrominated diphenyl ethers, commonly found in the indoor environment, alter hormonal homeostasis and are associated with early pregnancy loss and abnormal implantation in women undergoing ART (225). A recent study found reduced IVF PRs during the period of highest urinary bisphenol A (BPA), phthalate metabolites and parabens (226). Paternal urine concentration of certain phthalates for couples undergoing IVF or IUI are associated with significantly decreased odds of implantation and live birth (227). There is sparse evidence from interesting studies looking into pesticides, BPA, phthalates and heavy metals (table 2).

- Air pollution

Air pollution has been associated with an adverse effect on various sperm parameters in the ART setting (250-252) and may even influence sperm sex ratio (253) and sperm aneuploidy (254). For women, various air pollutants adversely affect fertility treatment outcomes, including the probability of intrauterine pregnancy and live birth (255-258). The results are evident even after short-term exposure (259, 260). Traffic pollution, in particular, has been linked to impaired outcomes (261, 262). Women who live closer to major roadways, enrolled in the EARTH study (263), had significantly decreased chance of implantation and live birth following IVF after accounting for confounders, while no adverse effect was documented for male partners (264).

- Electromagnetic field exposure
Exposure to electromagnetic field is rapidly increasing and its safety for reproduction needs to be explored. Rodent studies demonstrate an adverse effect on follicular development and ovarian reserve (265). In mice, cell phone related radiation affected embryo development (266). Interesting results come from in vitro studies on human and mouse sperm assessing various sources of radiation, from cell phones to microwave ovens (267) demonstrating adverse effect from every day habits such as use of Wifi-connected laptop for 4 hours (268). For men attending a fertility center, wireless internet use was adversely related to total sperm count and sperm motility (269). Cell phone use adversely affected the hormonal profile and semen quality with increasing frequency of use in observational studies (270-272) and a systematic review (273). Conversely, a cohort study on 153 men attending a fertility clinic, did not find an association between cell phone use and semen parameters (274).

**Other factors**

For men attending fertility clinics, several parameters have been sporadically shown to affect sperm parameters and sperm DNA integrity. These include exposure to noise and sedentary work of more than 6 hours/day (24), periodontal infections (275, 276), exposure to solvents, high temperatures, mechanical vibrations (242, 247, 277) and certain types of underwear; men wearing boxers had 25% higher sperm concentration, increased sperm count and lower FSH than those wearing tight underwear (278). Research in these fields is sparse and results should be interpreted with caution.

**Discussion**

This review provides an insight into the existing evidence demonstrating that lifestyle factors can affect outcomes for couples undergoing fertility treatment. As discussed, some associations are more evident than others. For many of these factors, the favorable outcomes could be attributed to the generally better well-being; a patient who is better nourished, normoweight, exercises, does not smoke or drink and has healthy habits is expected to have better ART outcome. It should be noted that this work explores associations and not clear causation. Associations can arise between variables in the presence and absence of a causal relationship (279).

Since fertility treatment involves numerous steps and processes, it is challenging to associate outcomes with a single factor. Stimulation protocols, culture media, pH and oxygen concentration, consumables such as Petri dishes, materials and culture surfaces in the ART laboratory can affect outcomes (280-283). Besides, success rates are also
related to the couple’s individual characteristics and type of infertility. Therefore, assessing for confounders and for potential bias is particularly challenging and clear causation can rarely be demonstrated. Also, the precise timing and duration required for a positive effect of lifestyle modifications on fertility treatment outcomes is currently speculated (284). Hypotheses include the “olive tree hypothesis” which advocates that toxins, such as smoking, affect mainly growing follicles and could be reversible in six months (285). Due to the nature of the question that this review attempts to answer, there are few randomized trials and most data are either retrospective, epidemiological, or based on questionnaires, prone to report and recollection bias. Furthermore, many studies do not report on LBRs, which is the most relevant outcome for clinical practice.

In the world of ART, progress is rapid; lots of new technologies are entering the laboratory at a fast pace and there is a lot of discussion and a strong market around adjuncts and supplements which promise to increase success rates (286). Going forwards with all these promising techniques is great but we should not forget the basics. Simple advice, based on the existing literature, such as weight loss, balanced diet, correction of vitamin deficiencies, smoking and alcohol cessation, stress management and avoidance of known pollutants, could make a difference in clinical outcomes (table 3). For couples seeking fertility treatment preconceptual care should not be overlooked. This also includes pre-pregnancy advice and investigations, which are essential for everyone trying to conceive (folic acid and vitamin D intake, rubella immunization and haemoglobinopathy screening, optimization of chronic conditions etc) (287).

- Preconceptual counseling

Preconceptual counseling is often not considered high priority (288, 289). Couples seem hesitant to seek lifestyle advice, mostly due to lack of awareness but also due to personal reasons (290, 291). As a result, even basic preconceptual advice such as folic acid supplementation is neglected by a significant percentage of patients (5, 292).

The need to incorporate preconceptual care in fertility programs is now recognized and clinics providing tailored fertility assessment and pro-fertility counseling for both men and women, have been successfully running (293, 294). The fertility status awareness tool (FertiSTAT) has been developed to permit women to check which are their reproductive risk factors and seek personalized counseling (295). Online material through a fertility education website has been successful in increasing knowledge around age and fertility, as well as ART in the short term
The results of individualized preconceptual care programs for subfertile couples in the Netherlands also seem promising (297). The LIFESTYLE study, a multicenter RCT, is designed to assess the cost-effectiveness of a lifestyle modification program for subfertile, overweight/obese women prior to fertility care versus fertility care alone (298). Also, the FAST study described tailored preconceptual counseling and ongoing encouragement in order to promote healthy lifestyle in infertile couples with promising results (299). This consists of assessment of risk factors, discussion regarding positive changes and telephone consultation to boost encouragement every one to two weeks.

Fertility teams should individually identify and address behaviors that could affect the reproductive potential and provide evidence-based recommendations and interventions for positive lifestyle modifications before any type of fertility treatment (294). Encouragement to adhere with advice should be offered throughout treatment. Information should be provided in various forms (verbal, written, online tools, applications, reliable websites) after an honest discussion in order to identify areas that need improvement (5). Emphasis should be given on the positive effect that these changes will bring to avoid cultivating feelings of guilt and self-blame, which may increase anxiety and dropout risk. This may be better achieved through a multidisciplinary team (MDT) approach in the fertility center. These MDTs, consisting of clinicians, fertility nurses, dieticians, psychologists, exercise advisors and others, should dedicate time to offer tailored preconceptual advice and holistic management to the infertile couple instead of a universal approach to all.

Conclusion

The preconceptual period is undeniably a delicate and important window for the couple and should not be overlooked during fertility counseling. There is space for more well designed studies to deeper investigate the observed associations between lifestyle factors and fertility treatment outcomes in order to offer clear advice. Future studies should also focus on how to incorporate efficiently this information in fertility counseling in a structured way, and which lifestyle modification strategies to adopt. Fertility MDTs may lead to optimal results by offering constant support, evidence-based advice and interventions to cover the couple’s individual needs before and throughout treatment.
Note from the authors: Additional tables with extensive references and detailed notes on the effect of each studied lifestyle factor on reproduction are available upon request directed to the corresponding author.

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Table 1. Evidence of the effect of dietary habits on reproductive outcomes.

<table>
<thead>
<tr>
<th>Diet</th>
<th>Recommendations/Conclusions</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>Adopt Mediterranean-type dietary pattern</td>
<td>(130, 131)</td>
</tr>
<tr>
<td></td>
<td>Total dairy food intake not associated with fertilization rates</td>
<td>(132)</td>
</tr>
<tr>
<td></td>
<td>Total fruit and vegetable intake unrelated to semen quality parameters</td>
<td>(133)</td>
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<tr>
<td></td>
<td>Poultry intake is positively associated with fertilization rates, whereas processed meat intake is negatively associated with fertilization rates among couples undergoing conventional IVF</td>
<td>(132)</td>
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<td></td>
<td>Low-fat dairy intake (particularly low-fat milk) is related to higher sperm concentration and progressive motility, whereas cheese intake is related to lower sperm concentration amongst past or current smokers</td>
<td>(134)</td>
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<tr>
<td></td>
<td>Avoidance of trans fatty acids</td>
<td>(135)</td>
</tr>
<tr>
<td></td>
<td>Avoidance of saturated fats and high intake of omega-3 polyunsaturated fats</td>
<td>(136, 137)</td>
</tr>
<tr>
<td></td>
<td>Health conscious diet - high intake of fruits, vegetables, fish and whole grains (diet rich in 1-C metabolites such as folate and B12 derived from vegetables, fruits and shellfish)</td>
<td>(138, 139)</td>
</tr>
<tr>
<td></td>
<td>Cereal and fruit consumption with frequent meals and reduced intake of red meat</td>
<td>(140)</td>
</tr>
<tr>
<td></td>
<td>Higher intake of fish but low intake of processed red meat</td>
<td>(134)</td>
</tr>
<tr>
<td></td>
<td>High intake of carbohydrates, fiber, folate, vitamin C, and lycopene and lower intakes of proteins and total fat</td>
<td>(141)</td>
</tr>
<tr>
<td></td>
<td>Low intake of yogurt, meat products and potatoes and high intake of lettuce, tomatoes and fruits</td>
<td>(142)</td>
</tr>
<tr>
<td></td>
<td>High intake of fruit and vegetables</td>
<td>(143)</td>
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<tr>
<td></td>
<td>High sea food consumption related to high blood mercury concentrations associated with infertility</td>
<td>(144)</td>
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<tr>
<td></td>
<td>Negative effect of high diet selenium</td>
<td>(145)</td>
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<tr>
<td></td>
<td>Negative effect of zinc deprived diet</td>
<td>(146)</td>
</tr>
<tr>
<td>Women</td>
<td>Dairy consumption has a favorable effect on live birth after ART in women &gt;35 years of age</td>
<td>(147)</td>
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<td></td>
<td>High consumption of whole grain before fertility treatment increases the chance of live birth after IVF and has a positive effect on endometrial thickness</td>
<td>(148)</td>
</tr>
<tr>
<td></td>
<td>Increased red meat intake was found to have adverse effect on IR and CPR while the consumption of fruits, vegetables and cereals favored embryo quality</td>
<td>(149)</td>
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<tr>
<td></td>
<td>Avoid high intakes of isoflavone (≥40 mg/day)</td>
<td>(150)</td>
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<tr>
<td></td>
<td>Increased ω-6 to ω-3 ratios are preferable</td>
<td>(151)</td>
</tr>
<tr>
<td></td>
<td>No association of vitamin B12 or folate with chance of pregnancy</td>
<td>(152)</td>
</tr>
<tr>
<td></td>
<td>Avoid fat-rich diet</td>
<td>(153)</td>
</tr>
<tr>
<td></td>
<td>Avoid high dietary glycemic load and carbohydrate intake</td>
<td>(154)</td>
</tr>
<tr>
<td></td>
<td>Adopt Mediterranean-type dietary pattern</td>
<td>(139, 155)</td>
</tr>
<tr>
<td></td>
<td>Increased preconception omega-3 polyunsaturated fatty acid intake</td>
<td>(156)</td>
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<tr>
<td></td>
<td>Avoid trans-unsaturated fats</td>
<td>(157)</td>
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<tr>
<td></td>
<td>Avoid high intake of low-fat dairy foods and prefer high-fat dairy foods</td>
<td>(158)</td>
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<tr>
<td>Table 2. Evidence demonstrating an effect of various pollutants on fertility treatment outcomes</td>
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<tr>
<td><strong>BPA</strong></td>
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<td>Reduced IVF PRs during the period of highest urinary bisphenol A (BPA), phthalate metabolites and parabens</td>
<td>(228)</td>
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<tr>
<td>Maternal and not paternal preconception BPA exposure was inversely associated with birth weight and head circumference for subfertile couples</td>
<td>(229)</td>
<td></td>
</tr>
<tr>
<td>BPA has estrogenic action and is detected in follicular fluid and amniotic fluid</td>
<td>(230)</td>
<td></td>
</tr>
<tr>
<td>Male BPA affected sperm quality and embryo development after IVF/ICSI</td>
<td>(231, 232)</td>
<td></td>
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<tr>
<td>Affects pick estradiol concentration, the number of retrieved oocytes, oocyte quality and fertilization</td>
<td>(231, 233)</td>
<td></td>
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<tr>
<td>Associated with reduced ovarian response, fertilization rate and blastocyst formation in a dose response manner</td>
<td>(234)</td>
<td></td>
</tr>
<tr>
<td>Increased levels of urinary BPA in a cohort of women seeking fertility treatment were associated with lower antral follicular count indicating accelerated follicle loss</td>
<td>(235)</td>
<td></td>
</tr>
<tr>
<td>A prospective cohort study of 235 women undergoing IVF/ICSI did not confirm an adverse impact of urinary BPA on any outcomes including implantation rate, CPR or LBR although an age-dependent relation was observed between BPA concentration and endometrial thickness</td>
<td>(228)</td>
<td></td>
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<td><strong>Phthalates</strong></td>
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<tr>
<td>Couples seeking fertility treatment are exposed to a wide range of phthalate compounds and seven compounds were isolated in &gt;94% of urine samples</td>
<td>(236)</td>
<td></td>
</tr>
<tr>
<td>Paternal urine concentration of certain phthalates for couples undergoing IVF or IUI are associated with significantly decreased odds of implantation</td>
<td>(227)</td>
<td></td>
</tr>
<tr>
<td>Phthalates found to be associated with failed implantation</td>
<td>(225)</td>
<td></td>
</tr>
<tr>
<td>Increased urine concentration of phthalate metabolites was associated with a significant decrease in antral follicular count in women seeking fertility treatment with the highest risk documented for younger women</td>
<td>(237)</td>
<td></td>
</tr>
</tbody>
</table>
Phthalates detected in follicular fluid
Phthalates adversely affected ART outcomes in terms of egg collection, PR and birth rate in 256 women enrolled in the EARTH study
Impaired oocyte quality
No association between phthalates and various ART end points
Prospective study of 599 couples undergoing IVF, 32% and 22% higher chance of clinical pregnancy and unsuccessful live birth observed with elevated levels of urinary MEHP and MEP in women, respectively
Weak association with oxidative stress in follicular fluid and DNA damage in granulosa cells

Pesticides
DDT and its metabolites are found in more than 70% of women seeking fertility treatment in some countries
Pesticide detection in follicular fluid was adversely associated with endometrial thickness, retrieved oocytes and fertilization and embryo cleavage rate after ICSI
DDT metabolites in follicular fluid associated with fertilization failure
Pesticide exposure in infertile men confers adverse effect on sperm, post-testicular glands and endocrine profile
Decreased implantation rates with occupational exposure to organic solvents and paradoxically increased implantation rates with paternal pesticide exposure

Heavy metals
Embryo development was influenced by the follicular fluid concentration of certain trace metals such as selenium, cadmium, zinc, lead and copper
Hair mercury correlates with fish consumption and was found to exceed the recommended reference for one third of women undergoing IVF
75% reduction in the probability for a retrieved oocyte to be in metaphase-II arrest for each microg/dl increase in blood lead concentration
Various heavy metals have been detected in follicular fluid and have been associated with impaired sperm parameters
Blood lead level, even at concentrations which are considered to be safe, negatively affected fertilization outcome although cadmium had the opposite effect
Skin lightening creams and dental amalgam increase exposure to mercury and smoking is strongly associated to cadmium accumulation in follicular fluid in a dose dependent manner

**Table 3.** Recommendations and proposed interventions on lifestyle factors for couples seeking fertility treatment based on the existing literature.

<table>
<thead>
<tr>
<th>Lifestyle factors</th>
<th>Recommendation</th>
<th>Proposed interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>Couples should optimize their BMI (20-25 kg/m²)</td>
<td>Women: calorie restriction or aerobic exercise,</td>
</tr>
</tbody>
</table>
before starting any type of fertility treatment.  

| Physical activity | Women: physical activity for 2.5-4 hours/week before IVF/ICSI. Exercise particularly important for women with PCOS. Avoid excessive exercise.  
Men: moderate exercise.  

| Smoking | Smoking cessation and avoid passive smoking.  

| Alcohol | Avoid alcohol regardless of alcohol type.  

| Caffeine | Women: up to 200 mg/day (2 average cups of coffee)  
Men: avoid excessive consumption - ideally < 272mg  

| Diet | Mediterranean diet pattern during fertility treatment and the preceding 6 months.  

| Supplements | No strong evidence to support the use of any antioxidants for nutritionally adequate men or women before or during fertility treatment. Folic acid is routinely proposed at a dose of 400mcg for women wishing to conceive.  

| Stress | Effort to minimize stress.  

| Complementary medicine | Not enough evidence to support the use of complementary medicine as an adjunct during fertility treatment.  

| Pollutants | Avoid known pollutants.  

| bariatric surgery for the extremes of BMI. Avoid central obesity. Counseling should take into account women’s age and age-related fertility decline. Limited evidence on the type of proposed intervention - individualized weight loss and weight maintenance programs for couples with dietician input.  

| Central obesity.  

| Counseling should take into account women’s age and age-related fertility decline. Limited evidence on the type of proposed intervention - individualized weight loss and weight maintenance programs for couples with dietician input.  

| Limited evidence regarding the type of exercise. For men, moderate aerobic exercise, resistance exercise or combination of the two for 24 weeks before fertility treatment in cases of male factor infertility. Avoid cycling for more than 5 hours/week before ART.  

| Smoking cessation interventions should be offered as well as support to maintain results throughout treatment and pregnancy.  

| Limited evidence on duration of alcohol abstinence. Advice to abstain from alcohol for both partners when starting treatment. For women there is some evidence of an effect of alcohol consumption even during the year before ART and for men from the month preceding ART.  

| Conflicted results on type of beverage. Limited evidence suggests avoidance of caffeinated soda, energy drinks and sugar-sweetened beverages.  

| Limited evidence on specific food categories. Interventions proposed include personalized online programs and pre-conceptual dietary interventions (reduce consumption of fats, processed meat and red meat) – more research needed, dietician input encouraged.  

| Measure vitamin D and treat deficiency/insufficiency in women planning ART (aim above 30 ng/ml). More research needed for other supplements such as inositol, coenzyme Q10, Vitamin E, Vitamin C, pentoxifylline, melatonin, N-acetyl-cysteine and combinations for both men and women.  

| Identification of couples that would benefit from stress management. Psychological support and evaluation should be offered throughout treatment. Unclear which intervention to propose – individualized and tailored management plans.  

| The majority of studies are inconclusive due to techniques that are not standardized. Acupuncture is better studied than other interventions and may be of value as analgesia during egg collection or as an adjunct to embryo transfer for women with poor previous ART outcomes - more research is needed.  

| Accumulating evidence on BPA, phthalates, pesticides and air pollutants including traffic pollution. Limited evidence on heavy metals.  


| Electromagnetic field exposure | Not enough evidence to link electromagnetic field exposure from different sources with impaired fertility treatment outcomes. | Sparse evidence suggesting adverse effect of increasing wireless internet and cell phone use on male fertility – more research needed, no results on LBRs. |

Essential points

- A large percentage of couples attending fertility clinics face multiple lifestyle issues but do not always receive appropriate preconceptual advice.
- The preconceptual period is undeniably a delicate and important window which should not be overlooked during fertility counseling.
- Simple lifestyle modifications could positively influence fertility treatment outcomes.
- Fertility teams should offer tailored, evidence-based preconceptual advice and targeted interventions to couples seeking fertility treatment.