

Diet and men's fertility: does diet affect sperm quality?

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Male contribution to a couple's fecundity is important, and identifying the dietary factors that can influence male fertility potential is of high importance. Despite this importance, there are currently no clear clinical guidelines for male patients seeking fertility treatment. In this review, we present the most up-to-date evidence about diet and male fertility in humans. We focus on the dietary factors necessary for production of healthy functioning sperm with high fertility potential. Based on this review, men may be encouraged to use antioxidant supplements and to follow dietary patterns favoring the consumption of seafood, poultry, nuts, whole grains, fruits, and vegetables. Evidence is strongest for recommending the use of antioxidant supplements to men in couples undergoing infertility treatment—although the specific antioxidants and doses remain unclear—and increasing consumption of omega-3 fatty acids from fish and nuts. (*Fertil Steril*® 2018;110:570–7. ©2018 by American Society for Reproductive Medicine.)

Key Words: Infertility, male diet/therapy, dietary supplements, vitamins/therapeutic use, semen analysis, food

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Approximately one in six couples who try to become pregnant fail to do so within a year, thus meeting the definition of infertility (1). Although male factor is identified in ~50% of couples seeking medical help with infertility (2, 3), infertility research has primarily focused on female factors. Nevertheless, three meta-analyses have documented collectively downward trends in sperm concentration and total sperm count over the past eight decades (4–6). The most recent meta-analyses, which included more than 185 studies of men without known fertility problems, found that sperm counts have declined in industrialized countries by 50%–60% from 1973 to 2011 (6). Although the underlying causes of this downward trend in semen quality are a matter of both active research and heated debate, concurrent trends in worsening diet quality

(7) and increasing obesity (8–10) could to some extent explain these trends.

Although there is strong and consistent evidence that overweight and obesity play a significant role in maintaining semen quality (10) and a couple's fertility (11), there are no clear dietary guidelines to counsel men in couples trying to become pregnant. In the present review, we aim to summarize the growing literature about the role of men's diet on fertility. Most of the literature has focused on the relationship between diet and semen quality. Although conventional semen analysis is a far from perfect fertility proxy for reproductive potential (12–17), it is considered to be the cornerstone of the male fertility evaluation (18) and does provide insight into male reproductive function. We will also consider the relation between diet and serum reproductive hormones as well as

the emerging literature on men's diet and couple-based outcomes, including measures of fecundity in studies of pregnancy planners and studies of pregnancy outcomes after the use of assisted reproductive technologies (ART). To facilitate that discussion, we will first review the literature that describes dietary factors that may directly affect semen quality as sperm mature, followed by a discussion of dietary factors that may affect spermatogenesis by altering the reproductive hormonal milieu, and close our discussion by reviewing how those findings fit into overall patterns of diet. We will then end the review by discussing the gaps in this growing literature and the implications for research and clinical practice.

DIET AND THE BUILDING BLOCKS FOR SPERM

Although there are a large number of complex steps in the transformation from spermatogonia to mature sperm, focusing on a few key changes can facilitate the discussion of how nutritional input affects this complex process. First, spermatozoa lose most of their cytoplasm before leaving the testis, and condensation of the sperm

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chromatin occurs after they progress from the caput epididymis in transit to the cauda epididymis. These processes include repeated oxidation reactions (19). The shuttle systems for removing and transferring reducing equivalents into the mitochondria are not operational during these reactions, essentially leaving sperm without intracellular defense mechanisms against oxidative damage. Only enzymatic and nonenzymatic antioxidants in seminal plasma provide cellular protection (20). At the same time, the fatty acid composition of the cell membrane changes, favoring the accumulation of long-chain polyunsaturated fatty acids (PUFAs). Although all three processes are essential for performing the sperm's function, they make sperm exceedingly susceptible to oxidative stress by simultaneously removing most of the nonspecific defense against oxidative damage (by loss of cytoplasm), concentrating the endogenous production of reactive oxygen species (ROS; by increasing concentration of mitochondria relative to cell size), and preferentially incorporating into the cell membrane a highly oxidizable substrate (PUFAs) (21, 22). Second, an adequate supply of substrates for DNA production is essential to meet the constant demands for new DNA of spermatogenesis.

Dietary Fats and Their Role in the Sperm Cell Membrane

The fatty acid composition of the sperm cell membrane is highly important for proper sperm function. The sperm cell membrane plays a critical role in key fertilization events, such as capacitation, acrosome reaction, and sperm-oocyte fusion (19). The amount of PUFAs, particularly docosahexaenoic acid (DHA), in the sperm cell membrane increases as the sperm matures (23). DHA represents 20% of the fatty acid content in mature sperm, compared with only 4% in immature germ cells (23). The relative content of DHA is higher in epididymal versus testicular sperm in mice (24). Similarly, human orchietomy specimens show that the proportion of PUFAs in cell membranes is higher in sperm recovered from the cauda than in sperm recovered from the caput epididymis (25).

The sperm cell membrane fatty acid composition is partly due to a highly specialized local metabolism. Sertoli cells express $\Delta 6$ -desaturase (the rate-limiting enzyme in the metabolism of PUFAs) and $\Delta 5$ -desaturase at levels similar to those in the liver (26). In addition, enzymes involved in the elongation of PUFAs are expressed in a very limited number of tissues, but are highly expressed in the testis (27–30). Furthermore, it has been observed that Sertoli cells can actively convert the 18- and 20-carbon PUFAs into their 22- and 24-carbon metabolites more efficiently than hepatocytes (31–33). Also in Sertoli cells, the enzymes involved in this pathway prefer the conversion of omega-3 fatty acids into 22- and 24-carbon metabolites over converting omega-6 fatty acids (31–33), explaining to some extent the high concentration of DHA in sperm. The proper functioning of this specialized machinery in the testis relies on an adequate supply of metabolic substrates obtained from diet. PUFAs can not be endogenously synthesized by humans and must therefore be obtained from consuming

nuts, seeds, and vegetable oils in the case of 18-carbon linoleic (LA) and α -linolenic acids (ALA), or seafood in the case of longer-chain omega-3 PUFAs such as eicosapentaenoic acid (EPA) and DHA.

Consuming these fatty acids or their food sources has been shown to modify the fatty acid composition of sperm and semen quality. Diets supplemented with fish oil, which is rich in EPA and DHA, increase testicular DHA concentrations in rodents (34–36) and sperm membrane DHA in humans (37). Sperm membrane DHA content has, in turn, been associated with higher sperm motility (37–43), normal morphology (37, 43), and concentration (37, 39, 42–45). Moreover, intake of these fatty acids and their food sources has been related to semen quality. In observational studies among fertility patients, higher intake of omega-3 PUFAs has been related to a greater proportion of morphologically normal sperm (46) and fish intake to total sperm count and normal sperm morphology (45). Although in a small trial ($n = 28$) among asthenospermic men, 3 months of DHA supplementation did not improve sperm motility (47), other trials are in agreement with the preponderance of the literature. A trial of long-chain omega-3 fatty acid (DHA + EPA) supplementation (1.84 g/d for 32 weeks) among 211 men with idiopathic oligoasthenoteratospermia resulted in a significant increase in total sperm count, sperm concentration, and percentages of motile and morphologically normal sperm (37). Walnuts, which contain large amounts of plant omega-3 fatty acids, have been related to higher sperm parameters. In a randomized controlled trial of young healthy men consuming a typical Western-style diet, men randomized to walnut supplementation of 75 g/d for 12 weeks had improvements in sperm vitality, motility, and morphology compared with control subjects (48). Recent studies further suggest that the benefit may extend beyond semen quality. In a prospective cohort of couples trying to become pregnant, men's fish intake was related to shorter time to pregnancy and lower risk of infertility (49).

Trans fatty acids and saturated fats, on the other hand, appear to have the effect on spermatogenesis opposite to that of PUFAs. Like PUFAs, *trans* fats—which are primarily found in commercially baked and fried foods—accumulate in the testis (50, 51), but unlike with PUFAs, sperm membrane levels and intake of these fatty acids has been consistently related to poor semen quality, particularly to lower counts (44, 46, 52, 53). In fact, nonhuman models suggest that diets supplemented with *trans* fats result not only in decreased spermatogenesis but can, in a dose-dependent manner, decrease production of testosterone, reduce testicular mass, and promote testicular degeneration (50, 54–56). Of note, the decision by the U.S. Food and Drug Administration to exclude *trans* fats from industrial origin from the list of substances Generally Regarded as Safe as of June 2018 will effectively eliminate this concern from the U.S. once the ruling is fully implemented. Saturated fats, however, will not disappear from the food supply. Given the pervasiveness of *trans* fats in the global food supply, particularly in the developing world, this will, however, remain a concern. Although evidence is thinner, two observational studies have found that saturated fat intake is

inversely related to total sperm count and concentration among fertility patients in the U.S. (46) and among healthy young men in Denmark (52).

Antioxidants as Essential Factors for Sperm Defense

As mentioned above, the combination of loss of cytoplasm, generation of ROS by the mitochondria, and preferential accumulation of a highly oxidizable substrate in its cell membrane make sperm highly susceptible to oxidative damage. This heightened susceptibility has generated enormous interest in the role of antioxidants in the management of subfertile men. Another paper in this issue of *Fertility and Sterility* (57) reviews the role of supplementing with antioxidants men and women undergoing infertility treatment. Briefly, the collective evidence of randomized trials of antioxidant supplementation among men in couples undergoing infertility treatment shows that supplementation improves semen quality, particularly motility, and may increase the probability of clinical pregnancy and live birth. Some of these effects are likely to be explained by direct scavenging of ROS by some antioxidants, including vitamin C, which is considered to be the principal antioxidant in seminal plasma, reducing ROS from a variety of sources as well as serving to recycle oxidized vitamin E (58). In addition, vitamin E directly neutralizes ROS in sperm plasma membranes (58). The effect of antioxidants may extend beyond their ability to prevent oxidation. For example, in observational studies, β -carotene intake has been associated with a lower prevalence of disomy of the sperm X chromosome (59).

One-Carbon Metabolism and Spermatogenesis

Folates and other nutrients also may play an important role in spermatogenesis by serving as either substrates or cofactors in one-carbon metabolism. Briefly, this metabolic pathway encompasses a series of related metabolic pathways where one-carbon moieties are transferred from donors to intermediate carriers and ultimately used in methylation reactions or in the synthesis of purines and thymidine which are subsequently used in DNA synthesis (60, 61). One-carbon metabolism takes place in the testes (62–64), and data suggest that genetic (65) or pharmacologic (66–68) disruption of this metabolic pathway has detrimental consequence on spermatogenesis. A meta-analysis on the association between *MTHFR* C677T and male factor infertility reported pooled odds ratios (ORs) (95% confidence interval [CIs]) for male-factor infertility of 1.39 (1.15–1.69) for TT homozygotes and 1.23 (1.08–1.41) for T allele carriers (69). In addition, a large study carried out in Korea reported an association between homozygosity for the variant G allele in *MTR* A2756G and nonobstructive azoospermia (OR 4.63 [1.40–15.31]) as well as an association between being a carrier (OR 1.75 [1.07–2.86]) or homozygous (OR 2.96 [1.51–5.82]) for the variant G allele in *MTRR* A66G and oligoasthenoteratospermia (70).

Folic acid intake affects sperm production. In a randomized trial, folic acid supplementation of 15 mg/d for 90 days led to a 53% increase in sperm concentration and a doubling

in the proportion of motile sperm (71). Likewise, in a randomized trial of folate (5 mg/d for 182 days), zinc, folate + zinc, or placebo, subfertile men assigned to the folate + zinc arm had a 74% increase in total normal sperm count compared with preintervention values and a 41% increase compared with postintervention values in the placebo arm which did not reach statistical significance (72). Neither folate and/or zinc had an effect on serum FSH, testosterone, or inhibin B concentrations (73). In a case-control study among fertility patients in Spain, men in the highest tertile of folate intake had an 87% lower odds of oligoteratospermia than men in the lowest tertile of intake (74). Similarly, two cross-sectional studies found a positive correlation between seminal plasma folate and vitamin B₁₂ and sperm concentration (75, 76). Among men who have previously fathered a pregnancy and have sperm counts $>20 \times 10^6$ /mL, seminal plasma folate is inversely related to sperm DNA fragmentation (77). Also, folate intake has been related to a lower frequency of sperm aneuploidy (59). In a study of healthy nonsmoking men, those with the highest folate intake (722–1,150 μ g/d) had a lower incidence of disomy X, sex nullisomy, disomy 21, and aggregate aneuploidy in their sperm (59). Moreover, in rodent models, folate-deficient diets result in differential sperm DNA methylation at sites associated with cancer and chronic human diseases, decreased pregnancy rates, increased postimplantation embryo loss, and increased gross anatomic abnormalities in their offspring (78).

DIET AS A VEHICLE FOR ENVIRONMENTAL TOXINS

For decades the study of potentially modifiable risk factors for infertility in general and poor semen quality in particular has been strongly influenced by and primarily focused on the identification of potential effects of environmental toxicants. Because of this, many studies have approached the study of selected dietary factors as potential vehicles for environmental chemicals. A particularly popular hypothesis has been to consider some dietary factors as sources of exogenous antiandrogenic or proestrogenic dietary exposures (from dairy, meat, and soy-derived products) that may affect spermatogenesis (79, 80).

Soy-Derived Products

Isoflavones are weakly estrogenic plant-derived polyphenolic compounds present in soybeans as well as soy-derived products (81–86) which can bind to estrogen receptors (87). In nonhuman models, isoflavones were associated with smaller testes in rats (88) and induced nongenomic adverse effects on sperm capacitation and acrosome reaction (89). However, in humans, the literature on soy or soy-derived products and male fertility is still scarce and inconsistent. For example, semen quality and reproductive hormone concentrations did not change after supplementation with 40 mg/d isoflavones for 2 months in 14 men compared with before supplementation (90). On the other hand, dietary isoflavone intake was associated with higher sperm count and motility and lower sperm DNA damage among 48 men with

abnormal semen parameters and 10 fertile control men (91). Another study showed the converse: Dietary intake of soy-derived foods was associated with lower sperm concentration among 99 men attending a fertility clinic (92). One may argue that Asian diets include high amounts of phytoestrogens from soy foods without any apparent deleterious effects on fertility. However, in a study from China assessing 609 men with idiopathic infertility and 469 fertile control men, higher urinary concentrations of isoflavones were associated with lower sperm concentration, total count, and motility and higher odds of idiopathic male infertility (93). On the other hand, men's soy intake was unrelated to the probability of live birth in couples undergoing infertility treatment with ART (94), and men's urinary isoflavone levels were unrelated to fecundity in a prospective cohort of pregnancy planners (95).

Dairy and Meat Products

Specific modern livestock production (96) and dairy farming (97) practices may induce dairy products and meat to act as vehicles for environmental estrogens. In most of the world, commercial milk is derived from pregnant cows (97, 98). Therefore, naturally occurring placental hormones such as estrogen are present in milk in measurable concentrations (99, 100) raising concerns regarding reproductive effects in consumers of milk and dairy products. In fact, it is estimated that dairy accounts for 60%–80% of dietary estrogen intake in Western countries (101). In boys, intake of milk and other dairy products has been associated with higher concentrations of prepubertal growth hormone and insulin-like growth factor 1 (IGF-1), a higher ratio of IGF-1 to insulin-like growth factor-binding protein 3 (102), increased excretion of estrone, estriol, estradiol, and pregnenediol (103), and a higher frequency of teenage acne (104). Moreover, in healthy young men, intake of dairy products has been related to lower concentrations of testosterone, FSH, and LH (103).

Literature on the relationship between dairy product intake and semen quality is inconclusive. Although some studies have suggested that dairy is a possible risk factor for poorer semen parameters (98, 104–107), other studies did not support this theory (105, 106, 108). In a case-control study comparing dietary habits of oligoasthenoteratospermic versus normospermic men attending a fertility clinic in Spain, case subjects had higher intake of full-fat dairy products (yogurt, whole milk, cheese, and semiskimmed milk) and lower intakes of skimmed milk than control subjects (105). In another case-control study of asthenozoospermic men in Iran, the odds of asthenozoospermia were marginally higher with greater intake of total dairy products and significantly lower with greater intake of skim milk (106). In a longitudinal cohort study ($n = 155$) among men attending a fertility clinic in Boston, Massachusetts, the intake of low-fat dairy products was associated with higher sperm concentration and better motility (109). In a cross-sectional study of a cohort of physically active young men, intake of full-fat dairy products, specifically cheese, was adversely related to normal sperm morphology and progressive sperm motility (107). In another cross-sectional study in men attending a fertility clinic in the

Netherlands, dairy intake was not related to semen quality (108). Although the evidence largely upholds the benefit of low-fat versus the harmful effects of full-fat dairy products, more studies, especially randomized trials, are still needed for a well supported conclusion.

In the United States and some other countries, anabolic sex steroids, including combinations of estrogen, progesterone, testosterone, and any of three synthetic hormones (zernanol, melengestrol acetate, and trenbolone acetate), are commonly administered for growth promotion 60–90 days before slaughter (96, 110). Therefore, hormonal residues are present in the meat products (110, 111), with the potential for reproductive consequences in meat and meat-product consumers (100, 112, 113). Studies are inconsistent about the relationship between meat intake and semen quality. Male offspring of U.S. women with high beef consumption during pregnancy had lower sperm concentration in adulthood (112). In a cross-sectional study, young college men in the U.S. who consumed higher amounts of processed meat had lower total sperm counts and total progressive motile counts (114). In another cross-sectional study from Spain, oligoasthenoteratospermic men had ~31% higher intake of processed red meat than control subjects but without any difference in unprocessed red meat intake between the two groups (105). Another study from Iran reported that the odds of asthenozoospermia were approximately twice as high in men in the highest intake tertile of processed red meat consumption compared with those in the lowest tertile, but red meat intake was unrelated to asthenozoospermia (106). A separate study among fertility patients in the Netherlands found that intake of meat products was unrelated to semen quality parameters (108). In a longitudinal study of men attending a fertility clinic in the U.S., processed meat intake was inversely related to sperm morphology (45). It should be pointed out that the Spanish and Dutch studies were conducted after the European Union ban on steroid hormones for beef cattle went into effect (110, 115), suggesting that the similar findings in the Spanish and U.S. studies are probably not due to hormonal residues.

Methylmercury in Fish

As discussed above, fish intake may have beneficial effects on semen quality and couple fecundity. However, contaminated fish and shellfish are the main exposure source of methylmercury, the most common organic mercury compound found in the environment (116). Both animal (117, 118) and in vitro (119, 120) studies have shown a detrimental effect of methylmercury on male reproductive health, such as impaired spermatogenesis (117), decreased sperm count and lower testicular weight (118), decreased sperm motility, and increased abnormal tail morphology (121). One possible explanation for these apparently contradictory findings is the fact that studies hardly ever consider simultaneously mercury and fish consumption in their relationship with semen parameters, probably leading to residual confounding. Few studies have addressed these issues simultaneously. In a recent study, hair mercury (the best biomarker for mercury exposure) was positively associated

with total sperm count, sperm concentration, and progressive motility in a cohort of men attending a fertility clinic. This association was attenuated after further adjustment for fish intake. Specifically, men in the highest quartile of hair mercury concentrations had 50%, 46%, and 31% higher sperm concentration, total sperm count, and progressive motility, respectively, compared with men in the lowest quartile. Among men whose fish intake was above the study population median, these associations were stronger (122). These results confirm exposure to methylmercury through fish intake and show the important role of diet while assessing the associations between heavy metals and semen parameters among men of couples seeking fertility care. Although these findings warrant further investigation, the data suggest that the beneficial effects of fish intake may outweigh the potential adverse effects that methylmercury may have on spermatogenesis.

Pesticide Residues

Fruits and vegetables are universally recommended as an essential component of a healthy diet (123). Nevertheless, they are also the main source of pesticide residues in the diet and the most important source of exposure to pesticides for most individuals in the general population (124). Fruits and vegetables with low to moderate pesticide residues, such as onions, avocados, and beans, are positively associated with semen parameters among young healthy men (125). In men attending a fertility clinic, total fruit and vegetable intake was unrelated to semen parameters, although intake of high-pesticide-residue fruits and vegetables, such as strawberries, spinach, and apples, was associated with poorer semen quality (125). On average, men in the highest quartile of high-pesticide-residue fruit and vegetable intake (≥ 1.5 servings/day) had 49% lower total sperm count and 32% lower percentage of morphologically normal sperm than men in the lowest quartile of intake (<0.5 servings/day). Low- to moderate-pesticide-residue fruit and vegetable intake was associated with a higher percentage of morphologically normal sperm (126).

DIET PATTERNS

Diet patterns have the most consistent association with semen quality. In recent reviews (127–129), a healthy dietary pattern, such as the Mediterranean pattern or patterns with high intakes of seafood, poultry, whole grains, legumes, skimmed milk, fruits, and vegetables, has been consistently associated with better semen parameters in studies in North America, Europe, the Middle East, and East Asia (106, 108, 127, 130, 131). Unhealthy dietary patterns that were high in fats, red and processed meats, refined grains, sweets and sweetened beverages were associated with poorer semen quality. Although different studies have reported improvements in one or more semen parameters that could be different from study to study, there was consistency of generally better semen quality. A more recent study in Greece reported that men who adhered more to the Mediterranean diet had lower likelihood of having abnormal sperm concentration, total sperm count, and

motility (132). Furthermore, the healthy pattern was associated with lower sperm DNA fragmentation (108). More recently, in addition to higher sperm concentrations, count, and motile sperms in men who adhered to a healthy diet pattern, this association was mainly present in men with lower total motile sperm counts of <10 million and poor semen quality (133).

Although the healthy dietary pattern is consistently associated with better semen quality, we have yet to elucidate the effect of individual food categories on men's reproduction.

CONCLUSION

Although the picture of the relationship between diet and men's fertility is far from complete, a number of broad patterns have emerged. First, increased intake of omega-3 fatty acids, either as supplements or from foods (from either nuts or fish) appears to have a positive effect on spermatogenesis. Supplementation with antioxidants and nutrients involved in the one-carbon metabolism pathway (folate, vitamin B₁₂, zinc) also appears to be beneficial. Evidence to suggest that environmental toxicants obtained through diet, including xenoestrogens from soy, dairy products, and beef, are harmful to men's reproductive potential is, at best, questionable. On the other hand, a robust body of evidence from observational studies spanning the globe has emerged suggesting that dietary patterns generally consistent with those already promoted for the prevention of heart disease and other chronic conditions may be beneficial for male fertility as well. Whether these findings hold up to scrutiny in randomized trials remains to be determined. Finally, more research is needed to understand how diet influences not only semen parameters and other proxies for male fertility, but also couple-based outcomes, including fecundity and outcomes of infertility treatments.

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