GYNECOLOGY

Dietary patterns and outcomes of assisted reproduction

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BACKGROUND: There is growing acceptance that nutrition may be related to fertility and specifically to assisted reproductive technologies success in women; however, there is still no specific dietary guidance.

OBJECTIVE: The objective of the study was to evaluate the relationship between pretreatment adherence to various dietary patterns and outcomes of assisted reproductive technologies.

STUDY DESIGN: We followed up 357 women enrolled in the prospective Environment and Reproductive Health (EARTH) study, who underwent 608 assisted reproductive technologies cycles (2007–2017). Using a validated food frequency questionnaire completed prior to treatment, we assessed adherence to the Mediterranean diet, the alternate Healthy Eating Index 2010, the Fertility Diet (developed based on risk factors for anovulatory infertility), and a profertility diet we developed based on factors previously related to assisted reproductive technologies outcomes (higher intake of supplemental 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 alternate Healthy Eating Index 2010 and Fertility Diet was not related to live birth following assisted reproductive technologies. Women in the second through the fourth quartiles of Mediterranean diet adherence had significantly higher probability of live birth (0.44, 95% confidence interval, 0.39–0.49) compared with women in the first quartile (0.31, 95% confidence interval, 0.25–0.39); however, there was no additional benefit of adherence to the Mediterranean diet above the second quartile. Increased adherence to the profertility diet was linearly associated with assisted reproductive technologies outcomes. The adjusted odds (95% confidence interval) of implantation, clinical pregnancy, and live birth were higher by 47% (21%, 77%), 43% (19%, 72%), and 53% (26%, 85%), respectively, per SD increase. The adjusted difference in the proportion of cycles resulting in live birth for women in the fourth vs first quartile of adherence to the profertility diet was 0.28 (95% confidence interval, 0.16–0.38). While the profertility diet was not related to estradiol levels, oocyte counts, or endometrial thickness, it was inversely associated with clinical pregnancy loss (odds ratio, 0.69, 95% confidence interval, 0.53–0.90 per SD increase).

CONCLUSION: Higher pretreatment adherence to the profertility diet was associated with an increased probability of live birth among women undergoing assisted reproductive technologies. 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.

Key words: assisted reproductive technology, dietary patterns, fertility, infertility

Assisted reproductive technologies (ART), including in vitro fertilization (IVF) and intracytoplasmic 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), 1 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 because 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 old) presenting at the Massachusetts General Hospital 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 to the present).[12] Approximately 55% of women referred by physicians ultimately enroll in the study; however, among referred women whom research nurses are able to contact, 78% enroll in the study.

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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.

Key findings

Women who adhere to a profertility 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 a higher likelihood of live birth following assisted reproductive technologies.

What does this add to what is known?

Given the stronger results we observed for this profertility diet vs a traditional Mediterranean diet, our results stress the importance of providing specific preconception guidance to women planning pregnancy above and beyond general recommendations for chronic disease prevention.

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 an FFQ and 14 women (3%) were excluded because they had started their ART cycle prior to the FFQ completion.

Some women reenrolled 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 Massachusetts General Hospital 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 vs 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 0−5 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, 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 the 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, percentage of energy from vegetable protein, high-fat dairy, iron, and multivitamins from the lowest to the highest category. For percentage of energy from animal protein, glycemic load, and low-fat dairy, the point assignment was reversed.

We also created our own, alternative profertility diet score based on foods and nutrients previously related to ART outcomes in this cohort and others (Table 1). Briefly, participants received 1−4 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 was administered approximately 36 hours before the scheduled oocyte retrieval to induce oocyte maturation. Following retrieval, oocytes were fertilized using conventional insemination or ICSI as clinically indicated.

Fertilization was determined 17−20 hours after insemination as the number of oocytes with 2 pronuclei. For cryothaw or donor egg recipient cycles, patients underwent endometrial

preparation protocols as clinically indicated. Following embryo transfer, all clinical outcomes were assessed identically for fresh, cryothaw, and donor egg recipient cycles. Successful implantation was defined as a serum β-human chorionic gonadotropin 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) (kilograms per square meter). 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 or more 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; because of 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 (eg, 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 odds ratio (OR; 95% confidence interval [CI]) of live birth per 1 SD increase in the dietary pattern score or predicted marginal probabilities for the average women in our cohort, plotted from the fifth to 95th percentile of exposure.

TABLE 1
Components and scoring system of the profertility diet

Component	Definition	Quartile scoring
Supplemental folic acid, μg/d	Total folic acid intake from nonfood sources	Q1 (1 pt): 0–399
		Q2 (2 pt): 400–500
		Q3 (3 pt): 501–800
		Q4 (4 pt): 801–2400
Vitamin B12, μg/d	Energy adjusted total B12 intake from diet and supplements	Q1 (1 pt): 0–8.9
		Q2 (2 pt): 9.0–11.7
		Q3 (3 pt): 11.8–15.8
		Q4 (4 pt): 15.9–947
Vitamin D, IU/d	Energy adjusted total vitamin D from food and supplements	Q1 (1 pt): 61–463
		Q2 (2 pt): 464–578
		Q3 (3 pt): 579–843
		Q4 (4 pt): 844–3847
Low-pesticide fruits and vegetables, servings/d[a]	Fruits and vegetables scoring <4 on the PRBS scale	Q1 (1 pt): 0.3–1.6
		Q2 (2 pt): 1.7–2.4
		Q3 (3 pt): 2.5–3.5
		Q4 (4 pt): 3.6–11.5
High-pesticide fruits and vegetables, servings/d[b]	Fruits and vegetables scoring ≥4 on the PRBS scale	Q1 (4 pt): 0.2–1.0
		Q2 (3 pt): 1.1–1.5
		Q3 (2 pt): 1.6–2.2
		Q4 (1 pt): 2.3–6.8
Whole grains, g/d	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 (2 pt): 20.7–33.1
		Q3 (3 pt): 33.2–50.9
		Q4 (4 pt): 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 (2 pt): 0.12–0.18
		Q3 (3 pt): 0.19–0.32
		Q4 (4 pt): 0.32–1.00

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TABLE 1
Components and scoring system of the profertility diet *(continued)*

Component	Definition	Quartile scoring
Dairy, servings/d	All milk, yogurt, cream, cheese, and ice cream	Q1 (1 pt): 0–1.2
		Q2 (2 pt):1.3–1.8
		Q3 (3 pt): 1.9–2.6
		Q4 (4 pt): 2.7–6.2
Soy foods, servings/d	Tofu, tempeh, miso soup, soy meat substitutes, soy dairy products, soy beans and nuts, and soy protein drinks and bars	Q1 (1 pt): 0
		Q2 (2 pt): 0.01–0.09
		Q3 (3 pt): 0.10–0.27
		Q4 (4 pt): 0.28–7.45
Range of profertility diet score: 9–36 points		

pt, point(s); *PRBS*, pesticide residual based scoring; *Q*, quartile.

[a] 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; [b] 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.

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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 (eg, 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 white (83%), and had at least a college degree (92%). Of the 608 initiated ART cycles, 500 (82%) were fresh cycles, 85 (14%) were autologous cryothaw cycles, and 23 (4%) were donor egg recipient cycles (Supplemental Figure 1). A total of 544 of the initiated cycles (89%) had at least 1 embryo transferred, with 343 (56%) resulting in implantation, 305 (50%) in clinical pregnancy, and 248 (41%) in live birth.

Women were followed up for 1 (55%), 2 (26%), 3 (13%), or 4–6 cycles (5%). 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 profertility diet (r = 0.27) (Supplemental Table 1).

Women with higher adherence to the profertility 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 Tables 2–4).

Higher adherence to the aHEI2010 and FD was not associated with clinical outcomes following ART (Table 3). While women in the second and third quartiles of the MedDiet had higher probability of live birth compared with

TABLE 2
Baseline characteristics of 357 women (375 unique FFQs) by quartile of pretreatment adherence to the profertility diet in the EARTH study

Characteristics	Profertliity diet				
Quartile (range)	Q1 (11–20)	Q2 (21–23)	Q3 (24–25)	Q4 (26–32)	*P* value[a]
Number of women/FFQs	103/105	90/97	78/82	86/91	
Personal characteristics					
Age, y	35.0 (3.8)	35.5 (4.0)	35.0 (4.1)	35.8 (4.2)	.52
Ever smoker, n (%)	28 (26.7)	28 (28.9)	20 (24.4)	24 (26.4)	.93
White, n (%)	87 (82.9)	82 (84.5)	66 (80.5)	79 (86.8)	.71
Education, n (%)					.11
High school or less	10 (9.5)	5 (5.2)	9 (11.0)	5 (5.5)	
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)	

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TABLE 2
Baseline characteristics of 357 women (375 unique FFQs) by quartile of pretreatment adherence to the profertility diet in the EARTH study *(continued)*

Characteristics	Profertliity diet				
Quartile (range)	Q1 (11–20)	Q2 (21–23)	Q3 (24–25)	Q4 (26–32)	*P* value[a]
BMI, kg/m^2	24.2 (4.6)	24.3 (4.4)	24.2 (3.8)	23.7 (4.1)	.48
Moderate to vigorous exercise, h/wk	2.9 (3.1)	4.1 (4.5)	4.2 (4.6)	4.7 (4.8)	.04
Baseline cycle characteristics					
Infertility diagnosis, n (%)					.76
Female factor	28 (26.7)	28 (28.9)	23 (28.1)	32 (35.2)	
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 (%)					.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)	.66
Embryo transfer day, n (%)[b]					.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 (%)[b]					.29
One embryo	16 (20.0)	22 (28.6)	21 (32.8)	16 (20.8)	
Two embryos	53 (66.3)	41 (53.3)	32 (50.0)	43 (55.8)	
Three or more embryos	11 (13.8)	14 (18.2)	11 (17.2)	18 (23.4)	
Dietary characteristics					
Total calories, kcal/d	1633 (490)	1651 (514)	1905 (624)	2042 (658)	< .001
Carbohydrates, % of kcal/d	48.0 (8.6)	48.5 (7.7)	49.1 (7.8)	50.7 (6.5)	.03
Protein, % of kcal/d	16.9 (3.0)	16.7 (2.8)	16.7 (2.7)	16.6 (2.7)	.88
Fat, % of kcal/d	33.0 (6.7)	33.3 (6.4)	33.1 (6.7)	32.3 (5.8)	.75
Alcohol, g/d	9.3 (12.7)	8.9 (10.2)	8.5 (8.7)	8.4 (9.2)	.94
Caffeine, mg/d	121 (101)	125 (94)	143 (132)	124 (108)	.76
Multivitamin use, n (%)	72 (68.6)	88 (92.6)	74 (91.4)	90 (98.9)	< .001
Duration of use ≥2 y	50 (69.4)	63 (71.6)	54 (73.0)	69 (76.7)	.76

BMI, body mass index; *FFQ*, food frequency questionnaire; *FSH*, follicle-stimulating hormone; *Q*, quartile.

[a] *P* values were calculated using a Kruskal-Wallis test for continuous variables and a χ^2 test for categorical variables; [b] Embryo transfer day and number were assessed only among fresh cycles with embryo transfer.

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women in the first quartile, there was not a significant linear trend across quartiles.

In a post hoc analysis, we grouped together women in quartiles 2–4 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 profertility diet was associated with significantly higher probability of implantation, clinical pregnancy, and live birth in a linear fashion (*p trend* < .001 for all).

The adjusted probabilities of live birth (95% CI) in increasing quartiles of adherence to the profertility diet were 0.33 (0.26–0.40), 0.32 (0.25–0.40), 0.48

TABLE 3
Association between pretreatment adherence to the Profertility 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

Variables	Women/cycles	Adjusted proportions (95% CI)[a]		
		Implantation	Clinical pregnancy	Live birth
Profertility 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)[b]	0.59 (0.50–0.68)[b]	0.48 (0.39–0.57)[b]
Q4 (26–32)	86/138	0.68 (0.59–0.76)[b]	0.61 (0.52–0.69)[b]	0.56 (0.47–0.64)[b]
P for trend		< .001	< .001	< .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)[b]	0.56 (0.47–0.64)[b]	0.47 (0.39–0.55)[b]
Q3 (32–33)	74/123	0.64 (0.55–0.72)[b]	0.57 (0.48–0.66)[b]	0.44 (0.36–0.53)[b]
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		.17	.25	.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		.12	.08	.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		.83	.89	.37

ART, assisted reproductive technologies; *CI*, confidence interval; *EARTH*, Environment and Reproductive Health; *Q*, quartile.

[a] 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, body mass index, smoking status, and moderate to vigorous exercise; [b] $P < .05$ for comparison of specific quartile vs quartile 1 (reference).

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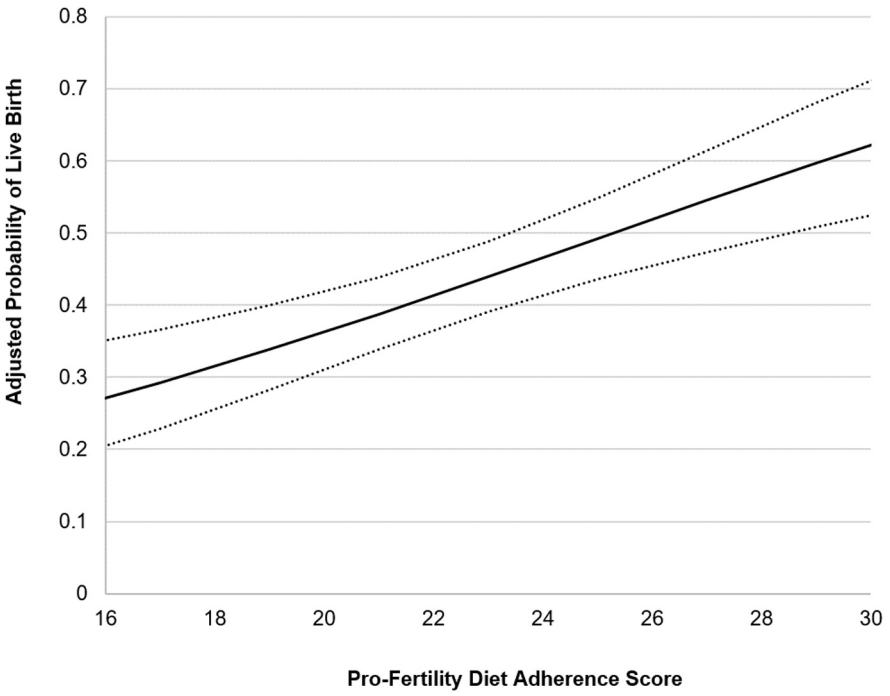
(0.39–0.57), and 0.56 (0.47–0.64), respectively (Table 3). When modelled continuously, each SD (4 points) increase in adherence to the profertility diet was associated with a 53% (26–85%) higher odds of live birth or approximately a 0.10 increase in the proportion of initiated cycles resulting in live birth (Figure). All the components of the profertility diet contributed to this positive association (Supplemental Figure 2).

Increasing adherence to the profertility 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 profertility 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

FIGURE
Association between pretreatment adherence to profertility diet and live birth



Association between pretreatment adherence to the profertility diet and probability of live birth following assisted reproductive technologies in the Environment and Reproductive Health (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% confidence interval) adjusted for calorie intake, age, body mass index, smoking status, and moderate to vigorous exercise.

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(<25 vs ≥ 25 kg/m^2), age (<37 vs ≥37 years), 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 profertility diet characterized by higher intake of supplemental folic acid, vitamin B12, vitamin D, low-pesticide fruits and vegetables, whole grains, seafood, dairy, and soy foods and a 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 profertility 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 FD were not consistently associated with ART outcomes.

To date, only 3 studies have examined the relation between pretreatment dietary patterns and ART outcomes. The first study followed up 161 Dutch couples undergoing IVF/ICSI and identified 2 dietary patterns using a 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 MedDiet (characterized by a high intake of vegetable oil, fish, legumes, and vegetables and a low intake of snacks).[10] Higher couple-level adherence to the MedDiet 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 (eg, ≥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 MedDiet 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 profertility diet has many food groups such as seafood, whole grains, and fruits and vegetables that overlap with the MedDiet 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 United States, 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 profertility diet vs. the

TABLE 4
Associations between pretreatment adherence to the profertility diet and early ART outcomes in 322 women (473 fresh ART cycles with egg retrieval) from the EARTH study

Adjusted means (95% CI)[a]	Profertility diet				*P* trend
	Q1 (11–20)	Q2 (21–23)	Q3 (24–25)	Q4 (26–32)	
Women/cycles	90/144	86/125	68/93	78/111	
Estradiol trigger levels, pmol/L	2206 (2031, 2381)	2208 (2028, 2388)	1977 (1772, 2182)	2123 (1928, 2317)	.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)	.69
Total oocyte yield, n	12.0 (11.0, 13.2)	10.7 (9.7, 11.8)	10.7 (9.6, 11.9)	10.9 (9.8, 12.1)	.20
Mature oocytes, n	10.3 (9.4, 11.4)	8.7 (7.8, 9.6)	8.9 (7.9, 9.9)	8.9 (8.0, 10.0)	.08
Fertilized embryos, n	7.2 (6.5, 8.1)	5.9 (5.2, 6.6)	6.3 (5.5, 7.2)	6.4 (5.7, 7.3)	.34

ART, assisted reproductive technologies; *CI*, confidence interval; *EARTH*, Environment and Reproductive Health; *Q*, quartile.

[a] 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.

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Mediterranean diet, the other main difference was the prioritization of certain nutrients above and beyond the typical components of a healthy diet.

Numerous studies, in addition to 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 IU/day) in our profertility 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 FD and ART outcomes suggests that dietary factors associated with a 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 profertility 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 1 or 2 of the components of the profertility diet were associated with ART success, it is unlikely that a single pathway is responsible for the observed effects. Moreover, because we observed associations between higher adherence to the profertility diet and a lower likelihood of failing prior to embryo transfer as well as a lower likelihood of having a clinical pregnancy loss, this suggests beneficial effects of the profertility 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. Because we based the development of the profertility 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 United States that includes a full dietary assessment tool. Despite the 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 profertility diet.

Because of 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. Because 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 United States compared with 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 that 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 subpopulation.

In conclusion, our findings suggest that women who adhere to a profertility 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 a higher likelihood of live birth following ART. Given the much stronger results we observed for the profertility diet vs the Mediterranean diet, our results stress the importance of providing specific preconception guidance to women planning pregnancy above and beyond general recommendations for chronic disease prevention. ■

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References

1. Ishihara O, Adamson GD, Dyer S, et al. International Committee for Monitoring Assisted Reproductive Technologies: world report on assisted reproductive technologies, 2007. Fertil Steril 2015;103:402–13.e11.

2. Zegers-Hochschild F, Mansour R, Ishihara O, et al. International Committee for Monitoring Assisted Reproductive Technology: world report on assisted reproductive technology, 2005. Fertil Steril 2014;101:366–78.

3. European Society for Human Reproduction and Embryology (ESHRE). The world's number of IVF and ICSI babies has now reached a calculated total of 5 million. Istanbul, Turkey: European Society of Human Reproduction and Embryology. 2012. Available at: http://www.eshre.eu/ESHRE/English/Press-Room/Press-Releases/Press-releases-2012/5-million-babies/page.aspx/1606. Accessed October 16, 2012.

4. De Geyter C. European IVF-monitoring of ART and development of a strategy for vigilance, *Presented at the annual meeting of the European Society for Human Reproduction*, Barcelona, Spain, 2018.

5. Kushnir VA, Barad DH, Albertini DF, Darmon SK, Gleicher N. Systematic review of worldwide trends in assisted reproductive technology, 2004–2013. Reprod Biol Endocrinol 2017;15:6.

6. Chambers GM, Sullivan EA, Ishihara O, Chapman MG, Adamson GD. The economic impact of assisted reproductive technology: a review of selected developed countries. Fertil Steril 2009;91:2281–94.

7. Harris JA, Menke MN, Haefner JK, Moniz MH, Perumalswami CR. Geographic access to assisted reproductive technology health care in the United States: a population-based cross-sectional study. Fertil Steril 2017;107:1023–7.

8. Gaskins AJ, Chavarro JE. Diet and fertility: a review. Am J Obstet Gynecol 2018;218:379–89.

9. Karayiannis D, Kontogianni MD, Mendorou C, Mastrominas M, Yiannakouris N. Adherence to the Mediterranean diet and IVF success rate among non-obese women attempting fertility. Hum Reprod 2018;33:494–502.

10. Vujkovic M, de Vries JH, Lindemans J, et al. The preconception Mediterranean dietary pattern in couples undergoing in vitro fertilization/intracytoplasmic sperm injection treatment increases the chance of pregnancy. Fertil Steril 2010;94:2096–101.

11. Twigt JM, Bolhuis ME, Steegers EA, et al. The preconception diet is associated with the chance of ongoing pregnancy in women undergoing IVF/ICSI treatment. Hum Reprod 2012;27:2526–31.

12. Messerlian C, Williams PL, Ford JB, et al. The Environment and Reproductive Health (EARTH) study: a prospective preconception cohort. Hum Reprod Open 2018;2018.

13. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26; discussion 1127-36.

14. US Department of Agriculture Agricultural Research Service. USDA National Nutrient Database for Standard Reference, release 25. Nutrient Data Laboratory home page; 2012.

15. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int JEpidemiol 1989;18:858–67.

16. Yuan C, Spiegelman D, Rimm EB, et al. Validity of a dietary questionnaire assessed by comparison with multiple weighed dietary records or 24-hour recalls. Am J Epidemiol 2017;185:570–84.

17. Panagiotakos DB, Pitsavos C, Arvaniti F, Stefanadis C. Adherence to the Mediterranean food pattern predicts the prevalence of hypertension, hypercholesterolemia, diabetes and obesity, among healthy adults; the accuracy of the MedDietScore. Prev Med 2007;44:335–40.

18. Chiuve SE, Fung TT, Rimm EB, et al. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr 2012;142:1009–18.

19. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Diet and lifestyle in the prevention of ovulatory disorder infertility. Obstet Gynecol 2007;110:1050–8.

20. Gaskins AJ, Afeiche MC, Wright DL, et al. Dietary folate and reproductive success among women undergoing assisted reproduction. Obstet Gynecol 2014;124:801–9.

21. Gaskins AJ, Chiu YH, Williams PL, et al. Association between serum folate and vitamin B-12 and outcomes of assisted reproductive technologies. Am J Clin Nutr 2015;102:943–50.

22. Szymanski W, Kazdepka-Zieminska A. [Effect of homocysteine concentration in follicular fluid on a degree of oocyte maturity]. Ginekol Pol 2003;74:1392–6.

23. Boxmeer JC, Macklon NS, Lindemans J, et al. IVF outcomes are associated with biomarkers of the homocysteine pathway in monofollicular fluid. Hum Reprod 2009;24:1059–66.

24. Abadia L, Gaskins AJ, Chiu YH, et al. Serum 25-hydroxyvitamin D concentrations and treatment outcomes of women undergoing assisted reproduction. Am J Clin Nutr 2016;104:729–35.

25. Chu J, Gallos I, Tobias A, Tan B, Eapen A, Coomarasamy A. Vitamin D and assisted reproductive treatment outcome: a systematic review and meta-analysis. Hum Reprod 2018;33:65–80.

26. Chiu YH, Williams PL, Gillman MW, et al. Association between pesticide residue intake from consumption of fruits and vegetables and pregnancy outcomes among women undergoing infertility treatment with assisted reproductive technology. JAMA Intern Med 2018;178:17–26.

27. Gaskins AJ, Chiu YH, Williams PL, et al. Maternal whole grain intake and outcomes of in vitro fertilization. Fertil Steril 2016;105:1503–10.e4.

28. Nassan FL, Chiu YH, Vanegas JC, et al. Intake of protein-rich foods in relation to outcomes of infertility treatment with assisted reproductive technologies. Am J Clin Nutr 2018;108:1104–12.

29. Braga DP, Halpern G, Setti AS, Figueira RC, Iaconelli A Jr, Borges E Jr. The impact of food intake and social habits on embryo quality and the likelihood of blastocyst formation. Reprod Biomed Online 2015;31:30–8.

30. Afeiche MC, Chiu YH, Gaskins AJ, et al. Dairy intake in relation to in vitro fertilization outcomes among women from a fertility clinic. Hum Reprod 2016;31:563–71.

31. Vanegas JC, Afeiche MC, Gaskins AJ, et al. Soy food intake and treatment outcomes of women undergoing assisted reproductive technology. Fertil Steril 2015;103:749–55.e2.

32. Unfer V, Casini ML, Gerli S, Costabile L, Mignosa M, Di Renzo GC. Phytoestrogens may improve the pregnancy rate in in vitro fertilization-embryo transfer cycles: a prospective, controlled, randomized trial. Fertil Steril 2004;82:1509–13.

33. Gaskins AJ, Williams PL, Keller MG, et al. Maternal physical and sedentary activities in relation to reproductive outcomes following IVF. Reprod Biomed Online 2016;33:513–21.

34. Fitzmaurice GM, Laird NM, Ware JH. Missing data and dropout. Chapter 14. Applied longitudinal analysis. Hoboken, NJ: John Wiley and Sons, Inc; 2004.

35. Searle SR, Speed FM, Milliken GA. Population marginal means in the linear model: an alternative to least square means. Am Statist 1980;34:216–21.
36. US Food and Drug Administration. Pesticide monitoring program, fiscal year 2012 pesticide report. Silver Spring (MD): US Food and Drug Administration; 2012.
37. Fantke P, Friedrich R, Jolliet O. Health impact and damage cost assessment of pesticides in Europe. Environ Int 2012;49:9–17.

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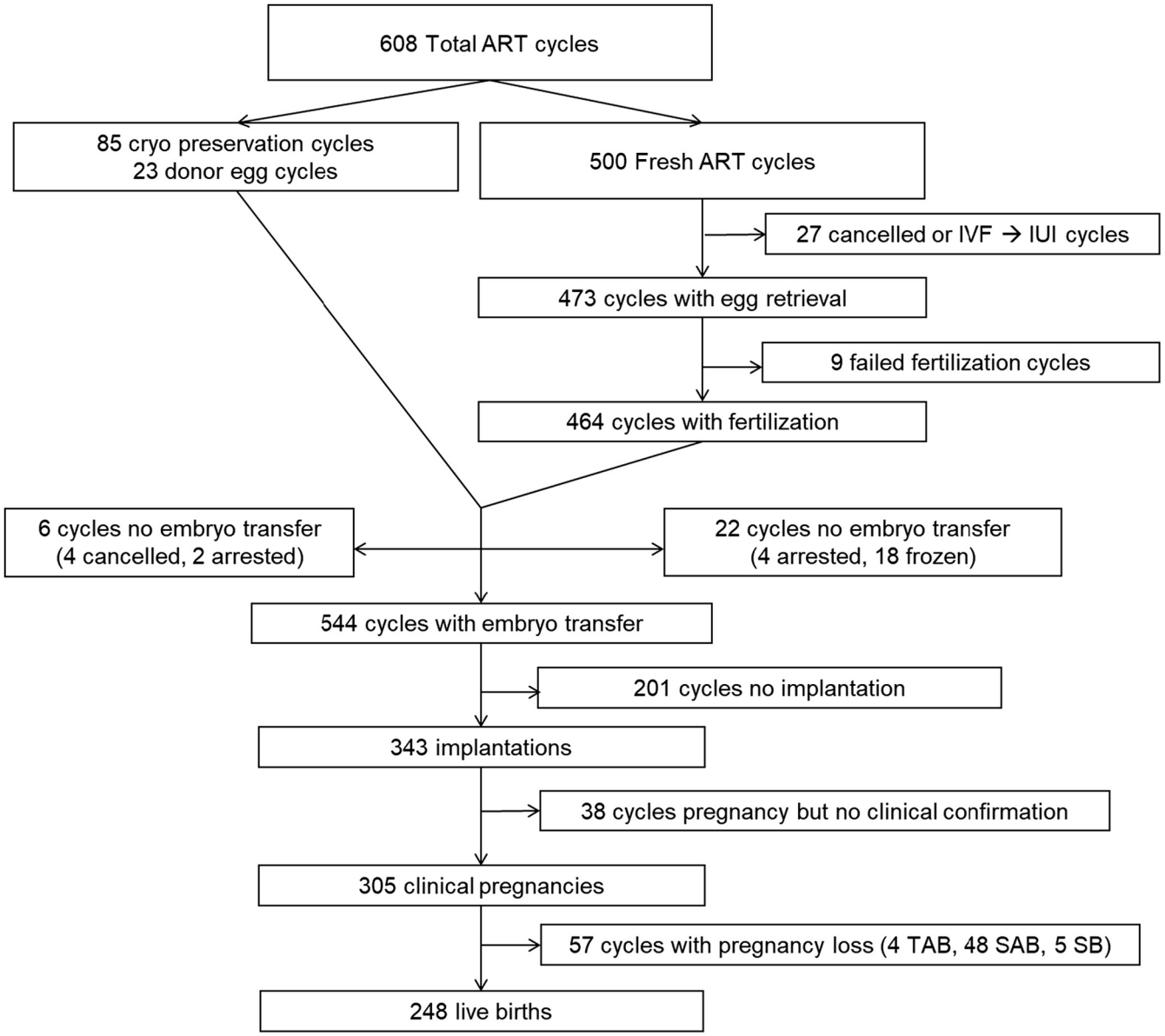
SUPPLEMENTAL FIGURE 1
Overview of ART cycles of preconception dietary patterns and ART



Overview of the 605 initiated ART cycles included in the analysis of preconception dietary patterns and ART outcomes in EARTH.

ART, assisted reproductive technology; *EARTH*, Environment and Reproductive Health; *IUI*, intrauterine insemination; *SAB*, spontaneous abortion; *SB*, stillbirth; *TAB*, therapeutic abortion.

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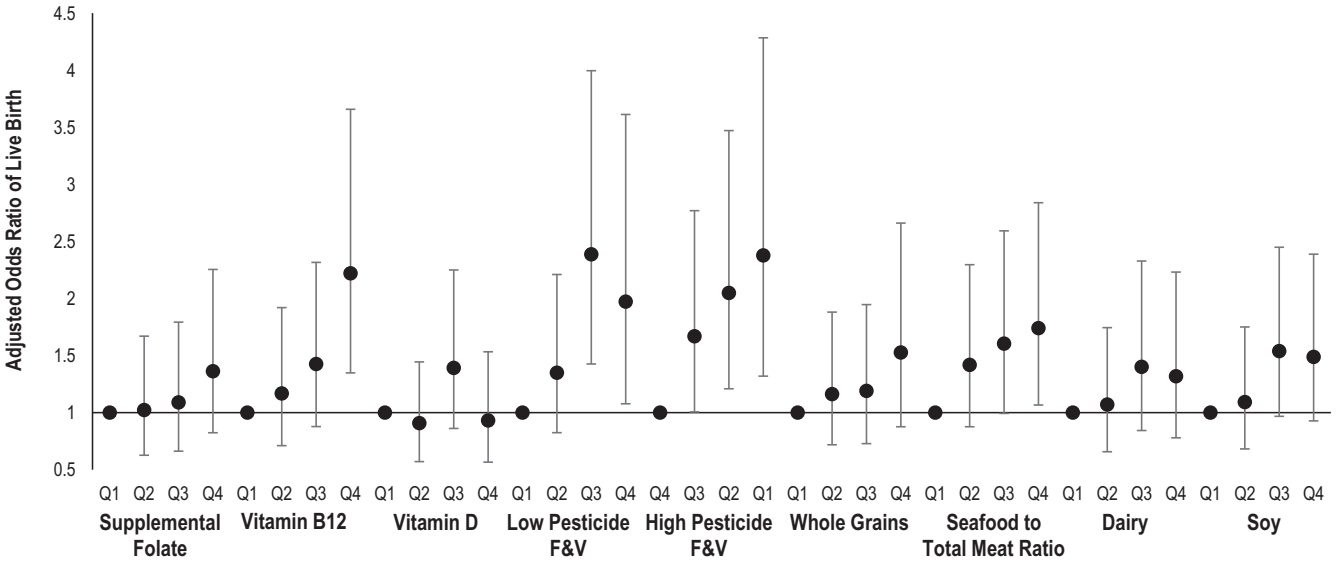
SUPPLEMENTAL FIGURE 2
Association between pretreatment adherence to profertility diet and live birth



Association between pretreatment adherence to components of the profertility diet and odds of live birth following ART in the EARTH study. Analyses were run using generalized linear mixed models with random intercepts, binomial distribution, and logit link function adjusted for calorie intake, age, body mass index, smoking status, and moderate to vigorous exercise. Each component was analyzed separately, not adjusting for the other components, with the exception of high- and low-pesticide fruits and vegetables.

EARTH, Environment and Reproductive Health; *F&V*, fruits and vegetables.

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SUPPLEMENTAL TABLE 1
Spearman correlations between adherence to several healthy dietary pattern scores and the Profertility Diet (n = 375 unique FFQs)

Diets	Profertility	MedDiet	aHEI2010	Fertility diet
Profertility	1.0	0.34	0.29	0.38
MedDiet		1.0	0.61	0.33
aHEI2010			1.0	0.45
Fertility diet				1.0

aHEI2010, alternate Healthy Eating Index 2010; *FFQ*, food frequency questionnaire; *MedDiet*, Mediterranean diet.

The MedDiet is based on the dietary intake of 11 items: vegetables, potatoes, legumes, fruits, whole grains, red meat, fish, poultry, alcohol, full-fat dairy, and olive oil (range, 0—55). The aHEI2010 is based on the dietary intake of 11 items: vegetables (excluding potatoes), fruit, whole grains, nuts and legumes, long-chain omega-3 fats, polyunsaturated fat, alcohol, sugar-sweetened beverages and fruit juice, red and processed meat, *trans*-fat, and sodium (range. 0—110). The fertility diet is based on the dietary intake of 8 items: ratio of monounsaturated fats to *trans*-fats, percentage of energy from vegetable protein, percentage energy from animal protein, high-fat dairy, iron, multivitamins, glycemic load, and low-fat dairy (range, 8— 40).

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SUPPLEMENTAL TABLE 2

Baseline characteristics of 357 women (375 unique FFQs) by quartile of pretreatment adherence to the Mediterranean diet in the EARTH study

Characteristics	Mediterranean diet (MedDiet)				
Quartile (range)	Q1 (17–28)	Q2 (29–31)	Q3 (32–33)	Q4 (34–44)	*P* value[a]
Number of women/FFQs	90/92	93/100	74/76	100/107	
Personal characteristics					
Age, y	35.7 (3.8)	34.9 (4.5)	35.2 (3.8)	35.5 (4.0)	.29
Ever smoker, n (%)	31 (33.7)	24 (24.0)	16 (21.1)	29 (27.1)	.27
White, n (%)	73 (79.4)	87 (87.0)	63 (82.9)	91 (85.1)	.52
Education, n (%)					.71
High school or less	8 (8.7)	7 (7.0)	8 (10.5)	6 (5.6)	
College	31 (24.0)	39 (39.0)	21 (27.6)	38 (35.5)	
Graduate school	53 (57.6)	54 (54.0)	47 (61.8)	63 (58.9)	
BMI, kg/m^2	24.2 (3.8)	24.8 (4.7)	24.3 (4.5)	23.2 (3.9)	.02
Moderate to vigorous exercise, h/wk	2.8 (3.4)	4.0 (4.3)	4.1 (4.1)	4.7 (4.9)	.005
Baseline cycle characteristics					
Infertility diagnosis, n (%)					.49
Female factor	30 (32.6)	36 (36.0)	22 (29.0)	29 (27.1)	
Male factor	32 (34.8)	27 (27.0)	19 (25.0)	33 (30.8)	
Unexplained	30 (32.6)	37 (37.0)	35 (46.1)	45 (42.1)	
Treatment protocol, n (%)					.32
Antagonist	16 (17.4)	6 (6.0)	14 (18.4)	12 (11.2)	
Flare	12 (13.0)	12 (12.0)	7 (9.2)	10 (9.4)	
Luteal phase agonist	54 (58.7)	72 (72.0)	49 (64.5)	76 (71.0)	
Egg donor or cryo cycle	10 (10.9)	10 (10.0)	6 (7.9)	9 (8.4)	
Day 3 FSH, IU/L	7.3 (1.7)	7.4 (3.1)	7.3 (2.2)	7.4 (2.8)	.69
Embryo transfer day, n (%)[b]					.66
Day 2	4 (5.7)	3 (3.9)	2 (3.0)	7 (8.2)	
Day 3	31 (44.3)	38 (48.7)	37 (56.1)	39 (45.9)	
Day 5	35 (50.0)	37 (47.4)	27 (40.9)	39 (45.9)	
Number of embryos transferred, n (%)[b]					.29
One embryo	19 (27.1)	13 (16.9)	17 (25.8)	26 (30.6)	
Two embryos	39 (55.7)	52 (67.5)	33 (50.0)	45 (52.9)	
Three or more embryos	12 (17.1)	12 (15.6)	16 (24.2)	14 (16.5)	
Dietary characteristics					
Total calories, kcal/d	1602 (551)	1725 (542)	1799 (564)	2030 (628)	< .001
Carbohydrates, kcal/d, %	47.6 (8.8)	47.5 (6.7)	50.9 (7.7)	50.3 (7.4)	< .001
Protein, kcal/d, %	16.9 (3.2)	17.0 (2.7)	16.9 (2.7)	16.2 (2.5)	.07

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SUPPLEMENTAL TABLE 2

Baseline characteristics of 357 women (375 unique FFQs) by quartile of pretreatment adherence to the Mediterranean diet in the EARTH study *(continued)*

Characteristics	Mediterranean diet (MedDiet)				
Quartile (range)	Q1 (17–28)	Q2 (29–31)	Q3 (32–33)	Q4 (34–44)	*P* value[a]
Fat, of kcal/d, %	33.7 (6.8)	33.8 (5.5)	30.8 (6.0)	33.0 (6.9)	< .001
Alcohol, g/d	7.6 (12.7)	9.0 (9.9)	9.4 (8.9)	9.1 (9.7)	.003
Caffeine, mg/d	143 (126)	119 (101)	122 (108)	127 (98)	.74
Multivitamin use, n (%)	76 (82.6)	87 (88.8)	66 (88.0)	12 (88.8)	.53
Duration of use ≥2 y	55 (72.4)	66 (75.9)	48 (72.7)	67 (70.5)	.88

BMI, body mass index; *EARTH*, Environment and Reproductive Health; *FFQ*, food frequency questionnaire; *Q*, quartile.

[a] *P* values were calculated using a Kruskal-Wallis test for continuous variables and a χ^2 test for categorical variables; [b] Embryo transfer day and number were assessed only among fresh cycles with embryo transfer.

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SUPPLEMENTAL TABLE 3

Baseline characteristics of 357 women (375 unique FFQs) by quartile of pretreatment adherence to the Alternate Healthy Eating Index 2010 in the EARTH Study

Characteristics	Alternate Healthy Eating Index 2010				
Quartile (range)	Q1 (32–60)	Q2 (61–67)	Q3 (68–74)	Q4 (75–99)	*P* value[a]
Number of women/FFQs	92/95	87/89	88/92	90/99	
Personal characteristics					
Age, y	35.1 (4.1)	35.2 (4.3)	35.5 (4.2)	35.5 (3.5)	.65
Ever smoker, n (%)	30 (31.6)	21 (23.6)	22 (23.9)	27 (27.3)	.58
White, n (%)	79 (83.2)	72 (82.0)	77 (83.7)	85 (85.9)	.91
Education, n (%)					.19
High school or less	13 (13.7)	4 (4.5)	5 (5.4)	7 (7.1)	
College	32 (33.7)	34 (38.2)	27 (29.4)	36 (36.4)	
Graduate school	50 (52.6)	51 (57.3)	60 (65.2)	56 (56.6)	
BMI, kg/m^2	24.1 (4.1)	24.5 (4.2)	24.1 (4.7)	23.7 (4.1)	.42
Moderate to vigorous exercise, h/wk	2.8 (3.6)	4.1 (4.1)	3.8 (4.4)	4.9 (4.8)	.001
Baseline cycle characteristics					
Infertility diagnosis, n (%)					.26
Female factor	31 (32.6)	31 (34.8)	30 (32.6)	25 (25.3)	
Male factor	32 (33.7)	27 (30.3)	28 (30.4)	24 (24.2)	
Unexplained	32 (33.7)	31 (34.8)	34 (37.0)	50 (50.5)	
Treatment protocol, n (%)					.10
Antagonist	9 (9.5)	10 (11.2)	11 (12.0)	18 (18.2)	
Flare	7 (7.4)	9 (10.1)	17 (18.5)	8 (8.1)	
Luteal phase agonist	68 (71.6)	62 (69.7)	53 (57.6)	68 (68.7)	
Egg donor or cryo cycle	11 (11.6)	8 (9.0)	11 (12.0)	5 (5.1)	
Day 3 FSH, IU/L	7.1 (2.4)	7.3 (1.9)	7.7 (3.3)	7.2 (2.3)	.87

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SUPPLEMENTAL TABLE 3

Baseline characteristics of 357 women (375 unique FFQs) by quartile of pretreatment adherence to the Alternate Healthy Eating Index 2010 in the EARTH Study *(continued)*

Characteristics	Alternate Healthy Eating Index 2010				
Quartile (range)	Q1 (32–60)	Q2 (61–67)	Q3 (68–74)	Q4 (75–99)	*P* value[a]
Embryo transfer day, n (%)[b]					.14
Day 2	4 (5.3)	2 (2.8)	3 (4.4)	7 (8.5)	
Day 3	32 (42.1)	31 (43.1)	42 (60.9)	40 (48.8)	
Day 5	40 (52.6)	39 (54.2)	24 (34.8)	35 (42.7)	
Number of embryos transferred, n (%)[b]					.45
One embryo	17 (22.4)	23 (31.9)	14 (20.6)	21 (25.6)	
Two embryos	49 (64.5)	34 (47.2)	41 (60.3)	45 (54.9)	
Three or more embryos	10 (13.2)	15 (20.8)	13 (19.1)	16 (19.5)	
Dietary characteristics					
Total calories, kcal/d	1675 (539)	1779 (609)	1853 (673)	1878 (541)	.09
Carbohydrates, of kcal/day%	49.8 (7.9)	49.6 (7.1)	50.0 (6.8)	46.8 (8.6)	.04
Protein, kcal/d, %	16.5 (2.8)	17.0 (2.9)	16.7 (2.7)	16.7 (2.7)	.64
Fat, kcal/d, %	32.5 (6.3)	32.1 (5.5)	31.9 (5.1)	35.1 (7.7)	.005
Alcohol, g/d	6.9 (12.6)	8.1 (9.0)	9.4 (9.8)	10.7 (9.5)	< .001
Caffeine, mg/d	119 (112)	118 (102)	138 (114)	135 (105)	.27
Multivitamin use, n (%)	80 (85.1)	79 (88.8)	79 (87.8)	86 (86.9)	.90
Duration of use ≥2 y	57 (71.3)	61 (77.2)	54 (68.4)	64 (74.4)	.62

BMI, body mass index; *EARTH*, Environment and Reproductive Health; *FFQ*, food frequency questionnaire; *FSH*, follicle-stimulating hormone; *Q*, quartile.

[a] *P* values were calculated using a Kruskal-Wallis test for continuous variables and a χ^2 test for categorical variables; [b] Embryo transfer day and number were assessed only among fresh cycles with embryo transfer.

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SUPPLEMENTAL TABLE 4

Baseline characteristics of 357 women (375 unique FFQs) by quartile of pretreatment adherence to the Fertility Diet in the EARTH study

Characteristics	Fertility diet				
Quartile (range)	Q1 (13-22)	Q2 (23-25)	Q3 (26-28)	Q4 (29-35)	*P* value[a]
Number of women/FFQs	99/100	93/98	89/95	76/82	
Personal characteristics					
Age, y	35.2 (4.2)	35.3 (4.0)	35.6 (4.1)	35.1 (3.8)	.95
Ever smoker, n (%)	21 (21.0)	30 (30.6)	23 (24.2)	26 (31.7)	.29
White, n (%)	84 (84.0)	81 (82.7)	76 (80.0)	73 (89.0)	.43
Education, n (%)					.004
High school or less	17 (17.0)	6 (6.1)	4 (4.2)	2 (2.4)	
College	32 (32.0)	30 (30.6)	38 (40.0)	29 (35.4)	
Graduate school	51 (51.0)	62 (63.3)	53 (55.8)	51 (62.2)	
BMI, kg/m^2	24.6 (4.9)	24.8 (4.3)	23.6 (3.8)	23.2 (3.6)	.03
Moderate to vigorous exercise, h/wk	3.3 (3.7)	4.4 (4.4)	4.4 (5.0)	3.6 (3.9)	.19

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SUPPLEMENTAL TABLE 4

Baseline characteristics of 357 women (375 unique FFQs) by quartile of pretreatment adherence to the Fertility Diet in the EARTH study *(continued)*

Characteristics	Fertility diet				
Quartile (range)	Q1 (13-22)	Q2 (23-25)	Q3 (26-28)	Q4 (29-35)	*P* value[a]
Baseline cycle characteristics					
Infertility diagnosis, n (%)					.51
Female factor	27 (27.0)	38 (38.8)	29 (30.5)	23 (28.1)	
Male factor	30 (30.0)	30 (30.6)	27 (28.4)	24 (29.3)	
Unexplained	43 (43.0)	30 (30.6)	39 (41.1)	35 (42.7)	
Treatment protocol, n (%)					.41
Antagonist	14 (14.0)	9 (9.2)	13 (13.7)	12 (14.6)	
Flare	9 (9.0)	11 (11.2)	11 (11.6)	10 (12.2)	
Luteal phase agonist	70 (70.0)	62 (63.3)	65 (68.4)	54 (65.9)	
Egg donor or cryo cycle	7 (7.0)	16 (16.3)	6 (6.3)	6 (7.3)	
Day 3 FSH, IU/L	7.0 (1.7)	7.5 (2.8)	7.7 (3.3)	7.1 (1.8)	.72
Embryo transfer day, n (%)[b]					.14
Day 2	2 (2.4)	5 (6.8)	2 (2.7)	7 (10.3)	
Day 3	36 (43.9)	41 (55.4)	35 (46.7)	33 (48.5)	
Day 5	44 (53.7)	28 (37.8)	38 (50.7)	28 (41.2)	
Number of embryos transferred, n (%)[b]					.75
One embryo	17 (20.7)	16 (21.9)	20 (26.7)	22 (32.4)	
Two embryos	48 (58.5)	44 (60.3)	42 (56.0)	35 (51.5)	
Three or more embryos	17 (20.7)	13 (17.8)	13 (17.3)	11 (16.2)	
Dietary characteristics					
Total calories, kcal/d	1845 (571)	1872 (637)	1740 (570)	1714 (592)	.13
Carbohydrates, kcal/d, %	49.7 (7.8)	48.6 (7.2)	49.9 (8.1)	47.6 (7.9)	.21
Protein, kcal/d, %	17.2 (2.6)	17.0 (2.8)	16.9 (3.1)	15.7 (2.4)	$<$ .001
Fat, kcal/d, %	31.6 (5.7)	32.9 (6.7)	32.5 (6.3)	35.1 (6.5)	.008
Alcohol, g/d	8.1 (11.5)	9.7 (11.3)	7.3 (7.4)	10.3 (10.7)	.07
Caffeine, mg/d	142 (118)	131 (115)	106 (91.1)	132 (104)	.18
Multivitamin use, n (%)	59 (60.2)	93 (95.9)	93 (97.9)	79 (96.3)	$<$ .001
Duration of use $\geq$2 y	42 (71.2)	67 (72.0)	72 (77.4)	55 (69.6)	.68

BMI, body mass index; *EARTH*, Environment and Reproductive Health; *FFQ*, food frequency questionnaire; *FSH*, follicle-stimulating hormone; *Q*, quartile.

[a] *P* values were calculated using a Kruskal-Wallis test for continuous variables and a χ^2 test for categorical variables; [b] Embryo transfer day and number were assessed only among fresh cycles with embryo transfer.

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SUPPLEMENTAL TABLE 5

Association between pretreatment adherence to the profertility diet and probability of failing at various points during an ART cycle in the EARTH Study

	Adjusted proportions (95% CI)[a]			
	Failing prior to embryo transfer (n = 608 cycles)	Total pregnancy loss (n = 343 cycles)[b]	Biochemical loss (n = 343 cycles)[c]	Clinical pregnancy loss (n = 305 cycles)[d]
Profertility diet				
Q1 (11–20)	0.13 (0.08–0.19)	0.28 (0.19–0.39)	0.12 (0.06–0.22)	0.18 (0.11–0.28)
Q2 (21–23)	0.13 (0.08–0.21)	0.38 (0.29–0.49)	0.12 (0.07–0.20)	0.28 (0.19–0.40)
Q3 (24–25)	0.06 (0.03–0.12)	0.26 (0.18–0.36)	0.09 (0.05–0.17)	0.18 (0.11–0.28)
Q4 (26–32)	0.06 (0.03–0.13)	0.16 (0.10–0.25)	0.09 (0.05–0.15)	0.08 (0.04–0.15)
P for trend	.03	.02	.60	.01
	Adjusted odds ratio (95% CI)[a]			
	Failing prior to embryo transfer (n = 608 cycles)	Total pregnancy loss (n = 343 cycles)[b]	Biochemical loss (n = 343 cycles)[c]	Clinical pregnancy loss (n = 305 cycles)[d]
Profertility diet (per 1 SD)	0.75 (0.57–0.98)	0.74 (0.60–0.92)	0.90 (0.67–1.19)	0.69 (0.54–0.90)

ART, assisted reproductive technologies; *CI*, confidence interval; *EARTH*, Environment and Reproductive Health; *Q*, quartile.

[a] Analyses were run using logistic regression models with generalized estimating equations. Data are presented as predicted marginal proportions (95% CI) or odds ratios (95% CI) adjusted for calorie intake, age, body mass index, smoking status, and moderate to vigorous exercise; [b] Defined as a positive beta-human chorionic gonadotropin that did not result in live birth; [c] Defined as a positive beta-human chorionic gonadotropin that did result in clinical pregnancy; [d] Defined as a clinical pregnancy that did not result in live birth.

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SUPPLEMENTAL TABLE 6

Sensitivity analyses for the associations between pre-treatment adherence to various dietary patterns and probability of live birth following ART in the EARTH study

	Adjusted proportion of live birth (95% CI)[a]				
Diets	Main analysis (n = 608 cycles)	Only first ART cycle (n = 357 cycles)	Only fresh cycles (n = 473 cycles)	Only cycles within 1 y of FFQ (n = 437 cycles)	Only cycles with embryo transfer (n = 544 cycles)
Profertility diet					
Q1 (11–20)	0.33 (0.26–0.40)	0.34 (0.25–0.44)	0.34 (0.26–0.42)	0.29 (0.21–0.38)	0.38 (0.30–0.46)
Q2 (21–23)	0.32 (0.25–0.40)	0.37 (0.27–0.47)	0.37 (0.28–0.46)	0.32 (0.24–0.42)	0.38 (0.30–0.47)
Q3 (24–25)	0.48 (0.39–0.57)[b]	0.51 (0.40–0.62)[b]	0.49 (0.39–0.60)[b]	0.49 (0.38–0.60)	0.52 (0.42–0.61)[b]
Q4 (26–32)	0.56 (0.47–0.64)[b]	0.56 (0.45–0.67)[b]	0.55 (0.45–0.65)[b]	0.56 (0.45–0.66)	0.60 (0.51–0.69)[b]
P for trend	< .001	< .001	.002	< .001	< .001
MedDiet					
Q1 (17–28)	0.31 (0.25–0.39)	0.35 (0.25–0.46)	0.35 (0.27–0.44)	0.31 (0.22–0.42)	0.35 (0.27–0.43)
Q2 (29–31)	0.47 (0.39–0.55)[b]	0.52 (0.42–0.62)[b]	0.50 (0.41–0.60)[b]	0.47 (0.37–0.57)[b]	0.55 (0.46–0.64)[b]
Q3 (32–33)	0.44 (0.36–0.53)[b]	0.42 (0.31–0.54)	0.41 (0.32–0.52)	0.41 (0.31–0.52)	0.48 (0.39–0.57)[b]
Q4 (34–44)	0.41 (0.34–0.49)	0.45 (0.35–0.55)	0.44 (0.35–0.53)	0.40 (0.31–0.50)	0.47 (0.39–0.56)[b]
P for trend	.06	.31	.26	.25	.05
aHEI2010					
Q1 (32–60)	0.44 (0.36–0.52)	0.51 (0.41–0.61)	0.44 (0.36–0.54)	0.49 (0.38–0.60)	0.48 (0.40–0.57)
Q2 (61–67)	0.42 (0.34–0.50)	0.47 (0.37–0.58)	0.47 (0.38–0.57)	0.39 (0.29–0.49)	0.47 (0.38–0.55)
Q3 (68–74)	0.40 (0.33–0.49)	0.35 (0.25–0.46)[b]	0.39 (0.30–0.49)	0.35 (0.26–0.46)	0.47 (0.38–0.56)
Q4 (75–99)	0.37 (0.29–0.45)	0.41 (0.31–0.51)	0.40 (0.31–0.50)	0.38 (0.30–0.48)	0.42 (0.34–0.51)
P for trend	.19	.07	.34	.15	.41
Fertility diet					
Q1 (13–22)	0.37 (0.30–0.45)	0.41 (0.32–0.52)	0.39 (0.31–0.48)	0.37 (0.28–0.47)	0.42 (0.34–0.51)
Q2 (23–25)	0.42 (0.35–0.50)	0.45 (0.35–0.56)	0.42 (0.33–0.51)	0.39 (0.30–0.49)	0.47 (0.38–0.55)
Q3 (26–28)	0.42 (0.34–0.50)	0.43 (0.33–0.53)	0.44 (0.35–0.54)	0.40 (0.30–0.50)	0.48 (0.39–0.57)
Q4 (29–35)	0.43 (0.34–0.52)	0.46 (0.34–0.57)	0.46 (0.36–0.56)	0.46 (0.35–0.57)	0.48 (0.38–0.58)
P for trend	.37	.67	.25	.25	.37

aHEI2010, alternate Healthy Eating Index 2010; *ART*, assisted reproductive technologies; *CI*, confidence interval; *EARTH*, Environment and Reproductive Health; *FFQ*, food frequency questionnaire; *MedDiet*, Mediterranean Diet; *Q*, quartile.

[a] Analyses used generalized linear mixed models with random intercepts, binomial distribution, and logit link. Data are presented as predicted marginal proportions (95% CI) adjusted for calorie intake, age, body mass index, smoking status, and moderate to vigorous exercise; [b] $P < .05$ for comparison of specific quartile vs quartile 1 (reference).

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