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 (cocaine, 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) ~~(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 $\geq$ 30 kg/m^2) (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 $\geq$25 kg/m^2 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 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/m^2) 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, 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 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-inos~~a~~itol, 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.

References

1. Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. Hum Reprod Update 2007;13:209-23.
2. Anderson K, Nisenblat V, Norman R. Lifestyle factors in people seeking infertility treatment - A review. Aust N Z J Obstet Gynaecol 2010;50:8-20.
3. Domar AD, Rooney KL, Milstein M, Conboy L. Lifestyle habits of 12,800 IVF patients: Prevalence of negative lifestyle behaviors, and impact of region and insurance coverage. Hum Fertil 2015;18:253-7.
4. Ferreira RC, Halpern G, Figueira Rde C, Braga DP, Iaconelli A, Jr., Borges E, Jr. Physical activity, obesity and eating habits can influence assisted reproduction outcomes. Womens Health (Lond Engl) 2010;6:517-24.
5. Gormack AA, Peek JC, Derraik JG, Gluckman PD, Young NL, Cutfield WS. Many women undergoing fertility treatment make poor lifestyle choices that may affect treatment outcome. Hum Reprod 2015;30:1617-24.
6. Alvarez S. Do some addictions interfere with fertility? Fertil Steril 2015;103:22-6.
7. Adashi EY, Cohen J, Hamberger L, Jones HW, Jr., de Kretser DM, Lunenfeld B *et al.* Public perception on infertility and its treatment: an international survey. The Bertarelli Foundation Scientific Board. Hum Reprod 2000;15:330-4.
8. Roth LK, Taylor HS. Risks of smoking to reproductive health: assessment of women's knowledge. Am J Obstet Gynecol 2001;184:934-9.
9. de Jong-Van den Berg LT, Hernandez-Diaz S, Werler MM, Louik C, Mitchell AA. Trends and predictors of folic acid awareness and periconceptional use in pregnant women. Am J Obstet Gynecol 2005;192:121-8.
10. Bunting L, Boivin J. Knowledge about infertility risk factors, fertility myths and illusory benefits of healthy habits in young people. Hum Reprod 2008;23:1858-64.
11. Vause TDR, Jones L, Evans M, Wilkie V, Leader A. Pre-conception health awareness in infertility patients. J Obstet Gynaecol Can 2009;31:717-20.
12. Messerlian C, Williams PL, Ford JB, Chavarro JE, Minguez-Alarcon L, Dadd R *et al.* The Environment and Reproductive Health (EARTH) Study: A Prospective Preconception Cohort. Human reprod open 2018;2018.
13. Domar AD, Smith K, Conboy L, Iannone M, Alper M. A prospective investigation into the reasons why insured United States patients drop out of in vitro fertilization treatment. Fertil Steril 2010;94:1457-9.
14. Chen TH, Chang SP, Tsai CF, Juang KD. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Hum Reprod 2004;19:2313-8.
15. Volgsten H, Skoog Svanberg A, Ekselius L, Lundkvist O, Sundstrom Poromaa I. Prevalence of psychiatric disorders in infertile women and men undergoing in vitro fertilization treatment. Hum Reprod 2008;23:2056-63.
16. Holley SR, Pasch LA, Bleil ME, Gregorich S, Katz PK, Adler NE. Prevalence and predictors of major depressive disorder for fertility treatment patients and their partners. Fertil Steril 2015;103:1332-9.
17. Pasch LA, Holley SR, Bleil ME, Shehab D, Katz PP, Adler NE. Addressing the needs of fertility treatment patients and their partners: are they informed of and do they receive mental health services? Fertil Steril 2016;106:209-15.

18. Haimovici F, Anderson JL, Bates GW, Racowsky C, Ginsburg ES, Simovici D *et al.* Stress, anxiety, and depression of both partners in infertile couples are associated with cytokine levels and adverse IVF outcome. American journal of reproductive immunology (New York, NY : 1989) 2018;79:e12832.
19. Massey AJ, Campbell BK, Raine-Fenning N, Pincott-Allen C, Perry J, Vedhara K. Relationship between hair and salivary cortisol and pregnancy in women undergoing IVF. Psychoneuroendocrinology 2016;74:397-405.
20. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res 2002;53:865-71.
21. Mor G, Cardenas I, Abrahams V, Guller S. Inflammation and pregnancy: the role of the immune system at the implantation site. Ann N Y Acad Sci 2011;1221:80-87.
22. Schaller MA, Griesinger G, Banz-Jansen C. Women show a higher level of anxiety during IVF treatment than men and hold different concerns: a cohort study. Arch Gynecol Obstet 2016;293:1137-45.
23. Vellani E, Colasante A, Mamazza L, Minasi MG, Greco E, Bevilacqua A. Association of state and trait anxiety to semen quality of in vitro fertilization patients: a controlled study. Fertil Steril 2013;99:1565-72.
24. Jurewicz J, Radwan M, Merecz-Kot D, Sobala W, Ligocka D, Radwan P *et al.* Occupational, life stress and family functioning: does it affect semen quality? Ann Hum Biol 2014;41:220-8.
25. Radwan M, Jurewicz J, Merecz-Kot D, Sobala W, Radwan P, Bochenek M *et al.* Sperm DNA damage-the effect of stress and everyday life factors. International journal of impotence research 2016;28:148-54.
26. Zorn B, Auger J, Velikonja V, Kolbezen M, Meden-Vrtovec H. Psychological factors in male partners of infertile couples: relationship with semen quality and early miscarriage. Int J Androl 2008;31:557-64.
27. Nouri K, Litschauer B, Sator M, Tiringer D, Ott J, Walch K *et al.* Decline of semen quality during IVF is not associated with subjective male stress. Asian J Androl 2014;16:597-601.
28. Ying L, Wu LH, Loke AY. The effects of psychosocial interventions on the mental health, pregnancy rates, and marital function of infertile couples undergoing in vitro fertilization: a systematic review. J Assist Reprod Genet 2016;33:689-701.
29. Darbandi S, Darbandi M, Khorram Khorshid HR, Sadeghi MR. Yoga Can Improve Assisted Reproduction Technology Outcomes in Couples With Infertility. Altern Ther Health Med 2018;24:50-5.
30. LoGiudice JA, Massaro J. The impact of complementary therapies on psychosocial factors in women undergoing in vitro fertilization (IVF): A systematic literature review. Applied Nursing Research 2018;39:220-8.
31. Chow KM, Cheung MC, Cheung IK. Psychosocial interventions for infertile couples: a critical review. J Clin Nurs 2016;25:2101-13.
32. Verkuijlen J, Verhaak C, Nelen WL, Wilkinson J, Farquhar C. Psychological and educational interventions for subfertile men and women. Cochrane Database Syst Rev 2016;31.
33. Boivin J. How does stress, depression and anxiety affect patients undergoing treatment? Curr Opin Obstet Gynecol 2019;31:195-9.
34. Pedro J, Frederiksen Y, Schmidt L, Ingerslev HJ, Zachariae R, Martins MV. Comparison of three infertility-specific measures in men and women going through assisted reproductive technology treatment. Journal of Health Psychology 2019;24:738-49.
35. Rooney KL, Domar AD. The impact of stress on fertility treatment. Curr Opin Obstet Gynecol 2016;28:198-201.
36. Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, Wang JX. Improving reproductive performance in overweight/obese women with effective weight management. Human Reproduction Update 2004;10:267-80.

37. Sheng Y, Lu G, Liu J, Liang X, Ma Y, Zhang X *et al.* Effect of body mass index on the outcomes of controlled ovarian hyperstimulation in Chinese women with polycystic ovary syndrome: a multicenter, prospective, observational study. Journal of assisted reproduction and genetics 2017;34:61-70.
38. Sermondade N, Huberlant S, Bourhis-Lefebvre V, Arbo E, Gallot V, Colombani M *et al.* Female obesity is negatively associated with live birth rate following IVF: a systematic review and meta-analysis. Hum Reprod Update 2019;25:439-51.
39. Zaadstra BM, Seidell JC, Van Noord PA, te Velde ER, Habbema JD, Vrieswijk B *et al.* Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. BMJ 1993;306:484-7.
40. Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. J Clin Endocrinol Metab 1999;84:1470-4.
41. Chavarro JE, Ehrlich S, Colaci DS, Wright DL, Toth TL, Petrozza JC *et al.* Body mass index and short-term weight change in relation to treatment outcomes in women undergoing assisted reproduction. Fertil Steril 2012;98:109-16.
42. Li MC, Minguez-Alarcon L, Arvizu M, Chiu YH, Ford JB, Williams PL *et al.* Waist circumference in relation to outcomes of infertility treatment with assisted reproductive technologies. Am J Obstet Gynecol 2019;220:578.e1-.e13.
43. Bellver J, De los Santos MJ, Alamá P, Castelló D, Privitera L, Galliano D *et al.* Day-3 embryo metabolomics in the spent culture media is altered in obese women undergoing in vitro fertilization. Fertility and sterility 2015;103:1407-15.e1.
44. Leary C, Leese HJ, Sturmey RG. Human embryos from overweight and obese women display phenotypic and metabolic abnormalities. Human Reproduction 2015;30:122-32.
45. Petersen GL, Schmidt L, Pinborg A, Kamper-Jorgensen M. The influence of female and male body mass index on live births after assisted reproductive technology treatment: a nationwide register-based cohort study. Fertil Steril 2013;99:1654-62.
46. Mushtaq R, Pundir J, Achilli C, Naji O, Khalaf Y, El-Toukhy T. Effect of male body mass index on assisted reproduction treatment outcome: an updated systematic review and meta-analysis. Reprod Biomed Online 2018;36:459-71.
47. Chavarro JE, Toth TL, Wright DL, Meeker JD, Hauser R. Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic. Fertil Steril 2010;93:2222-31.
48. Dupont C, Faure C, Sermondade N, Boubaya M, Eustache F, Clement P *et al.* Obesity leads to higher risk of sperm DNA damage in infertile patients. Asian J Androl 2013;15:622-5.
49. Veron GL, Tissera AD, Bello R, Beltramone F, Estofan G, Molina RI *et al.* Impact of age, clinical conditions, and lifestyle on routine semen parameters and sperm kinematics. Fertil Steril 2018;110:68-75.e4.
50. Raad G, Azouri J, Rizk K, Zeidan NS, Azouri J, Grandjean V *et al.* Adverse effects of paternal obesity on the motile spermatozoa quality. PLoS One 2019;14:e0211837.
51. Bakos HW, Henshaw RC, Mitchell M, Lane M. Paternal body mass index is associated with decreased blastocyst development and reduced live birth rates following assisted reproductive technology. Fertil Steril 2011;95:1700-4.
52. Anifandis G, Dafopoulos K, Messini CI, Polyzos N, Messinis IE. The BMI of men and not sperm parameters impact on embryo quality and the IVF outcome. Andrology 2013;1:85-9.
53. Fejes I, Koloszar S, Szollosi J, Zavaczki Z, Pal A. Is semen quality affected by male body fat distribution? Andrologia 2005;37:155-9.

54. Best D, Avenell A, Bhattacharya S. How effective are weight-loss interventions for improving fertility in women and men who are overweight or obese? A systematic review and meta-analysis of the evidence. Human Reproduction Update 2017;23:681-705.
55. Hakonsen LB, Thulstrup AM, Aggerholm AS, Olsen J, Bonde JP, Andersen CY *et al.* Does weight loss improve semen quality and reproductive hormones? Results from a cohort of severely obese men. Reprod Health 2011;8:24.
56. Faure C, Dupont C, Baraibar MA, Ladouce R, Cedrin-Durnerin I, Wolf JP *et al.* In Subfertile Couple, Abdominal Fat Loss in Men Is Associated with Improvement of Sperm Quality and Pregnancy: A Case-Series. PLoS One 2014;9:e86300.
57. Moran LJ, Noakes M, Clifton PM, Tomlinson L, Galletly C, Norman RJ. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003;88:812-9.
58. Mutsaerts MA, van Oers AM, Groen H, Burggraaff JM, Kuchenbecker WK, Perquin DA *et al.* Randomized Trial of a Lifestyle Program in Obese Infertile Women. N Engl J Med 2016;374:1942-53.
59. Einarsson S, Bergh C, Friberg B, Pinborg A, Klajnbard A, Karlström P-O *et al.* Weight reduction intervention for obese infertile women prior to IVF: a randomized controlled trial. Human Reproduction 2017;32:1621-30.
60. Mutsaerts MA, Kuchenbecker WK, Mol BW, Land JA, Hoek A. Dropout is a problem in lifestyle intervention programs for overweight and obese infertile women: a systematic review. Hum Reprod 2013;28:979-86.
61. Tsur A, Orvieto R, Haas J, Kedem A, Machtinger R. Does bariatric surgery improve ovarian stimulation characteristics, oocyte yield, or embryo quality? Journal of Ovarian Research 2014;7:116.
62. Milone M, Sosa Fernandez LM, Sosa Fernandez LV, Manigrasso M, Elmore U, De Palma GD *et al.* Does Bariatric Surgery Improve Assisted Reproductive Technology Outcomes in Obese Infertile Women? Obesity Surgery 2017;27:2106-12.
63. Sanchez-Garrido MA, Ruiz-Pino F, Velasco I, Barroso A, Fernandois D, Heras V *et al.* Intergenerational Influence of Paternal Obesity on Metabolic and Reproductive Health Parameters of the Offspring: Male-Preferential Impact and Involvement of Kiss1-Mediated Pathways. Endocrinology 2017;159:1005-18.
64. Perng W, Oken E. Maternal obesity and associated offspring diabetes mellitus. Nature Reviews Endocrinology 2019;15:630-2.
65. Rodríguez-González GL, Reyes-Castro LA, Bautista CJ, Beltrán AA, Ibáñez CA, Vega CC *et al.* Maternal obesity accelerates rat offspring metabolic ageing in a sex-dependent manner. The Journal of Physiology 2019;597:5549-63.
66. Glenn T, Harris AL, Lindheim SR. Impact of obesity on male and female reproductive outcomes. Curr Opin Obstet Gynecol 2019;31:201-6.
67. Ethics ETFo, Law i, Dondorp W, de Wert G, Pennings G, Shenfield F *et al.* Lifestyle-related factors and access to medically assisted reproduction†. Human Reproduction 2010;25:578-83.
68. Goldman RH, Farland LV, Thomas AM, Zera CA, Ginsburg ES. The combined impact of maternal age and body mass index on cumulative live birth following in vitro fertilization. Am J Obstet Gynecol 2019;221:617.e1-.e13.
69. Evenson KR, Calhoun KC, Herring AH, Pritchard D, Wen F, Steiner AZ. Association of physical activity in the past year and immediately after in vitro fertilization on pregnancy. Fertil Steril 2014;101:1047-54.e5.
70. Karimzadeh MA, Javedani M. An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate-metformin in patients with polycystic ovary syndrome. Fertil Steril 2010;94:216-20.

71. Palomba S, Falbo A, Giallauria F, Russo T, Rocca M, Tolino A *et al.* Six weeks of structured exercise training and hypocaloric diet increases the probability of ovulation after clomiphene citrate in overweight and obese patients with polycystic ovary syndrome: a randomized controlled trial. Hum Reprod 2010;25:2783-91.
72. Palomba S, Falbo A, Valli B, Morini D, Villani MT, Nicoli A *et al.* Physical activity before IVF and ICSI cycles in infertile obese women: an observational cohort study. Reprod Biomed Online 2014;29:72-9.
73. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS, Jr. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N Engl J Med 1991;325:147-52.
74. Redman LM. Physical activity and its effects on reproduction. Reprod Biomed Online 2006;12:579-86.
75. Zhai J, Liu CX, Tian ZR, Jiang QH, Sun YP. Effects of metformin on the expression of GLUT4 in endometrium of obese women with polycystic ovary syndrome. Biol Reprod 2012;87.
76. Warren MP, Perlroth NE. The effects of intense exercise on the female reproductive system. The Journal of endocrinology 2001;170:3-11.
77. Rao M, Zeng Z, Tang L. Maternal physical activity before IVF/ICSI cycles improves clinical pregnancy rate and live birth rate: a systematic review and meta-analysis. Reprod Biol Endocrinol 2018;16:018-0328.
78. Morris SN, Missmer SA, Cramer DW, Powers RD, McShane PM, Hornstein MD. Effects of lifetime exercise on the outcome of in vitro fertilization. Obstet Gynecol 2006;108:938-45.
79. Gaskins AJ, Afeiche MC, Hauser R, Williams PL, Gillman MW, Tanrikut C *et al.* Paternal physical and sedentary activities in relation to semen quality and reproductive outcomes among couples from a fertility center. Hum Reprod 2014;29:2575-82.
80. Hajizadeh Maleki B, Tartibian B. Combined aerobic and resistance exercise training for improving reproductive function in infertile men: a randomized controlled trial. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 2017;42:1293-306.
81. Hajizadeh Maleki B, Tartibian B. Moderate aerobic exercise training for improving reproductive function in infertile patients: A randomized controlled trial. Cytokine 2017;92:55-67.
82. Hajizadeh Maleki B, Tartibian B. Resistance exercise modulates male factor infertility through anti-inflammatory and antioxidative mechanisms in infertile men: A RCT. Life sciences 2018;203:150-60.
83. Wise LA, Cramer DW, Hornstein MD, Ashby RK, Missmer SA. Physical activity and semen quality among men attending an infertility clinic. Fertil Steril 2011;95:1025-30.
84. Huisman M, Kunst AE, Mackenbach JP. Educational inequalities in smoking among men and women aged 16 years and older in 11 European countries. Tobacco Control 2005;14:106-13.
85. Sansone A, Di Dato C, de Angelis C, Menafra D, Pozza C, Pivonello R *et al.* Smoke, alcohol and drug addiction and male fertility. Reprod Biol Endocrinol 2018;16:3.
86. Pieraccini G, Furlanetto S, Orlandini S, Bartolucci G, Giannini I, Pinzauti S *et al.* Identification and determination of mainstream and sidestream smoke components in different brands and types of cigarettes by means of solid-phase microextraction–gas chromatography–mass spectrometry. Journal of Chromatography A 2008;1180:138-50.
87. Frederiksen Y, Farver-Vestergaard I, Skovgård NG, Ingerslev HJ, Zachariae R. Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: a systematic review and meta-analysis. BMJ Open 2015;5.
88. Zenzes MT. Smoking and reproduction: gene damage to human gametes and embryos. Hum Reprod Update 2000;6:122-31.
89. Talbot P, Riveles K. Smoking and reproduction: the oviduct as a target of cigarette smoke. Reprod Biol Endocrinol 2005;3:52.

90. Soares SR, Melo MA. Cigarette smoking and reproductive function. Curr Opin Obstet Gynecol 2008;20:281-91.
91. Dechanet C, Anahory T, Mathieu Daude JC, Quantin X, Reyftmann L, Hamamah S *et al.* Effects of cigarette smoking on reproduction. Hum Reprod Update 2011;17:76-95.
92. Penzias AS. Recurrent IVF failure: other factors. Fertil Steril 2012;97:1033-8.
93. Vanegas JC, Chavarro JE, Williams PL, Ford JB, Toth TL, Hauser R *et al.* Discrete survival model analysis of a couple's smoking pattern and outcomes of assisted reproduction. Fertility research and practice 2017;3.
94. Klonoff Cohen H, Natarajan L, Marrs R, Yee B. Effects of female and male smoking on success rates of IVF and gamete intra-Fallopian transfer. Human Reproduction 2001;16:1382-90.
95. Zhang RP, Zhao WZ, Chai BB, Wang QY, Yu CH, Wang HY *et al.* The effects of maternal cigarette smoking on pregnancy outcomes using assisted reproduction technologies: An updated meta-analysis. Journal of gynecology obstetrics and human reproduction 2018;47:461-8.
96. Lutterodt MC, Sorensen KP, Larsen KB, Skouby SO, Andersen CY, Byskov AG. The number of oogonia and somatic cells in the human female embryo and fetus in relation to whether or not exposed to maternal cigarette smoking. Hum Reprod 2009;24:2558-66.
97. Ye X, Skjaerven R, Basso O, Baird DD, Eggesbo M, Cupul Uicab LA *et al.* In utero exposure to tobacco smoke and subsequent reduced fertility in females. Hum Reprod 2010;25:2901-6.
98. Anderson RA, McIlwain L, Coutts S, Kinnell HL, Fowler PA, Childs AJ. Activation of the aryl hydrocarbon receptor by a component of cigarette smoke reduces germ cell proliferation in the human fetal ovary. Mol Hum Reprod 2014;20:42-8.
99. Fowler PA, Childs AJ, Courant F, MacKenzie A, Rhind SM, Antignac JP *et al.* In utero exposure to cigarette smoke dysregulates human fetal ovarian developmental signalling. Hum Reprod 2014;29:1471-89.
100. Benedict MD, Missmer SA, Vahratian A, Berry KF, Vitonis AF, Cramer DW *et al.* Secondhand tobacco smoke exposure is associated with increased risk of failed implantation and reduced IVF success. Hum Reprod 2011;26:2525-31.
101. Wdowiak A, Lewicka M, Plewka K, Bakalczuk G. Nicotinism and quality of embryos obtained in in-vitro fertilization programmes. AAEM Annals of Agricultural and Environmental Medicine 2013;20:82-5.
102. Li J, Wu Q, Wu XK, Zhou ZM, Fu P, Chen XH *et al.* Effect of exposure to second-hand smoke from husbands on biochemical hyperandrogenism, metabolic syndrome and conception rates in women with polycystic ovary syndrome undergoing ovulation induction. Hum Reprod 2018;33:617-25.
103. Neal MS, Hughes EG, Holloway AC, Foster WG. Sidestream smoking is equally as damaging as mainstream smoking on IVF outcomes. Human Reproduction 2005;20:2531-5.
104. Cui X, Jing X, Wu X, Wang Z, Li Q. Potential effect of smoking on semen quality through DNA damage and the downregulation of Chk1 in sperm. Molecular medicine reports 2016;14:753-61.
105. Bundhun PK, Janoo G, Bhurtu A, Teeluck AR, Soogund MZS, Pursun M *et al.* Tobacco smoking and semen quality in infertile males: a systematic review and meta-analysis. BMC public health 2019;19:36.
106. Jenkins TG, James ER, Alonso DF, Hoidal JR, Murphy PJ, Hotaling JM *et al.* Cigarette smoking significantly alters sperm DNA methylation patterns. Andrology 2017;5:1089-99.
107. Hughes EG, Lamont DA, Beecroft ML, Wilson DM, Brennan BG, Rice SC. Randomized trial of a "stage-of-change" oriented smoking cessation intervention in infertile and pregnant women. Fertil Steril 2000;74:498-503.
108. Klonoff Cohen H, Lam Kruglick P, Gonzalez C. Effects of maternal and paternal alcohol consumption on the success rates of in vitro fertilization and gamete intrafallopian transfer. Fertility and sterility 2003;79:330-9.

109. Condorelli RA, Calogero AE, Vicari E, La Vignera S. Chronic consumption of alcohol and sperm parameters: our experience and the main evidences. Andrologia 2015;47:368-79.
110. Rossi BV, Berry KF, Hornstein MD, Cramer DW, Ehrlich S, Missmer SA. Effect of Alcohol Consumption on In Vitro Fertilization. Obstetrics and gynecology 2011;117:136-42.
111. Nicolau P, Miralpeix E, Sola I, Carreras R, Checa MA. Alcohol consumption and in vitro fertilization: a review of the literature. Gynecol Endocrinol 2014;30:759-63.
112. Minguez-Alarcon L, Chavarro JE, Gaskins AJ. Caffeine, alcohol, smoking, and reproductive outcomes among couples undergoing assisted reproductive technology treatments. Fertil Steril 2018;110:587-92.
113. Al-Saleh I, El-Doush I, Grisellhi B, Coskun S. The effect of caffeine consumption on the success rate of pregnancy as well various performance parameters of in-vitro fertilization treatment. Med Sci Monit 2010;16:CR598-605.
114. Klonoff-Cohen H, Bleha J, Lam-Kruglick P. A prospective study of the effects of female and male caffeine consumption on the reproductive endpoints of IVF and gamete intra-Fallopian transfer. Human Reproduction 2002;17:1746-54.
115. Lyngso J, Kesmodel US, Bay B, Ingerslev HJ, Nybo Andersen AM, Ramlau-Hansen CH. Impact of female daily coffee consumption on successful fertility treatment: a Danish cohort study. Fertil Steril 2019;112:120-9.e2.
116. Ricci E, Viganò P, Cipriani S, Somigliana E, Chiaffarino F, Bulfoni A *et al.* Coffee and caffeine intake and male infertility: a systematic review. Nutr J 2017;16:37.
117. Choi JH, Ryan LM, Cramer DW, Hornstein MD, Missmer SA. Effects of Caffeine Consumption by Women and Men on the Outcome of In Vitro Fertilization. Journal of Caffeine Research 2011;1:29-34.
118. Machtinger R, Gaskins AJ, Mansur A, Adir M, Racowsky C, Baccarelli AA *et al.* Association between preconception maternal beverage intake and in vitro fertilization outcomes. Fertility and sterility 2017;108:1026-33.
119. Abadia L, Chiu YH, Williams PL, Toth TL, Souter I, Hauser R *et al.* The association between pre-treatment maternal alcohol and caffeine intake and outcomes of assisted reproduction in a prospectively followed cohort. Hum Reprod 2017;32:1846-54.
120. Karmon AE, Toth TL, Chiu YH, Gaskins AJ, Tanrikut C, Wright DL *et al.* Male caffeine and alcohol intake in relation to semen parameters and in vitro fertilization outcomes among fertility patients. Andrology 2017;5:354-61.
121. Parazzini F, Marchini M, Tozzi L, Mezzopane R, Fedele L. Risk factors for unexplained dyspermia in infertile men: a case-control study. Archives of andrology 1993;31:105-13.
122. Marshburn PB, Sloan CS, Hammond MG. Semen quality and association with coffee drinking, cigarette smoking, and ethanol consumption. Fertility and sterility 1989;52:162-5.
123. Oldereid NB, Rui H, Purvis K. Life styles of men in barren couples and their relationship to sperm quality. International journal of fertility 1992;37:343-9.
124. Lyngsø J, Ramlau-Hansen CH, Bay B, Ingerslev HJ, Hulman A, Kesmodel US. Association between coffee or caffeine consumption and fecundity and fertility: a systematic review and dose–response meta-analysis. Clinical Epidemiology 2017;9:699-719.
125. Karmon AE, Toth TL, Chiu YH, Gaskins AJ, Tanrikut C, Wright DL *et al.* Male caffeine and alcohol intake in relation to semen parameters and in vitro fertilization outcomes among fertility patients. Andrology 2017;5:354-61.
126. Pichini S, De Luca R, Pellegrini M, Marchei E, Rotolo MC, Spoletini R *et al.* Hair and urine testing to assess drugs of abuse consumption in couples undergoing assisted reproductive technology (ART). Forensic Sci Int 2012;218:57-61.

127. Klonoff-Cohen HS, Natarajan L, Chen RV. A prospective study of the effects of female and male marijuana use on in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT) outcomes. Am J Obstet Gynecol 2006;194:369-76.
128. Nassan FL, Arvizu M, Mínguez-Alarcón L, Gaskins AJ, Williams PL, Petrozza JC *et al.* Marijuana smoking and outcomes of infertility treatment with assisted reproductive technologies. Human Reproduction 2019;34:1818-29.
129. Kermack AJ, Calder PC, Houghton FD, Godfrey KM, Macklon NS. A randomised controlled trial of a preconceptional dietary intervention in women undergoing IVF treatment (PREPARE trial). BMC women's health 2014;14:130.
130. Ricci E, Bravi F, Noli S, Ferrari S, De Cosmi V, La Vecchia I *et al.* Mediterranean diet and the risk of poor semen quality: cross-sectional analysis of men referring to an Italian Fertility Clinic. Andrology 2019;7:156-62.
131. Karayiannis D, Kontogianni MD, Mendorou C, Douka L, Mastrominas M, Yiannakouris N. Association between adherence to the Mediterranean diet and semen quality parameters in male partners of couples attempting fertility. Hum Reprod 2017;32:215-22.
132. Xia W, Chiu YH, Williams PL, Gaskins AJ, Toth TL, Tanrikut C *et al.* Men's meat intake and treatment outcomes among couples undergoing assisted reproduction. Fertil Steril 2015;104:972-9.
133. Chiu YH, Afeiche MC, Gaskins AJ, Williams PL, Petrozza JC, Tanrikut C *et al.* Fruit and vegetable intake and their pesticide residues in relation to semen quality among men from a fertility clinic. Human Reproduction 2015;30:1342-51.
134. Afeiche MC, Bridges ND, Williams PL, Gaskins AJ, Tanrikut C, Petrozza JC *et al.* Dairy intake and semen quality among men attending a fertility clinic. Fertil Steril 2014;101:1280-7.
135. Chavarro JE, Minguez-Alarcon L, Mendiola J, Cutillas-Tolin A, Lopez-Espin JJ, Torres-Cantero AM. Trans fatty acid intake is inversely related to total sperm count in young healthy men. Hum Reprod 2014;29:429-40.
136. Attaman JA, Toth TL, Furtado J, Campos H, Hauser R, Chavarro JE. Dietary fat and semen quality among men attending a fertility clinic. Hum Reprod 2012;27:1466-74.
137. Olsen J, Ramlau-Hansen CH. Dietary fats may impact semen quantity and quality. Asian J Androl 2012;14:511-2.
138. Vujkovic M, de Vries JH, Dohle GR, Bonsel GJ, Lindemans J, Macklon NS *et al.* Associations between dietary patterns and semen quality in men undergoing IVF/ICSI treatment. Human Reproduction 2009;24:1304-12.
139. Vujkovic M, de Vries JH, Lindemans J, Macklon NS, van der Spek PJ, Steegers EA *et al.* The preconception Mediterranean dietary pattern in couples undergoing in vitro fertilization/intracytoplasmic sperm injection treatment increases the chance of pregnancy. Fertil Steril 2010;94:2096-101.
140. Braga DP, Halpern G, Figueira Rde C, Setti AS, Iaconelli A, Jr., Borges E, Jr. Food intake and social habits in male patients and its relationship to intracytoplasmic sperm injection outcomes. Fertil Steril 2012;97:53-9.
141. Mendiola J, Torres Cantero A, Vioque Js, Moreno Grau J, Ten J, Roca M *et al.* A low intake of antioxidant nutrients is associated with poor semen quality in patients attending fertility clinics. Fertility and sterility 2010;93:1128-33.
142. Mendiola J, Torres Cantero A, Moreno Grau J, Ten J, Roca M, Moreno Grau S *et al.* Food intake and its relationship with semen quality: a case-control study. Fertility and sterility 2009;91:812-8.
143. Wong W, Zielhuis G, Thomas CMG, Merkus HMWM, Steegers-Theunissen RgPM. New evidence of the influence of exogenous and endogenous factors on sperm count in man. European journal of obstetrics & gynecology and reproductive biology 2003;110:49-54.

144. Choy CM, Lam CW, Cheung LT, Briton-Jones CM, Cheung LP, Haines CJ. Infertility, blood mercury concentrations and dietary seafood consumption: a case-control study. Bjog 2002;109:1121-5.
145. Hawkes WC, Turek PJ. Effects of dietary selenium on sperm motility in healthy men. J Androl 2001;22:764-72.
146. Hunt CD, Johnson PE, Herbel J, Mullen LK. Effects of dietary zinc depletion on seminal volume and zinc loss, serum testosterone concentrations, and sperm morphology in young men. Am J Clin Nutr 1992;56:148-57.
147. Afeiche MC, Chiu YH, Gaskins AJ, Williams PL, Souter I, Wright DL *et al.* Dairy intake in relation to in vitro fertilization outcomes among women from a fertility clinic. Hum Reprod 2016;31:563-71.
148. Gaskins AJ, Chiu YH, Williams PL, Keller MG, Toth TL, Hauser R *et al.* Maternal whole grain intake and outcomes of in vitro fertilization. Fertil Steril 2016;105:1503-10.
149. Braga DP, Halpern G, Setti AS, Figueira RC, Iaconelli A, Jr., Borges E, Jr. The impact of food intake and social habits on embryo quality and the likelihood of blastocyst formation. Reprod Biomed Online 2015;31:30-8.
150. Jacobsen BK, Jaceldo-Siegl K, Knutsen SF, Fan J, Oda K, Fraser GE. Soy isoflavone intake and the likelihood of ever becoming a mother: the Adventist Health Study-2. Int J Womens Health 2014;6:377-84.
151. Jungheim ES, Frolova AI, Jiang H, Riley JK. Relationship Between Serum Polyunsaturated Fatty Acids and Pregnancy in Women Undergoing In Vitro Fertilization. The Journal of Clinical Endocrinology and Metabolism 2013;98:E1364-E8.
152. Haggarty P, McCallum H, McBain H, Andrews K, Duthie S, McNeill G *et al.* Effect of B vitamins and genetics on success of in-vitro fertilisation: prospective cohort study. Lancet (London, England) 2006;367:1513-9.
153. Kazemi A, Ramezanzadeh F, Nasr-Esfahani MH, Saboor Yaraghi AA, Ahmadi M. Does dietary fat intake influence oocyte competence and embryo quality by inducing oxidative stress in follicular fluid? Iran J Reprod Med 2013;11:1005-12.
154. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. A prospective study of dietary carbohydrate quantity and quality in relation to risk of ovulatory infertility. Eur J Clin Nutr 2009;63:78-86.
155. Toledo E, Lopez-del Burgo C, Ruiz-Zambrana A, Donazar M, Navarro-Blasco I, Martinez-Gonzalez MA *et al.* Dietary patterns and difficulty conceiving: a nested case-control study. Fertil Steril 2011;96:1149-53.
156. Hammiche F, Vujkovic M, Wijburg W, de Vries JH, Macklon NS, Laven JS *et al.* Increased preconception omega-3 polyunsaturated fatty acid intake improves embryo morphology. Fertil Steril 2011;95:1820-3.
157. Chavarro J, Rich Edwards J, Rosner B, Willett W. Dietary fatty acid intakes and the risk of ovulatory infertility. The American journal of clinical nutrition 2007;85:231-7.
158. Chavarro JE, Rich-Edwards JW, Rosner B, Willett WC. A prospective study of dairy foods intake and anovulatory infertility. Human Reproduction 2007;22:1340-7.
159. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Dietary fatty acid intakes and the risk of ovulatory infertility. Am J Clin Nutr 2007;85:231-7.
160. Chavarro J, Rich Edwards J, Rosner B, Willett W. Protein intake and ovulatory infertility. American journal of obstetrics and gynecology 2008;198:210-7.
161. Twigt JM, Bolhuis MEC, Steegers EAP, Hammiche F, van Inzen WG, Laven JSE *et al.* The preconception diet is associated with the chance of ongoing pregnancy in women undergoing IVF/ICSI treatment. Human Reproduction 2012;27:2526-31.
162. Ruder E, Hartman T, Reindollar R, Goldman M. Female dietary antioxidant intake and time to pregnancy among couples treated for unexplained infertility. Fertility and sterility 2014;101:759-66.

163. Vujkovic M, de Vries JH, Lindemans J, Macklon NS, van der Spek PJ, Steegers EAP *et al.* The preconception Mediterranean dietary pattern in couples undergoing in vitro fertilization/intracytoplasmic sperm injection treatment increases the chance of pregnancy. Fertility and sterility 2010;94:2096-101.
164. Karayiannis D, Kontogianni MD, Mendorou C, Mastrominas M, Yiannakouris N. Adherence to the Mediterranean diet and IVF success rate among non-obese women attempting fertility. Hum Reprod 2018;33:494-502.
165. van Dijk MR, Oostingh EC, Koster MPH, Willemsen SP, Laven JSE, Steegers-Theunissen RPM. The use of the mHealth program Smarter Pregnancy in preconception care: rationale, study design and data collection of a randomized controlled trial. BMC Pregnancy and Childbirth 2017;17:46.
166. Suliga E, Gluszek S. The relationship between diet, energy balance and fertility in men. International journal for vitamin and nutrition research Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung Journal international de vitaminologie et de nutrition 2019:1-13.
167. Dressler N, Chandra A, Aguirre Dávila L, Spineli LM, Schippert C, von Versen-Höynck F. BMI and season are associated with vitamin D deficiency in women with impaired fertility: a two-centre analysis. Archives of gynecology and obstetrics 2015:1-8.
168. Pacis MM, Fortin CN, Zarek SM, Mumford SL, Segars JH. Vitamin D and assisted reproduction: should vitamin D be routinely screened and repleted prior to ART? A systematic review. Journal of assisted reproduction and genetics 2015;32:323-35.
169. Ozkan S, Jindal S, Greenseid K, Shu J, Zeitlian G, Hickmon C *et al.* Replete vitamin D stores predict reproductive success following in vitro fertilization. Fertility and sterility 2010;94:1314-9.
170. Chu J, Gallos I, Tobias A, Tan B, Eapen A, Coomarasamy A. Vitamin D and assisted reproductive treatment outcome: a systematic review and meta-analysis. Hum Reprod 2018;33:65-80.
171. Zhao J, Huang X, Xu B, Yan Y, Zhang Q, Li Y. Whether vitamin D was associated with clinical outcome after IVF/ICSI: a systematic review and meta-analysis. Reproductive Biology and Endocrinology 2018;16:13.
172. Boisen IM, Bøllehuus Hansen L, Mortensen LJ, Lanske B, Juul A, Blomberg Jensen M. Possible influence of vitamin D on male reproduction. The Journal of Steroid Biochemistry and Molecular Biology 2017;173:215-22.
173. de Angelis C, Galdiero M, Pivonello C, Garifalos F, Menafra D, Cariati F *et al.* The role of vitamin D in male fertility: A focus on the testis. Reviews in endocrine & metabolic disorders 2017;18:285-305.
174. Blomberg Jensen M, Lawaetz JG, Petersen JH, Juul A, Jorgensen N. Effects of Vitamin D Supplementation on Semen Quality, Reproductive Hormones, and Live Birth Rate: A Randomized Clinical Trial. J Clin Endocrinol Metab 2018;103:870-81.
175. Ota K, Dambaeva S, Han AR, Beaman K, Gilman-Sachs A, Kwak-Kim J. Vitamin D deficiency may be a risk factor for recurrent pregnancy losses by increasing cellular immunity and autoimmunity. Hum Reprod 2014;29:208-19.
176. Khalessi N, Kalani M, Araghi M, Farahani Z. The Relationship between Maternal Vitamin D Deficiency and Low Birth Weight Neonates. J Family Reprod Health 2015;9:113-7.
177. Miliku K, Vinkhuyzen A, Blanken LM, McGrath JJ, Eyles DW, Burne TH *et al.* Maternal vitamin D concentrations during pregnancy, fetal growth patterns, and risks of adverse birth outcomes. Am J Clin Nutr 2016;103:1514-22.
178. Baker BC, Hayes D, Jones RL. Effects of micronutrients on placental function: evidence from clinical studies to animal models. Reproduction 2018;29:18-0130.
179. Dovnik A, Mujezinovic F. The Association of Vitamin D Levels with Common Pregnancy Complications. Nutrients 2018;10.

180. Agarwal A, Durairajanayagam D, du Plessis SS. Utility of antioxidants during assisted reproductive techniques: an evidence based review. Reproductive Biology and Endocrinology : RB&E 2014;12:112.
181. Showell MG, Mackenzie-Proctor R, Jordan V, Hart RJ. Antioxidants for female subfertility. Cochrane Database Syst Rev 2017;7:Cd007807.
182. Youssef MAFM, Abdelmoty HI, Elashmwi HA, Abduljawad EM, Elghamary N, Magdy A *et al.* Oral antioxidants supplementation for women with unexplained infertility undergoing ICSI/IVF: Randomized controlled trial. Human fertility 2015;18:38-42.
183. Fatemi F, Mohammadzadeh A, Sadeghi MR, Akhondi MM, Mohammadmoradi S, Kamali K *et al.* Role of vitamin E and D3 supplementation in Intra-Cytoplasmic Sperm Injection outcomes of women with polycystic ovarian syndrome: A double blinded randomized placebo-controlled trial. Clin Nutr ESPEN 2017;18:23-30.
184. Arhin SK, Zhao Y, Lu X, Chetry M, Lu J. Effect of micronutrient supplementation on IVF outcomes: a systematic review of the literature. Reproductive biomedicine online 2017;35:715-22.
185. Zhou X, Liu F, Zhai S. Effect of L-carnitine and/or L-acetyl-carnitine in nutrition treatment for male infertility: a systematic review. Asia Pacific journal of clinical nutrition 2007;16 Suppl 1:383-90.
186. Smits RM, Mackenzie-Proctor R, Yazdani A, Stankiewicz MT, Jordan V, Showell MG. Antioxidants for male subfertility. Cochrane Database Syst Rev 2019;3:Cd007411.
187. Bentov Y, Hannam T, Jurisicova A, Esfandiari N, Casper R. Coenzyme Q10 Supplementation and Oocyte Aneuploidy in Women Undergoing IVF-ICSI Treatment. Clinical Medicine Insights: Reproductive Health 2014;8:31-6.
188. El Refaeey A, Selem A, Badawy A. Combined coenzyme Q10 and clomiphene citrate for ovulation induction in clomiphene-citrate-resistant polycystic ovary syndrome. Reprod Biomed Online 2014;29:119-24.
189. Xu Y, Nisenblat V, Lu C, Li R, Qiao J, Zhen X *et al.* Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. Reproductive Biology and Endocrinology : RB&E 2018;16:29.
190. Nadjarzadeh A, Sadeghi MR, Amirjannati N, Vafa MR, Motevalian SA, Gohari MR *et al.* Coenzyme Q10 improves seminal oxidative defense but does not affect on semen parameters in idiopathic oligoasthenoteratozoospermia: a randomized double-blind, placebo controlled trial. J Endocrinol Invest 2011;34:e224-8.
191. Nadjarzadeh A, Shidfar F, Amirjannati N, Vafa MR, Motevalian SA, Gohari MR *et al.* Effect of Coenzyme Q10 supplementation on antioxidant enzymes activity and oxidative stress of seminal plasma: a double-blind randomised clinical trial. Andrologia 2014;46:177-83.
192. Balercia G, Buldreghini E, Vignini A, Tiano L, Paggi F, Amoroso S *et al.* Coenzyme Q10 treatment in infertile men with idiopathic asthenozoospermia: a placebo-controlled, double-blind randomized trial. Fertility and sterility 2009;91:1785-92.
193. Safarinejad MR, Safarinejad S, Shafiei N. Effects of the reduced form of coenzyme Q10 (ubiquinol) on semen parameters in men with idiopathic infertility: a double-blind, placebo controlled, randomized study. J Urol 2012;188:526-31.
194. Safarinejad M. Efficacy of coenzyme Q10 on semen parameters, sperm function and reproductive hormones in infertile men. The Journal of urology 2009;182:237-48.
195. Lafuente R, Gonzalez-Comadran M, Sola I, Lopez G, Brassesco M, Carreras R *et al.* Coenzyme Q10 and male infertility: a meta-analysis. J Assist Reprod Genet 2013;30:1147-56.
196. Ikematsu H, Nakamura K, Harashima S, Fujii K, Fukutomi N. Safety assessment of coenzyme Q10 (Kaneka Q10) in healthy subjects: a double-blind, randomized, placebo-controlled trial. Regul Toxicol Pharmacol 2006;44:212-8.

197. Miner SA, Robins S, Zhu YJ, Keeren K, Gu V, Read SC *et al.* Evidence for the use of complementary and alternative medicines during fertility treatment: a scoping review. BMC Complement Altern Med 2018;18:158.
198. El-Toukhy T, Khalaf Y. A new study of acupuncture in IVF: pointing in the right direction. Reprod Biomed Online 2010;21:278-9.
199. Meldrum DR, Fisher AR, Butts SF, Su HI, Sammel MD. Acupuncture--help, harm, or placebo? Fertil Steril 2013;99:1821-4.
200. Zheng CH, Huang GY, Zhang MM, Wang W. Effects of acupuncture on pregnancy rates in women undergoing in vitro fertilization: a systematic review and meta-analysis. Fertil Steril 2012;97:599-611.
201. Cheong YC, Dix S, Hung Yu Ng E, Ledger WL, Farquhar C. Acupuncture and assisted reproductive technology. Cochrane Database of Systematic Reviews 2013.
202. Qian Y, Xia XR, Ochin H, Huang C, Gao C, Gao L *et al.* Therapeutic effect of acupuncture on the outcomes of in vitro fertilization: a systematic review and meta-analysis. Arch Gynecol Obstet 2017;295:543-58.
203. Schwarze JE, Ceroni JP, Ortega-Hrepich C, Villa S, Crosby J, Pommer R. Does acupuncture the day of embryo transfer affect the clinical pregnancy rate? Systematic review and meta-analysis. JBRA Assist Reprod 2018;22:363-8.
204. Kwan I, Bhattacharya S, Knox F, McNeil A. Pain relief for women undergoing oocyte retrieval for assisted reproduction. Cochrane Database Syst Rev 2013;31.
205. Jo J, Lee YJ. Effectiveness of acupuncture in women with polycystic ovarian syndrome undergoing in vitro fertilisation or intracytoplasmic sperm injection: a systematic review and meta-analysis. Acupunct Med 2017;35:162-70.
206. Smith CA, Armour M, Shewamene Z, Tan HY, Norman RJ, Johnson NP. Acupuncture performed around the time of embryo transfer: a systematic review and meta-analysis. Reprod Biomed Online 2019;38:364-79.
207. Zhang M, Huang G, Lu F, Paulus WE, Sterzik K. Influence of acupuncture on idiopathic male infertility in assisted reproductive technology. J Huazhong Univ Sci Technolog Med Sci 2002;22:228-30.
208. Dieterle S, Li C, Greb R, Bartzsch F, Hatzmann W, Huang D. A prospective randomized placebo-controlled study of the effect of acupuncture in infertile patients with severe oligoasthenozoospermia. Fertil Steril 2009;92:1340-3.
209. Cakmak YO, Akpinar IN, Ekinci G, Bekiroglu N. Point- and frequency-specific response of the testicular artery to abdominal electroacupuncture in humans. Fertil Steril 2008;90:1732-8.
210. Jerng UM, Jo JY, Lee S, Lee JM, Kwon O. The effectiveness and safety of acupuncture for poor semen quality in infertile males: a systematic review and meta-analysis. Asian J Androl 2014;16:884-91.
211. Okhowat J, Murtinger M, Schuff M, Wogatzky J, Spitzer D, Vanderzwalmen P *et al.* Massage therapy improves in vitro fertilization outcome in patients undergoing blastocyst transfer in a cryo-cycle. Altern Ther Health Med 2015;21:16-22.
212. Revelli A, La Sala GB, Gennarelli G, Scatigna L, Racca C, Massobrio M. Seasonality and human in vitro fertilization outcome. Gynecol Endocrinol 2005;21:12-7.
213. Wunder DM, Limoni C, Birkhauser MH. Lack of seasonal variations in fertilization, pregnancy and implantation rates in women undergoing IVF. Hum Reprod 2005;20:3122-9.
214. Kirshenbaum M, Ben-David A, Zilberberg E, Elkan-Miller T, Haas J, Orvieto R. Influence of seasonal variation on in vitro fertilization success. PLoS One 2018;13:e0199210-e.
215. Stolwijk AM, Reuvers MJ, Hamilton CJ, Jongbloet PH, Hollanders JM, Zielhuis GA. Seasonality in the results of in-vitro fertilization. Hum Reprod 1994;9:2300-5.
216. Braga DP, Setti A, Figueira Rde C, Iaconelli A, Jr., Borges E, Jr. Seasonal variability in the fertilization rate of women undergoing assisted reproduction treatments. Gynecol Endocrinol 2012;28:549-52.

217. Wood S, Quinn A, Troupe S, Kingsland C, Lewis-Jones I. Seasonal variation in assisted conception cycles and the influence of photoperiodism on outcome in in vitro fertilization cycles. Hum Fertil 2006;9:223-9.
218. Vandekerckhove F, Van der Veken H, Tilleman K, De Croo I, Van den Abbeel E, Gerris J *et al.* Seasons in the sun: the impact on IVF results one month later. Facts, Views & Vision in ObGyn 2016;8:75-83.
219. Rojansky N, Benshushan A, Meirsdorf S, Lewin A, Laufer N, Safran A. Seasonal variability in fertilization and embryo quality rates in women undergoing IVF. Fertil Steril 2000;74:476-81.
220. Jarrell JF, Villeneuve D, Franklin C, Bartlett S, Wrixon W, Kohut J *et al.* Contamination of human ovarian follicular fluid and serum by chlorinated organic compounds in three Canadian cities. Cmaj 1993;148:1321-7.
221. Younglai EV, Foster WG, Hughes EG, Trim K, Jarrell JF. Levels of environmental contaminants in human follicular fluid, serum, and seminal plasma of couples undergoing in vitro fertilization. Arch Environ Contam Toxicol 2002;43:121-6.
222. Al-Hussaini TK, Abdelaleem AA, Elnashar I, Shabaan OM, Mostafa R, El-Baz MAH *et al.* The effect of follicullar fluid pesticides and polychlorinated biphenyls concentrations on intracytoplasmic sperm injection (ICSI) embryological and clinical outcome. Eur J Obstet Gynecol Reprod Biol 2018;220:39-43.
223. Petro EM, Leroy JL, Covaci A, Fransen E, De Neubourg D, Dirtu AC *et al.* Endocrine-disrupting chemicals in human follicular fluid impair in vitro oocyte developmental competence. Hum Reprod 2012;27:1025-33.
224. Minguez-Alarcon L, Souter I, Chiu YH, Williams PL, Ford JB, Ye X *et al.* Urinary concentrations of cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester, a metabolite of the non-phthalate plasticizer di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH), and markers of ovarian response among women attending a fertility center. Environ Res 2016;151:595-600.
225. Johnson PI, Altshul L, Cramer DW, Missmer SA, Hauser R, Meeker JD. Serum and follicular fluid concentrations of polybrominated diphenyl ethers and in-vitro fertilization outcome. Environ Int 2012;45:9-14.
226. Minguez-Alarcon L, Messerlian C, Bellavia A, Gaskins AJ, Chiu YH, Ford JB *et al.* Urinary concentrations of bisphenol A, parabens and phthalate metabolite mixtures in relation to reproductive success among women undergoing in vitro fertilization. Environ Int 2019;126:355-62.
227. Dodge LE, Williams PL, Williams MA, Missmer SA, Souter I, Calafat AM *et al.* Associations between paternal urinary phthalate metabolite concentrations and reproductive outcomes among couples seeking fertility treatment. Reproductive toxicology 2015;58:184-93.
228. Mínguez-Alarcón L, Gaskins AJ, Chiu Y-H, Williams PL, Ehrlich S, Chavarro JE *et al.* Urinary bisphenol A concentrations and association with in vitro fertilization outcomes among women from a fertility clinic. Human Reproduction 2015;30:2120-8.
229. Mustieles V, Williams PL, Fernandez MF, Minguez-Alarcon L, Ford JB, Calafat AM *et al.* Maternal and paternal preconception exposure to bisphenols and size at birth. Hum Reprod 2018;33:1528-37.
230. Ikezuki Y, Tsutsumi O, Takai Y, Kamei Y, Taketani Y. Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. Hum Reprod 2002;17:2839-41.
231. Bloom MS, vom Saal FS, Kim D, Taylor JA, Lamb JD, Fujimoto VY. Serum unconjugated bisphenol A concentrations in men may influence embryo quality indicators during in vitro fertilization. Environmental toxicology and pharmacology 2011;32:319-23.
232. Knez J, Kranvogl R, Breznik BP, Voncina E, Vlaisavljevic V. Are urinary bisphenol A levels in men related to semen quality and embryo development after medically assisted reproduction? Fertil Steril 2014;101:215-21.e5.

233. Mok-Lin E, Ehrlich S, Williams PL, Petrozza J, Wright DL, Calafat AM *et al.* Urinary bisphenol A concentrations and ovarian response among women undergoing IVF. International journal of andrology 2010;33:385-93.
234. Ehrlich S, Williams PL, Missmer SA, Flaws JA, Ye X, Calafat AM *et al.* Urinary bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF. Human Reproduction 2012;27:3583-92.
235. Souter I, Smith KW, Dimitriadis I, Ehrlich S, Williams PL, Calafat AM *et al.* The association of bisphenol-A urinary concentrations with antral follicle counts and other measures of ovarian reserve in women undergoing infertility treatments. Reprod Toxicol 2013;42:224-31.
236. Al-Saleh I, Coskun S, El-Doush I, Billedo G, Mashhour A, Jaroudi K *et al.* Outcome of in-vitro fertilization treatment and DDT levels in serum and follicular fluid. Med Sci Monit 2009;15:BR320-33.
237. Messerlian C, Souter I, Gaskins AJ, Williams PL, Ford JB, Chiu Y-H *et al.* Urinary phthalate metabolites and ovarian reserve among women seeking infertility care. Human Reproduction 2016;31:75-83.
238. Du YY, Fang YL, Wang YX, Zeng Q, Guo N, Zhao H *et al.* Follicular fluid and urinary concentrations of phthalate metabolites among infertile women and associations with in vitro fertilization parameters. Reprod Toxicol 2016;61:142-50.
239. Hauser R, Gaskins AJ, Souter I, Smith KW, Dodge LE, Ehrlich S *et al.* Urinary Phthalate Metabolite Concentrations and Reproductive Outcomes among Women Undergoing in Vitro Fertilization: Results from the EARTH Study. Environ Health Perspect 2016;124:831-9.
240. Machtinger R, Gaskins AJ, Racowsky C, Mansur A, Adir M, Baccarelli AA *et al.* Urinary concentrations of biomarkers of phthalates and phthalate alternatives and IVF outcomes. Environ Int 2018;111:23-31.
241. Al-Saleh I, Coskun S, Al-Doush I, Al-Rajudi T, Al-Rouqi R, Abduljabbar M *et al.* Exposure to phthalates in couples undergoing in vitro fertilization treatment and its association with oxidative stress and DNA damage. Environ Res 2019;169:396-408.
242. Oliva A, Spira A, Multigner L. Contribution of environmental factors to the risk of male infertility. Human Reproduction 2001;16:1768-76.
243. Tielemans E, van Kooij R, Looman C, Burdorf A, te Velde E, Heederik D. Paternal occupational exposures and embryo implantation rates after IVF. Fertil Steril 2000;74:690-5.
244. Wdowiak A, Wdowiak E, Bojar I. Evaluation of trace metals in follicular fluid in ICSI-treated patients. Annals of agricultural and environmental medicine : AAEM 2017;25:213-8.
245. Wright DL, Afeiche MC, Ehrlich S, Smith K, Williams PL, Chavarro JE *et al.* Hair mercury concentrations and in vitro fertilization (IVF) outcomes among women from a fertility clinic. Reprod Toxicol 2015;51:125-32.
246. Bloom MS, Parsons PJ, Steuerwald AJ, Schisterman EF, Browne RW, Kim K *et al.* Toxic trace metals and human oocytes during in vitro fertilization (IVF). Reproductive toxicology 2010;29:298-305.
247. De Fleurian G, Perrin J, Ecochard R, Dantony E, Lanteaume A, Achard V *et al.* Occupational exposures obtained by questionnaire in clinical practice and their association with semen quality. J Androl 2009;30:566-79.
248. Al-Saleh I, Coskun S, Mashhour A, Shinwari N, El-Doush I, Billedo G *et al.* Exposure to heavy metals (lead, cadmium and mercury) and its effect on the outcome of in-vitro fertilization treatment. International Journal of Hygiene and Environmental Health 2008;211:560-79.
249. Zenzes MT, Krishnan S, Krishnan B, Zhang H, Casper RF. Cadmium accumulation in follicular fluid of women in in vitro fertilization-embryo transfer is higher in smokers. Fertil Steril 1995;64:599-603.
250. Jurewicz J, Dziewirska E, Radwan M, Hanke W. Air pollution from natural and anthropic sources and male fertility. Reprod Biol Endocrinol 2018;16:109.

251. Huang X, Zhang B, Wu L, Zhou Y, Li Y, Mao X *et al.* Association of Exposure to Ambient Fine Particulate Matter Constituents With Semen Quality Among Men Attending a Fertility Center in China. Environmental science & technology 2019;53:5957-65.
252. Wdowiak A, Wdowiak E, Bien A, Bojar I, Iwanowicz-Palus G, Raczkiewicz D. Air pollution and semen parameters in men seeking fertility treatment for the first time. International journal of occupational medicine and environmental health 2019;32:387-99.
253. Radwan M, Dziewirska E, Radwan P, Jakubowski L, Hanke W, Jurewicz J. Air Pollution and Human Sperm Sex Ratio. American journal of men's health 2018;12:907-12.
254. Jurewicz J, Radwan M, Sobala W, Polanska K, Radwan P, Jakubowski L *et al.* The relationship between exposure to air pollution and sperm disomy. Environ Mol Mutagen 2015;56:50-9.
255. Legro RS, Sauer MV, Mottla GL, Richter KS, Li X, Dodson WC *et al.* Effect of air quality on assisted human reproduction. Hum Reprod 2010;25:1317-24.
256. Checa Vizcaino MA, Gonzalez-Comadran M, Jacquemin B. Outdoor air pollution and human infertility: a systematic review. Fertil Steril 2016;106:897-904.
257. Choe SA, Jun YB, Lee WS, Yoon TK, Kim SY. Association between ambient air pollution and pregnancy rate in women who underwent IVF. Hum Reprod 2018;33:1071-8.
258. Conforti A, Mascia M, Cioffi G, De Angelis C, Coppola G, De Rosa P *et al.* Air pollution and female fertility: a systematic review of literature. Reproductive biology and endocrinology : RB&E 2018;16:117.
259. Perin PM, Maluf M, Czeresnia CE, Nicolosi Foltran Januario DA, Nascimento Saldiva PH. Effects of exposure to high levels of particulate air pollution during the follicular phase of the conception cycle on pregnancy outcome in couples undergoing in vitro fertilization and embryo transfer. Fertil Steril 2010;93:301-3.
260. Carre J, Gatimel N, Moreau J, Parinaud J, Leandri R. Influence of air quality on the results of in vitro fertilization attempts: A retrospective study. Eur J Obstet Gynecol Reprod Biol 2017;210:116-22.
261. Gaskins AJ, Fong KC, Abu Awad Y, Di Q, Minguez-Alarcon L, Chavarro JE *et al.* Time-Varying Exposure to Air Pollution and Outcomes of in Vitro Fertilization among Couples from a Fertility Clinic. Environ Health Perspect 2019;127:77002.
262. Quraishi SM, Lin PC, Richter KS, Hinckley MD, Yee B, Neal-Perry G *et al.* Ambient Air Pollution Exposure and Fecundability in Women Undergoing In Vitro Fertilization. Environmental epidemiology (Philadelphia, Pa) 2019;3.
263. Gaskins AJ, Hart JE, Minguez-Alarcon L, Chavarro JE, Laden F, Coull BA *et al.* Residential proximity to major roadways and traffic in relation to outcomes of in vitro fertilization. Environ Int 2018;115:239-46.
264. Nassan FL, Chavarro JE, Minguez-Alarcon L, Williams PL, Tanrikut C, Ford JB *et al.* Residential distance to major roadways and semen quality, sperm DNA integrity, chromosomal disomy, and serum reproductive hormones among men attending a fertility clinic. Int J Hyg Environ Health 2018;221:830-7.
265. Roshangar L, Hamdi BA, Khaki AA, Rad JS, Soleimani-Rad S. Effect of low-frequency electromagnetic field exposure on oocyte differentiation and follicular development. Advanced Biomedical Research 2014;3:76.
266. Fatehi D, Anjomshoa M, Mohammadi M, Seify M, Rostamzadeh A. Biological effects of cell-phone radiofrequency waves exposure on fertilization in mice; an in vivo and in vitro study. Middle East Fertility Society Journal 2018;23:148-53.
267. Kesari KK, Agarwal A, Henkel R. Radiations and male fertility. Reproductive biology and endocrinology : RB&E 2018;16:118.
268. Avendano C, Mata A, Sanchez Sarmiento CA, Doncel GF. Use of laptop computers connected to internet through Wi-Fi decreases human sperm motility and increases sperm DNA fragmentation. Fertil Steril 2012;97:39-45.e2.

269. Yildirim ME, Kaynar M, Badem H, Cavis M, Karatas OF, Cimentepe E. What is harmful for male fertility: cell phone or the wireless Internet? The Kaohsiung journal of medical sciences 2015;31:480-4.
270. Wdowiak A, Wdowiak L, Wiktor H. Evaluation of the effect of using mobile phones on male fertility. Annals of agricultural and environmental medicine:AAEM 2007;14:169-72.
271. Agarwal A, Desai NR, Makker K, Varghese A, Mouradi R, Sabanegh E *et al.* Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an in vitro pilot study. Fertil Steril 2009;92:1318-25.
272. Gutschi T, Mohamad Al-Ali B, Shamloul R, Pummer K, Trummer H. Impact of cell phone use on men's semen parameters. Andrologia 2011;43:312-6.
273. Adams JA, Galloway TS, Mondal D, Esteves SC, Mathews F. Effect of mobile telephones on sperm quality: a systematic review and meta-analysis. Environ Int 2014;70:106-12.
274. Lewis RC, Minguez-Alarcon L, Meeker JD, Williams PL, Mezei G, Ford JB *et al.* Self-reported mobile phone use and semen parameters among men from a fertility clinic. Reprod Toxicol 2017;67:42-7.
275. Bieniek KW, Riedel HH. Bacterial foci in the teeth, oral cavity, and jaw—secondary effects (remote action) of bacterial colonies with respect to bacteriospermia and subfertility in males. Andrologia 1993;25:159-62.
276. Klinger A, Hain B, Yaffe H, Schonberger O. Periodontal status of males attending an in vitro fertilization clinic. Journal of Clinical Periodontology 2011;38:542-6.
277. Tielemans E, Burdorf A, te Velde ER, Weber RF, van Kooij RJ, Veulemans H *et al.* Occupationally related exposures and reduced semen quality: a case-control study. Fertil Steril 1999;71:690-6.
278. Minguez-Alarcon L, Gaskins AJ, Chiu YH, Messerlian C, Williams PL, Ford JB *et al.* Type of underwear worn and markers of testicular function among men attending a fertility center. Hum Reprod 2018;33:1749-56.
279. Altman N, Krzywinski M. Association, correlation and causation. Nature Methods 2015;12:899-900.
280. Sommer AP, Haddad MK, Fecht H-J. It is time for a change: Petri Dishes weaken cells. Journal of Bionic Engineering 2012;9:353-7.
281. Swain JE. Optimizing the culture environment in the IVF laboratory: impact of pH and buffer capacity on gamete and embryo quality. Reprod Biomed Online 2010;21:6-16.
282. Swain JE, Smith GD. Advances in embryo culture platforms: novel approaches to improve preimplantation embryo development through modifications of the microenvironment. Hum Reprod Update 2011;17:541-57.
283. Chronopoulou E, Harper JC. IVF culture media: past, present and future. Hum Reprod Update 2015;21:39-55.
284. Rooney KL, Domar AD. The impact of lifestyle behaviors on infertility treatment outcome. Curr Opin Obstet Gynecol 2014;26:181-5.
285. de Ziegler D, Santulli P, Seroka A, Decanter C, Meldrum DR, Chapron C. In women, the reproductive harm of toxins such as tobacco smoke is reversible in 6 months: basis for the “olive tree” hypothesis. Fertility and sterility 2013;100:927-8.
286. Harper J, Magli MC, Lundin K, Barratt CL, Brison D. When and how should new technology be introduced into the IVF laboratory? Hum Reprod 2012;27:303-13.
287. Seshadri S, Oakeshott P, Nelson-Piercy C, Chappell LC. Prepregnancy care. BMJ 2012;344:e3467.:10.1136/bmj.e3467.
288. Heyes T, Long S, Mathers N. Preconception care: Practice and beliefs of primary care workers. Family Practice 2004;21:22-7.
289. Nekuei N, Nasr Esfahani MH, Kazemi A. Preconception counseling in couples undergoing fertility treatment. Int J Fertil Steril 2012;6:79-86.

290. Morgan MA, Hawks D, Zinberg S, Schulkin J. What obstetrician-gynecologists think of preconception care. Matern Child Health J 2006;10:S59-65.
291. van der Zee B, de Beaufort ID, Steegers EA, Denktas S. Perceptions of preconception counselling among women planning a pregnancy: a qualitative study. Fam Pract 2013;30:341-6.
292. Ludwig AK, Katalinic A, Steinbicker V, Diedrich K, Ludwig M. Antenatal care in singleton pregnancies after ICSI as compared to spontaneous conception: data from a prospective controlled cohort study in Germany. Hum Reprod 2006;21:713-20.
293. Ockhuijsen HD, Gamel CJ, van den Hoogen A, Macklon NS. Integrating preconceptional care into an IVF programme. J Adv Nurs 2012;68:1156-65.
294. Hvidman HW, Petersen KB, Larsen EC, Macklon KT, Pinborg A, Nyboe Andersen A. Individual fertility assessment and pro-fertility counselling; should this be offered to women and men of reproductive age? Hum Reprod 2015;30:9-15.
295. Bunting L, Boivin J. Development and preliminary validation of the fertility status awareness tool: FertiSTAT. Hum Reprod 2010;25:1722-33. doi: 10.093/humrep/deq087. Epub 2010 Apr 21.
296. Daniluk JC, Koert E. Fertility awareness online: the efficacy of a fertility education website in increasing knowledge and changing fertility beliefs. Hum Reprod 2015;30:353-63.
297. Hammiche F, Laven JS, van Mil N, de Cock M, de Vries JH, Lindemans J *et al.* Tailored preconceptional dietary and lifestyle counselling in a tertiary outpatient clinic in The Netherlands. Hum Reprod 2011;26:2432-41.
298. Mutsaerts MA, Groen H, ter Bogt NC, Bolster JH, Land JA, Bemelmans WJ *et al.* The LIFESTYLE study: costs and effects of a structured lifestyle program in overweight and obese subfertile women to reduce the need for fertility treatment and improve reproductive outcome. A randomised controlled trial. BMC Womens Health 2010;10.
299. Homan G, Litt J, Norman RJ. The FAST study: Fertility Assessment and advice Targeting lifestyle choices and behaviours: a pilot study. Human Reproduction 2012;27:2396-404.

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 (cocaine, 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 $\geq$ 30 kg/m^2) (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 $\geq$25 kg/m^2 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 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/m^2) 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

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 (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

(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.

References

1. Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. Hum Reprod Update 2007;13:209-23.
2. Anderson K, Nisenblat V, Norman R. Lifestyle factors in people seeking infertility treatment - A review. Aust N Z J Obstet Gynaecol 2010;50:8-20.
3. Domar AD, Rooney KL, Milstein M, Conboy L. Lifestyle habits of 12,800 IVF patients: Prevalence of negative lifestyle behaviors, and impact of region and insurance coverage. Hum Fertil 2015;18:253-7.
4. Ferreira RC, Halpern G, Figueira Rde C, Braga DP, Iaconelli A, Jr., Borges E, Jr. Physical activity, obesity and eating habits can influence assisted reproduction outcomes. Womens Health (Lond Engl) 2010;6:517-24.
5. Gormack AA, Peek JC, Derraik JG, Gluckman PD, Young NL, Cutfield WS. Many women undergoing fertility treatment make poor lifestyle choices that may affect treatment outcome. Hum Reprod 2015;30:1617-24.
6. Alvarez S. Do some addictions interfere with fertility? Fertil Steril 2015;103:22-6.
7. Adashi EY, Cohen J, Hamberger L, Jones HW, Jr., de Kretser DM, Lunenfeld B *et al.* Public perception on infertility and its treatment: an international survey. The Bertarelli Foundation Scientific Board. Hum Reprod 2000;15:330-4.
8. Roth LK, Taylor HS. Risks of smoking to reproductive health: assessment of women's knowledge. Am J Obstet Gynecol 2001;184:934-9.
9. de Jong-Van den Berg LT, Hernandez-Diaz S, Werler MM, Louik C, Mitchell AA. Trends and predictors of folic acid awareness and periconceptional use in pregnant women. Am J Obstet Gynecol 2005;192:121-8.
10. Bunting L, Boivin J. Knowledge about infertility risk factors, fertility myths and illusory benefits of healthy habits in young people. Hum Reprod 2008;23:1858-64.
11. Vause TDR, Jones L, Evans M, Wilkie V, Leader A. Pre-conception health awareness in infertility patients. J Obstet Gynaecol Can 2009;31:717-20.
12. Messerlian C, Williams PL, Ford JB, Chavarro JE, Minguez-Alarcon L, Dadd R *et al.* The Environment and Reproductive Health (EARTH) Study: A Prospective Preconception Cohort. Human reprod open 2018;2018.
13. Domar AD, Smith K, Conboy L, Iannone M, Alper M. A prospective investigation into the reasons why insured United States patients drop out of in vitro fertilization treatment. Fertil Steril 2010;94:1457-9.
14. Chen TH, Chang SP, Tsai CF, Juang KD. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. Hum Reprod 2004;19:2313-8.
15. Volgsten H, Skoog Svanberg A, Ekselius L, Lundkvist O, Sundstrom Poromaa I. Prevalence of psychiatric disorders in infertile women and men undergoing in vitro fertilization treatment. Hum Reprod 2008;23:2056-63.
16. Holley SR, Pasch LA, Bleil ME, Gregorich S, Katz PK, Adler NE. Prevalence and predictors of major depressive disorder for fertility treatment patients and their partners. Fertil Steril 2015;103:1332-9.
17. Pasch LA, Holley SR, Bleil ME, Shehab D, Katz PP, Adler NE. Addressing the needs of fertility treatment patients and their partners: are they informed of and do they receive mental health services? Fertil Steril 2016;106:209-15.

18. Haimovici F, Anderson JL, Bates GW, Racowsky C, Ginsburg ES, Simovici D *et al.* Stress, anxiety, and depression of both partners in infertile couples are associated with cytokine levels and adverse IVF outcome. American journal of reproductive immunology (New York, NY : 1989) 2018;79:e12832.
19. Massey AJ, Campbell BK, Raine-Fenning N, Pincott-Allen C, Perry J, Vedhara K. Relationship between hair and salivary cortisol and pregnancy in women undergoing IVF. Psychoneuroendocrinology 2016;74:397-405.
20. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res 2002;53:865-71.
21. Mor G, Cardenas I, Abrahams V, Guller S. Inflammation and pregnancy: the role of the immune system at the implantation site. Ann N Y Acad Sci 2011;1221:80-87.
22. Schaller MA, Griesinger G, Banz-Jansen C. Women show a higher level of anxiety during IVF treatment than men and hold different concerns: a cohort study. Arch Gynecol Obstet 2016;293:1137-
23. Vellani E, Colasante A, Mamazza L, Minasi MG, Greco E, Bevilacqua A. Association of state and trait anxiety to semen quality of in vitro fertilization patients: a controlled study. Fertil Steril 2013;99:1565-72.
24. Jurewicz J, Radwan M, Merecz-Kot D, Sobala W, Ligocka D, Radwan P *et al.* Occupational, life stress and family functioning: does it affect semen quality? Ann Hum Biol 2014;41:220-8.
25. Radwan M, Jurewicz J, Merecz-Kot D, Sobala W, Radwan P, Bochenek M *et al.* Sperm DNA damage-the effect of stress and everyday life factors. International journal of impotence research 2016;28:148-54.
26. Zorn B, Auger J, Velikonja V, Kolbezen M, Meden-Vrtovec H. Psychological factors in male partners of infertile couples: relationship with semen quality and early miscarriage. Int J Androl 2008;31:557-64.
27. Nouri K, Litschauer B, Sator M, Tiringer D, Ott J, Walch K *et al.* Decline of semen quality during IVF is not associated with subjective male stress. Asian J Androl 2014;16:597-601.
28. Ying L, Wu LH, Loke AY. The effects of psychosocial interventions on the mental health, pregnancy rates, and marital function of infertile couples undergoing in vitro fertilization: a systematic review. J Assist Reprod Genet 2016;33:689-701.
29. Darbandi S, Darbandi M, Khorram Khorshid HR, Sadeghi MR. Yoga Can Improve Assisted Reproduction Technology Outcomes in Couples With Infertility. Altern Ther Health Med 2018;24:50-5.
30. LoGiudice JA, Massaro J. The impact of complementary therapies on psychosocial factors in women undergoing in vitro fertilization (IVF): A systematic literature review. Applied Nursing Research 2018;39:220-8.
31. Chow KM, Cheung MC, Cheung IK. Psychosocial interventions for infertile couples: a critical review. J Clin Nurs 2016;25:2101-13.
32. Verkuijlen J, Verhaak C, Nelen WL, Wilkinson J, Farquhar C. Psychological and educational interventions for subfertile men and women. Cochrane Database Syst Rev 2016;31.
33. Boivin J. How does stress, depression and anxiety affect patients undergoing treatment? Curr Opin Obstet Gynecol 2019;31:195-9.
34. Pedro J, Frederiksen Y, Schmidt L, Ingerslev HJ, Zachariae R, Martins MV. Comparison of three infertility-specific measures in men and women going through assisted reproductive technology treatment. Journal of Health Psychology 2019;24:738-49.
35. Rooney KL, Domar AD. The impact of stress on fertility treatment. Curr Opin Obstet Gynecol 2016;28:198-201.
36. Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, Wang JX. Improving reproductive performance in overweight/obese women with effective weight management. Human Reproduction Update 2004;10:267-80.

37. Sheng Y, Lu G, Liu J, Liang X, Ma Y, Zhang X *et al.* Effect of body mass index on the outcomes of controlled ovarian hyperstimulation in Chinese women with polycystic ovary syndrome: a multicenter, prospective, observational study. Journal of assisted reproduction and genetics 2017;34:61-70.
38. Sermondade N, Huberlant S, Bourhis-Lefebvre V, Arbo E, Gallot V, Colombani M *et al.* Female obesity is negatively associated with live birth rate following IVF: a systematic review and meta-analysis. Hum Reprod Update 2019;25:439-51.
39. Zaadstra BM, Seidell JC, Van Noord PA, te Velde ER, Habbema JD, Vrieswijk B *et al.* Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. BMJ 1993;306:484-7.
40. Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. J Clin Endocrinol Metab 1999;84:1470-4.
41. Chavarro JE, Ehrlich S, Colaci DS, Wright DL, Toth TL, Petrozza JC *et al.* Body mass index and short-term weight change in relation to treatment outcomes in women undergoing assisted reproduction. Fertil Steril 2012;98:109-16.
42. Li MC, Minguez-Alarcon L, Arvizu M, Chiu YH, Ford JB, Williams PL *et al.* Waist circumference in relation to outcomes of infertility treatment with assisted reproductive technologies. Am J Obstet Gynecol 2019;220:578.e1-.e13.
43. Bellver J, De los Santos MJ, Alamá P, Castelló D, Privitera L, Galliano D *et al.* Day-3 embryo metabolomics in the spent culture media is altered in obese women undergoing in vitro fertilization. Fertility and sterility 2015;103:1407-15.e1.
44. Leary C, Leese HJ, Sturmey RG. Human embryos from overweight and obese women display phenotypic and metabolic abnormalities. Human Reproduction 2015;30:122-32.
45. Petersen GL, Schmidt L, Pinborg A, Kamper-Jorgensen M. The influence of female and male body mass index on live births after assisted reproductive technology treatment: a nationwide register-based cohort study. Fertil Steril 2013;99:1654-62.
46. Mushtaq R, Pundir J, Achilli C, Naji O, Khalaf Y, El-Toukhy T. Effect of male body mass index on assisted reproduction treatment outcome: an updated systematic review and meta-analysis. Reprod Biomed Online 2018;36:459-71.
47. Chavarro JE, Toth TL, Wright DL, Meeker JD, Hauser R. Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic. Fertil Steril 2010;93:2222-31.
48. Dupont C, Faure C, Sermondade N, Boubaya M, Eustache F, Clement P *et al.* Obesity leads to higher risk of sperm DNA damage in infertile patients. Asian J Androl 2013;15:622-5.
49. Veron GL, Tissera AD, Bello R, Beltramone F, Estofan G, Molina RI *et al.* Impact of age, clinical conditions, and lifestyle on routine semen parameters and sperm kinematics. Fertil Steril 2018;110:68-75.
50. Raad G, Azouri J, Rizk K, Zeidan NS, Azouri J, Grandjean V *et al.* Adverse effects of paternal obesity on the motile spermatozoa quality. PLoS One 2019;14:e0211837.
51. Bakos HW, Henshaw RC, Mitchell M, Lane M. Paternal body mass index is associated with decreased blastocyst development and reduced live birth rates following assisted reproductive technology. Fertil Steril 2011;95:1700-4.
52. Anifandis G, Dafopoulos K, Messini CI, Polyzos N, Messinis IE. The BMI of men and not sperm parameters impact on embryo quality and the IVF outcome. Andrology 2013;1:85-9.
53. Fejes I, Koloszar S, Szollosi J, Zavaczki Z, Pal A. Is semen quality affected by male body fat distribution? Andrologia 2005;37:155-9.

54. Best D, Avenell A, Bhattacharya S. How effective are weight-loss interventions for improving fertility in women and men who are overweight or obese? A systematic review and meta-analysis of the evidence. Human Reproduction Update 2017;23:681-705.
55. Hakonsen LB, Thulstrup AM, Aggerholm AS, Olsen J, Bonde JP, Andersen CY *et al.* Does weight loss improve semen quality and reproductive hormones? Results from a cohort of severely obese men. Reprod Health 2011;8:24.
56. Faure C, Dupont C, Baraibar MA, Ladouce R, Cedrin-Durnerin I, Wolf JP *et al.* In Subfertile Couple, Abdominal Fat Loss in Men Is Associated with Improvement of Sperm Quality and Pregnancy: A Case-Series. PLoS One 2014;9:e86300.
57. Moran LJ, Noakes M, Clifton PM, Tomlinson L, Galletly C, Norman RJ. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003;88:812-9.
58. Mutsaerts MA, van Oers AM, Groen H, Burggraaff JM, Kuchenbecker WK, Perquin DA *et al.* Randomized Trial of a Lifestyle Program in Obese Infertile Women. N Engl J Med 2016;374:1942-53.
59. Einarsson S, Bergh C, Friberg B, Pinborg A, Klajnbard A, Karlström P-O *et al.* Weight reduction intervention for obese infertile women prior to IVF: a randomized controlled trial. Human Reproduction 2017;32:1621-30.
60. Mutsaerts MA, Kuchenbecker WK, Mol BW, Land JA, Hoek A. Dropout is a problem in lifestyle intervention programs for overweight and obese infertile women: a systematic review. Hum Reprod 2013;28:979-86.
61. Tsur A, Orvieto R, Haas J, Kedem A, Machtinger R. Does bariatric surgery improve ovarian stimulation characteristics, oocyte yield, or embryo quality? Journal of Ovarian Research 2014;7:116.
62. Milone M, Sosa Fernandez LM, Sosa Fernandez LV, Manigrasso M, Elmore U, De Palma GD *et al.* Does Bariatric Surgery Improve Assisted Reproductive Technology Outcomes in Obese Infertile Women? Obesity Surgery 2017;27:2106-12.
63. Sanchez-Garrido MA, Ruiz-Pino F, Velasco I, Barroso A, Fernandois D, Heras V *et al.* Intergenerational Influence of Paternal Obesity on Metabolic and Reproductive Health Parameters of the Offspring: Male-Preferential Impact and Involvement of Kiss1-Mediated Pathways. Endocrinology 2017;159:1005-18.
64. Perng W, Oken E. Maternal obesity and associated offspring diabetes mellitus. Nature Reviews Endocrinology 2019;15:630-2.
65. Rodríguez-González GL, Reyes-Castro LA, Bautista CJ, Beltrán AA, Ibáñez CA, Vega CC *et al.* Maternal obesity accelerates rat offspring metabolic ageing in a sex-dependent manner. The Journal of Physiology 2019;597:5549-63.
66. Glenn T, Harris AL, Lindheim SR. Impact of obesity on male and female reproductive outcomes. Curr Opin Obstet Gynecol 2019;31:201-6.
67. Ethics ETFo, Law i, Dondorp W, de Wert G, Pennings G, Shenfield F *et al.* Lifestyle-related factors and access to medically assisted reproduction†. Human Reproduction 2010;25:578-83.
68. Goldman RH, Farland LV, Thomas AM, Zera CA, Ginsburg ES. The combined impact of maternal age and body mass index on cumulative live birth following in vitro fertilization. Am J Obstet Gynecol 2019;221:617.e1-.e13.
69. Evenson KR, Calhoun KC, Herring AH, Pritchard D, Wen F, Steiner AZ. Association of physical activity in the past year and immediately after in vitro fertilization on pregnancy. Fertil Steril 2014;101:1047-54.e5.
70. Karimzadeh MA, Javedani M. An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate-metformin in patients with polycystic ovary syndrome. Fertil Steril 2010;94:216-20.

71. Palomba S, Falbo A, Giallauria F, Russo T, Rocca M, Tolino A *et al.* Six weeks of structured exercise training and hypocaloric diet increases the probability of ovulation after clomiphene citrate in overweight and obese patients with polycystic ovary syndrome: a randomized controlled trial. Hum Reprod 2010;25:2783-91.
72. Palomba S, Falbo A, Valli B, Morini D, Villani MT, Nicoli A *et al.* Physical activity before IVF and ICSI cycles in infertile obese women: an observational cohort study. Reprod Biomed Online 2014;29:72-9.
73. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS, Jr. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N Engl J Med 1991;325:147-52.
74. Redman LM. Physical activity and its effects on reproduction. Reprod Biomed Online 2006;12:579-86.
75. Zhai J, Liu CX, Tian ZR, Jiang QH, Sun YP. Effects of metformin on the expression of GLUT4 in endometrium of obese women with polycystic ovary syndrome. Biol Reprod 2012;87.
76. Warren MP, Perlroth NE. The effects of intense exercise on the female reproductive system. The Journal of endocrinology 2001;170:3-11.
77. Rao M, Zeng Z, Tang L. Maternal physical activity before IVF/ICSI cycles improves clinical pregnancy rate and live birth rate: a systematic review and meta-analysis. Reprod Biol Endocrinol 2018;16:018-0328.
78. Morris SN, Missmer SA, Cramer DW, Powers RD, McShane PM, Hornstein MD. Effects of lifetime exercise on the outcome of in vitro fertilization. Obstet Gynecol 2006;108:938-45.
79. Gaskins AJ, Afeiche MC, Hauser R, Williams PL, Gillman MW, Tanrikut C *et al.* Paternal physical and sedentary activities in relation to semen quality and reproductive outcomes among couples from a fertility center. Hum Reprod 2014;29:2575-82.
80. Hajizadeh Maleki B, Tartibian B. Combined aerobic and resistance exercise training for improving reproductive function in infertile men: a randomized controlled trial. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme 2017;42:1293-306.
81. Hajizadeh Maleki B, Tartibian B. Moderate aerobic exercise training for improving reproductive function in infertile patients: A randomized controlled trial. Cytokine 2017;92:55-67.
82. Hajizadeh Maleki B, Tartibian B. Resistance exercise modulates male factor infertility through anti-inflammatory and antioxidative mechanisms in infertile men: A RCT. Life sciences 2018;203:150-60.
83. Wise LA, Cramer DW, Hornstein MD, Ashby RK, Missmer SA. Physical activity and semen quality among men attending an infertility clinic. Fertil Steril 2011;95:1025-30.
84. Huisman M, Kunst AE, Mackenbach JP. Educational inequalities in smoking among men and women aged 16 years and older in 11 European countries. Tobacco Control 2005;14:106-13.
85. Sansone A, Di Dato C, de Angelis C, Menafra D, Pozza C, Pivonello R *et al.* Smoke, alcohol and drug addiction and male fertility. Reprod Biol Endocrinol 2018;16:3.
86. Pieraccini G, Furlanetto S, Orlandini S, Bartolucci G, Giannini I, Pinzauti S *et al.* Identification and determination of mainstream and sidestream smoke components in different brands and types of cigarettes by means of solid-phase microextraction–gas chromatography–mass spectrometry. Journal of Chromatography A 2008;1180:138-50.
87. Frederiksen Y, Farver-Vestergaard I, Skovgård NG, Ingerslev HJ, Zachariae R. Efficacy of psychosocial interventions for psychological and pregnancy outcomes in infertile women and men: a systematic review and meta-analysis. BMJ Open 2015;5.
88. Zenzes MT. Smoking and reproduction: gene damage to human gametes and embryos. Hum Reprod Update 2000;6:122-31.
89. Talbot P, Riveles K. Smoking and reproduction: the oviduct as a target of cigarette smoke. Reprod Biol Endocrinol 2005;3:52.

90. Soares SR, Melo MA. Cigarette smoking and reproductive function. Curr Opin Obstet Gynecol 2008;20:281-91.
91. Dechanet C, Anahory T, Mathieu Daude JC, Quantin X, Reyftmann L, Hamamah S *et al.* Effects of cigarette smoking on reproduction. Hum Reprod Update 2011;17:76-95.
92. Penzias AS. Recurrent IVF failure: other factors. Fertil Steril 2012;97:1033-8.
93. Vanegas JC, Chavarro JE, Williams PL, Ford JB, Toth TL, Hauser R *et al.* Discrete survival model analysis of a couple's smoking pattern and outcomes of assisted reproduction. Fertility research and practice 2017;3.
94. Klonoff Cohen H, Natarajan L, Marrs R, Yee B. Effects of female and male smoking on success rates of IVF and gamete intra-Fallopian transfer. Human Reproduction 2001;16:1382-90.
95. Zhang RP, Zhao WZ, Chai BB, Wang QY, Yu CH, Wang HY *et al.* The effects of maternal cigarette smoking on pregnancy outcomes using assisted reproduction technologies: An updated meta-analysis. Journal of gynecology obstetrics and human reproduction 2018;47:461-8.
96. Lutterodt MC, Sorensen KP, Larsen KB, Skouby SO, Andersen CY, Byskov AG. The number of oogonia and somatic cells in the human female embryo and fetus in relation to whether or not exposed to maternal cigarette smoking. Hum Reprod 2009;24:2558-66.
97. Ye X, Skjaerven R, Basso O, Baird DD, Eggesbo M, Cupul Uicab LA *et al.* In utero exposure to tobacco smoke and subsequent reduced fertility in females. Hum Reprod 2010;25:2901-6.
98. Anderson RA, McIlwain L, Coutts S, Kinnell HL, Fowler PA, Childs AJ. Activation of the aryl hydrocarbon receptor by a component of cigarette smoke reduces germ cell proliferation in the human fetal ovary. Mol Hum Reprod 2014;20:42-8.
99. Fowler PA, Childs AJ, Courant F, MacKenzie A, Rhind SM, Antignac JP *et al.* In utero exposure to cigarette smoke dysregulates human fetal ovarian developmental signalling. Hum Reprod 2014;29:1471-89.
100. Benedict MD, Missmer SA, Vahratian A, Berry KF, Vitonis AF, Cramer DW *et al.* Secondhand tobacco smoke exposure is associated with increased risk of failed implantation and reduced IVF success. Hum Reprod 2011;26:2525-31.
101. Wdowiak A, Lewicka M, Plewka K, Bakalczuk G. Nicotinism and quality of embryos obtained in in-vitro fertilization programmes. AAEM Annals of Agricultural and Environmental Medicine 2013;20:82-5.
102. Li J, Wu Q, Wu XK, Zhou ZM, Fu P, Chen XH *et al.* Effect of exposure to second-hand smoke from husbands on biochemical hyperandrogenism, metabolic syndrome and conception rates in women with polycystic ovary syndrome undergoing ovulation induction. Hum Reprod 2018;33:617-25.
103. Neal MS, Hughes EG, Holloway AC, Foster WG. Sidestream smoking is equally as damaging as mainstream smoking on IVF outcomes. Human Reproduction 2005;20:2531-5.
104. Cui X, Jing X, Wu X, Wang Z, Li Q. Potential effect of smoking on semen quality through DNA damage and the downregulation of Chk1 in sperm. Molecular medicine reports 2016;14:753-61.
105. Bundhun PK, Janoo G, Bhurtu A, Teeluck AR, Soogund MZS, Pursun M *et al.* Tobacco smoking and semen quality in infertile males: a systematic review and meta-analysis. BMC public health 2019;19:36.
106. Jenkins TG, James ER, Alonso DF, Hoidal JR, Murphy PJ, Hotaling JM *et al.* Cigarette smoking significantly alters sperm DNA methylation patterns. Andrology 2017;5:1089-99.
107. Hughes EG, Lamont DA, Beecroft ML, Wilson DM, Brennan BG, Rice SC. Randomized trial of a "stage-of-change" oriented smoking cessation intervention in infertile and pregnant women. Fertil Steril 2000;74:498-503.
108. Klonoff Cohen H, Lam Kruglick P, Gonzalez C. Effects of maternal and paternal alcohol consumption on the success rates of in vitro fertilization and gamete intrafallopian transfer. Fertility and sterility 2003;79:330-9.

109. Condorelli RA, Calogero AE, Vicari E, La Vignera S. Chronic consumption of alcohol and sperm parameters: our experience and the main evidences. Andrologia 2015;47:368-79.
110. Rossi BV, Berry KF, Hornstein MD, Cramer DW, Ehrlich S, Missmer SA. Effect of Alcohol Consumption on In Vitro Fertilization. Obstetrics and gynecology 2011;117:136-42.
111. Nicolau P, Miralpeix E, Sola I, Carreras R, Checa MA. Alcohol consumption and in vitro fertilization: a review of the literature. Gynecol Endocrinol 2014;30:759-63.
112. Minguez-Alarcon L, Chavarro JE, Gaskins AJ. Caffeine, alcohol, smoking, and reproductive outcomes among couples undergoing assisted reproductive technology treatments. Fertil Steril 2018;110:587-92.
113. Al-Saleh I, El-Doush I, Grisellhi B, Coskun S. The effect of caffeine consumption on the success rate of pregnancy as well various performance parameters of in-vitro fertilization treatment. Med Sci Monit 2010;16:CR598-605.
114. Klonoff-Cohen H, Bleha J, Lam-Kruglick P. A prospective study of the effects of female and male caffeine consumption on the reproductive endpoints of IVF and gamete intra-Fallopian transfer. Human Reproduction 2002;17:1746-54.
115. Lyngso J, Kesmodel US, Bay B, Ingerslev HJ, Nybo Andersen AM, Ramlau-Hansen CH. Impact of female daily coffee consumption on successful fertility treatment: a Danish cohort study. Fertil Steril 2019;112:120-9.e2.
116. Ricci E, Viganò P, Cipriani S, Somigliana E, Chiaffarino F, Bulfoni A *et al.* Coffee and caffeine intake and male infertility: a systematic review. Nutr J 2017;16:37.
117. Choi JH, Ryan LM, Cramer DW, Hornstein MD, Missmer SA. Effects of Caffeine Consumption by Women and Men on the Outcome of In Vitro Fertilization. Journal of Caffeine Research 2011;1:29-34.
118. Machtinger R, Gaskins AJ, Mansur A, Adir M, Racowsky C, Baccarelli AA *et al.* Association between preconception maternal beverage intake and in vitro fertilization outcomes. Fertility and sterility 2017;108:1026-33.
119. Abadia L, Chiu YH, Williams PL, Toth TL, Souter I, Hauser R *et al.* The association between pre-treatment maternal alcohol and caffeine intake and outcomes of assisted reproduction in a prospectively followed cohort. Hum Reprod 2017;32:1846-54.
120. Karmon AE, Toth TL, Chiu YH, Gaskins AJ, Tanrikut C, Wright DL *et al.* Male caffeine and alcohol intake in relation to semen parameters and in vitro fertilization outcomes among fertility patients. Andrology 2017;5:354-61.
121. Parazzini F, Marchini M, Tozzi L, Mezzopane R, Fedele L. Risk factors for unexplained dyspermia in infertile men: a case-control study. Archives of andrology 1993;31:105-13.
122. Marshburn PB, Sloan CS, Hammond MG. Semen quality and association with coffee drinking, cigarette smoking, and ethanol consumption. Fertility and sterility 1989;52:162-5.
123. Oldereid NB, Rui H, Purvis K. Life styles of men in barren couples and their relationship to sperm quality. International journal of fertility 1992;37:343-9.
124. Lyngsø J, Ramlau-Hansen CH, Bay B, Ingerslev HJ, Hulman A, Kesmodel US. Association between coffee or caffeine consumption and fecundity and fertility: a systematic review and dose–response meta-analysis. Clinical Epidemiology 2017;9:699-719.
125. Karmon AE, Toth TL, Chiu YH, Gaskins AJ, Tanrikut C, Wright DL *et al.* Male caffeine and alcohol intake in relation to semen parameters and in vitro fertilization outcomes among fertility patients. Andrology 2017;5:354-61.
126. Pichini S, De Luca R, Pellegrini M, Marchei E, Rotolo MC, Spoletini R *et al.* Hair and urine testing to assess drugs of abuse consumption in couples undergoing assisted reproductive technology (ART). Forensic Sci Int 2012;218:57-61.

127. Klonoff-Cohen HS, Natarajan L, Chen RV. A prospective study of the effects of female and male marijuana use on in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT) outcomes. Am J Obstet Gynecol 2006;194:369-76.
128. Nassan FL, Arvizu M, Mínguez-Alarcón L, Gaskins AJ, Williams PL, Petrozza JC *et al.* Marijuana smoking and outcomes of infertility treatment with assisted reproductive technologies. Human Reproduction 2019;34:1818-29.
129. Kermack AJ, Calder PC, Houghton FD, Godfrey KM, Macklon NS. A randomised controlled trial of a preconceptional dietary intervention in women undergoing IVF treatment (PREPARE trial). BMC women's health 2014;14:130.
130. Ricci E, Bravi F, Noli S, Ferrari S, De Cosmi V, La Vecchia I *et al.* Mediterranean diet and the risk of poor semen quality: cross-sectional analysis of men referring to an Italian Fertility Clinic. Andrology 2019;7:156-62.
131. Karayiannis D, Kontogianni MD, Mendorou C, Douka L, Mastrominas M, Yiannakouris N. Association between adherence to the Mediterranean diet and semen quality parameters in male partners of couples attempting fertility. Hum Reprod 2017;32:215-22.
132. Xia W, Chiu YH, Williams PL, Gaskins AJ, Toth TL, Tanrikut C *et al.* Men's meat intake and treatment outcomes among couples undergoing assisted reproduction. Fertil Steril 2015;104:972-9.
133. Chiu YH, Afeiche MC, Gaskins AJ, Williams PL, Petrozza JC, Tanrikut C *et al.* Fruit and vegetable intake and their pesticide residues in relation to semen quality among men from a fertility clinic. Human Reproduction 2015;30:1342-51.
134. Afeiche MC, Bridges ND, Williams PL, Gaskins AJ, Tanrikut C, Petrozza JC *et al.* Dairy intake and semen quality among men attending a fertility clinic. Fertil Steril 2014;101:1280-7.
135. Chavarro JE, Minguez-Alarcon L, Mendiola J, Cutillas-Tolin A, Lopez-Espin JJ, Torres-Cantero AM. Trans fatty acid intake is inversely related to total sperm count in young healthy men. Hum Reprod 2014;29:429-40.
136. Attaman JA, Toth TL, Furtado J, Campos H, Hauser R, Chavarro JE. Dietary fat and semen quality among men attending a fertility clinic. Hum Reprod 2012;27:1466-74.
137. Olsen J, Ramlau-Hansen CH. Dietary fats may impact semen quantity and quality. Asian J Androl 2012;14:511-2.
138. Vujkovic M, de Vries JH, Dohle GR, Bonsel GJ, Lindemans J, Macklon NS *et al.* Associations between dietary patterns and semen quality in men undergoing IVF/ICSI treatment. Human Reproduction 2009;24:1304-12.
139. Vujkovic M, de Vries JH, Lindemans J, Macklon NS, van der Spek PJ, Steegers EA *et al.* The preconception Mediterranean dietary pattern in couples undergoing in vitro fertilization/intracytoplasmic sperm injection treatment increases the chance of pregnancy. Fertil Steril 2010;94:2096-101.
140. Braga DP, Halpern G, Figueira Rde C, Setti AS, Iaconelli A, Jr., Borges E, Jr. Food intake and social habits in male patients and its relationship to intracytoplasmic sperm injection outcomes. Fertil Steril 2012;97:53-9.
141. Mendiola J, Torres Cantero A, Vioque Js, Moreno Grau J, Ten J, Roca M *et al.* A low intake of antioxidant nutrients is associated with poor semen quality in patients attending fertility clinics. Fertility and sterility 2010;93:1128-33.
142. Mendiola J, Torres Cantero A, Moreno Grau J, Ten J, Roca M, Moreno Grau S *et al.* Food intake and its relationship with semen quality: a case-control study. Fertility and sterility 2009;91:812-8.
143. Wong W, Zielhuis G, Thomas CMG, Merkus HMWM, Steegers-Theunissen RgPM. New evidence of the influence of exogenous and endogenous factors on sperm count in man. European journal of obstetrics & gynecology and reproductive biology 2003;110:49-54.

144. Choy CM, Lam CW, Cheung LT, Briton-Jones CM, Cheung LP, Haines CJ. Infertility, blood mercury concentrations and dietary seafood consumption: a case-control study. Bjog 2002;109:1121-5.
145. Hawkes WC, Turek PJ. Effects of dietary selenium on sperm motility in healthy men. J Androl 2001;22:764-72.
146. Hunt CD, Johnson PE, Herbel J, Mullen LK. Effects of dietary zinc depletion on seminal volume and zinc loss, serum testosterone concentrations, and sperm morphology in young men. Am J Clin Nutr 1992;56:148-57.
147. Afeiche MC, Chiu YH, Gaskins AJ, Williams PL, Souter I, Wright DL *et al.* Dairy intake in relation to in vitro fertilization outcomes among women from a fertility clinic. Hum Reprod 2016;31:563-71.
148. Gaskins AJ, Chiu YH, Williams PL, Keller MG, Toth TL, Hauser R *et al.* Maternal whole grain intake and outcomes of in vitro fertilization. Fertil Steril 2016;105:1503-10.
149. Braga DP, Halpern G, Setti AS, Figueira RC, Iaconelli A, Jr., Borges E, Jr. The impact of food intake and social habits on embryo quality and the likelihood of blastocyst formation. Reprod Biomed Online 2015;31:30-8.
150. Jacobsen BK, Jaceldo-Siegl K, Knutsen SF, Fan J, Oda K, Fraser GE. Soy isoflavone intake and the likelihood of ever becoming a mother: the Adventist Health Study-2. Int J Womens Health 2014;6:377-84.
151. Jungheim ES, Frolova AI, Jiang H, Riley JK. Relationship Between Serum Polyunsaturated Fatty Acids and Pregnancy in Women Undergoing In Vitro Fertilization. The Journal of Clinical Endocrinology and Metabolism 2013;98:E1364-E8.
152. Haggarty P, McCallum H, McBain H, Andrews K, Duthie S, McNeill G *et al.* Effect of B vitamins and genetics on success of in-vitro fertilisation: prospective cohort study. Lancet (London, England) 2006;367:1513-9.
153. Kazemi A, Ramezanzadeh F, Nasr-Esfahani MH, Saboor Yaraghi AA, Ahmadi M. Does dietary fat intake influence oocyte competence and embryo quality by inducing oxidative stress in follicular fluid? Iran J Reprod Med 2013;11:1005-12.
154. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. A prospective study of dietary carbohydrate quantity and quality in relation to risk of ovulatory infertility. Eur J Clin Nutr 2009;63:78-86.
155. Toledo E, Lopez-del Burgo C, Ruiz-Zambrana A, Donazar M, Navarro-Blasco I, Martinez-Gonzalez MA *et al.* Dietary patterns and difficulty conceiving: a nested case-control study. Fertil Steril 2011;96:1149-53.
156. Hammiche F, Vujkovic M, Wijburg W, de Vries JH, Macklon NS, Laven JS *et al.* Increased preconception omega-3 polyunsaturated fatty acid intake improves embryo morphology. Fertil Steril 2011;95:1820-3.
157. Chavarro J, Rich Edwards J, Rosner B, Willett W. Dietary fatty acid intakes and the risk of ovulatory infertility. The American journal of clinical nutrition 2007;85:231-7.
158. Chavarro JE, Rich-Edwards JW, Rosner B, Willett WC. A prospective study of dairy foods intake and anovulatory infertility. Human Reproduction 2007;22:1340-7.
159. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Dietary fatty acid intakes and the risk of ovulatory infertility. Am J Clin Nutr 2007;85:231-7.
160. Chavarro J, Rich Edwards J, Rosner B, Willett W. Protein intake and ovulatory infertility. American journal of obstetrics and gynecology 2008;198:210-7.
161. Twigt JM, Bolhuis MEC, Steegers EAP, Hammiche F, van Inzen WG, Laven JSE *et al.* The preconception diet is associated with the chance of ongoing pregnancy in women undergoing IVF/ICSI treatment. Human Reproduction 2012;27:2526-31.
162. Ruder E, Hartman T, Reindollar R, Goldman M. Female dietary antioxidant intake and time to pregnancy among couples treated for unexplained infertility. Fertility and sterility 2014;101:759-66.

163. Vujkovic M, de Vries JH, Lindemans J, Macklon NS, van der Spek PJ, Steegers EAP *et al.* The preconception Mediterranean dietary pattern in couples undergoing in vitro fertilization/intracytoplasmic sperm injection treatment increases the chance of pregnancy. Fertility and sterility 2010;94:2096-101.
164. Karayiannis D, Kontogianni MD, Mendorou C, Mastrominas M, Yiannakouris N. Adherence to the Mediterranean diet and IVF success rate among non-obese women attempting fertility. Hum Reprod 2018;33:494-502.
165. van Dijk MR, Oostingh EC, Koster MPH, Willemsen SP, Laven JSE, Steegers-Theunissen RPM. The use of the mHealth program Smarter Pregnancy in preconception care: rationale, study design and data collection of a randomized controlled trial. BMC Pregnancy and Childbirth 2017;17:46.
166. Suliga E, Gluszek S. The relationship between diet, energy balance and fertility in men. International journal for vitamin and nutrition research Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung Journal international de vitaminologie et de nutrition 2019:1-13.
167. Dressler N, Chandra A, Aguirre Dávila L, Spineli LM, Schippert C, von Versen-Höynck F. BMI and season are associated with vitamin D deficiency in women with impaired fertility: a two-centre analysis. Archives of gynecology and obstetrics 2015:1-8.
168. Pacis MM, Fortin CN, Zarek SM, Mumford SL, Segars JH. Vitamin D and assisted reproduction: should vitamin D be routinely screened and repleted prior to ART? A systematic review. Journal of assisted reproduction and genetics 2015;32:323-35.
169. Ozkan S, Jindal S, Greenseid K, Shu J, Zeitlian G, Hickmon C *et al.* Replete vitamin D stores predict reproductive success following in vitro fertilization. Fertility and sterility 2010;94:1314-9.
170. Chu J, Gallos I, Tobias A, Tan B, Eapen A, Coomarasamy A. Vitamin D and assisted reproductive treatment outcome: a systematic review and meta-analysis. Hum Reprod 2018;33:65-80.
171. Zhao J, Huang X, Xu B, Yan Y, Zhang Q, Li Y. Whether vitamin D was associated with clinical outcome after IVF/ICSI: a systematic review and meta-analysis. Reproductive Biology and Endocrinology 2018;16:13.
172. Boisen IM, Bøllehuus Hansen L, Mortensen LJ, Lanske B, Juul A, Blomberg Jensen M. Possible influence of vitamin D on male reproduction. The Journal of Steroid Biochemistry and Molecular Biology 2017;173:215-22.
173. de Angelis C, Galdiero M, Pivonello C, Garifalos F, Menafra D, Cariati F *et al.* The role of vitamin D in male fertility: A focus on the testis. Reviews in endocrine & metabolic disorders 2017;18:285-305.
174. Blomberg Jensen M, Lawaetz JG, Petersen JH, Juul A, Jorgensen N. Effects of Vitamin D Supplementation on Semen Quality, Reproductive Hormones, and Live Birth Rate: A Randomized Clinical Trial. J Clin Endocrinol Metab 2018;103:870-81.
175. Ota K, Dambaeva S, Han AR, Beaman K, Gilman-Sachs A, Kwak-Kim J. Vitamin D deficiency may be a risk factor for recurrent pregnancy losses by increasing cellular immunity and autoimmunity. Hum Reprod 2014;29:208-19.
176. Khalessi N, Kalani M, Araghi M, Farahani Z. The Relationship between Maternal Vitamin D Deficiency and Low Birth Weight Neonates. J Family Reprod Health 2015;9:113-7.
177. Miliku K, Vinkhuyzen A, Blanken LM, McGrath JJ, Eyles DW, Burne TH *et al.* Maternal vitamin D concentrations during pregnancy, fetal growth patterns, and risks of adverse birth outcomes. Am J Clin Nutr 2016;103:1514-22.
178. Baker BC, Hayes D, Jones RL. Effects of micronutrients on placental function: evidence from clinical studies to animal models. Reproduction 2018;29:18-0130.
179. Dovnik A, Mujezinovic F. The Association of Vitamin D Levels with Common Pregnancy Complications. Nutrients 2018;10.

180. Agarwal A, Durairajanayagam D, du Plessis SS. Utility of antioxidants during assisted reproductive techniques: an evidence based review. Reproductive Biology and Endocrinology : RB&E 2014;12:112.
181. Showell MG, Mackenzie-Proctor R, Jordan V, Hart RJ. Antioxidants for female subfertility. Cochrane Database Syst Rev 2017;7:Cd007807.
182. Youssef MAFM, Abdelmoty HI, Elashmwi HA, Abduljawad EM, Elghamary N, Magdy A *et al.* Oral antioxidants supplementation for women with unexplained infertility undergoing ICSI/IVF: Randomized controlled trial. Human fertility 2015;18:38-42.
183. Fatemi F, Mohammadzadeh A, Sadeghi MR, Akhondi MM, Mohammadmoradi S, Kamali K *et al.* Role of vitamin E and D3 supplementation in Intra-Cytoplasmic Sperm Injection outcomes of women with polycystic ovarian syndrome: A double blinded randomized placebo-controlled trial. Clin Nutr ESPEN 2017;18:23-30.
184. Arhin SK, Zhao Y, Lu X, Chetry M, Lu J. Effect of micronutrient supplementation on IVF outcomes: a systematic review of the literature. Reproductive biomedicine online 2017;35:715-22.
185. Zhou X, Liu F, Zhai S. Effect of L-carnitine and/or L-acetyl-carnitine in nutrition treatment for male infertility: a systematic review. Asia Pacific journal of clinical nutrition 2007;16 Suppl 1:383-90.
186. Smits RM, Mackenzie-Proctor R, Yazdani A, Stankiewicz MT, Jordan V, Showell MG. Antioxidants for male subfertility. Cochrane Database Syst Rev 2019;3:Cd007411.
187. Bentov Y, Hannam T, Jurisicova A, Esfandiari N, Casper R. Coenzyme Q10 Supplementation and Oocyte Aneuploidy in Women Undergoing IVF-ICSI Treatment. Clinical Medicine Insights: Reproductive Health 2014;8:31-6.
188. El Refaeey A, Selem A, Badawy A. Combined coenzyme Q10 and clomiphene citrate for ovulation induction in clomiphene-citrate-resistant polycystic ovary syndrome. Reprod Biomed Online 2014;29:119-24.
189. Xu Y, Nisenblat V, Lu C, Li R, Qiao J, Zhen X *et al.* Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. Reproductive Biology and Endocrinology : RB&E 2018;16:29.
190. Nadjarzadeh A, Sadeghi MR, Amirjannati N, Vafa MR, Motevalian SA, Gohari MR *et al.* Coenzyme Q10 improves seminal oxidative defense but does not affect on semen parameters in idiopathic oligoasthenoteratozoospermia: a randomized double-blind, placebo controlled trial. J Endocrinol Invest 2011;34:e224-8.
191. Nadjarzadeh A, Shidfar F, Amirjannati N, Vafa MR, Motevalian SA, Gohari MR *et al.* Effect of Coenzyme Q10 supplementation on antioxidant enzymes activity and oxidative stress of seminal plasma: a double-blind randomised clinical trial. Andrologia 2014;46:177-83.
192. Balercia G, Buldreghini E, Vignini A, Tiano L, Paggi F, Amoroso S *et al.* Coenzyme Q10 treatment in infertile men with idiopathic asthenozoospermia: a placebo-controlled, double-blind randomized trial. Fertility and sterility 2009;91:1785-92.
193. Safarinejad MR, Safarinejad S, Shafiei N. Effects of the reduced form of coenzyme Q10 (ubiquinol) on semen parameters in men with idiopathic infertility: a double-blind, placebo controlled, randomized study. J Urol 2012;188:526-31.
194. Safarinejad M. Efficacy of coenzyme Q10 on semen parameters, sperm function and reproductive hormones in infertile men. The Journal of urology 2009;182:237-48.
195. Lafuente R, Gonzalez-Comadran M, Sola I, Lopez G, Brassesco M, Carreras R *et al.* Coenzyme Q10 and male infertility: a meta-analysis. J Assist Reprod Genet 2013;30:1147-56.
196. Ikematsu H, Nakamura K, Harashima S, Fujii K, Fukutomi N. Safety assessment of coenzyme Q10 (Kaneka Q10) in healthy subjects: a double-blind, randomized, placebo-controlled trial. Regul Toxicol Pharmacol 2006;44:212-8.

197. Miner SA, Robins S, Zhu YJ, Keeren K, Gu V, Read SC *et al.* Evidence for the use of complementary and alternative medicines during fertility treatment: a scoping review. BMC Complement Altern Med 2018;18:158.
198. El-Toukhy T, Khalaf Y. A new study of acupuncture in IVF: pointing in the right direction. Reprod Biomed Online 2010;21:278-9.
199. Meldrum DR, Fisher AR, Butts SF, Su HI, Sammel MD. Acupuncture--help, harm, or placebo? Fertil Steril 2013;99:1821-4.
200. Zheng CH, Huang GY, Zhang MM, Wang W. Effects of acupuncture on pregnancy rates in women undergoing in vitro fertilization: a systematic review and meta-analysis. Fertil Steril 2012;97:599-611.
201. Cheong YC, Dix S, Hung Yu Ng E, Ledger WL, Farquhar C. Acupuncture and assisted reproductive technology. Cochrane Database of Systematic Reviews 2013.
202. Qian Y, Xia XR, Ochin H, Huang C, Gao C, Gao L *et al.* Therapeutic effect of acupuncture on the outcomes of in vitro fertilization: a systematic review and meta-analysis. Arch Gynecol Obstet 2017;295:543-58.
203. Schwarze JE, Ceroni JP, Ortega-Hrepich C, Villa S, Crosby J, Pommer R. Does acupuncture the day of embryo transfer affect the clinical pregnancy rate? Systematic review and meta-analysis. JBRA Assist Reprod 2018;22:363-8.
204. Kwan I, Bhattacharya S, Knox F, McNeil A. Pain relief for women undergoing oocyte retrieval for assisted reproduction. Cochrane Database Syst Rev 2013;31.
205. Jo J, Lee YJ. Effectiveness of acupuncture in women with polycystic ovarian syndrome undergoing in vitro fertilisation or intracytoplasmic sperm injection: a systematic review and meta-analysis. Acupunct Med 2017;35:162-70.
206. Smith CA, Armour M, Shewamene Z, Tan HY, Norman RJ, Johnson NP. Acupuncture performed around the time of embryo transfer: a systematic review and meta-analysis. Reprod Biomed Online 2019;38:364-79.
207. Zhang M, Huang G, Lu F, Paulus WE, Sterzik K. Influence of acupuncture on idiopathic male infertility in assisted reproductive technology. J Huazhong Univ Sci Technolog Med Sci 2002;22:228-30.
208. Dieterle S, Li C, Greb R, Bartzsch F, Hatzmann W, Huang D. A prospective randomized placebo-controlled study of the effect of acupuncture in infertile patients with severe oligoasthenozoospermia. Fertil Steril 2009;92:1340-3.
209. Cakmak YO, Akpinar IN, Ekinci G, Bekiroglu N. Point- and frequency-specific response of the testicular artery to abdominal electroacupuncture in humans. Fertil Steril 2008;90:1732-8.
210. Jerng UM, Jo JY, Lee S, Lee JM, Kwon O. The effectiveness and safety of acupuncture for poor semen quality in infertile males: a systematic review and meta-analysis. Asian J Androl 2014;16:884-91.
211. Okhowat J, Murtinger M, Schuff M, Wogatzky J, Spitzer D, Vanderzwalmen P *et al.* Massage therapy improves in vitro fertilization outcome in patients undergoing blastocyst transfer in a cryo-cycle. Altern Ther Health Med 2015;21:16-22.
212. Revelli A, La Sala GB, Gennarelli G, Scatigna L, Racca C, Massobrio M. Seasonality and human in vitro fertilization outcome. Gynecol Endocrinol 2005;21:12-7.
213. Wunder DM, Limoni C, Birkhauser MH. Lack of seasonal variations in fertilization, pregnancy and implantation rates in women undergoing IVF. Hum Reprod 2005;20:3122-9.
214. Kirshenbaum M, Ben-David A, Zilberberg E, Elkan-Miller T, Haas J, Orvieto R. Influence of seasonal variation on in vitro fertilization success. PLoS One 2018;13:e0199210-e.
215. Stolwijk AM, Reuvers MJ, Hamilton CJ, Jongbloet PH, Hollanders JM, Zielhuis GA. Seasonality in the results of in-vitro fertilization. Hum Reprod 1994;9:2300-5.
216. Braga DP, Setti A, Figueira Rde C, Iaconelli A, Jr., Borges E, Jr. Seasonal variability in the fertilization rate of women undergoing assisted reproduction treatments. Gynecol Endocrinol 2012;28:549-52.

217. Wood S, Quinn A, Troupe S, Kingsland C, Lewis-Jones I. Seasonal variation in assisted conception cycles and the influence of photoperiodism on outcome in in vitro fertilization cycles. Hum Fertil 2006;9:223-9.
218. Vandekerckhove F, Van der Veken H, Tilleman K, De Croo I, Van den Abbeel E, Gerris J *et al.* Seasons in the sun: the impact on IVF results one month later. Facts, Views & Vision in ObGyn 2016;8:75-83.
219. Rojansky N, Benshushan A, Meirsdorf S, Lewin A, Laufer N, Safran A. Seasonal variability in fertilization and embryo quality rates in women undergoing IVF. Fertil Steril 2000;74:476-81.
220. Jarrell JF, Villeneuve D, Franklin C, Bartlett S, Wrixon W, Kohut J *et al.* Contamination of human ovarian follicular fluid and serum by chlorinated organic compounds in three Canadian cities. Cmaj 1993;148:1321-7.
221. Younglai EV, Foster WG, Hughes EG, Trim K, Jarrell JF. Levels of environmental contaminants in human follicular fluid, serum, and seminal plasma of couples undergoing in vitro fertilization. Arch Environ Contam Toxicol 2002;43:121-6.
222. Al-Hussaini TK, Abdelaleem AA, Elnashar I, Shabaan OM, Mostafa R, El-Baz MAH *et al.* The effect of follicullar fluid pesticides and polychlorinated biphenyls concentrations on intracytoplasmic sperm injection (ICSI) embryological and clinical outcome. Eur J Obstet Gynecol Reprod Biol 2018;220:39-43.
223. Petro EM, Leroy JL, Covaci A, Fransen E, De Neubourg D, Dirtu AC *et al.* Endocrine-disrupting chemicals in human follicular fluid impair in vitro oocyte developmental competence. Hum Reprod 2012;27:1025-33.
224. Minguez-Alarcon L, Souter I, Chiu YH, Williams PL, Ford JB, Ye X *et al.* Urinary concentrations of cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester, a metabolite of the non-phthalate plasticizer di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH), and markers of ovarian response among women attending a fertility center. Environ Res 2016;151:595-600.
225. Johnson PI, Altshul L, Cramer DW, Missmer SA, Hauser R, Meeker JD. Serum and follicular fluid concentrations of polybrominated diphenyl ethers and in-vitro fertilization outcome. Environ Int 2012;45:9-14.
226. Minguez-Alarcon L, Messerlian C, Bellavia A, Gaskins AJ, Chiu YH, Ford JB *et al.* Urinary concentrations of bisphenol A, parabens and phthalate metabolite mixtures in relation to reproductive success among women undergoing in vitro fertilization. Environ Int 2019;126:355-62.
227. Dodge LE, Williams PL, Williams MA, Missmer SA, Souter I, Calafat AM *et al.* Associations between paternal urinary phthalate metabolite concentrations and reproductive outcomes among couples seeking fertility treatment. Reproductive toxicology 2015;58:184-93.
228. Mínguez-Alarcón L, Gaskins AJ, Chiu Y-H, Williams PL, Ehrlich S, Chavarro JE *et al.* Urinary bisphenol A concentrations and association with in vitro fertilization outcomes among women from a fertility clinic. Human Reproduction 2015;30:2120-8.
229. Mustieles V, Williams PL, Fernandez MF, Minguez-Alarcon L, Ford JB, Calafat AM *et al.* Maternal and paternal preconception exposure to bisphenols and size at birth. Hum Reprod 2018;33:1528-37.
230. Ikezuki Y, Tsutsumi O, Takai Y, Kamei Y, Taketani Y. Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. Hum Reprod 2002;17:2839-41.
231. Bloom MS, vom Saal FS, Kim D, Taylor JA, Lamb JD, Fujimoto VY. Serum unconjugated bisphenol A concentrations in men may influence embryo quality indicators during in vitro fertilization. Environmental toxicology and pharmacology 2011;32:319-23.
232. Knez J, Kranvogl R, Breznik BP, Voncina E, Vlaisavljevic V. Are urinary bisphenol A levels in men related to semen quality and embryo development after medically assisted reproduction? Fertil Steril 2014;101:215-21.e5.

233. Mok-Lin E, Ehrlich S, Williams PL, Petrozza J, Wright DL, Calafat AM *et al.* Urinary bisphenol A concentrations and ovarian response among women undergoing IVF. International journal of andrology 2010;33:385-93.
234. Ehrlich S, Williams PL, Missmer SA, Flaws JA, Ye X, Calafat AM *et al.* Urinary bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF. Human Reproduction 2012;27:3583-92.
235. Souter I, Smith KW, Dimitriadis I, Ehrlich S, Williams PL, Calafat AM *et al.* The association of bisphenol-A urinary concentrations with antral follicle counts and other measures of ovarian reserve in women undergoing infertility treatments. Reprod Toxicol 2013;42:224-31.
236. Al-Saleh I, Coskun S, El-Doush I, Billedo G, Mashhour A, Jaroudi K *et al.* Outcome of in-vitro fertilization treatment and DDT levels in serum and follicular fluid. Med Sci Monit 2009;15:BR320-33.
237. Messerlian C, Souter I, Gaskins AJ, Williams PL, Ford JB, Chiu Y-H *et al.* Urinary phthalate metabolites and ovarian reserve among women seeking infertility care. Human Reproduction 2016;31:75-83.
238. Du YY, Fang YL, Wang YX, Zeng Q, Guo N, Zhao H *et al.* Follicular fluid and urinary concentrations of phthalate metabolites among infertile women and associations with in vitro fertilization parameters. Reprod Toxicol 2016;61:142-50.
239. Hauser R, Gaskins AJ, Souter I, Smith KW, Dodge LE, Ehrlich S *et al.* Urinary Phthalate Metabolite Concentrations and Reproductive Outcomes among Women Undergoing in Vitro Fertilization: Results from the EARTH Study. Environ Health Perspect 2016;124:831-9.
240. Machtinger R, Gaskins AJ, Racowsky C, Mansur A, Adir M, Baccarelli AA *et al.* Urinary concentrations of biomarkers of phthalates and phthalate alternatives and IVF outcomes. Environ Int 2018;111:23-31.
241. Al-Saleh I, Coskun S, Al-Doush I, Al-Rajudi T, Al-Rouqi R, Abduljabbar M *et al.* Exposure to phthalates in couples undergoing in vitro fertilization treatment and its association with oxidative stress and DNA damage. Environ Res 2019;169:396-408.
242. Oliva A, Spira A, Multigner L. Contribution of environmental factors to the risk of male infertility. Human Reproduction 2001;16:1768-76.
243. Tielemans E, van Kooij R, Looman C, Burdorf A, te Velde E, Heederik D. Paternal occupational exposures and embryo implantation rates after IVF. Fertil Steril 2000;74:690-5.
244. Wdowiak A, Wdowiak E, Bojar I. Evaluation of trace metals in follicular fluid in ICSI-treated patients. Annals of agricultural and environmental medicine : AAEM 2017;25:213-8.
245. Wright DL, Afeiche MC, Ehrlich S, Smith K, Williams PL, Chavarro JE *et al.* Hair mercury concentrations and in vitro fertilization (IVF) outcomes among women from a fertility clinic. Reprod Toxicol 2015;51:125-32.
246. Bloom MS, Parsons PJ, Steuerwald AJ, Schisterman EF, Browne RW, Kim K *et al.* Toxic trace metals and human oocytes during in vitro fertilization (IVF). Reproductive toxicology 2010;29:298-305.
247. De Fleurian G, Perrin J, Ecochard R, Dantony E, Lanteaume A, Achard V *et al.* Occupational exposures obtained by questionnaire in clinical practice and their association with semen quality. J Androl 2009;30:566-79.
248. Al-Saleh I, Coskun S, Mashhour A, Shinwari N, El-Doush I, Billedo G *et al.* Exposure to heavy metals (lead, cadmium and mercury) and its effect on the outcome of in-vitro fertilization treatment. International Journal of Hygiene and Environmental Health 2008;211:560-79.
249. Zenzes MT, Krishnan S, Krishnan B, Zhang H, Casper RF. Cadmium accumulation in follicular fluid of women in in vitro fertilization-embryo transfer is higher in smokers. Fertil Steril 1995;64:599-603.
250. Jurewicz J, Dziewirska E, Radwan M, Hanke W. Air pollution from natural and anthropic sources and male fertility. Reprod Biol Endocrinol 2018;16:109.

251. Huang X, Zhang B, Wu L, Zhou Y, Li Y, Mao X *et al.* Association of Exposure to Ambient Fine Particulate Matter Constituents With Semen Quality Among Men Attending a Fertility Center in China. Environmental science & technology 2019;53:5957-65.
252. Wdowiak A, Wdowiak E, Bien A, Bojar I, Iwanowicz-Palus G, Raczkiewicz D. Air pollution and semen parameters in men seeking fertility treatment for the first time. International journal of occupational medicine and environmental health 2019;32:387-99.
253. Radwan M, Dziewirska E, Radwan P, Jakubowski L, Hanke W, Jurewicz J. Air Pollution and Human Sperm Sex Ratio. American journal of men's health 2018;12:907-12.
254. Jurewicz J, Radwan M, Sobala W, Polanska K, Radwan P, Jakubowski L *et al.* The relationship between exposure to air pollution and sperm disomy. Environ Mol Mutagen 2015;56:50-9.
255. Legro RS, Sauer MV, Mottla GL, Richter KS, Li X, Dodson WC *et al.* Effect of air quality on assisted human reproduction. Hum Reprod 2010;25:1317-24.
256. Checa Vizcaino MA, Gonzalez-Comadran M, Jacquemin B. Outdoor air pollution and human infertility: a systematic review. Fertil Steril 2016;106:897-904.
257. Choe SA, Jun YB, Lee WS, Yoon TK, Kim SY. Association between ambient air pollution and pregnancy rate in women who underwent IVF. Hum Reprod 2018;33:1071-8.
258. Conforti A, Mascia M, Cioffi G, De Angelis C, Coppola G, De Rosa P *et al.* Air pollution and female fertility: a systematic review of literature. Reproductive biology and endocrinology : RB&E 2018;16:117.
259. Perin PM, Maluf M, Czeresnia CE, Nicolosi Foltran Januario DA, Nascimento Saldiva PH. Effects of exposure to high levels of particulate air pollution during the follicular phase of the conception cycle on pregnancy outcome in couples undergoing in vitro fertilization and embryo transfer. Fertil Steril 2010;93:301-3.
260. Carre J, Gatimel N, Moreau J, Parinaud J, Leandri R. Influence of air quality on the results of in vitro fertilization attempts: A retrospective study. Eur J Obstet Gynecol Reprod Biol 2017;210:116-22.
261. Gaskins AJ, Fong KC, Abu Awad Y, Di Q, Minguez-Alarcon L, Chavarro JE *et al.* Time-Varying Exposure to Air Pollution and Outcomes of in Vitro Fertilization among Couples from a Fertility Clinic. Environ Health Perspect 2019;127:77002.
262. Quraishi SM, Lin PC, Richter KS, Hinckley MD, Yee B, Neal-Perry G *et al.* Ambient Air Pollution Exposure and Fecundability in Women Undergoing In Vitro Fertilization. Environmental epidemiology (Philadelphia, Pa) 2019;3.
263. Gaskins AJ, Hart JE, Minguez-Alarcon L, Chavarro JE, Laden F, Coull BA *et al.* Residential proximity to major roadways and traffic in relation to outcomes of in vitro fertilization. Environ Int 2018;115:239-46.
264. Nassan FL, Chavarro JE, Minguez-Alarcon L, Williams PL, Tanrikut C, Ford JB *et al.* Residential distance to major roadways and semen quality, sperm DNA integrity, chromosomal disomy, and serum reproductive hormones among men attending a fertility clinic. Int J Hyg Environ Health 2018;221:830-7.
265. Roshangar L, Hamdi BA, Khaki AA, Rad JS, Soleimani-Rad S. Effect of low-frequency electromagnetic field exposure on oocyte differentiation and follicular development. Advanced Biomedical Research 2014;3:76.
266. Fatehi D, Anjomshoa M, Mohammadi M, Seify M, Rostamzadeh A. Biological effects of cell-phone radiofrequency waves exposure on fertilization in mice; an in vivo and in vitro study. Middle East Fertility Society Journal 2018;23:148-53.
267. Kesari KK, Agarwal A, Henkel R. Radiations and male fertility. Reproductive biology and endocrinology : RB&E 2018;16:118.
268. Avendano C, Mata A, Sanchez Sarmiento CA, Doncel GF. Use of laptop computers connected to internet through Wi-Fi decreases human sperm motility and increases sperm DNA fragmentation. Fertil Steril 2012;97:39-45.e2.

269. Yildirim ME, Kaynar M, Badem H, Cavis M, Karatas OF, Cimentepe E. What is harmful for male fertility: cell phone or the wireless Internet? The Kaohsiung journal of medical sciences 2015;31:480-4.
270. Wdowiak A, Wdowiak L, Wiktor H. Evaluation of the effect of using mobile phones on male fertility. Annals of agricultural and environmental medicine:AAEM 2007;14:169-72.
271. Agarwal A, Desai NR, Makker K, Varghese A, Mouradi R, Sabanegh E *et al.* Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an in vitro pilot study. Fertil Steril 2009;92:1318-25.
272. Gutschi T, Mohamad Al-Ali B, Shamloul R, Pummer K, Trummer H. Impact of cell phone use on men's semen parameters. Andrologia 2011;43:312-6.
273. Adams JA, Galloway TS, Mondal D, Esteves SC, Mathews F. Effect of mobile telephones on sperm quality: a systematic review and meta-analysis. Environ Int 2014;70:106-12.
274. Lewis RC, Minguez-Alarcon L, Meeker JD, Williams PL, Mezei G, Ford JB *et al.* Self-reported mobile phone use and semen parameters among men from a fertility clinic. Reprod Toxicol 2017;67:42-7.
275. Bieniek KW, Riedel HH. Bacterial foci in the teeth, oral cavity, and jaw—secondary effects (remote action) of bacterial colonies with respect to bacteriospermia and subfertility in males. Andrologia 1993;25:159-62.
276. Klinger A, Hain B, Yaffe H, Schonberger O. Periodontal status of males attending an in vitro fertilization clinic. Journal of Clinical Periodontology 2011;38:542-6.
277. Tielemans E, Burdorf A, te Velde ER, Weber RF, van Kooij RJ, Veulemans H *et al.* Occupationally related exposures and reduced semen quality: a case-control study. Fertil Steril 1999;71:690-6.
278. Minguez-Alarcon L, Gaskins AJ, Chiu YH, Messerlian C, Williams PL, Ford JB *et al.* Type of underwear worn and markers of testicular function among men attending a fertility center. Hum Reprod 2018;33:1749-56.
279. Altman N, Krzywinski M. Association, correlation and causation. Nature Methods 2015;12:899-900.
280. Sommer AP, Haddad MK, Fecht H-J. It is time for a change: Petri Dishes weaken cells. Journal of Bionic Engineering 2012;9:353-7.
281. Swain JE. Optimizing the culture environment in the IVF laboratory: impact of pH and buffer capacity on gamete and embryo quality. Reprod Biomed Online 2010;21:6-16.
282. Swain JE, Smith GD. Advances in embryo culture platforms: novel approaches to improve preimplantation embryo development through modifications of the microenvironment. Hum Reprod Update 2011;17:541-57.
283. Chronopoulou E, Harper JC. IVF culture media: past, present and future. Hum Reprod Update 2015;21:39-55.
284. Rooney KL, Domar AD. The impact of lifestyle behaviors on infertility treatment outcome. Curr Opin Obstet Gynecol 2014;26:181-5.
285. de Ziegler D, Santulli P, Seroka A, Decanter C, Meldrum DR, Chapron C. In women, the reproductive harm of toxins such as tobacco smoke is reversible in 6 months: basis for the “olive tree” hypothesis. Fertility and sterility 2013;100:927-8.
286. Harper J, Magli MC, Lundin K, Barratt CL, Brison D. When and how should new technology be introduced into the IVF laboratory? Hum Reprod 2012;27:303-13.
287. Seshadri S, Oakeshott P, Nelson-Piercy C, Chappell LC. Prepregnancy care. BMJ 2012;344:e3467.:10.1136/bmj.e3467.
288. Heyes T, Long S, Mathers N. Preconception care: Practice and beliefs of primary care workers. Family Practice 2004;21:22-7.
289. Nekuei N, Nasr Esfahani MH, Kazemi A. Preconception counseling in couples undergoing fertility treatment. Int J Fertil Steril 2012;6:79-86.

290. Morgan MA, Hawks D, Zinberg S, Schulkin J. What obstetrician-gynecologists think of preconception care. Matern Child Health J 2006;10:S59-65.
291. van der Zee B, de Beaufort ID, Steegers EA, Denktas S. Perceptions of preconception counselling among women planning a pregnancy: a qualitative study. Fam Pract 2013;30:341-6.
292. Ludwig AK, Katalinic A, Steinbicker V, Diedrich K, Ludwig M. Antenatal care in singleton pregnancies after ICSI as compared to spontaneous conception: data from a prospective controlled cohort study in Germany. Hum Reprod 2006;21:713-20.
293. Ockhuijsen HD, Gamel CJ, van den Hoogen A, Macklon NS. Integrating preconceptional care into an IVF programme. J Adv Nurs 2012;68:1156-65.
294. Hvidman HW, Petersen KB, Larsen EC, Macklon KT, Pinborg A, Nyboe Andersen A. Individual fertility assessment and pro-fertility counselling; should this be offered to women and men of reproductive age? Hum Reprod 2015;30:9-15.
295. Bunting L, Boivin J. Development and preliminary validation of the fertility status awareness tool: FertiSTAT. Hum Reprod 2010;25:1722-33. doi: 10.093/humrep/deq087. Epub 2010 Apr 21.
296. Daniluk JC, Koert E. Fertility awareness online: the efficacy of a fertility education website in increasing knowledge and changing fertility beliefs. Hum Reprod 2015;30:353-63.
297. Hammiche F, Laven JS, van Mil N, de Cock M, de Vries JH, Lindemans J *et al.* Tailored preconceptional dietary and lifestyle counselling in a tertiary outpatient clinic in The Netherlands. Hum Reprod 2011;26:2432-41.
298. Mutsaerts MA, Groen H, ter Bogt NC, Bolster JH, Land JA, Bemelmans WJ *et al.* The LIFESTYLE study: costs and effects of a structured lifestyle program in overweight and obese subfertile women to reduce the need for fertility treatment and improve reproductive outcome. A randomised controlled trial. BMC Womens Health 2010;10.
299. Homan G, Litt J, Norman RJ. The FAST study: Fertility Assessment and advice Targeting lifestyle choices and behaviours: a pilot study. Human Reproduction 2012;27:2396-404.

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

Diet		
Men	**Recommendations/Conclusions**	**Evidence**
	Adopt Mediterranean-type dietary pattern	(130, 131)
	Total dairy food intake not associated with fertilization rates	(132)
	Total fruit and vegetable intake unrelated to semen quality parameters	(133)
	Poultry intake is positively associated with fertilization rates, whereas processed meat intake is negatively associated with fertilization rates among couples undergoing conventional IVF	(132)
	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	(134)
	Avoidance of trans fatty acids	(135)
	Avoidance of saturated fats and high intake of omega-3 polyunsaturated fats	(136, 137)
	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)	(138, 139)
	Cereal and fruit consumption with frequent meals and reduced intake of red meat	(140)
	Higher intake of fish but low intake of processed red meat	(134)
	High intake of carbohydrates, fiber, folate, vitamin C, and lycopene and lower intakes of proteins and total fat	(141)
	Low intake of yogurt, meat products and potatoes and high intake of lettuce, tomatoes and fruits	(142)
	High intake of fruit and vegetables	(143)
	High sea food consumption related to high blood mercury concentrations associated with infertility	(144)
	Negative effect of high diet selenium	(145)
	Negative effect of zinc deprived diet	(146)
Women		
	Dairy consumption has a favorable effect on live birth after ART in women >35 years of age	(147)
	High consumption of whole grain before fertility treatment increases the chance of live birth after IVF and has a positive effect on endometrial thickness	(148)
	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	(149)
	Avoid high intakes of isoflavone ($\geq$40 mg/day)	(150)
	Increased ω-6 to ω-3 ratios are preferable	(151)
	No association of vitamin B12 or folate with chance of pregnancy	(152)
	Avoid fat-rich diet	(153)
	Avoid high dietary glycemic load and carbohydrate intake	(154)
	Adopt Mediterranean-type dietary pattern	(139, 155)
	Increased preconception omega-3 polyunsaturated fatty acid intake	(156)
	Avoid trans-unsaturated fats	(157)
	Avoid high intake of low-fat dairy foods and prefer high-fat dairy foods	(158)

	High seafood consumption related to high blood mercury concentrations associated with infertility	(144)
	Lower intake of trans fat with greater intake of mono-unsaturated fat, lower intake of animal protein with greater vegetable protein intake, higher intake of high-fiber and low glycemic carbohydrates, greater preference for high-fat dairy products and higher non-heme iron intake	(157, 159)
	Replace animal sources of protein with vegetable sources of protein	(160)
	Adherence to recommendations of the Netherlands Nutrition Centre associated with an increased chance of ongoing pregnancy after the first IVF/ICSI treatment	(161)
	Shorter time to pregnancy was observed among women with unexplained infertility with BMI<25 with increasing vitamin C, women with BMI ≥25 with increasing b-carotene, women <35 years old with increasing b-carotene and vitamin C, and women ≥35 years old with increasing vitamin E	(162)
ART; assisted reproductive technology, BMI; body mass index, CPR; clinical pregnancy rate, ICSI; intracytoplasmic sperm injection; IR; implantation rate, IVF; in vitro fertilization		

Table 2. Evidence demonstrating an effect of various pollutants on fertility treatment outcomes

BPA	
Reduced IVF PRs during the period of highest urinary bisphenol A (BPA), phthalate metabolites and parabens	(228)
Maternal and not paternal preconception BPA exposure was inversely associated with birth weight and head circumference for subfertile couples	(229)
BPA has estrogenic action and is detected in follicular fluid and amniotic fluid	(230)
Male BPA affected sperm quality and embryo development after IVF/ICSI	(231, 232)
Affects pick estradiol concentration, the number of retrieved oocytes, oocyte quality and fertilization	(231, 233)
Associated with reduced ovarian response, fertilization rate and blastocyst formation in a dose response manner	(234)
Increased levels of urinary BPA in a cohort of women seeking fertility treatment were associated with lower antral follicular count indicating accelerated follicle loss	(235)
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	(228)
Phthalates	
Couples seeking fertility treatment are exposed to a wide range of phthalate compounds and seven compounds were isolated in >94% of urine samples	(236)
Paternal urine concentration of certain phthalates for couples undergoing IVF or IUI are associated with significantly decreased odds of implantation	(227)
Phthalates found to be associated with failed implantation	(225)
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	(237)

Phthalates detected in follicular fluid	(238)
Phthalates adversely affected ART outcomes in terms of egg collection, PR and birth rate in 256 women enrolled in the EARTH study	(239)
Impaired oocyte quality	(240)
No association between phthalates and various ART end points	(238, 240)
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	(241)
Weak association with oxidative stress in follicular fluid and DNA damage in granulosa cells	(241)
Pesticides	
DDT and its metabolites are found in more than 70% of women seeking fertility treatment in some countries	(236)
Pesticide detection in follicular fluid was adversely associated with endometrial thickness, retrieved oocytes and fertilization and embryo cleavage rate after ICSI	(222)
DDT metabolites in follicular fluid associated with fertilization failure	(221)
Pesticide exposure in infertile men confers adverse effect on sperm, post-testicular glands and endocrine profile	(242)
Decreased implantation rates with occupational exposure to organic solvents and paradoxically increased implantation rates with paternal pesticide exposure	(243)
Heavy metals	
Embryo development was influenced by the follicular fluid concentration of certain trace metals such as selenium, cadmium, zinc, lead and copper	(244)
Hair mercury correlates with fish consumption and was found to exceed the recommended reference for one third of women undergoing IVF	(245)
75% reduction in the probability for a retrieved oocyte to be in metaphase-II arrest for each microg/dl increase in blood lead concentration	(246)
Various heavy metals have been detected in follicular fluid and have been associated with impaired sperm parameters	(247)
Blood lead level, even at concentrations which are considered to be safe, negatively affected fertilization outcome although cadmium had the opposite effect	(248)
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	(248, 249)
ART; assisted reproductive technology, BPA; bisphenol A, CPR; clinical pregnancy rate, DDT; Dichlorodiphenyltrichloroethane EARTH; Environment and Reproductive Health study, ICSI; intracytoplasmic sperm injection; IVF; in vitro fertilization, LBR. Live birth rate; MEHP; monoethylhexyl phthalic acid; MEP; monoethyl phthalate	

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

Lifestyle factors	Recommendation	Proposed interventions
BMI	Couples should optimize their BMI (20-25kg/m^2)	Women: calorie restriction or aerobic exercise,

	before starting any type of fertility treatment.	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.
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.	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	Smoking cessation and avoid passive smoking.	Smoking cessation interventions should be offered as well as support to maintain results throughout treatment and pregnancy.
Alcohol	Avoid alcohol regardless of alcohol type.	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.
Caffeine	Women: up to 200 mg/day (2 average cups of coffee) Men: avoid excessive consumption - ideally < 272mg	Conflicted results on type of beverage. Limited evidence suggests avoidance of caffeinated soda, energy drinks and sugar-sweetened beverages.
Diet	Mediterranean diet pattern during fertility treatment and the preceding 6 months.	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.
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.	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.
Stress	Effort to minimize stress.	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.
Complementary medicine	Not enough evidence to support the use of complementary medicine as an adjunct during fertility treatment.	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.
Pollutants	Avoid known pollutants.	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.

ART; assisted reproductive technology, BMI; body mass index, BPA; bisphenol A, DDT; Dichlorodiphenyltrichloroethane; ICSI; intracytoplasmic sperm injection; IVF; in vitro fertilization, LBR. Live birth rate, PCOS; polycystic ovary syndrome

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.