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Diet and Fertility: A Review

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Abstract

The literature on the relation between diet and human fertility has greatly expanded over the last decade resulting in the identification of a few clear patterns. Intake of supplemental folic acid, particularly at doses higher than those recommended for the prevention of neural tube defects, has been consistently related to lower frequency of infertility, lower risk of pregnancy loss and greater success in infertility treatment. On the other hand, and despite promising evidence from animal models, vitamin D does not appear to exert an important role in human fertility in the absence of deficiency. Antioxidant supplementation does not appear to offer any benefits to women undergoing infertility treatment, but it appears to be beneficial when it is the male partner who is supplemented. However, the available evidence does not allow discerning which specific antioxidants, nor at which doses, are responsible for this benefit. Long chain omega 3 fatty acids appear to improve female fertility although it remains unclear to what extent contamination of shared food sources, such as fish with high levels of environmental toxicants, can dampen this benefit. Last, adherence to healthy diets favoring seafood, poultry, whole grains, fruits and vegetables, are related to better fertility in women and better semen quality in men. The cumulative evidence has also piled against popular hypotheses. Dairy and soy, once proposed as reproductive toxicants, have not been consistently related to poor fertility. In fact, soy and soy supplements appear to exert a beneficial effect among women undergoing infertility treatment. Similarly, as data from large, high-quality studies continues to accumulate, the evidence of a potentially deleterious effect of moderate alcohol and caffeine intake on the ability to become pregnant seems less solid than it once did. While a complete picture of the role of nutrition on fertility is far from complete, much progress has been made. The most salient gaps in the current evidence include jointly considering female and male diets, and testing the most consistent findings in randomized trials.

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Introduction

Identifying modifiable lifestyle factors, such as diet, that influence human fertility is of major clinical and public health significance. Infertility, the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse, affects 15–25% of couples in western countries.[1, 2] Impaired fecundity, which encompasses infertility and difficulty carrying a pregnancy to term, is estimated to affect twice as many couples.[3] Medical treatment for impaired fecundity is also on the rise. The use of assisted reproductive technologies (ART) in the United States has steadily increased from approximately 60,000 cycles in 1995[4] to 209,000 cycles in 2015,[5] although improvements in live birth rates per initiated cycle over the last decade have been small in comparison. Comparable data for intrauterine insemination and ovulation induction procedures are lacking but given that these procedures are even more common, it's estimated they account for 2–6 times more births than ART in the United States.[6]

The high prevalence of impaired fecundity combined with the high financial costs of and limited geographic access to infertility treatment motivate the need to identify modifiable predictors of couple fertility.[7, 8] While there is a growing acceptance that nutrition may be related to reproductive performance in both men and women,[9] there is still no official guidance for reproductive-aged couples. The purpose of this review is to summarize the epidemiologic literature on nutrition and fertility and offer practical dietary recommendations based on the best available evidence. Highlights and gaps in the literature are summarized in Table 1 for female diet and Table 2 for male diet.

Micronutrients

Antioxidants

A 2013 Cochrane review of randomized controlled trials (RCTs) of antioxidant supplementation during the course of infertility treatment concluded that the current evidence does not show benefits of antioxidant supplementation for increasing pregnancy or live birth rates.[10] The authors pointed out many deficiencies of the available evidence including high risk of bias, incomplete reporting, and high variability of the interventions tested in the trials.[10] For example, the trials included in the meta-analysis testing the effect of "antioxidants" against placebo included interventions as dissimilar as multiple micronutrient blends (including proprietary blends with undisclosed ingredients), pentoxifyline, *N*-acetyl-cysteine, melatonin, L-arginine, vitamin E, myo-inositol, vitamin C, vitamin D+calcium and omega-3 polyunsaturated fatty acids, many of which are not even technically antioxidants. Furthermore, no two trials included in the meta-analysis tested the same intervention (i.e. same compound at same dose against same comparator) making it nearly impossible to draw strong conclusions from this systematic review other than the

need of more high quality trials large enough to test effects on clinically relevant outcomes such as live birth rates.

B Vitamins

More promising nutrients in the context of beneficial effects on fertility might possibly be folate (or folic acid) and vitamin B12. While the impact of folate deficiency and defects in folate and homocysteine metabolism on neural tube defects (NTDs) are established,[11] the evidence on the effects of folate on fertility is less clear. One of the first studies supporting a link between folate and fertility was the Hungarian NTDs RCT which showed that of the women randomized to the pre-conception multivitamin supplement (containing 800 μg of folic acid) 71.3% conceived compared 67.9% of the women randomized to the placebo-like trace element supplement during a 14-month follow-up period.[12] Similarly, in a small RCT, of the subfertile women who took a multivitamin (containing 400 μg of folic acid) for 3 months, 26% had a pregnancy compared to 10% of women in the placebo group.[13] Among women participating in the Nurses' Health Study II (NHS-II) cohort, women who consumed ≥6 multivitamin tablets per week had a 41% (95% CI 25, 54%) lower risk of ovulatory infertility compared to non-consumers with folic acid appearing to explain most of this association.[14] Moreover, it was estimated that 20% (95% CI 11, 28%) of the ovulatory infertility cases could be avoided if women consumed 3 or more multivitamins per week. Consistent with this finding, folate intake was related to a lower frequency of sporadic anovulation in a prospective cohort of young healthy women (adjusted odds ratio=0.36 [95% CI 0.14, 0.92] comparing women in highest to lowest tertile of folic acid).[15] Most recently, folic acid supplement use was also associated with shorter time to pregnancy among a large cohort of Danish pregnancy planners (adjusted fecundability ratio=1.15 [95% CI 1.06, 1.25]).[16]

Studies from infertility cohorts also suggest that folate could have beneficial effects on fertility. For instance, carriers of the T allele in position 677 of the MTHFR gene (which leads to lower enzyme activity) had decreased ovarian responsiveness to follicle-stimulating hormone, fewer oocytes retrieved,[17] and granulosa cells that produced less estradiol (basal and stimulated) compared to wild type allele carriers.[18] A Polish *in vitro* fertilization (IVF) cohort study also found that women who received a folic acid supplement prior to treatment had better quality oocytes and a higher degree of mature oocytes compared to women who did not receive folic acid.[19] Similarly, among a cohort of US women undergoing IVF, with nearly universal compliance to preconception folic acid supplement use guidelines and no evidence of folate or B12 deficiency, the probability of live birth was 20% (8, 31%) higher among women consuming >800 μg/day of supplemental compared to women consuming <400 μg/day. Similarly, in this same cohort, women in the highest quartile of serum folate and vitamin B12 levels had 1.62 (95% CI 0.99, 2.65) and 2.04 (95% CI 1.14, 3.62) times the probability of live birth compared to women in the lowest quartiles.[20, 21] While three other cohort studies of folate and clinical outcomes of IVF from European populations did not show this benefit,[22–24] they excluded women failing prior to embryo transfer, which could have systematically biased their findings towards the null if folate does indeed prevent early failures prior to embryo transfer, as suggested by findings from the US cohort[20] and Dutch studies relating markers of folate and B12 status with greater day 3 embryo quality.[25,26]

Nevertheless, there has been plenty of controversy surrounding the evidence on folate and pregnancy maintenance. Only a couple years after the Hungarian RCT findings were published on the beneficial effects of a multivitamin supplement on likelihood of conception, the full report on all pregnancy outcomes was released which suggested that pre-conception folic acid use increased the risk of fetal death (RR=1.16 [95% CI 1.01, 1.30]).[27] This was further supported by a re-analysis of the UK Medical Research Council study (RR=1.15, p-value=0.18) and an observational cohort study in California (RR=1.14 [95% CI 0.96, 1.35]) which also found similar increased risks (albeit not statistically significant).[28, 29] These results were later challenged due to methodological errors[30, 31] and a subsequent trial from India did not replicate these findings (RR=0.44).[32] Thus, the most recent Cochrane review concluded that there was no evidence across three randomized and quasi-randomized trials of any difference in the risk of total fetal loss (RR=1.00 [95% CI 0.75, 1.34]), early or late miscarriage (RR=0.99 [95% CI 0.72, 1.38]), or stillbirth (RR=1.03 [95% CI 0.51, 2.09]) comparing women supplemented with folic acid compared to none.[33] Results from observational folic-acid intervention studies in China (RR= 0.97 [95% CI 0.84, 1.12])[34] and Brazil (RR=0.80, p-value=0.49)[35] have also since provided strong evidence that periconceptional folic acid use did not increase miscarriage rates. Moreover, three recent cohort studies have shown that the use of folic acid prior to or during early pregnancy is, in fact, associated with a reduced risk of miscarriage (aOR=0.43 [95% CI 0.30, 0.60] and aOR=0.37 [95% CI 0.19, 0.72] for folic acid or vitamin use during pregnancy versus none; aRR=0.80 [95% CI 0.71, 0.90] for >730 μg/day of supplemental folate vs none),[36–38] and an additional prospective cohort found that increased adherence to preconception multivitamin supplements (one of the main sources of folic acid in the US population) was also related to a lower risk of miscarriage (aHR=0.45 [95% CI 0.25, 0.80]).[39]

The vast literature on folate and fertility endpoints suggests that higher intake of preconception supplemental folate may increase a woman's chances of becoming pregnant and, possibly, to carry a pregnancy to term. Interestingly, in several of these studies, beneficial effects of folate on fertility and fecundity were observed at levels well above those that are currently recommended for the prevention of NTDs.

Vitamin D

Over the last decade, the potential effects of vitamin D on fertility have been of great research interest as *in vitro* studies found that the vitamin D receptor is expressed in the ovary,[40, 41] the endometrium,[40] and the placenta.[42] Animal studies have also pointed to a possible role of vitamin D in fertility as female rodents fed a vitamin D deficient diets and female rodents with knockouts for *VDR* and *1α-hydroxylase* (which catalyses the hydroxylation of 25(OH)D into the biologically active $1,25(OH)_2D$) were shown to have reduced fertility[43, 44] as a result of uterine hypoplasia, impaired follicular development and anovulation.[45–47]

Among women trying to get pregnant in the NHS-II cohort, higher intake of vitamin D (as estimated through a food frequency questionnaire) was not associated with risk of ovulatory infertility after multivariable adjustment. Similarly, among a large cohort of women with 1–2 prior pregnancy losses and no history of infertility, there were no associations between

baseline serum vitamin D levels or vitamin D deficiency (<20 ng/mL) and fecundability.[48] A cohort study among 153 Danish pregnancy planners also found no associations between pre-conception plasma 25-hydroxyvitamin D concentrations and chances of conceiving or overall risk of miscarriage; however, women who had a miscarriage after gestational week 10 had lower first trimester plasma vitamin D concentrations compared with those who did not have a miscarriage.[49] These findings should be interpreted with caution though as it was only based on a small number of cases (n=3) and three other studies found no associations between early pregnancy concentrations of serum 25(OH)D and risk of miscarriage.[50–52] Similarly, a recently published meta-analysis found no association between vitamin D insufficiency and risk of spontaneous abortion (RR=1.04 [95% CI 0.95, 1.13]).[53] Finally, one case-control study, compared early pregnancy levels of vitamin D between women who took 12–24 months to get pregnant compared to age-matched women conceiving in less than 1 year and found no associations.[54]

Despite the limited studies on vitamin D and fertility from the general population, there has been explosion in the number of studies over the past 7 years exploring this association among subfertile women undergoing medical treatment. The first study on vitamin D and fertility after IVF reported that pregnancy rates were almost four fold higher in women who were vitamin D sufficient compared to those who were vitamin D deficient.[55] While a handful of subsequent studies have yielded similar, positive findings,[56–59] a similar number of studies have found no associations[60–64] and one study even observed a negative association.[65] A small randomized controlled trial from Iran among women with insufficient serum vitamin D levels (<30 ng/ml) undergoing a cryopreservation cycle found that vitamin D supplementation of 50,000 IU/week, for 6–8 weeks, was not associated with clinical pregnancy rates.[66] Similarly, a small RCT among PCOS women undergoing intrauterine insemination found no significant differences in pregnancy outcomes[67] despite observational evidence that higher serum vitamin D levels might predict greater reproductive success among PCOS women undergoing ovulation induction.[68] Two studies have investigated the association between vitamin D levels and IVF outcomes among egg donor recipients and while one found a significant increase in clinical pregnancy rates with increasing vitamin D levels[69], suggesting a specific effect of 25(OH)D on endometrial receptivity, the second study could not confirm this association.[70]

At present, little can be conclusively drawn from the results on vitamin D and fertility given the heterogeneity of findings. While vitamin D deficiency might possibly be detrimental to fertility, it is unclear whether higher levels of vitamin D confer additional benefit once sufficiency has been achieved.

Fatty Acids

In vitro studies have shown that fatty acids are important substrates in early reproductive events including oocyte maturation[71] and embryo implantation.[72] Moreover, animal and human studies suggest that polyunsaturated fatty acids (PUFAs) may specifically impact fertility, through effects on oocyte quality and embryo implantation[73, 74] while trans fatty acids may promote greater insulin resistance [75] which could adversely affect ovulatory function.[76]

Results from the NHS-II cohort demonstrated that *trans* fatty acids (TFA) intake was associated with a greater risk of self-reported ovulatory infertility after adjustment for potential confounders (aRR=1.73 [95% CI: 1.09, 2.73] for a 2% increase in energy from TFA);[77] however intakes of saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), total PUFAs, omega 3 PUFAs, and omega 6 PUFAS were not associated with ovulatory infertility. Among two prospective time to pregnancy studies, women in the highest quartile of TFA intake had reduced fecundability in the North American cohort (FR=0.86 [95% CI: 0.71, 1.04]) but not the Danish cohort (FR=1.04 [95% CI: 0.86, 1.25]), although intake in Denmark was low.[78] Additionally, in the North America cohort, women in the lowest quartile of omega-3 PUFA intake had lower fecundability than women in the other quartiles (FR=1.19 [95% CI 1.02, 1.39]) while no association was found in Denmark, where low intake was rare.[78] Docosapentaenoic acid (DPA), an omega 3 PUFA that is structurally similar to eicosapentaenoic acid (EPA), was associated with reduced risk of anovulation in a cohort of healthy, regularly menstruating women (aRR=0.42 [95% CI 0.18, 0.95] for tertile 3 vs. tertile 1), with similar inverse trends for the other long-chain omega 3 fatty acids.[79]

Among 46 overweight and obese women undergoing IVF in Australia, intake of PUFAs, specifically omega-6 PUFAs and linoleic acid (LA) and possibly omega-3 PUFA, was higher among women who achieved pregnancy;[80] however there were no differences in fat intake comparing women who did and did not have live births. Two studies from the US and one from Iran have investigated the association between serum fatty acids concentrations and outcomes of IVF. The first US cohort found that women with lower serum α-linolenic (ALA) had a higher chance of pregnancy while the second found that only an increased LA to ALA ratio was associated with a higher chance of pregnancy.[81] A cohort study among 105 women underdoing intracytoplasmic sperm injection (ICSI) in Iran found that serum levels of EPA were significantly higher in women who achieved pregnancy compared to those who did not.[82]

While synthesizing these results is difficult given the large differences across studies in terms of populations and assessment of fatty acid status, the conclusions overall appear to suggest that higher intake of PUFAs, specifically long chain omega 3 fatty acids, and lower intake of trans fatty acids may be beneficial for enhancing female fertility.

Dairy

Dairy foods have been suggested as potential reproductive toxicants due to their high content of galactose, which in mice was shown to decrease ovulation and lead to premature ovarian failure, [83, 84] and their potential to contain high amounts of environmental estrogens.[85] In 1994 an ecological study among 31 countries was published showing that the decline in fertility with age is steeper among populations with higher per capita milk consumption.[86] However, a subsequent case-control study found that women consuming three or more glasses of milk per day had a 70% lower risk of infertility than women who did not consume milk.[87] In NHS-II, the largest prospective cohort to date, no relation was found between total intake of dairy foods and risk of ovulatory infertility (aRR=1.12 [95% CI 0.69,1.82] comparing ≥4 vs. <1 serving per day) yet this overall null finding was due to the fact that

full-fat dairy foods were associated with lower risk of ovulatory infertility (aRR=0.73 [95% CI 0.52, 1.01] comparing ≥1 serving per day vs. ≤1 servings per week) while low-fat dairy foods were associated with higher risk of ovulatory infertility (aRR=1.85 [95% CI 1.24, 2.77] comparing ≥2 servings per day vs. ≤1 servings per week).[88] A prospective cohort of women undergoing assisted reproduction in the US found that among women ≥35 years of age, those in the highest quartile of pre-treatment dairy food intake had a multivariable-adjusted probability of live birth of 55% (95% CI 39, 69%) compared to 23% (95% CI 11, 42%) among women in the lowest quartile.[89] And while this relationship was only present among older women, the association did not differ between full-fat and low-fat dairy foods.[89] Finally, in the most recent study on pre-conception dairy intake and time to pregnancy, associations between dairy intake and fecundity were small and inconsistent between the Danish and American cohorts (pooled FR=1.11 [95% CI: 0.94, 1.31] comparing ≥18 vs. <7 servings per week).[90] Taken together, given the conflicting findings, no strong conclusions regarding the effect of maternal dairy intake on fertility can be made although the evidence supporting dairy as a potential reproductive toxicant (similar to animal studies) is weak.

Meats, fish and soy

Intake of protein sources have received attention in the context of fertility mostly due to their potential to contain high levels of environmental contaminants, which could adversely affect reproductive health. While red meats can be good sources of protein and other essential nutrients, they also contain high levels of saturated fat and can serve as a vehicles for exposure to hormonal residues, antibiotics, and polybrominated diphenyl ethers.[91, 92] Similarly, while seafood is recognized good source of long chain omega 3 fatty acids, it can also be a primary route of exposure to organochlorines, dioxins, and mercury.[93] Moreover, while soy-based products are generally healthy alternatives to animal proteins in terms of cardiovascular and metabolic benefits, some have raised concerns regarding the potential adverse reproductive consequences of soy phyotoestrogens.[94]

Among women from the NHS-II cohort, one additional serving of meat (red meats, chicken, turkey, processed meats and fish) per day, while holding calories constant, was associated with a 32% (95% CI 8, 62%) increase in the risk of ovulatory infertility.[95] Similarly, among women from an infertility cohort, consumption of red meat prior to IVF had a negative influence on embryo development and the likelihood of clinical pregnancy; however, higher fish intake was associated with higher likelihood of blastocyst formation.[96] A case-control study from Hong Kong found that infertile females with unexplained infertility had higher blood mercury concentrations compared to their fertile counterparts.[97] Moreover, higher seafood consumption was associated with elevated blood mercury concentrations in this population. A retrospective time to pregnancy study among pregnant Canadian women found that women with higher mercury concentrations in blood (>1.2 μg/L) or hair (>0.24 ppm) had lower fecundability (FOR=0.22 [95% CI 0.07, 0.72]).[98] A subsequent prospective cohort study of women undergoing IVF in the US, however, did not find any associations between hair mercury levels and any of the intermediate or clinical IVF endpoints.[99] A retrospective cohort study comparing two groups of Swedish women differentially exposed to fatty fish contaminated with persistent organochlorine compounds found no association with time to pregnancy; however, within each group, the consumption of locally caught fatty

fish appeared to have a protective, rather than hazardous, effect on time to pregnancy (success odds ratio=1.27 [95% CI 0.96, 1.69] and 1.36 [95% CI 0.96, 1.94] for women in the east and west coast group, respectively, comparing high to low consumers).[100] In contrast, a retrospective time to pregnancy study among women residing in counties surrounding Lakes Erie and Ontario (two bodies of water with high polychlorinated biphenyls contamination) found that maternal consumption of fish for 3–6 years compared to none was associated with reduced fecundability (conditional FR=0.75 [95% CI 0.51, 0.91)].[101]

Soy, as the main source of phytoestrogens for humans, has received a large degree of attention as a potential reproductive toxicant given well documented and dramatic deleterious reproductive effects due to intake of phytoestrogens initially described in sheep[102] and subsequently identified in other mammals.[103, 104] Evidence from human studies, while limited, has so far not shown little evidence of harm for females. Despite findings from a small study suggesting that soy supplements could improve ovulation,[105] a large cross-sectional analysis with retrospective diet assessment of women participating in the Adventist Health Study found that women with the highest intake of soy isoflavones (~25 times higher than typical intake in Western populations) were 13% (95% CI 2, 26%) more likely to have never been pregnant.[94] However, a prospective cohort study of pregnancy planners in the US found no relation between female urinary isoflavones (a biomarker of soy intake) and fecundity among couples trying to become pregnant (adjusted FORs ranged from 1.02 to 1.05 for a 1 log nmol/L increase in various urinary isoflavones).[106] Furthermore, all published studies evaluating soy intake or phytoestrogen supplements among couples undergoing infertility treatments to date have found them to be beneficial. In a prospective cohort of women undergoing IVF in the US, the odds of achieving a live birth during ART were 77% higher for women with the highest intake of soy isoflavones (mean: 12mg/d; range: 8–28mg/d) than for women who did not consume any soy products.[107] Similarly, isoflavone supplements (120mg/d of isoflavones) increased live birth rates (36.7% versus 13.6%) an RCT among couples undergoing infertility treatment with clomiphene citrate + timed intercourse.[108] Higher doses (1,500mg/d) have also been shown to increase endometrial thickness and ongoing pregnancy rates in women undergoing IUI (20.0% vs. 4.4%)[109] and clinical pregnancy rates in women undergoing IVF (39.3% vs. 20.9%).[110]

At present, there is limited evidence on the association between red or white meat intake and fertility; however the available studies both point to a potential detrimental association between higher red meat intake and higher risk of infertility and adverse embryo development. In regards to fish, the picture is more complicated as the degree of environmental contamination may potentially modify this relationship. Thus, fish from waters with a high degree of environmental pollution as well as those with a high degree of mercury should generally be avoided as the consequences of these environmental toxicants on fertility may outweigh the potential health benefits from the fish alone. Finally, intake of soy supplements and products does not appear to harm fertility as suggested by animal studies, and may in fact confer benefits as suggested by a handful of small studies from infertility cohorts.

Dietary Patterns

To date, two studies have examined the relation between pre-conception dietary patterns and risk of infertility.[111, 112] In the NHS-II, women in the highest quintile of an investigator-generated "fertility diet" score which prioritizes higher intakes of protein from vegetable sources, full-fat dairy foods, iron, the ratio of MUFAs to trans fats and more frequent use of multivitamins and lower intakes of protein from animal sources, dietary glycemic load, and low fat dairy foods had a 66% (95% CI 52, 77%) lower risk of ovulatory disorder infertility and a 27% (95% CI 5–43%) lower risk of infertility due to other causes compared to women in the lowest quintile..[111] Similarly, a nested case-control study among women in the Seguimiento Universidad de Navarra (SUN) project, found that women with the highest adherence to a Mediterranean-style diet, characterized by higher intakes of vegetables, fruit, fish, poultry, low fat dairy and olive oil, had 0.56 (95% CI 0.35–0.95) times the odds of seeking medical help for difficulty getting pregnant.[112] Two studies from *in vitro* fertilization cohorts further confirm that healthy pre-conception dietary patterns might have a positive impact on fertility.[113, 114] In two separate cohorts, it was shown that higher adherence to the Dutch dietary recommendations (characterized by high intake of whole grains, monounsaturated or polyunsaturated oils, vegetables, fruit, meat or meat replacers, and fish)[114] and higher adherence to a "Mediterranean" diet (characterized by high intake of vegetable oil, fish, legumes, and vegetables and low intake of snacks) prior to treatment was associated with increased probability of pregnancy following IVF (aOR=1.65 [95% CI 1.08, 2.52] for the Dutch dietary pattern and aOR=1.4 [95% CI: 1.0, 1.9] for the Mediterranean dietary pattern).[113] However, despite the increasing evidence suggesting that a healthy pre-conception diet might increase fecundity (or a woman's chances of becoming pregnant) results from the NHS-II cohort found no relationship between pre-pregnancy adherence to several healthy dietary patterns prior to pregnancy and risk of pregnancy loss.[115]

Alcohol and caffeine

Intakes of caffeine and alcohol are, unquestionably, the most studied dietary factors as potential disruptors of fertility with more than 30 studies on this topic to date. Results, however, are inconsistent, with multiple studies showing deleterious effects of caffeine[116–125] and alcohol,[126–132] but just as many studies showing no association[125, 126, 133–143144, 145] or even improved fertility with consumption of certain caffeinated or alcoholic beverages.[134, 139, 146] One potential explanation for these inconsistencies is the fact that most of the studies are retrospective, and thus subject to recall and other types of bias. In fact, systematic reviews on the relation between caffeine and reproductive outcomes have noted that adverse effects of caffeine on reproductive health, including fertility, are more often reported in retrospective studies and studies of low methodological quality;[147, 148] a similar situation may be at play for studies linking alcohol to decreased fertility. While concerns regarding adverse effects of maternal alcohol intake on fetal development are warranted,[149, 150] as are also concerns of increased risk of pregnancy loss with caffeine intake,[39, 151, 152] whether intake of these substances have a deleterious effect on the ability to become pregnant is questionable. In addition, the evidence among couples undergoing ART or other infertility treatments remains relatively slim.[153]

Paternal Diet

The role of paternal diet on semen quality and couple fertility has been recently examined and summarized in several systematic reviews.[154–157] Some general trends are worth brief mention. First, a Cochrane review of randomized trials of antioxidant supplementation for men in couples undergoing infertility treatment found evidence of benefit for antioxidant supplements in improving semen quality and clinical pregnancy rates.[154] Despite the evidence for benefit, the large heterogeneity of study designs in the trials included in the meta-analysis, along with the expansive definition of "antioxidants" used for the meta-analysis does not make it possible to identify individual agents, combination of agents, or doses responsible for the observed effects. Second, "healthy" dietary patterns (such as the Mediterranean diet pattern and diets characterized by higher intakes of seafood, poultry, whole grains, fruits and vegetables in non-Mediterranean countries) have been consistently associated with better semen parameters, in a wide range of studies in North America, Europe, the Middle East and East Asia. [155, 158] "Unhealthy" diets (rich in red and processed meats, potatoes, sweets and sweetened beverages) have had the opposite relation. Whether these findings can be confirmed in randomized trials remains to be determined. Third, intake of *trans* and saturated fats has consistently been related to poor semen quality;[159–162] *trans* fat intake has also been related to other markers of poor testicular function[163] – including lower testosterone and lower testicular volume – in agreement with animal models.[164–166] Last, moderate intake of alcohol and caffeine do not have a meaningful impact on semen quality.[157, 167] It is important to keep in mind that while much of the research on diet and male fertility has used clinical semen quality parameters as study outcomes, and these remain the cornerstone for the clinical evaluation of the man's contribution to a couple's fertility, they are poor predictors of fertility.[168, 169] Hence, associations with semen quality do not imply associations with fertility, and vice versa, as demonstrated by several recent studies among couples undergoing infertility treatment.[170–172]

Conclusions

The literature on the relation between diet and human fertility has greatly expanded over the last decade and led to the emergence of some clear patterns. Intake of supplemental folic acid has been consistently related to numerous markers of female fertility– from lower frequency of anovulation to higher reproductive success in the setting of ART– suggesting that the reproductive benefits of folate extend beyond the prevention of NTDs. On the other hand, despite promising evidence from animal models, vitamin D does not appear to exert an important role in human fertility in the absence of deficiency. While supplementation with antioxidants does not appear to offer any benefits to women undergoing infertility treatment, it does appears to be beneficial when the male partner is supplemented. However, the available evidence does not allow discerning which specific antioxidants, nor at which doses, are responsible for this benefit. Higher intake of long chain omega 3 fatty acids appears to improve female fertility although it remains unclear whether environmental contamination of fish, their most common food source, can dampen (or even counteract) this benefit. Last, adherence to healthy diets favoring fish, poultry, whole grains, fruits and vegetables, are related to better fertility in women and better semen quality in men. While a complete picture of the role of nutrition on fertility is far from complete, much progress has

been made. Future efforts should concentrate on solidifying emerging evidence and jointly considering female and male diets. Furthermore, to overcome the limitations inherent to observational research based on validated diet assessment tools or nutritional biomarkers, it is essential that the most consistent associations are tested in adequately powered randomized controlled trials.

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Table 1

Overview of the literature on the relation between diet and female fertility

	What is the bottom line?	**What are the gaps in the evidence?**	**I want to read more but do not have much time.**
Antioxidant supplements	Antioxidant supplements most likely do not make a difference	Too few studies have tested the exact same intervention so it is difficult to draw strong conclusions	Ref. 10
Folic acid, vitamin B12	Folic acid may increase fertility and live birth rates in ART. Doses higher than recommended for NTD prevention may offer the greatest benefit as might the additional intake of vitamin B12	No randomized trials have tested the doses related with greatest benefit in observational studies	Ref. 16 and 20 or 21
Vitamin D	Vitamin D does not have a major impact on fertility within the observed range of supplementation/adequate serum levels	Most published work has focused on women with vitamin D intakes or serum concentrations within or very close to normal range; an adverse effect of severe deficiency on fertility cannot be ruled out	Ref. 53 and 61 or 63
Dietary fats	*Trans* fatty acids (even at current intake levels in the US) are related to lower fertility while long chain omega-3 fatty acids have the opposite relation	The role of *trans* fatty acids will become an untestable hypothesis as they are phased out of the US food supply, but they may still be relevant elsewhere Trials of omega-3 fatty acid supplementation are needed	Ref 77, 78, 81, 82
Dairy	Dairy foods probably do not have an important influence on fertility	Very few studies have addressed this question	Ref 89, 90
Meats	Intake of red meats and fish with high levels of environmental contamination may be of concern	Very few studies have addressed this question	Ref 95, 96, 101
Soy, isoflavones	Soy intake does not help or hurt couples trying to conceive on their own; however, isoflavone intake may increase live birth rates in ART	Only one study to date among pregnancy planners Vast range of doses in ART studies yet all show similar effects	Ref. 106, 110
Diet patterns	“Healthy” diets have been consistently related to better fertility and higher live birth rates in ART across multiple studies. “Unhealthy” diets have consistently had the opposite relation.	Definition of healthy and unhealthy diets changes slightly from study to study. No randomized trials to date.	Ref. 111, 113
Alcohol, caffeine	Most large, well designed studies have not detected associations between higher alcohol or caffeine intake and lower fertility	Since randomized trials of alcohol/caffeine will likely be judged as unethical, there is a need for more large, high quality prospective cohort studies to clarify this issue.	Ref 144, 145, 153

Table 2

Overview of the literature on the relation between diet and male fertility

	What is the bottom line?	**What are the gaps in the evidence?**	**I want to read more but do not have much time.**
Antioxidant supplements	Supplementing men in couples undergoing ART with antioxidants may increase live birth rates	Based on the current literature, it is not possible to say, what antioxidants (or combinations) or at what doses are responsible for this benefit.	Ref 154
Diet patterns	"Healthy" diets have been consistently related to better semen quality across a wide range of populations. "Unhealthy" diets have consistently had the opposite relation	Definitions of healthy and unhealthy diets change slightly from study to study. No randomized trials to date. Effect on semen quality does not imply effect on couple fertility.	Ref 155
Dietary fats	Intake of saturated and *trans* fats has consistently been related to lower semen quality and other markers of poor testicular function.	No randomized trials to date. Effect on semen quality does not imply effect on couple fertility.	Ref 159, 161, 163
Alcohol, caffeine	Alcohol and caffeine do not have an important impact on semen quality within usual ranges of intake. The exception is alcohol intake at levels associated with liver disease.	Effect on semen quality does not imply effect on couple fertility.	Ref 157