# Female dietary antioxidant intake and time to pregnancy among couples treated for unexplained infertility

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**Objective:** To determine whether increased antioxidant intake in women is associated with shorter time to pregnancy (TTP) among a cohort of couples being treated for unexplained infertility.
**Design:** Secondary data analysis of a randomized controlled trial.
**Setting:** Academic medical center associated with a private infertility center.
**Patients:** Females with unexplained infertility.
**Interventions:** None.
**Main Outcome Measure(s):** The time it took to establish a pregnancy that led to a live birth.
**Result(s):** Mean nutrient intake exceeded the estimated average requirement (EAR) for vitamins C and E. No differences in mean intake of any of the antioxidants were noted between women who delivered a live-born infant during the study period vs. those who did not. In multivariable models, intake of $\beta$-carotene from dietary supplements was associated with shorter TTP among women with body mass index (BMI) $\geq 25$ kg/m$^2$ (hazard ratio [HR] 1.29, 95% confidence interval [CI] 1.09–1.53) and women $<35$ y (HR 1.19, 95% CI 1.01–1.41). Intake of vitamin C from dietary supplements was associated with shorter TTP among women with BMI $<25$ kg/m$^2$ (HR 1.09, 95% CI 1.03–1.15) and women $<35$ y (HR 1.10, 95% CI 1.02–1.18). Intake of vitamin E from dietary supplements among women $\geq 35$ y also was associated with shorter TTP (HR 1.07, 95% CI 1.01–1.13).
**Conclusion(s):** Shorter TTP was observed among women with BMI $<25$ kg/m$^2$ with increasing vitamin C, women with BMI $\geq 25$ kg/m$^2$ with increasing $\beta$-carotene, women $<35$ y with increasing $\beta$-carotene and vitamin C, and women $\geq 35$ y with increasing vitamin E.
**Clinical Trial Registration Number:** NCT00260091. (Fertil Steril® 2014;101:759–66. ©2014 by American Society for Reproductive Medicine.)
**Key Words:** Diet, antioxidants, oxidative stress, unexplained infertility, nutritional epidemiology

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The role of dietary antioxidant intake in conception and birth outcome is a topic of emerging interest. A growing body of evidence suggests that oxidative stress (OS) and low antioxidant status may be associated with infertility of both known and idiopathic origin (1). Lower total antioxidant status (TAS) is observed in serum of women with polycystic ovarian syndrome (a known risk factor for female infertility) and the peritoneal fluid of women with idiopathic infertility compared with fertile control women (2, 3). In vivo, antioxidants scavenge reactive oxygen species (ROS) and other radical species. Oxidative stress occurs when scavenging capacity is exceeded, either because of decreased antioxidant intake or increased antioxidant

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utilization due to excessive production of ROS. Furthermore, characteristics associated with decreased fertility, such as advanced maternal age and obesity, are also associated with increased oxidative stress (4–6).

Other than for folate, specific dietary guidance for women trying to conceive is not included as part of the Institute of Medicine's dietary reference intake (DRI) reports (7). Some, but not all, antioxidants have increased DRIs during pregnancy. For example, the maternal requirement for vitamin C is increased because of hemodilution and active transfer to the fetus (7). Certain populations, such as cigarette smokers and heavy users of alcohol, may have further increased vitamin C requirements during pregnancy as a result of increased lipid peroxidation (7). In contrast, an increased vitamin E requirement during pregnancy is not supported.

The preponderance of lay literature suggesting that dietary factors influence female fertility is based on limited scientific research that primarily investigates specific types of infertility, such as ovulatory infertility (8) or the relationship between glucose control and fertility (9, 10), although one recent investigation suggests that women's adherence to national dietary recommendations increases the chance of ongoing pregnancy in couples undergoing IVF/intracytoplasmic sperm injection treatment (11). In the present study, we explored antioxidant intake of the female partner in relation to the time it takes a couple to conceive a pregnancy that resulted in a live birth. Given that body mass index (BMI) and age affect fertility and the potential for variation in micronutrient intake among these subgroups (12, 13), we examined diet by age and diet by BMI interactions. We hypothesized that higher intakes of antioxidants $\beta$-carotene, vitamin C, and vitamin E are associated with a shorter time to conception among a cohort of couples being treated for unexplained infertility.

## MATERIALS AND METHODS

### Participants

Women participating in The Fast Track and Standard Treatment (FASTT) trial (n = 503) who reported reliable dietary information (n = 441, defined as those reporting 500–5,000 kcal/d intake) and started treatment (n = 437; 87%) were included in the present analyses. FASTT was a randomized controlled clinical trial conducted to evaluate an accelerated treatment strategy for couples with unexplained infertility that consisted of three cycles of clomiphene citrate/intrauterine insemination (CC/IUI) and up to six cycles of IVF compared with a step-wise treatment course of three cycles of CC/IUI, three cycles of gonadotropin/IUI, and up to six cycles of IVF. The study protocol was approved by the Institutional Review Boards at all participating institutions, and every study participant gave written informed consent. An independent Data and Safety Monitoring Board met annually. No conflicts of interest exist for the authors of the present investigation.

Details of the study were previously published (14). Briefly, all couples in which the woman was 21–39 years old who sought care for unexplained infertility at Boston IVF or Harvard Vanguard Medical Associates from September 14, 2001, to August 31, 2005, were screened. Eligibility criteria included 12 months of unsuccessful attempted conception; at least one ovary and ipsilateral patent fallopian tube confirmed by hysterosalpingogram or laparoscopy; no pelvic pathology, ectopic pregnancy, or previous infertility treatment (with the exception of up to three cycles of clomiphene citrate without IUI). Sufficient ovarian reserve, demonstrated by cycle day 3 FSH and $E_2$ values of $<15$ mIU/mL and $<100$ pg/mL, respectively, and a sperm concentration of $\geq 15$ million total motile sperm or $\geq 5$ million total motile sperm from the male partner at reflex IUI preparation were required. Exclusion criteria included the presence of hydrosalpinges, stage III/IV endometriosis, use of donor sperm, or the need for assisted reproductive technology procedures other than IVF. Randomization was performed with the use of permuted blocks of varying sizes, stratified by woman's age ($<35$ y vs. $\geq 35$ y), laparoscopy within the past year (yes or no), and study site (Boston IVF or Harvard Vanguard Medical Associates). The closing date of the study for delivery of at least one live-born baby was April 30, 2006. Main study results indicated an increased rate of pregnancy in the accelerated arm of the trial, with fewer treatment cycles and at less cost, than in the conventional treatment arm (14).

### Assessment of Dietary Intake and Supplement Use

Participants completed a paper-based validated 110-item food frequency questionnaire (FFQ) at study baseline (15). The FFQ ascertained energy and macro- and micronutrient intake from diet and dietary supplements. Intake of caffeine was not available. Participants were asked to select from 11 options for typical frequency of food and beverage intake, ranging from never to $\geq 6$ times per day. In addition, participants selected from five options for frequency of intake of a variety of dietary supplements ($<1$ d/mo, 1–3 d/mo, 1–3 d/wk, 4–6 d/wk, every day) and six options for range of dosage, including an option for "I don't know." To reduce extraneous variation in non–energy-bearing nutrient intakes, dietary intake was adjusted for total energy intake with the use of the nutrient residual method (16). In total, we examined three categories of nutrient intake: total nutrient intake (from diet and supplement sources), dietary nutrient intake (diet sources only), and dietary supplements alone.

### Assessment of Covariates

Nondiet covariates with known or suspected association with fertility were self-reported as part of the baseline personal health history questionnaire. These included age, smoking, physical activity, height, and weight. BMI was calculated as kilograms per square meter from the self-reported height and weight.

### Assessment of Birth Outcome

The outcome of interest was length of time from the date of randomization to the date of pregnancy resulting in a live birth. Time to pregnancy was determined from the date of randomization to the date of conception of a pregnancy resulting in a live birth and quantified in months (including fractions of a month) for analyses. Analyses were conducted

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