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Dietary Patterns and Outcomes of Assisted Reproduction

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Abstract

Background.—There is growing acceptance that nutrition may be related to fertility, and specifically to ART success in women; however, there is still no specific dietary guidance.

Objective.—To evaluate the relationship between pre-treatment adherence to various dietary patterns and outcomes of assisted reproductive technologies (ART).

Study Design.—We followed 357 women enrolled in the prospective Environment and Reproductive Health (EARTH) Study, who underwent 608 ART cycles (2007-2017). Using a validated food frequency questionnaire completed prior to treatment, we assessed adherence to the Mediterranean Diet (MedDiet), the alternate Healthy Eating Index 2010 (aHEI2010), the Fertility Diet (FD) (developed based on risk factors for anovulatory infertility), and a "pro-fertility" diet we developed based on factors previously related to ART outcomes (higher intake of supplemental

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folic acid, vitamin B12, vitamin D, low rather than high pesticide residue produce, whole grains, dairy, soy foods, and seafood rather than other meats).

Results.—Higher adherence to the aHEI2010 and FD was not related to live birth following ART. Women in the 2nd thru 4th quartiles of MedDiet adherence had significantly higher probability of live birth (0.44 95% CI 0.39, 0.49) compared to women in 1st quartile (0.31 95% 0.25, 0.39); however there was no additional benefit of adherence to the MedDiet above the 2nd quartile. Increased adherence to the "pro-fertility" diet was linearly associated with ART outcomes. The adjusted odds (95% CI) of implantation, clinical pregnancy, and live birth were higher by 47% (21%, 77%), 43% (19%, 72%), and 53% (26%, 85%), respectively, per standard deviation (SD) increase. The adjusted difference in the proportion of cycles resulting in live birth for women in the 4th vs. 1st quartile of adherence to the "pro-fertility" diet was 0.28 (95% CI 0.16, 0.38). While the "pro-fertility" diet was not related to estradiol levels, oocyte counts, or endometrial thickness, it was inversely associated with clinical pregnancy loss (OR: 0.69, 95% CI 0.53, 0.90 per SD increase).

Conclusions.—Higher pre-treatment adherence to the "pro-fertility" diet was associated with increased probability of live birth among women undergoing ART. Commonly recommended dietary advice such as adhering to the Mediterranean Diet may not provide the most appropriate guidance for women undergoing infertility treatment in the United States.

Keywords

dietary patterns; fertility; infertility; assisted reproductive technology

Introduction.

Assisted reproductive technologies (ART), including *in vitro* fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI), have become one of the main treatment modalities for couples facing fertility problems. In the first 25 years of ART (1978-2003), one million babies were born. By 2005, this tally had doubled.[1-3] This upswing in the use of ART has only further escalated in the past decade such that now it is estimated that >8 million babies have been born to date.[4] Despite the increased utilization of ART, improvements in live birth rates per initiated cycle have been limited and remain around 30-40%.[5] These modest success rates combined with the high financial costs and limited geographic access to infertility treatments motivates the need to identify modifiable predictors of live birth following ART.[6,7]

There is growing acceptance that nutrition may be related to fertility, and specifically to ART success, in women.[8] However, there is still no specific official dietary guidance. Evidence linking diet to fertility is also largely based on studies of single nutrients or foods as opposed to dietary patterns. From a clinical and public health perspective, the analysis of dietary patterns tends to be more applicable to formulating dietary guidance since they more closely parallel the real world conditions. Therefore, our goal was to evaluate the relationship between pretreatment adherence to various dietary patterns and outcomes of ART. Based on prior research,[9-11] our hypothesis was healthy dietary patterns, particularly ones prioritizing intake of supplemental folic acid, vitamin B12, vitamin D, fruits, vegetables, and seafood would be related to higher likelihood of ART success.

Materials and Methods.

Study Population.

Eligible women (18-46 years) presenting at the Massachusetts General Hospital (MGH) Fertility Center were invited to enroll in the Environment and Reproductive Health (EARTH) Study, an ongoing prospective cohort aimed at identifying determinants of fertility (2004-present).[12] Approximately 55% of women referred by physicians ultimately enroll in the study; however, among referred women who research nurses are able to contact, 78% enroll in the study. A food frequency questionnaire (FFQ) was introduced in 2007. For this analysis, women were eligible if they had completed at least 1 ART cycle between February 2007 and December 2017 (n=478). Of these, 116 women (24%) were excluded because they had not completed a FFQ and 14 women (3%) were excluded because they had started their ART cycle prior to FFQ completion. Some women re-enrolled in the study years after their initial entry and completed a second FFQ (n=18). For these women, their cycles initiated after receipt of the second FFQ were assigned to this FFQ. The study was approved by the Institutional Review Boards of the MGH and the Harvard T. H. Chan School of Public Health. All participants provided written informed consent.

Diet Assessment.

Diet was assessed before ART initiation using a validated FFQ.[13] Women were asked to report how often, on average, they consumed specified amounts of each food and beverage included in the questionnaire during the previous year. Multivitamin and supplement users were asked to specify brand, dose, and frequency of use. We calculated nutrient intake by multiplying the intake frequency for each food or supplement by its nutrient content and summing nutrient contributions across all items. Nutrient content of each item is obtained from the US Department of Agriculture with supplemental information from manufacturers.[14] Validation studies comparing nutrient and food intakes assessed by the FFQ versus multiple diet records found a mean correlation coefficient between food items of 0.52 (range: 0.08 for spinach to 0.87 for beer) and between nutrients of 0.53 (range: 0.36 for lauric acid to 0.77 for alcohol).[13, 15, 16]

Adherence scores to the Mediterranean diet (MedDiet), alternate Healthy Eating Index 2010 (aHEI-2010), and Fertility Diet (FD) were computed for each FFQ. The MedDiet score is based on dietary intake of 11 items: vegetables, potatoes, legumes, fruit, whole grains, high fat dairy, red meat, fish, poultry, olive oil, and alcohol.[17] Women were assigned 0 to 5 points based on increasing intake of each component, with the exception of red meats, poultry, and full fat, which was scored in reverse. For alcohol, intakes from 0.1-700 mL per day were scored in reverse and women consuming no alcohol received zero points. The aHEI-2010 score is based on 11 components and points are given on a scale from 0 to 10.[18] Higher intake of vegetables (excluding potatoes), fruit, whole grains, nuts and legumes, long-chain omega 3 fats, polyunsaturated fat (PUFA), and alcohol received higher scores. The scoring was reversed for higher intake of sugar-sweetened beverages and fruit juice, red and processed meat, *trans* fat, and sodium. The FD score is based on the dietary factors associated with lowest risk of anovulatory infertility in the Nurses' Health Study II cohort.[19] Points from 1 to 5 were assigned for increasing the ratio of monounsaturated fatty acids to *trans* fat, percent of energy from vegetable protein, high-fat dairy, iron, and multivitamins from the lowest to the highest category. For percent of energy from animal protein, glycemic load, and low-fat dairy, the point assignment was reversed. We also created our own, alternative "pro-fertility" diet score based on foods and nutrients previously related to ART outcomes in this cohort and others (Table 1). Briefly, participants received 1 to 4 points based on increasing intake of supplemental folic acid,[20-23] vitamin B12,[20, 21, 23] vitamin D,[24, 25] low pesticide fruits and vegetables,[26] whole grains,[27] seafood,[28, 29] dairy,[30] and soy foods.[31, 32] Scoring was reversed for intake of high pesticide fruits and vegetables.[26] The total score ranged from 9 to 36 points.

Outcome Assessment.

For fresh ART cycles, patients underwent luteal-phase gonadotropin-releasing hormone (GnRH) agonist protocol, follicular-phase GnRH-agonist/Flare protocol, or GnRH-antagonist protocol as clinically indicated. During stimulation, patients were monitored for serum estradiol, follicle size, and endometrial thickness. Human chorionic gonadotropin (hCG) was administered approximately 36 hours before scheduled oocyte-retrieval to induce oocyte maturation. Following retrieval, oocytes were fertilized using conventional insemination or ICSI as clinically indicated. Fertilization was determined 17-20h after insemination as the number of oocytes with two pronuclei (2PN). For cryo-thaw or donor egg recipient cycles, patients underwent endometrial preparation protocols as clinically indicated. Following embryo transfer, all clinical outcomes were assessed identically for fresh, cryo-thaw, and donor egg recipient cycles. Successful implantation was defined as a serum β-hCG level >6 mIU/mL typically measured 17 days (range 15–20 days) after egg retrieval, clinical pregnancy as the presence of an intrauterine pregnancy confirmed by ultrasound at 6 weeks gestation, and live birth as the birth of a neonate on or after 24 weeks gestation.

Covariate Assessment.

At enrollment, height and weight were measured by a trained research nurse to calculate body mass index (BMI) (kg/m^2). Participants completed a detailed take-home questionnaire regarding lifestyle factors, reproductive health, and medical history. Time spent in leisure time physical activities was assessed using a validated questionnaire[33] in which women reported the average time per week they spent during the preceding year on 11 different activities using 13 response categories ranging from "never" to "40+ hours per week". Clinical information including infertility diagnosis and protocol type was abstracted from electronic medical records.

Statistical Analysis.

Spearman correlation coefficients were used to describe the measure of dependence between the dietary pattern scores. Women were classified into quartiles based on their score for each dietary pattern; due to discrete points in scores, quartiles may have included slightly more or less than 25% of women. Descriptive statistics were calculated for demographic, reproductive, and dietary characteristics according to these quartiles. Multivariable generalized linear mixed models were used to evaluate the association between dietary patterns and ART outcomes, with a random intercept to account for within-person correlations in outcomes and unbalanced design (e.g. different number of cycles per woman).[34] A normal distribution and identity link function were specified for peak estradiol and endometrial thickness, a Poisson distribution and log link function were specified for oocyte counts, and a binomial distribution and logit link function were specified for clinical outcomes. Tests for trend across quartiles were conducted using a variable with the median dietary pattern score in each quartile. Results are presented as population marginal means, adjusted for covariates at their mean level for continuous covariates and weighted by relative frequency for categorical covariates.[35] The dietary patterns were also evaluated as continuous linear variables and, when appropriate based on meeting linearity assumptions, results are expressed as the OR (95% CI) of live birth per 1 standard deviation (SD) increase in the dietary pattern score or predicted marginal probabilities for the average women in our cohort, plotted from the 5th to 95th percentile of exposure.

Confounding was evaluated using prior knowledge and descriptive statistics from our cohort through the use of directed acyclic graphs. Variables retained in the final multivariable models were any factors associated with the exposure and the outcome that were not intermediate variables on the pathway (e.g. calorie intake, age, BMI, smoking status, and moderate-to-vigorous exercise). Effect modification by various demographic and reproductive characteristics was tested using cross-product terms in the final multivariable models.

Results.

The 357 women in our cohort had an average (SD) age of 35.3 (4.0) years and BMI of 24.1 (4.3) kg/m^2. Most had never smoked (73%), were Caucasian (83%), and had at least a college degree (92%). Of the 608 initiated ART cycles, 500 (82%) were fresh cycles, 85 (14%) were autologous cryo-thaw cycles, and 23 (4%) were donor egg recipient cycles (Supplemental Figure 1). A total of 544 (89%) of the initiated cycles had at least one embryo transferred with 343 (56%) resulting in implantation, 305 (50%) in clinical pregnancy, and 248 (41%) in live birth. Women were followed for 1 (55%), 2 (26%), 3 (13%), or 4-6 (5%) cycles. Dietary patterns were modestly correlated with one another with the highest correlation observed between the MedDiet and aHEI2010 patterns (r=0.63) and the lowest correlation observed between the aHEI2010 and the “pro-fertility” diet (r=0.27) (Supplemental Table 1). Women with higher adherence to the “pro-fertility” diet had, on average, higher calorie intake and moderate-to-vigorous physical activity; however all other characteristics were similar across quartiles including intakes of macronutrients, alcohol, and caffeine (Table 2). These differences were similar across adherence to the other dietary patterns (Supplemental Table 2, 3, 4).

Higher adherence to the aHEI2010 and Fertility Diet were not associated with clinical outcomes following ART (Table 3). While women in the second and third quartile of the MedDiet had higher probability of live birth compared to women in the 1st quartile, there was not a significant linear trend across quartiles. In a post-hoc analysis, we grouped together women in quartiles 2 thru 4 and found they had significantly higher probability of live birth (0.44 95% CI 0.39, 0.49) compared to women in the first quartile (0.31 95% CI 0.25, 0.39). Increasing adherence to the “pro-fertility” diet was associated with significantly higher probability of implantation, clinical pregnancy, and live birth in a linear fashion (p-trend<0.001 for all). The adjusted probabilities of live birth (95% CI) in increasing quartiles of adherence to the “pro-fertility” diet were 0.33 (0.26, 0.40), 0.32 (0.25, 0.40), 0.48 (0.39, 0.57), and 0.56 (0.47, 0.64), respectively (Table 3). When modelled continuously, each SD (4 point) increase in adherence to the “pro-fertility” diet was associated with a 53% (26%, 85%) higher odds of live birth or approximately a 0.10 increase in the proportion of initiated cycles resulting in live birth (Figure 1). All the components of the “pro-fertility” diet contributed to this positive association (Supplemental Figure 2)

Increasing adherence to the “pro-fertility” diet was unrelated to estradiol trigger levels, endometrial thickness, total or mature oocyte yield, or number of embryos (Table 4). However, women with higher adherence to the “pro-fertility” diet had a lower odds of failure prior to embryo transfer (OR=0.75 95% CI 0.57, 0.98 per 1 SD increase) and lower risk of clinical pregnancy loss (OR=0.69 95% CI 0.54, 0.90 per 1 SD increase) (Supplemental Table 5).

Results were consistent when we restricted the analysis to the first ART cycle per woman (n=357), fresh cycles only (n=473), cycles started within 1 year of the FFQ (n=437), and cycles with an embryo transfer (n=547) (Supplemental Table 6). We also observed similar findings for the MedDiet and aHEI2010 scores regardless of whether we included the alcohol component. Furthermore, we saw no evidence of effect modification by BMI (<25 vs. ≥25 kg/m^2), age (<37 vs. ≥37 yrs), race (White vs. other), education (≤college vs. graduate degree), or initial infertility diagnosis (male vs. female vs. unexplained) for any of the dietary patterns, despite being moderate to strong predictors of ART success.

Comment.

In this prospective cohort of women undergoing ART, higher adherence to a “pro-fertility” diet characterized by higher intake supplemental folic acid, vitamin B12, vitamin D, low pesticide fruits and vegetables, whole grains, seafood, dairy, and soy foods and lower intake of high pesticide fruits and vegetables, had higher odds of live birth. This association appeared to be driven by the fact that women with higher adherence to the “pro-fertility” diet had fewer cycles that failed prior to embryo transfer and fewer cycles that resulted in pregnancy loss. While adherence to the MedDiet appeared to be beneficial for live birth following ART, there was no additional benefit above the second quartile of adherence. The aHEI-2010 and the Fertility Diet were not consistently associated with ART outcomes.

To date, only three studies have examined the relation between pre-treatment dietary patterns and ART outcomes. The first study followed 161 Dutch couples undergoing IVF/ICSI and identified two dietary patterns using principal component analysis: a "health conscious-low processed" dietary pattern (characterized by high intakes of fruits, vegetables, fish, and whole grains and low intakes of snacks, meats, and mayonnaise) and a “Mediterranean” diet (characterized by high intake of vegetable oil, fish, legumes, and vegetables and low intake of snacks).[10] Higher couple-level adherence to the "Mediterranean" diet was associated with increased probability of pregnancy; however, there were no associations between higher adherence to the "health conscious–low processed" diet and IVF outcomes. In a subsequent study among 199 Dutch women undergoing IVF/ICSI, adherence to the Dutch dietary recommendations (e.g. ≥4 servings of whole grains daily, the use of monounsaturated or polyunsaturated oils, ≥200 g of vegetables daily, ≥2 servings of fruit daily, ≥3 servings of meat or meat replacers weekly, and ≥1 serving fish weekly) among women (but not men) was associated with an increased probability of pregnancy following IVF/ICSI.[11] Finally, in the most recent cohort study of 244 women undergoing IVF in Greece, higher adherence to a Mediterranean diet based on the same index we used in our study was associated with higher probability of clinical pregnancy and live birth, but not with any intermediate outcome.[9]

While our "pro-fertility" diet has many food groups such as seafood, whole grains, and fruits and vegetables that overlap with the Mediterranean diet and could explain some of the similar findings, we did not find a strong association between the MedDiet and ART outcomes. This could be due to the fact that in the general US population, fruits and vegetables serve as the primary route of exposure to pesticides[36] and therefore at least in the US intake of highly contaminated produce may counteract any potential reproductive benefits. The European Union has more strict legislation governing the use of pesticides on food products- outlawing at least 5 pesticides that are known to be used abundantly on US farms- which could explain some of the divergence in our findings with the previous studies.[37] Beyond the differences in how high vs. low pesticide fruits and vegetables were scored in the "pro-fertility" diet vs. the Mediterranean diet, the other main difference was the prioritization of certain nutrients above and beyond the typical components of a healthy diet. Numerous studies, besides our own, have published on the reproductive benefits of folic acid,[22] vitamin B12,[23] vitamin D,[25] and soy.[32] Therefore, it was not surprising that the addition of these components to our food-based dietary score, may have improved its ability to predict the probability of live birth following ART. The optimal intakes of supplemental folic acid (>800 μg/day), B12 (>15.8 μg/day), and vitamin D (>843 lU/day) in our "pro-fertility" diet score were also higher than the current recommended dietary allowances for these nutrients during pregnancy. This suggests that women undergoing ART may gain additional benefit with higher consumption of these nutrients. The fact that we saw no association with the Fertility Diet and ART outcomes suggests that dietary factors associated with risk of developing anovulatory infertility may differ from those that predict ART success.

From a biological perspective, we hypothesize that there are many different pathways through which the "pro-fertility" diet may be acting to promote fertility in women undergoing ART including the enhancing the body's capability to synthesize, repair, and methylate DNA, suppress oxidative stress and support antioxidant defense, reduce systematic inflammation, and regulate glucose and insulin metabolism. Given that all rather than just one or two of the components of the "pro-fertility" diet were associated with ART success, it is unlikely that a single pathway is responsible for the observed effects. Moreover, as we observed associations between higher adherence to the "pro-fertility" diet and lower likelihood of failing prior to embryo transfer as well as lower likelihood of having a clinical pregnancy loss, this suggests beneficial effects of the "pro-fertility" diet on a wide range of very early and later ART outcomes including response to ovarian stimulation, early embryo development, and pregnancy maintenance.

Limitations of our study are recognized. First and foremost was the lack of an independent validation study. Since we based the development of the “pro-fertility” diet on previous findings from this cohort, it would have been more desirable to test the robustness of this score in a separate group of women. However, we were unable to identify an analogous study of women undergoing ART in the US that includes a full dietary assessment tool. Despite use of a validated FFQ, self-report of diet is subject to measurement error. Furthermore, data on whether individual fruits and vegetables were consumed as organic or conventional was not collected, possibly leading to exposure misclassification of women according to the “pro-fertility” diet. Due to the prospective nature of our study, however, any measurement error would not be expected to differ with regard to the outcomes and would result in an attenuation of the observed associations. As this was an observational study, there remains the possibility of residual confounding by factors that were not measured or were poorly measured in our study. Finally, the generalizability of our results to women presenting at infertility clinics worldwide is unclear, particularly given the differences in use of pesticides on fruits and vegetables and the fortification of grain products in the US compared to other countries.

Despite these limitations, the strengths of our study include the prospective design and the standardized assessment of a wide variety of participant characteristics including a comprehensive dietary assessment which included the novel quantification of the pesticides in fruits and vegetables. By studying a population of women undergoing ART, we were also able to utilize an efficient study design with sufficient power to investigate dietary influences on clinically relevant, yet previously unobservable, outcomes in a potentially vulnerable sub-population.

In conclusion, our findings suggest that women who adhere to a “pro-fertility” diet prioritizing intake of supplemental folic acid, vitamin B12, vitamin D, low pesticide fruits and vegetables, whole grains, seafood, dairy, and soy foods and limiting intake of high pesticide fruits and vegetables have higher likelihood of live birth following ART. Given the much stronger results we observed for the “pro-fertility” diet versus the Mediterranean Diet, our results stress the importance of providing specific pre-conception guidance to women planning pregnancy above and beyond general recommendations for chronic disease prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Condensation: Women prioritizing supplemental folic acid, vitamin B12, vitamin D, low pesticide fruits and vegetables, whole grains, seafood, dairy, and soy and limit high pesticide fruits and vegetables have higher likelihood of ART success.

AJOG at a Glance:

Why was this study conducted?

- There is growing acceptance that nutrition may be related to fertility, and specifically to infertility treatment success in women; however, there is still no specific dietary guidance.

What are the key findings?

- Women who adhere to a “pro-fertility” diet prioritizing intake of supplemental folic acid, vitamin B12, vitamin D, low pesticide fruits and vegetables, whole grains, seafood, dairy, and soy foods and limiting intake of high pesticide fruits and vegetables have higher likelihood of live birth following ART.

What does this study add to what is already known?

- Given the stronger results we observed for this “pro-fertility” diet versus a traditional Mediterranean Diet, our results stress the importance of providing specific pre-conception guidance to women planning pregnancy above and beyond general recommendations for chronic disease prevention.

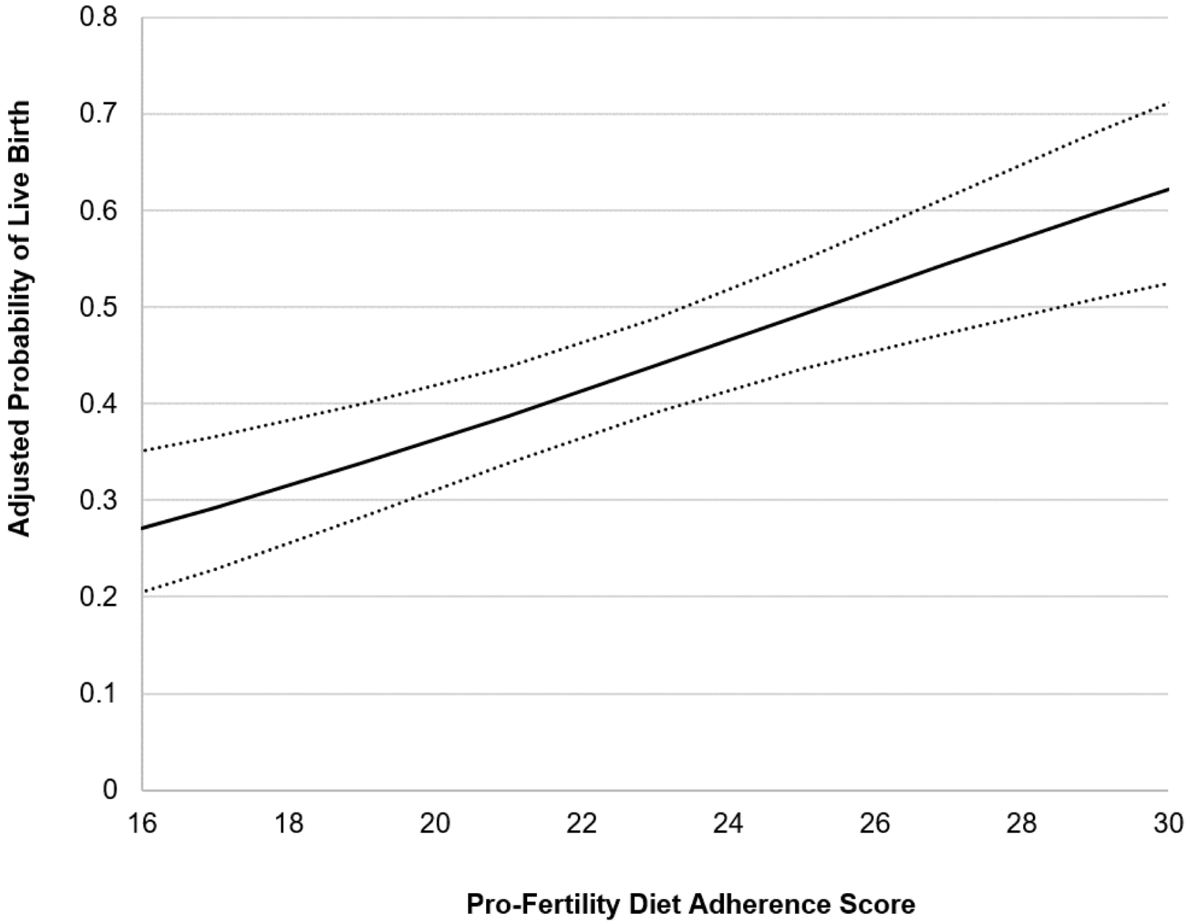

Figure 1.

Association between pre-treatment adherence to the Pro-Fertility Diet and probability of live birth following ART in the EARTH Study. Analyses were conducted using generalized linear mixed models with random intercepts (to account for multiple cycles per woman), a binomial distribution, and logit link function. Data are presented as predicted marginal proportions (95% CI) adjusted for calorie intake, age, BMI, smoking status, and moderate to vigorous exercise.

Table 1.

Components and scoring system of the Pro-Fertility Diet.

Component	Definition	Quartile Scoring
Supplemental folic acid (μg/day)	Total folic acid intake from non-food sources	Q1 (1 pt): 0-399 Q2 (2pt): 400-500 Q3 (3pt): 501-800 Q4 (4pt): 801-2400
Vitamin B12 (μg/day)	Energy adjusted total B12 intake from diet and supplements	Q1 (1 pt): 0-8.9 Q2 (2pt): 9.0-11.7 Q3 (3pt): 11.8-15.8 Q4 (4pt): 15.9-947
Vitamin D (IU/day)	Energy adjusted total vitamin D from food and supplements	Q1 (1 pt): 61-463 Q2 (2pt): 464-578 Q3 (3pt): 579-843 Q4 (4pt): 844-3847
Low pesticide fruits and vegetables[1] (servings/day)	Fruits and vegetables scoring <4 on the PRBS scale	Q1 (1 pt): 0.3-1.6 Q2 (2pt): 1.7-2.4 Q3 (3pt): 2.5-3.5 Q4 (4pt): 3.6-11.5
High pesticide fruits and vegetables[2] (servings/day)	Fruits and vegetables scoring ≥4 on the PRBS scale	Q1 (4pt): 0.2-1.0 Q2 (3pt): 1.1-1.5 Q3 (2pt): 1.6-2.2 Q4 (1 pt): 2.3-6.8
Whole grains (g/day)	Total dry weight of whole grain in all grain-containing foods (rice, bread, pasta, and breakfast cereals)	Q1 (1 pt): 0.4-20.6 Q2 (2pt): 20.7-33.1 Q3 (3pt): 33.2-50.9 Q4 (4pt): 51.0-196
Ratio of seafood to total meat intake	All fish and shellfish intake divided by total intake of red, processed, and organ meats, chicken, and seafood	Q1 (1 pt): 0-0.11 Q2 (2pt): 0.12-0.18 Q3 (3pt): 0.19-0.32 Q4 (4pt): 0.32-1.00
Dairy (servings/day)	All milk, yogurt, cream, cheese, and ice cream	Q1 (1 pt): 0-1.2 Q2 (2pt): 1.3-1.8 Q3 (3pt): 1.9-2.6 Q4 (4pt): 2.7-6.2
Soy foods (servings/day)	Tofu, tempeh, miso soup, soy meat substitutes, soy dairy products, soy beans & nuts, and soy protein drinks & bars	Q1 (1 pt): 0 Q2 (2pt): 0.01-0.09 Q3 (3pt): 0.10-0.27 Q4 (4pt): 0.28-7.45
Range of Pro-Fertility Diet Score: 9-36 points		

Abbreviations: PRBS, pesticide residual based scoring.

[1] Low pesticide fruits and vegetables include: peas or lima beans, dried plums or prunes, onions, beans or lentils, avocado, corn, cabbage or cole slaw, orange juice, tomato sauce, apple juice or cider, cauliflower, grapefruit, cantaloupe, tofu, bananas, eggplant, summer squash, zucchini, yam or sweet potatoes, oranges, broccoli, carrots, head lettuce, and leaf lettuce.

[2] High pesticide fruits and vegetables include: tomatoes, apple sauce, blueberries, kale, mustard, or chard greens, winter squash, fresh apples or pears, string beans, grapes or raisins, potatoes, raw or cooked spinach, peaches or plums, strawberries, celery, and green, yellow, or red bell peppers.

Table 2.

Baseline characteristics of 357 women (375 unique FFQs) by quartile of pre-treatment adherence to the Pro-Fertility Diet in the EARTH Study.

	Pro-Fertility Diet				
Quartile (Range) **Number of Women/FFQs**	**Q1 (11-20)** **103/105**	**Q2 (21-23)** **90/97**	**Q3 (24-25)** **78/82**	**Q4 (26-32)** **86/91**	**p-value**[1]
Personal Characteristics					
Age, years	35.0 (3.8)	35.5 (4.0)	35.0 (4.1)	35.8 (4.2)	0.52
Ever smoker, n (%)	28 (26.7)	28 (28.9)	20 (24.4)	24 (26.4)	0.93
White, n (%)	87 (82.9)	82 (84.5)	66 (80.5)	79 (86.8)	0.71
Education, n (%)					
High school or less	10 (9.5)	5 (5.2)	9 (11.0)	5 (5.5)	0.11
College	37 (35.2)	40 (41.2)	30 (36.6)	22 (24.2)	
Graduate school	58 (55.2)	52 (53.6)	43 (52.4)	64 (70.3)	
BMI, kg/m^2	24.2 (4.6)	24.3 (4.4)	24.2 (3.8)	23.7 (4.1)	0.48
Moderate to vigorous exercise, hrs/wk	2.9 (3.1)	4.1 (4.5)	4.2 (4.6)	4.7 (4.8)	0.04
Baseline Cycle Characteristics					
Infertility diagnosis, n (%)					
Female factor	28 (26.7)	28 (28.9)	23 (28.1)	32 (35.2)	0.76
Male factor	38 (36.2)	31 (32.0)	24 (29.3)	24 (26.4)	
Unexplained	39 (37.1)	38 (39.2)	35 (42.7)	35 (38.5)	
Treatment protocol, n (%)					0.56
Antagonist	13 (13.7)	10 (11.1)	13 (18.3)	12 (14.3)	
Flare	10 (10.5)	15 (16.7)	5 (7.0)	11 (13.1)	
Luteal phase agonist	72 (75.8)	65 (72.2)	53 (74.7)	61 (72.6)	
Egg Donor or Cryo Cycle	11 (10.1)	7 (7.3)	12 (11.5)	5 (7.8)	
Day 3 FSH, IU/L	7.1 (2.0)	7.1 (1.8)	7.2 (2.3)	8.0 (3.7)	0.66
Embryo Transfer Day, n (%)[2]					0.69
Day 2	5 (6.3)	4 (5.2)	3 (4.6)	4 (5.2)	
Day 3	32 (40.0)	37 (48.1)	36 (55.4)	40 (52.0)	
Day 5	43 (53.8)	36 (46.8)	26 (40.0)	33 (42.9)	
Number of Embryos Transferred, n (%)[2]					0.29
1 embryo	16 (20.0)	22 (28.6)	21 (32.8)	16 (20.8)	
2 embryos	53 (66.3)	41 (53.3)	32 (50.0)	43 (55.8)	
3+ embryos	11 (13.8)	14 (18.2)	11 (17.2)	18 (23.4)	
Dietary Characteristics					
Total Calories, kcal/day	1633 (490)	1651 (514)	1905 (624)	2042 (658)	<0.001
Carbohydrates, % of kcal/day	48.0 (8.6)	48.5 (7.7)	49.1 (7.8)	50.7 (6.5)	0.03
Protein, % of kcal/day	16.9 (3.0)	16.7 (2.8)	16.7 (2.7)	16.6 (2.7)	0.88
Fat, % of kcal/day	33.0 (6.7)	33.3 (6.4)	33.1 (6.7)	32.3 (5.8)	0.75
Alcohol, g/day	9.3 (12.7)	8.9 (10.2)	8.5 (8.7)	8.4 (9.2)	0.94
Caffeine, mg/day	121 (101)	125 (94)	143 (132)	124 (108)	0.76

	Pro-Fertility Diet				
Quartile (Range) **Number of Women/FFQs**	**Q1 (11-20)** **103/105**	**Q2 (21-23)** **90/97**	**Q3 (24-25)** **78/82**	**Q4 (26-32)** **86/91**	**p-value**[1]
Multivitamin Use, n (%)	72 (68.6)	88 (92.6)	74 (91.4)	90 (98.9)	<0.001
Duration of Use ≥2 years	50 (69.4)	63 (71.6)	54 (73.0)	69 (76.7)	0.76

Abbreviations: FFQ; food frequency questionnaire; Q, quartile.

[1] P-values were calculated using a Kruskal-Wallis test for continuous variables and a chi-square test for categorical variables.

[2] Embryo transfer day and number were only assessed among fresh cycles with embryo transfer.

Table 3.

Association between pre-treatment adherence to the Pro-Fertility Diet, the Mediterranean Diet, the Alternate Healthy Eating Index 2010, and the Fertility Diet and probability of implantation, clinical pregnancy, and live birth following ART in the EARTH Study.

		Adjusted Proportions (95% CI)[1]		
	Women/Cycles	**Implantation**	**Clinical Pregnancy**	**Live Birth**
Pro-Fertility Diet				
Q1 (11-20)	103/182	0.46 (0.39, 0.54)	0.40 (0.33, 0.48)	0.33 (0.26, 0.40)
Q2 (21-23)	90/165	0.53 (0.45, 0.61)	0.46 (0.38, 0.54)	0.32 (0.25, 0.40)
Q3 (24-25)	78/123	0.65 (0.56, 0.73) *	0.59 (0.50, 0.68) *	0.48 (0.39, 0.57) *
Q4 (26-32)	86/138	0.68 (0.59, 0.76) *	0.61 (0.52, 0.69) *	0.56 (0.47, 0.64) *
P for trend		<0.001	<0.001	<0.001
Mediterranean Diet				
Q1 (17-28)	90/170	0.49 (0.41, 0.57)	0.43 (0.35, 0.50)	0.31 (0.25, 0.39)
Q2 (29-31)	93/150	0.62 (0.53, 0.69) *	0.56 (0.47, 0.64) *	0.47 (0.39, 0.55) *
Q3 (32-33)	74/123	0.64 (0.55, 0.72) *	0.57 (0.48, 0.66) *	0.44 (0.36, 0.53) *
Q4 (34-44)	100/165	0.55 (0.47, 0.63)	0.48 (0.40, 0.56)	0.41 (0.34, 0.49)
P for trend		0.17	0.25	0.06
Alternate Healthy Eating Index 2010				
Q1 (32-60)	92/158	0.62 (0.54, 0.69)	0.55 (0.47, 0.63)	0.44 (0.36, 0.52)
Q2 (61-67)	87/151	0.59 (0.50, 0.67)	0.51 (0.43, 0.59)	0.42 (0.34, 0.50)
Q3 (68-74)	88/148	0.53 (0.44, 0.61)	0.50 (0.42, 0.59)	0.40 (0.33, 0.49)
Q4 (75-99)	90/151	0.54 (0.46, 0.62)	0.45 (0.37, 0.53)	0.37 (0.29, 0.45)
P for trend		0.12	0.08	0.19
Fertility Diet				
Q1 (13-22)	99/168	0.54 (0.46, 0.62)	0.48 (0.41, 0.56)	0.37 (0.30, 0.45)
Q2 (23-25)	93/168	0.58 (0.50, 0.66)	0.53 (0.45, 0.60)	0.42 (0.35, 0.50)
Q3 (26-28)	89/145	0.62 (0.53, 0.69)	0.52 (0.44, 0.61)	0.42 (0.34, 0.50)
Q4 (29-35)	76/127	0.54 (0.45, 0.63)	0.47 (0.39, 0.56)	0.43 (0.34, 0.52)
P for trend		0.83	0.89	0.37

[1] Analyses were run using generalized linear mixed models with random intercepts, binomial distribution, and logit link function. Data are presented as predicted marginal proportions (95% CI) adjusted for calorie intake, age, BMI, smoking status, and moderate to vigorous exercise.

[*] P-value < 0.05 for comparison of specific quartile versus quartile 1 (reference).

Table 4.

Associations between pre-treatment adherence to the Pro-Fertility Diet and early ART outcomes in 322 women (473 fresh ART cycles with egg retrieval) from the EARTH Study.

Adjusted Means (95% CI)[1]	**Pro-Fertility Diet**				
Women/Cycles	**Q1 (11-20) 90/144**	**Q2 (21-23) 86/125**	**Q3 (24-25) 68/93**	**Q4 (26-32) 78/111**	**P trend**
Estradiol Trigger Levels, pmol/L	2206 (2031, 2381)	2208 (2028, 2388)	1977 (1772, 2182)	2123 (1928, 2317)	0.21
Endometrial Thickness, mm	10.2 (9.7, 10.6)	10.5 (10.0, 10.9)	10.6 (10.0, 11.1)	10.1 (9.6, 10.6)	0.69
Total Oocyte Yield, number	12.0 (11.0, 13.2)	10.7 (9.7, 11.8)	10.7 (9.6, 11.9)	10.9 (9.8, 12.1)	0.20
Mature Oocytes, number	10.3 (9.4, 11.4)	8.7 (7.8, 9.6)	8.9 (7.9, 9.9)	8.9 (8.0, 10.0)	0.08
Fertilized Embryos, number	7.2 (6.5, 8.1)	5.9 (5.2, 6.6)	6.3 (5.5, 7.2)	6.4 (5.7, 7.3)	0.34

[1] All analyses were conducted using generalized linear mixed models with random intercepts, normal (for endometrial thickness and estradiol levels) or Poisson (for oocyte and embryo counts) distribution and identity (for endometrial thickness and E2 levels) or log (for oocyte or embryo counts) link function. Data are presented as predicted marginal means adjusted for calorie intake, age, BMI, smoking status, and moderate to vigorous exercise.