Diet and female fertility: doctor, what should I eat?

Yu-Han Chiu, M.D., Sc.D.,[a] Jorge E. Chavarro, M.D., ScD,[a,b,c] and Irene Souter, M.D.[d]

[a] Department of Nutrition and [b] Department of Epidemiology, Harvard T.H. Chan School of Public Health; [c] Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; and [d] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Harvard Medical School, Massachusetts General Hospital Fertility Center, Boston, Massachusetts

Fecundity is the capacity to produce offspring. Identifying dietary factors that influence human fecundity is of major clinical and public health significance. This review focuses on the evidence from epidemiologic literature for the relationships between key nutritional factors and female reproductive potential. According to existing data, women trying to achieve pregnancy are encouraged to increase consumption of whole grains, omega-3 fatty acids, fish, and soy and to reduce consumption of *trans* fats and red meat. In addition, a daily multivitamin that contains folic acid before and during pregnancy may not only prevent birth defects, but also improve the chance of achieving and maintaining a pregnancy. In contrast, there is limited evidence supporting an association between vitamin D and human fecundity outcomes despite promising evidence from nonhuman studies. Questions for future research included the roles of other types of fat (especially omega-6 and monounsaturated fats) and protein (especially white meat and seafood) on female fertility; particular attention should also be paid to exposure to environmental contaminants in foods. Although much work remains, this review accrued best available evidence to provide practical dietary recommendations for women trying to conceive. (Fertil Steril® 2018;110:560–9. ©2018 by American Society for Reproductive Medicine.)

Key Words: Diet, dietary patterns, micronutrients, macronutrients, female fertility

It is estimated that infertility affects 15.5% of reproductive-age women in the United States (1), and 30% of pregnancies are lost after implantation (2). Although assisted reproductive technologies (ART) become a common treatment choice, because of the financial and emotional challenges associated with ART, emerging scientific efforts focus on the identification of modifiable factors, such as diet and lifestyles, that may affect fertility. Dietary factors have been implicated in the pathology of multiple disorders (3–6), and the idea that dietary changes may boost fertility appears to be promising.

Human fecundity is difficult to assess directly. Therefore, most researchers rely on proxy measures, such as assessment of time to pregnancy (a shorter time indicating a higher fecundity) and whether a pregnancy, pregnancy loss, or live birth occurs among pregnancy planners or women undergoing ART. Other commonly used fecundity proxies include medically determined causes of infertility, reproductive hormonal profiles and menstrual irregularities (to assess ovulatory function), and ovarian antral follicle counts as well as serum levels of antimüllerian hormone (to assess ovarian reserve). In this review, we summarize the evidence from human studies relating diet to these markers of fecundity for the purpose of providing a tool to counsel patients trying to achieve pregnancy.

Received May 8, 2018; accepted May 23, 2018.
J.E.C. and I.S. should be considered similar in author order.
Y.-H.C. has nothing to disclose. J.E.C. has nothing to disclose. I.S. has nothing to disclose.
Supported by grants P30ES000002, R01ES009718, R01ES022955, and P30DK046200 from the National Institutes of Health.
Reprint requests: Irene Souter, M.D., Massachusetts General Hospital Fertility Center, Yawkey 10-A, 55 Fruit Street, Boston, MA 02114 (E-mail: isouter@partners.org).

Fertility and Sterility® Vol. 110, No. 4, September 2018 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2018.05.027

MICRONUTRIENTS

Folic Acid

Folate, involved in the synthesis of DNA (7), is crucial in gametogenesis, fertilization, and pregnancy (8, 9). Therefore, folate (natural form of vitamin B9) or folic acid (synthetic form of vitamin B9) may play an important role in human reproduction.

Folic acid and the risk for spontaneous abortion. Since the early 1990, the U.S. Public Health Service and Centers for Disease Control and Prevention have recommended that all women of childbearing age take a daily supplement containing 0.4–0.8 mg folic acid to prevent neural tube defects (10). In the mid-1990s, controversy over the safety of folic acid supplementation arose when three studies reported increased spontaneous abortion (SAB) rates among folic acid users (11–13). The validity of these findings was later challenged on methodologic grounds (14, 15), and in the most recent Cochrane review (16), on the basis of three randomized trials

(11, 17, 18), daily folic acid (0.8 mg in one study and 4 mg in two studies) plus multivitamin supplementation before and during pregnancy did not increase SAB rates among users versus nonusers. Similarly, a large population-based study in China found no increased risk for SAB among daily consumers of folic acid (19), and a Brazilian multicenter trial reported no difference in SAB rates between high and low folic acid supplementation groups (0.4 vs. 4 mg/d) (20). Interestingly, recent data from observational studies, including a large prospective cohort of healthy women in the Nurse's Healthy Study II (NHS-II), suggested a reduced SAB risk among women using folic acid before or during early pregnancy, particularly at intake levels well above those recommended for the prevention of neural tube defects (21–23).

Folic acid, fecundity, and ovulatory infertility. The associations between folic supplementation and infertility have also been examined in three prospective cohort studies, which in general suggested a protective effect. Specifically, among women from the NHS-II study, multivitamin users had approximately one-third lower risk of developing ovulatory infertility compared to nonusers, and folic acids appeared to explain most of this association (24). Similarly, folate intake was related to a lower frequency of sporadic anovulation in a prospective cohort of young healthy women (the Biocycle study) (25) and to a shorter time to pregnancy among pregnancy planners in a large Danish cohort (26).

Folic acid and ART outcomes. Studies among subfertile women generally suggest a favorable effect of folate supplementation on ART outcomes. In a small randomized controlled trial (RCT) of subfertile women, women who took a daily multivitamin (containing 0.4 mg folic acid) had 16% higher probability of pregnancy than women in the placebo group (27). In addition, in two studies, the *MTHFR* 677T allele mutation (leading to lower MTHFR enzyme activity and lower serum folate levels) was associated with poor ovarian response, fewer retrieved oocytes (28), and lower granulosa-cell E_2 production than the wild-type allele (29). Furthermore, in a prospective ART cohort in Boston (EARTH study), women consuming >0.8 mg/d folate compared with those consuming <0.4 mg/d, before conception, had a higher probability of live birth (30). In this same study, higher serum levels of folate and vitamin B_{12} measured during the stimulation phase of the cycle were associated with a higher probability of live birth (31). Nonetheless, the results from three European cohort studies of folate and ART outcomes did not show similar benefits (32–34). The latter results, however, should be interpreted with caution considering they excluded women who failed before embryo transfer. If folates affect early ART outcomes, as suggested by some studies (30, 35–37), then excluding these women could bias the results toward the null.

Summary. Overall, current evidence generally supports folic acid supplementation before and during pregnancy, because it appears that folate is not associated with higher risks of SAB but may instead improve a woman's chance of achieving and maintaining a pregnancy. Benefits seem to appear at intakes above those recommended for the prevention of neural tube defects, but trials testing these doses in relation to fertility are lacking.

Vitamin D

Accruing literature suggests that vitamin D may modulate reproductive processes. Vitamin D receptors are widely distributed across the reproductive system, including ovaries, uterus, and endometrium (38). Animal studies have shown that female rodents fed a vitamin D deficient diets, as well as knockouts for vitamin D receptors and 1α-hydroxylase (enzyme responsible for converting circulating 25-hydroxy vitamin D_3 [25(OH]D) to its biologically active form) have reduced fertility (39–43). Furthermore, vitamin D stimulates ovarian steroidogenesis, promotes follicular maturation, and regulates HOXA10 expression (involved in successful implantation) (44, 45), and its deficiency may be involved in the pathogenesis of polycystic ovary syndrome (PCOS).

Vitamin D and reproductive outcomes. Despite a promising role of vitamin D in reproduction in nonhuman animal studies, studies evaluating the relation between vitamin D and fecundity in healthy human populations generally show no strong associations. Among women participating in the NHS-II study, vitamin D intake was unrelated to anovulatory infertility (46). Similarly, vitamin D concentrations were not associated with either the overall probability of conception (among healthy Danish women) (47) or conception in less than 1 year (among Italian women undergoing routine aneuploidy screening) (48). Furthermore, a meta-analysis (49) of 10,630 pregnant women from five cohort studies (50–54) revealed no association between low 25(OH)D levels and SAB risks, although extremely low levels (<20 ng/mL) were associated with increased early SAB risk in a subgroup analysis of two studies (50, 53).

Vitamin D and ART outcomes. Results concerning a possible role of vitamin D on ART outcomes are inconsistent. In a recent meta-analysis of 11 cohort studies (five prospective [55–59] and six retrospective [60–65]) of women undergoing ART (66), Chu et al. found that women replete in vitamin D, compared with women with either deficient or insufficient vitamin D levels, had higher probability of clinical pregnancy and live birth. No association of vitamin D with probability of miscarriage was noted (66). Similarly, a post hoc analysis of an RCT in PCOS patients found that serum 25(OH)D <30 versus >30 ng/mL was associated with lower live birth rates (67). In contrast, three small observational studies, not included in this meta-analysis, found no association between serum or follicular fluid vitamin D concentrations and ART outcomes (68–70). Furthermore, findings from two small RCTs did not support the administration of vitamin D to improve pregnancy outcomes (71, 72). Neither weekly supplementation of 50,000 IU vitamin D for 6–8 weeks to deficient women (71) nor administration of megadose vitamin D (300,000 IU) to women with PCOS improved reproductive outcomes (72). In the latter, a significant increase in endometrial thickness was noted but did not translate to a significantly higher probability of pregnancy (72).

Summary. Despite there being promising mechanisms through which vitamin D can affect reproduction, evidence from epidemiologic studies remains inconclusive, though