Maternal and Pediatric Nutrition

Dietary Energy Density and Fertility: Results from the Lifestyle and Fertility Study

Terryl J Hartman,[1,2] June L Fung,[3] Pao Ying Hsiao,[4] Wenyi Fan,[5] Diane C Mitchell,[6] and Marlene B Goldman[3]

[1]Department of Epidemiology, Rollins School of Public Health, Atlanta, GA, USA; [2]Emory Prevention Research Center , Atlanta, GA, USA; [3]Department of Obstetrics and Gynecology, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA; [4]Department of Food and Nutrition, Indiana University of Pennsylvania, Indiana, PA, USA; [5]Department of Biostatistics, Emory University, Atlanta, GA, USA; and [6]Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA, USA

ABSTRACT

Background: Diet is a modifiable lifestyle factor linked with fertility in a growing number of studies.

Objective: The objective of this study was to evaluate the association between dietary energy density (ED), a summary measure of diet quality that estimates the amount of energy per unit food (kcal/g) consumed, and conception and pregnancy outcomes.

Methods: A prospective cohort study of couples planning their first pregnancy was conducted in the Northeast region of the USA. Dietary data were collected prior to conception via 3 unannounced interviewer-administered 24-h dietary recalls. Multivariable-adjusted logistic regression (ORs and Cox proportional hazards models [RR] and 95% CIs) were estimated for continuous and categorical (tertile [T]) variables of dietary ED.

Results: The majority of women ($n = 80$; 61%) achieved clinical pregnancy. Median time to conception of a clincal pregnancy(TTC) for those who conceived was 4.64 mo with an IQR of 4.37 mo. ED modeled as a continuous variable was not associated with clinical pregnancy, live birth, or TTC after controlling for race, physical activity, and male partner's ED. When ED was categorized to consider nonlinear associations, 60%, 73%, and 50% of the participants in the tertiles (from lowest ED to highest) achieved clinical pregnancy. In multivariable logistic analyses with the middle group as the referent (ED = 1.37–1.60), membership in the highest ED group (ED >1.60) was associated with lower odds of clinical pregnancy (OR = 0.30; 95% CI: 0.11, 0.81, $P = 0.02$). In Cox proportional hazards analyses, membership in the highest ED group was associated with significantly longer TTC compared with the middle category (HR = 0.41; 95% CI: 0.21,0.82, $P = 0.01$).

Conclusions: These results suggest that high dietary ED is associated with reduced fertility. This study evaluated associations between dietary energy density and the probability of conceiving clinical pregnancy, having a live birth, and the time to conception among couples planning pregnancy. *Curr Dev Nutr* 2021;5:nzab075.

Keywords: diet, energy density, calorie density, fertility, pregnancy

Manuscript received February 1, 2021. Initial review completed April 20, 2021. Revision accepted April 26, 2021. Published online April 28, 2021.

Research reported in this publication was supported by the *Eunice Kennedy Shriver* National Institute of Child Health & Human Development of the NIH under Award Numbers R01HD049762 and R01HD049762S1. The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of the NIH.

Author disclosures: The authors report no conflicts of interest.

Address correspondence to TJH (e-mail: tjhartm@emory.edu).

Abbreviations used: AHEI-P, Alternative Healthy Eating Index for Pregnancy; ED, energy density; NDSR, Nutrition Data System for Research software; T, tertile; TTC, time to conception of a clinical pregnancy.

Introduction

Infertility is the failure to conceive after 12 mo of regular unprotected sexual intercourse (1). Impaired fecundity additionally includes difficulty carrying an infant to full term (1). There is a 20–25% probability of conception per month for healthy young couples with no known infertility conditions (1). Nevertheless, data from the US National Survey of Family Growth indicate that ∼6% and 15–18% of women aged under 35 y experience infertility and impaired fecundity, respectively (2). For nearly 1/3 of infertile couples the origin remains unknown (3).

Diet is a modifiable lifestyle factor linked with fertility in a growing number of studies (4). A recent review of the epidemiologic literature on nutrition and fertility concluded that, based on the limited data available, concordance with overall healthful dietary patterns higher in fish, poultry, whole grains, vegetables, and fruits may be positively associated with female fertility and improved semen quality in males (4). The review also highlighted that no prospective studies have jointly assessed measures of female and male diet quality on infertility or impaired fecundity.

In the current study, we evaluated the association between dietary energy density (ED), assessed prior to attempting conception, on the probability of conceiving a clinical pregnancy and having a live birth, and the time to conception among couples planning their first pregnancy. We hypothesized that higher ED would be associated with unfavorable outcomes. Dietary ED is a summary measure of diet quality that estimates the amount of energy per unit food (kcal/g) consumed (5). Low-ED diets are generally lower in fat and higher in fiber, fruits, and vegetables (6), consistent with the healthful dietary patterns that have been linked to better fertility (4). Consuming an energy-dense diet has been positively associated with body weight in both children and adults and may be a contributing factor to risk of chronic disease (7–10).

Methods

Design and study participants

The Lifestyle and Fertility Study (ISIS) was a multisite, prospective cohort study of healthy, nulliparous couples with no known infertility conditions, planning their first pregnancy. Other eligibility criteria for women included having regular menstrual periods and using contraception at the time of enrollment, and no history of polycystic ovary syndrome or PCOS, endometriosis, or serious medical conditions such as diabetes, cancer, or heart disease. We conducted preliminary telephone screening on 802 female participants between May 2008 and June 2012 at sites in Boston, MA, Lebanon, NH, and University Park, PA. Of these, 536 did not meet our eligibility criteria, 85 were not interested in participating, and the remaining 181 were invited for in-person screening. After in-person screening, 135 were interested in participating and eligible for enrollment. A total of 132 women aged 18–39 y and their male partners (all but 1, i.e. $n = 131$) were enrolled. Between the screening and the baseline visits 2 women became pregnant and 1 decided not to participate. The protocol was approved by the participating institutions' human subjects review boards and all participants provided written informed consent. The study was conducted according to the guidelines laid down in the Declaration of Helsinki. The study was registered at clinicaltrials.gov as NCT00642590.

Data collection

Demographic characteristics, medical history, and lifestyle factors, including dietary intake, were self-reported at baseline (before attempting conception). Height (without shoes) and weight (in light clothing) were measured by trained technicians and used to calculate BMI (kg/m^2). Physical activity was ascertained at baseline and scored as meeting guidelines set by the US Department of Health and Human Services (yes/no) (10, 11). Frequency of intercourse was captured prospectively. Couples were followed from the start of the study protocol until they either achieved a clinically confirmed pregnancy, completed 6 menstrual cycles of attempted conception, or were lost to follow-up.

Pregnancy outcome

We followed our participants to determine whether they conceived or not for 6 menstrual cycles with daily urine collection. Pregnancy ($n = 80/52$ for yes/no pregnancy) was determined by a positive pregnancy test (human chorionic gonadotropin or hCG $\geq$20 mIU/mL; AIM MidStream OTC Professional, Craig Medical Distribution, Inc.) and confirmed clinically by each female participant's physician either using a urine test, blood test, and/or ultrasound. Clinical pregnancies were followed to delivery ($n = 69$) or loss ($n = 11$) and the date recorded. Live birth was defined as a gasp, heartbeat, or sign of life at birth. Time to conception of a clinical pregnancy (TTC) was defined as the length of time from the date the couple began attempting conception (day 1 of the first menstrual cycle after the baseline visit) to the date of the last menstrual period plus 14 d for those who conceived a clinical pregnancy during the study. There were a total of 47 participants who completed follow-up, but did not conceive a clinical pregnancy. Five participants did not have follow-up to determine outcome and were censored at date of last contact.

Dietary assessment

Dietary intake was assessed at baseline using a standardized multipass process including a series of 3, unannounced, telephone 24-h dietary recalls administered on nonconsecutive days (2 weekdays, 1 weekend day) by trained interviewers at the Diet Assessment Center, Penn State University (University Park, PA). Dietary intake assessment was attempted in all participants; however, 2 males did not provide dietary data. Dietary recalls included all foods, beverages, and supplements consumed by participants over the previous 24-h period. The Nutrition Data System for Research software (NDSR, Version 2012, Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN [12]) was used for data entry and nutritional analyses. NDSR output data were used to calculate average daily energy intake (in kcal) and average amount of food consumed (in g) for each participant from food alone, excluding beverages (e.g. differentiating between milk used in cereal compared with milk consumed as a beverage) (13). Beverages have a high water content, and the weight of the beverages, even caloric beverages, like regular soda (has an ED of 0.34 kcal/g which is lower than most vegetables) generally lowers the overall ED of the diet. Dietary ED was calculated as mean energy (kcal)/mean total amount (g) consumed (5).

Statistical analysis

Statistical analyses were performed using SAS Institute, Inc. software (version 9.3). Dietary ED was evaluated as both a continuous variable and categorized into tertiles of intake with the middle tertile serving as the referent. Descriptive statistics were conducted for tertiles of ED and presented as mean $\pm$ SD for continuous and percentages for categorical variables. Multivariable-adjusted logistic regression models (ORs and 95% CIs) were estimated for odds of clinical pregnancy and live birth by continuous and categories of ED. Time to clinical pregnancy was evaluated in Cox proportional hazards regression models. In these models, lower HRs (RR; 95% CI) can be interpreted as less likely to achieve pregnancy (longer TTC). The associations between pregnancy outcomes and dietary ED were evaluated in a series of multivariate models that adjusted for race/ethnicity (white, other), male partner's dietary ED (continuous), physical activity (meeting guidelines versus not), and then with the addition of prepregnancy BMI (continuous kg/m^2) or total energy intake (kcal/d). For categorical ED, the middle tertile (T2) was designated as the referent. A number of other potential covariates were evaluated but did not appreciably contribute to model fit or interpretation and were not included in final models. These variables included female educational status (<college, college degree, graduate degree), household income (<\$60,000, \$60,000–99,999, $\geq$\$100,000), female smoking status (ever versus never), total and *trans* fat intakes (per cent kcal), animal and vegetable protein intake (g/d), and alcohol use (g/d). Attempts at conception per cycle were available for all

TABLE 1 Baseline characteristics of females by tertiles (range) of dietary energy density

Characteristics[1]	T1 (*n* = 44) (0.85–1.36)	T2 (*n* = 44) (1.37–1.60)	T3 (*n* = 44) (1.61–2.66)	*P* value	Overall
Age, y (mean ± SD)	29.7 ± 3.2	29.8 ± 2.7	29.9 ± 3.7	0.92	29.8 ± 3.2
Race, *n* (%)				0.004	
White	28 (21.2)	38 (28.8)	39 (29.6)		105 (79.6)
African American	3 (2.3)	1 (0.8)	3 (2.3)		7 (5.3)
Asian	12 (9.1)	2 (1.5)	2 (1.5)		16 (12.1)
Other/unknown	1 (0.8)	3 (2.3)	0 (0)		4 (3.0)
Education, *n* (%)				0.08	
<College degree	5 (3.8)	1 (0.8)	9 (6.8)		15 (11.4)
College degree	15 (11.4)	19 (14.4)	18 (13.6)		52 (39.4)
Graduate degree	24 (18.2)	24 (18.2)	17 (12.9)		65 (49.2)
Income,[2] *n* (%)				0.36	
<$60,000	15 (11.6)	7 (5.4)	13 (10.1)		35 (27.1)
$60,000–$99,999	11 (8.5)	16 (12.4)	14 (10.9)		41 (31.8)
≥$100,000	16 (12.4)	20 (15.5)	17 (13.2)		53 (41.1)
Smoking status, *n* (%)				0.69	
Never	37 (28.0)	34 (25.8)	33 (25.0)		104 (78.8)
Past use	7 (5.3)	10 (7.6)	10 (7.6)		27 (20.5)
Current use	0 (0)	0 (0)	1 (0.8)		1 (0.8)
Alcohol use, *n* (%)				0.30	
No	12 (9.1)	7 (5.3)	7 (5.3)		26 (19.7)
Yes	32 (24.2)	37 (28.0)	37 (28.0)		106 (80.3)
Activity score (PA), *n* (%)				0.43	
Inactive	9 (6.8)	14 (10.6)	10 (7.6)		33 (25)
Active	35 (26.5)	30 (22.7)	34 (25.8)		99 (75)
BMI, kg/m^2, mean ± SD	24.0 ± 5.4	24.4 ± 5.4	24.6 ± 5.4	0.86	24.3 ± 5.4
Pregnancy outcomes					
Attempts,[3] mean/cycle ± SD	5.7 ± 3.3	7.9 ± 5.5	6.2 ± 3.4	0.04	6.6 ± 4.3
Pregnancy, *n* (% yes)	26 (19.7)	32 (24.2)	22 (16.7)	0.09	80 (60.6)
TTC, mo, mean ± SD	3.3 ± 2.6	3.1 ± 2.1	3.8 ± 2.8	0.37	3.4 ± 2.5
Live birth, *n* (% yes)	23 (17.4)	27 (20.5)	19 (14.5)	0.23	69 (52.3)
Dietary intake, mean ± SD					
Energy, kcal	1461 ± 381	1755 ± 384	1963 ± 523	<0.0001	1726 ± 478
Protein, % kcal	16.5 ± 4.0	16.0 ± 3.2	15.9 ± 3.9	0.65	16.1 ± 3.7
Animal, g/1000 kcal	24.0 ± 11.0	23.7 ± 8.2	24.4 ± 9.6	0.83	24.3 ± 9.6
Vegetable, g/1000 kcal	17.6 ± 4.3	16.5 ± 3.7	14.5 ± 3.5	0.001	16.2 ± 4.0
Carbohydrate, % kcal	55.2 ± 7.7	50.5 ± 6.5	48.6 ± 7.6	<0.0001	51.4 ± 7.7
Fat, % kcal	26.9 ± 5.8	30.9 ± 5.4	33.3 ± 5.7	<0.0001	30.4 ± 6.2
Trans fat, g/1000 kcal	0.9 ± 0.6	1.2 ± 0.5	1.6 ± 0.8	<0.0001	1.3 ± 0.7
Fiber, g/1000 kcal	15.1 ± 5.1	13.0 ± 4.9	10.2 ± 4.0	<0.0001	12.8 ± 5.1
Male energy density	1.5 ± 0.3	1.7 ± 0.4	1.9 ± 0.4	<0.0001	1.7 ± 0.4

[1]Values are mean ± SD for continuous variables or *n* (%) for categorical variables; *n* = 132 for most variables.
[2]3 participants reported unknown incomes.
[3]9 participants did not report pregnancy attempts.
PA, physical activity; TTC, time to conception of a clinical pregnancy in months.

but 9 couples who became pregnant in a short time period (<1 mo); thus, this variable was considered in sensitivity analyses. In Cox models, potential effect modification by age and BMI was evaluated by modeling multiplicative interaction terms between variables for ED and time.

Results

The majority of participants (n = 80 women; 61%) achieved clinical pregnancy. Among those who conceived, the median TTC was 4.64 mo with an IQR of 4.37 mo (data not presented). Compared with women consuming lower-ED diets, those who consumed higher-ED diets were more likely to be Caucasian (**Table 1**). Male partners of women reporting higher ED diets also reported higher ED diets. As expected, women consuming higher-ED diets reported intakes higher in total energy, total and *trans* fat, and lower in dietary fiber. From the lowest to the highest category (tertile) of ED, 60% (26/44), 73% (32/44), and 50% (22/44) of the participants achieved clinical pregnancy.

In logistic regression analyses (**Table 2**), ED modeled as a continuous variable was not significantly associated with either clinical pregnancy or live birth after adjustment for maternal race and activity level and male dietary ED. In the categorical ED analysis, women reporting ED diets in the highest tertile (T3: ED >1.60) were significantly less likely to achieve pregnancy ($OR_{T3versus2}$ = 0.29; 95% CI: 0.11, 0.76, P <0.01) than women in the middle category of ED (ED = 1.37–1.60). There was

TABLE 2 Association between energy density and odds of clinical pregnancy ($n = 80$) and live birth ($n = 69$) for participants of the Lifestyle and Fertility study

	Clinical pregnancy			Live birth		
Model	OR	95% CI	*P* value	OR	95% CI	*P* value
ED continuous						
ED (Model 1)	0.87	(0.33, 2.31)	0.79	0.80	(0.31, 2.06)	0.64
ED + race + male ED + PA (Model 2)	0.38	(0.12, 1.24)	0.11	0.40	(0.13, 1.26)	0.12
Model 2 + BMI (Model 3)	0.38	(0.12, 1.24)	0.11	0.39	(0.12, 1.26)	0.12
Model 2 + total energy (Model 4)	0.44	(0.12, 1.69)	0.23	0.60	(0.16, 2.22)	0.44
Above Model (4) + attempts[2]	0.22	(0.04, 1.08)	0.06	0.39	(0.08, 1.90)	0.24
ED categorical[1]						
ED + race + male ED + PA (Model 5)[1]						
ED low (<1.37)	0.84	(0.32, 2.21)	0.72	1.10	(0.44, 2.80)	0.84
ED high (>1.6)	0.29	(0.11, 0.76)	<0.01	0.43	(0.17, 1.07)	0.07
Model 5 + BMI (Model 6)[1]						
ED low (<1.37)	0.83	(0.32, 2.18)	0.70	1.09	(0.43, 2.77)	0.85
ED high (>1.6)	0.30	(0.11, 0.78)	0.01	0.44	(0.17, 1.10)	0.08
Model 5 + total energy (Model 7)[1]						
ED low (<1.37)	0.80	(0.30, 2.19)	0.67	0.93	(0.35, 2.47)	0.89
ED High (>1.6)	0.30	(0.11, 0.81)	0.02	0.49	(0.19, 1.24)	0.13
Above Model (7) + attempts[2]						
ED low (<1.37)	0.99	(0.32, 3.09)	0.99	1.06	(0.35, 3.17)	0.92
ED high (>1.6)	0.26	(0.09, 0.77)	0.02	0.50	(0.17, 1.40)	0.18

[1]For categorical ED the referent is the middle tertile (ED 1.37–1.60). All variables are female except for male ED. BMI is measured prepregnancy. OR <1 means odds of pregnancy/live birth are lower.
[2]Sensitivity analyses – conception attempts are missing for 9 couples.
ED, energy density; PA, physical activity.

also a suggestion that the high-ED group was less likely to have a live birth ($OR_{T3versus2} = 0.43$; 95% CI: 0.17, 1.07, $P = 0.07$). The addition of either female prepregnancy BMI or total energy to these models did not appreciably alter our overall conclusions. Women consuming the lowest ED diets (T_1) showed some evidence that they were less likely to achieve pregnancy compared with the middle tertile ($OR_{T1versus2} = 0.84$; 95% CI: 0.32, 2.21, $P = 0.72$), but results did not reach statistical significance. In multivariable Cox proportional hazards regression models (Table 3), higher dietary ED (continuous) among females was associated with longer TTC which approached statistical significance (HR = 0.48; 95% CI: 0.21, 1.14, $P = 0.10$). In multivariable analyses with the middle ED group as the referent, membership in the highest ED group (categorical) was associated with significantly longer TTC ($HR_{T3versus2} = 0.41$; 95% CI: 0.21, 0.80, $P < 0.01$). The estimated TTC for women in the lowest ED group (ED = 0.85–1.36) was longer than the reference group; but results were not statistically significant ($HR_{T1versus2} = 0.77$; 95% CI: 0.41, 1.42, $P = 0.40$). When we further adjusted the categorical ED models by female prepregnancy BMI or total energy intake the results changed little. In addition, in sensitivity analyses, when we considered the addition of total or *trans* fat, or animal or vegetable protein, each in turn, to our models, the results for ED did not meaningfully change (data not presented) and our overall conclusions remained the same. Lastly, results for multivariate logistic and time to conception analyses did not differ by either age or prepregnancy BMI.

Discussion

In the first study to examine the role of dietary ED in achieving pregnancy, we observed that women who consumed high-ED diets preconceptually were less likely to achieve clinical pregnancy and experienced longer TTC. In addition, there was a suggestion that women who consumed high-ED diets prior to pregnancy were less likely to have a live birth; however, our numbers were more limited for those analyses and results should be interpreted cautiously.

Relatively few studies have examined the influence of preconceptual overall dietary quality on fertility. In general, our results are consistent with those of other investigators who noted that healthful dietary patterns promote fertility among healthy women without a history of infertility. Three previous studies have evaluated the association between preconceptual dietary patterns and fertility among healthy women planning pregnancy (14–16). Chavarro and colleagues (14) reported that among 17,544 women in the Nurses' Health Study II (NHSII), diets featuring more vegetable protein and high-fat dairy sources, more MUFAs and fewer *trans* fatty acids, lower glycemic load, and including regular multivitamin supplements, were associated with a lower risk of ovulatory disorder infertility. Toledo and colleagues (15) found that greater concurrence (highest quartile – Q4) with a Mediterranean-type dietary pattern derived through factor analysis was associated with a lower risk of difficulty becoming pregnant ($OR_{Q4versus1} = -0.56$; 95% CI: 0.35, 0.90, $P = 0.01$) in a Spanish nested case-control study ($n = 485$). In contrast, we recently reported in the Lifestyle and Fertility Study that greater adherence with the Alternative Healthy Eating Index for Pregnancy (AHEI-P) was not significantly associated with achieving clinical pregnancy or TTC, even after adjustment for covariates (16). Although these are seemingly contradictory results, these 2 measures of diet quality likely capture different constructs. The AHEI-P is an *a priori* summary dietary index that includes several subscales scored individually and summed which focus on foods (e.g. vegetables, fruits, whole grains, sugar-sweetened beverages, nuts and legumes, red and

TABLE 3 Association between energy density and time to conception for participants of the Lifestyle and Fertility study

Model	HR	95% CI	*P* value
ED continuous			
ED (Model 1)	0.86	(0.42, 1.71)	0.66
ED + race + male ED + PA (Model 2)	0.48	(0.20, 1.14)	0.10
Model 2 + BMI (Model 3)	0.50	(0.21, 1.18)	0.12
Model 2 + total energy (Model 4)	0.54	(0.21, 1.41)	0.21
Above Model (4) + attempts[2]	0.51	(0.19, 1.32)	0.16
ED categorical[1]			
ED + race + Male ED + PA (Model 5)[1]			
ED low (<1.37)	0.77	(0.41, 1.42)	0.40
ED high (>1.6)	0.41	(0.21, 0.80)	0.009
Model 5 + BMI (Model 6)[1]			
ED low (<1.37)	0.76	(0.41, 1.40)	0.38
ED high (>1.6)	0.42	(0.22, 0.82)	0.01
Model 5 + total energy (Model 7)[1]			
ED low (<1.37)	0.67	(0.34, 1.30)	0.24
ED high (>1.6)	0.42	(0.22, 0.82)	0.01
Above model (5) + attempts[2]			
ED low (<1.37)	0.87	(0.46, 1.68)	0.69
ED high (>1.6)	0.44	(0.23, 0.87)	0.02

[1]For categorical ED the referent is the middle tertile (ED 1.37–1.60). All variables are female except for male ED. BMI is measured prepregnancy. HR <1 means TTC is longer. HR <1 means delayed TTC.
[2]Sensitivity analyses – conception attempts are missing for 9 couples.
ED, energy density; PA, physical activity.

processed meats), macronutrients (PUFA-, *trans*-, and ω-3 fatty acids), and sodium, including components for nutrients important for pregnancy (e.g. calcium, folate, and iron) (17).

Dietary ED may play a role in fertility through interactions of modifiable dietary factors including total energy intake, diet composition, nutrient intakes as well as other characteristics of foods. Of the macronutrients, fat has the most influence on ED because it contributes the most energy by weight. Not surprisingly, consumption of high-ED diets contributes to increased energy intake and has been associated with obesity (10, 18, 19). Obese women (BMI $\geq$30) experience endocrine dysregulation and in previous research have demonstrated higher risk of infertility (20, 21). In our population, prepregnancy BMI and dietary ED were only modestly correlated (Spearman correlation 0.08; $P = 0.35$), and the associations we observed between consuming a high-ED diet and unfavorable fertility outcomes remained significant after adjustment for BMI or total energy intake (Tables 2 and 3). Notably, previous studies have shown that metabolic consequences associated with high-fat and high-ED diets such as unfavorable lipid profiles, insulin resistance, inflammation, and oxidative stress (19, 22, 23) might impact fertility, independent of obesity (24–26). Dietary patterns characterized by higher fat consumption and lower intakes of fiber-rich foods like fruits, vegetables, and whole grains also tend to be lower in antioxidants. A 2013 Cochrane review (27) evaluated 28 antioxidant trials and concluded that supplemental oral antioxidants were not associated with increased live birth or clinical pregnancy rates, but did not address antioxidant intake contributed by diet. There are many possibilities through which dietary antioxidants might influence fertility (28, 29). Clearly, this is an area that deserves further study. Finally, converging lines of evidence suggest that foods, particularly energy-dense, high-fat animal products, fast and processed foods, may be important routes of exposure to environmental contaminants, including those which are potential endocrine disruptors and may disrupt hormonally mediated physiological processes important in fertility (30–34). This is also an area in need of future research.

In addition to high-ED diets there is a possibility that very low-ED diets may also have negative effects on conception. Women consuming the lowest ED diets (T1) showed some evidence of reduced fertility compared with the middle tertile, but results were not significant. Low-ED diets are generally higher in fiber and were so in this population. Previous studies have observed that diets higher in fiber may influence menstrual function and ability to conceive (35). For example, Andrews and colleagues reported a modestly positive association between higher intakes of dietary fiber and luteal phase deficiency, a menstrual cycle disturbance associated with recurrent miscarriages and infertility (36, 37), (OR = 1.10; 95% CI: 0.99, 1.23, $P = 0.07$) after adjustment for age, per cent body fat, and total energy intake, among 246 women in the BioCycle Study.

Strengths of our study include its prospective design, including dietary intake and lifestyle characteristics collected prior to attempting pregnancy, measured weight and height that allowed us to accurately assess BMI, and confirmation of clinical pregnancy. All women were nulliparous and planning their first pregnancy. We assessed dietary intake in detail with repeated, unannounced telephone 24-h recalls among both women and their male partners. Mean ED in this population of women (mean ED = 1.5) was comparable to that reported for US women at similar BMIs ($\sim$1.4) (10). Limitations are that this study was modest in size and includes mostly non-Hispanic white, healthy, and better-educated women aged 18–39 y planning pregnancy. These factors may have some implications for the generalizability of our observations to more diverse populations of women.

In summary, results of our study suggest that higher ED diets may be associated with lower probability of conceiving a clinical pregnancy and longer time to conception among couples planning their first pregnancy. Additional research is needed to corroborate these findings and to identify potential underlying mechanisms for dietary ED in fertility-related outcomes. Future research in large, well-characterized prospective birth cohorts may wish to explore whether dietary ED is associated with additional maternal pregnancy-related outcomes, including gestational weight gain and pregnancy complications such as pre-eclampsia or gestational diabetes, or with infant characteristics, such as preterm birth and birth size.

Acknowledgments

We are grateful to the couples who participated in the study.

The authors' responsibilities were as follows—all authors: participated in the study concept and research design; WF and TJH: analyzed the data; TJH: had primary responsibility for writing the manuscript; all authors: contributed to interpretation of data and read, edited, and approved the final manuscript.

Data Availability

The data underlying this article may be shared at a later date upon reasonable request to the corresponding author and after final approval by the principal investigator.

References

1. Fritz MAS L. Clinical Gynecology and Infertility, 8th ed. Philadelphia, PA: Lippincott, Williams and Wilkins. 2011.
2. Key statistics from the National Survey of Family Growth: National Center for Health Statistics, Centers for Disease Control and Prevention. 2015.
3. Gelbaya TA, Potdar N, Jeve YB, Nardo LG. Definition and epidemiology of unexplained infertility. Obstet Gynecol Surv 2014;69(2):109–15.
4. Gaskins AJ, Chavarro JE. Diet and fertility: a review. Am J Obstet Gynecol 2018;218(4):379–89.
5. Vernarelli JA, Mitchell DC, Rolls BJ, Hartman TJ. Methods for calculating dietary energy density in a nationally representative sample. Procedia Food Science 2013;2:68–74.
6. Vernarelli JA, Mitchell DC, Hartman TJ, Rolls BJ. Dietary energy density is associated with body weight status and vegetable intake in U.S. children. J Nutr 2011;141(12):2204–10.
7. Hartman TJ, Gapstur SM, Gaudet MM, Shah R, Flanders WD, Wang Y, McCullough ML. Dietary energy density and postmenopausal breast cancer incidence in the Cancer Prevention Study II Nutrition Cohort. J Nutr 2016;146(10):2045–50.
8. Hartman TJ, McCullough ML, Hodge JM, Gaudet MM, Wang Y, Gapstur SM. Dietary energy density, glycemic load, glycemic index, and risk for endometrial cancer in the CPS-II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev 2018;27(1):113–5.
9. Jones JA, Hartman TJ, Klifa CS, Coffman DL, Mitchell DC, Vernarelli JA, Snetselaar LG, Van Horn L, Stevens VJ, Robson AM, et al. Dietary energy density is positively associated with breast density among young women. Journal of the Academy of Nutrition and Dietetics 2015;115(3): 353–9.
10. Vernarelli JA, Mitchell DC, Rolls BJ, Hartman TJ. Dietary energy density is associated with obesity and other biomarkers of chronic disease in US adults. Eur J Nutr 2015;54(1):59–65.
11. US Department of Health and Human Services. Physical Activity Guidelines for Americans. Washington, DC. 2008.
12. NDS-R, 2010ed. Minneapolis, MN: Nutrition Coordinating Center. 2012.
13. Johnson L, Wilks DC, Lindroos AK, Jebb SA. Reflections from a systematic review of dietary energy density and weight gain: is the inclusion of drinks valid? Obes Rev 2009;10(6):681–92.
14. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Diet and lifestyle in the prevention of ovulatory disorder infertility. Obstetrics & Gynecology 2007;110(5):1050–8.
15. Toledo E, Lopez-del Burgo C, Ruiz-Zambrana A, Donazar M, Navarro-Blasco I, Martinez-Gonzalez MA, de Irala J. Dietary patterns and difficulty conceiving: a nested case-control study. Fertil Steril 2011;96(5):1149–53.
16. Hsiao PY, Fung JL, Mitchell DC, Hartman TJ, Goldman MB. Dietary quality, as measured by the Alternative Healthy Eating Index for Pregnancy (AHEI-P) in couples planning their first pregnancy. Public Health Nutr 2019;22(18):3385–94.
17. Poon AK, Yeung E, Boghossian N, Albert PS Zhang C. Maternal dietary patterns during third trimester in association with birthweight characteristics and early infant growth. Scientifica 2013;2013:786409.
18. Rolls BJ. The relationship between dietary energy density and energy intake. Physiol Behav 2009;97(5):609–15.
19. Hingle MD, Wertheim BC, Neuhouser ML, Tinker LF, Howard BV, Johnson K, Liu S, Phillips LS, Qi L, Sarto G, et al. Association between dietary energy density and incident type 2 diabetes in the Women's Health Initiative. Journal of the Academy of Nutrition and Dietetics 2017;117(5):778–785.e1.
20. Panth N, Gavarkovs A, Tamez M, Mattei J. The influence of diet on fertility and the implications for public health nutrition in the United States. Frontiers in Public Health 2018;6:211.
21. Rich-Edwards JW, Spiegelman D, Garland M, Hertzmark E, Hunter DJ, Colditz GA, Willett WC, Wand H, Manson JE. Physical activity, body mass index, and ovulatory disorder infertility. Epidemiology 2002;13(2):184–90.
22. Manna P, Jain SK. Obesity, oxidative stress, adipose tissue dysfunction, and the associated health risks: causes and therapeutic strategies. Metabolic Syndrome and Related Disorders 2015;13(10):423–44.
23. Wang J, Luben R, Khaw KT, Bingham S, Wareham NJ, Forouhi NG. Dietary energy density predicts the risk of incident type 2 diabetes: the European Prospective Investigation of Cancer (EPIC)-Norfolk Study. Diabetes Care 2008;31(11):2120–5.
24. Pugh SJ, Schisterman EF, Browne RW, Lynch AM, Mumford SL, Perkins NJ, Silver R, Sjaarda L, Stanford JB, Wactawski-Wende J, et al. Preconception maternal lipoprotein levels in relation to fecundability. Hum Reprod 2017;32(5):1055–63.
25. Wise LA, Rothman KJ, Mikkelsen EM, Sorensen HT, Riis A, Hatch EE. An internet-based prospective study of body size and time-to-pregnancy. Hum Reprod 2010;25(1):253–64.
26. Grieger JA, Grzeskowiak LE, Smithers LG, Bianco-Miotto T, Leemaqz SY, Andraweera P, Poston L, McCowan LM, Kenny LC, Myers J, et al. Metabolic syndrome and time to pregnancy: a retrospective study of nulliparous women. BJOG: An International Journal of Obstetrics & Gynaecology 2019;126(7):852–62.
27. Showell MG, Brown J, Clarke, , Hart RJ. Antioxidants for female subfertility. Cochrane Database Syst Rev 2013;(8):CD007807.
28. Ruder EH, Hartman TJ, Blumberg J, Goldman MB. Oxidative stress and antioxidants: exposure and impact on female fertility. Hum Reprod Update 2008;14(4):345–57.
29. Ruder EH, Hartman TJ, Goldman MB. Impact of oxidative stress on female fertility. Curr Opin Obstet Gynecol 2009;21(3):219–22.
30. Arrebola JP, Castano A, Esteban M, Bartolome M, Perez-Gomez B Ramos JJ. Differential contribution of animal and vegetable food items on persistent organic pollutant serum concentrations in Spanish adults. Data from BIOAMBIENT.ES project. Sci Total Environ 2018;634:235–42.
31. Darnerud PO, Atuma S, Aune M, Bjerselius R, Glynn A, Grawe KP, Becker W. Dietary intake estimations of organohalogen contaminants (dioxins, PCB, PBDE and chlorinated pesticides, e.g. DDT) based on Swedish market basket data. Food Chem Toxicol 2006;44(9):1597–606.
32. Minguez-Alarcon L, Messerlian C, Bellavia A, Gaskins AJ, Chiu YH, Ford JB, Azevedo AR, Petrozza JC, Calafat AM, Hauser R, et al. Urinary concentrations of bisphenol A, parabens and phthalate metabolite mixtures in relation to reproductive success among women undergoing in vitro fertilization. Environ Int 2019;126:355–62.

33. Ehrlich S, Williams PL, Missmer SA, Flaws JA, Ye X, Calafat AM, Petrozza JC, Wright D, Hauser R. Urinary bisphenol A concentrations and early reproductive health outcomes among women undergoing IVF. Hum Reprod 2012;27(12):3583–92.
34. Mok-Lin E, Ehrlich S, Williams PL, Petrozza J, Wright DL, Calafat AM, Ye X, Hauser R. Urinary bisphenol A concentrations and ovarian response among women undergoing IVF. Int J Androl 2010;33(2):385–93.
35. Harlow SD, Ephross SA. Epidemiology of menstruation and its relevance to women's health. Epidemiol Rev 1995;17(2):265–86.
36. Li TC, Spuijbroek MD, Tuckerman E, Anstie B, Loxley M, Laird S. Endocrinological and endometrial factors in recurrent miscarriage. BJOG 2000;107(12):1471–9.
37. Potdar N, Konje JC. The endocrinological basis of recurrent miscarriages. Curr Opin Obstet Gynecol 2005;17(4):424–8.