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Original Articles

Diet and Lifestyle in the Prevention of Ovulatory Disorder Infertility

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Abstract

OBJECTIVE: To evaluate the relation of a dietary pattern and other lifestyle practices to risk of ovulatory disorder infertility.

METHODS: We followed a cohort of 17,544 women without a history of infertility for 8 years as they tried to become pregnant or became pregnant. A dietary score based on factors previously

related to lower ovulatory disorder infertility (higher consumption of monounsaturated rather than trans fats, vegetable rather than animal protein sources, low glycemic carbohydrates, high fat dairy, multivitamins, and iron from plants and supplements) and other lifestyle information was prospectively related to the incidence of infertility.

RESULTS: Increasing adherence to a “fertility diet” pattern was associated with a lower risk of ovulatory disorder infertility. The multivariable-adjusted relative risk of ovulatory disorder infertility comparing women in the highest with women in the lowest quintile of the “fertility diet” pattern score was 0.34 (95% confidence interval 0.23–0.48; *P* for trend <.001). This inverse relation was similar in subgroups defined by women’s age, parity, and body weight. A combination of five or more low-risk lifestyle factors, including diet, weight control, and physical activity was associated with a 69% lower risk of ovulatory disorder infertility and an estimated population attributable risk of 66% (95% confidence interval 29–86%).

CONCLUSION: Following a “fertility diet” pattern may favorably influence fertility in otherwise healthy women. Further, the majority of infertility cases due to ovulation disorders may be preventable through modifications of diet and lifestyle.

LEVEL OF EVIDENCE: II

Infertility is a common condition affecting one of six couples during their reproductive lifetime.¹ Among these couples, problems with ovulation can be identified in 18–30% of the cases.^{1–3} Although treatment options for infertility are available, their large cost^{4,5} and frequency of adverse events^{6,7} have motivated the identification of potentially modifiable risk factors. We have previously found that body weight,^{8,9} physical activity,⁹ and dietary factors, such as intakes of specific fatty acids,¹⁰ protein (Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Protein intake and ovulatory infertility. *Am J Obstet Gynecol*. In press), carbohydrates (Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. A prospective study of dietary carbohydrate quantity and quality in relation to risk of ovulatory infertility. *Eur J Clin Nutr*. In press), dairy foods,¹¹ iron,¹² and multivitamins,¹³ are related to infertility due to ovulation disorders. These findings suggest that an overall dietary and lifestyle pattern aimed at increasing the intake of certain micronutrients and improving insulin sensitivity through the modification of diet composition, weight control, and increased physical activity may help prevent ovulatory disorder infertility. However, the degree to which a fertility-promoting dietary pattern, by itself or in combination with changes in body weight and physical activity, may reduce infertility is unknown, as is the proportion of cases that could be prevented. To address these questions, we conducted a prospective observational analysis of diet, physical activity, and body weight in relation to incident infertility due to ovulation disorders among apparently healthy women enrolled in the Nurses’ Health Study II.

MATERIALS AND METHODS

The Nurses’ Health Study II is prospective cohort study started in 1989 when more than 116,000 female registered nurses aged 25–42 years completed a mailed baseline questionnaire. Participants

have been followed biennially since then with mailed questionnaires. The study was approved by the Institutional Review Board of Brigham and Women's Hospital.

Follow-up for the current analysis started in 1991, when diet was first measured, and concluded in 1999. Every 2 years participants were asked if they had tried to become pregnant for more than 1 year without success since the previous questionnaire administration and to indicate whether their inability to conceive was caused by tubal blockage, ovulatory disorder, endometriosis, cervical mucus factor, male factor, or was not found, was not investigated, or was due to another reason. In a validation study among members of this cohort, self-reported diagnosis of ovulatory disorder infertility was confirmed by review of medical records in 95% of the cases.⁸ Women were also asked if they became pregnant during the preceding 2-year period, including pregnancies resulting in miscarriages or induced abortions. Using this information, we identified a cohort of women most likely attempting to become pregnant. Only married women (whose pregnancies are more likely to be intentional¹⁴) without a history of infertility and with available information on diet, physical activity, height, and weight were eligible to enter the analysis. These women contributed information to the analysis during each 2-year period in which they reported a pregnancy or a failed pregnancy attempt and were followed until they reported infertility from any cause, reached menopause, or underwent a sterilization procedure (themselves or their partner), whichever came first. We excluded the 10 diabetic women meeting these criteria. In total, we identified 17,544 women without a history of infertility who tried to become pregnant or became pregnant during the study period.

Reports of infertility due to ovulatory disorder were considered cases. All other events (pregnancies—resulting in live births, miscarriages, or induced abortions—and infertility due to other causes) were considered noncases.

We calculated body mass index (weight in kilograms divided by height squared in meters) (BMI) using height reported in the 1989 baseline questionnaire and weight reported in the most recent follow-up questionnaire. Self-reported height and weight have high validity in this and similar cohorts.^{15,16} Physical activity information was collected in 1991 and 1997 using a previously validated instrument,¹⁷ in which women reported the average time spent in eight different activities. We summed the contribution of each activity to obtain the average daily time spent in moderate (4–5.9 metabolic equivalents/h) and vigorous physical activities (6 metabolic equivalents/h or more).

Dietary information was collected in 1991 and 1995 using a validated food-frequency questionnaire.^{18,19} This questionnaire has been previously found to validly estimate nutrient intakes 4 years in the past.²⁰ Participants were asked to report how often, on average, they consumed each of the foods, beverages, and supplements included in the food-frequency questionnaire during the previous year. The questionnaire offered nine options for frequency of intake for each food that ranged from “never or less than once per month” to “six or more times per day.” The nutrient content of each food and specified portion size was obtained from a nutrient database derived from the U.S. Department of Agriculture,²¹ with supplemental information from other sources.²² Dietary glycemic load was calculated as the product of total carbohydrate intake

times the average dietary glyceic index.¹⁹

We maintained a strictly prospective analysis of these factors in relation to infertility. Body mass index information from 1991 was related to cases reported in 1993; the 1993 BMI information was used for cases reported in 1995, and so forth. Physical activity data reported in 1991 were related to the 1991–1997 follow-up period, and the data reported in 1997 were related to the remainder of follow-up. For dietary variables we calculated cumulative averaged intakes to reduce measurement error due to within-person variation over time.²³ Thus, the 1991 diet was related to cases reported in 1993 and 1995, and the average of the 1991 and 1995 diets was related to cases reported in 1997 and 1999.

A summary “fertility diet” score was calculated for each woman based on variables we had earlier found to predict ovulatory disorder infertility, assigning the highest score to the category with the lowest risk. Thus, for increasing monounsaturated/trans fat ratio, vegetable protein, high-fat dairy, iron, and multivitamins, we assigned from 1 to 5 points from the lowest to the highest category. For animal protein, glyceic load, and low-fat dairy, the point assignment was reversed; women in the lowest intake category received 5 points and women in the highest stratum received 1 point (Table 1). Points for each of the variables were added to obtain the “fertility diet” score, which ranged from 8 to 40. The median score was 24 points. Women were divided into five groups according to quintiles of this score.

Variable	1	2	3	4	5
Ratio of monounsaturated to trans fat	Lowest 10%	10%–20%	20%–30%	30%–40%	Highest 10%
Vegetable protein (% of energy)	Lowest 10%	10%–20%	20%–30%	30%–40%	Highest 10%
Animal protein (% of energy)	Highest 10%	30%–40%	20%–30%	10%–20%	Lowest 10%
Iron (mg)	Lowest 10%	10%–20%	20%–30%	30%–40%	Highest 10%
Glyceic load	Highest 10%	30%–40%	20%–30%	10%–20%	Lowest 10%
Low-fat dairy (servings/wk)	Highest 10%	30%–40%	20%–30%	10%–20%	Lowest 10%
High-fat dairy (servings/d)	Lowest 10%	10%–20%	20%–30%	30%–40%	Highest 10%
Multivitamins (tablets/wk)	Lowest 10%	10%–20%	20%–30%	30%–40%	Highest 10%

Table 1

We also dichotomized vigorous physical activity levels, BMI, and each dietary factor to identify women with the lowest risk of ovulatory disorder infertility. The cutoff points were for vigorous physical activity, more than 30 min/d; for BMI, 20–24.99 kg/m²; for the ratio of monounsaturated to trans fat, the highest 10% of distribution; for animal protein, less than 10% of energy; for vegetable protein, more than 7% of energy; for iron, more than 40 mg; for glyceic load, the bottom 10% of the distribution; for low-fat dairy, less than 1 serving/wk; for high-fat dairy, 1 or more serving/d; and for multivitamins, 6 or more tablets/wk. Women were divided into six groups according to the number of lifestyle factors followed from 0 to 5 or more.

The relative risk (RR, calculated as an odds ratio) of ovulatory disorder infertility in relation to dietary and lifestyle factors was estimated using logistic regression. The generalized estimating equation approach²⁴ with an exchangeable working correlation structure was used to account for the within-person correlation in outcomes at different time periods. We divided women into groups according to levels of fertility diet score, the number of fertility-friendly lifestyle habits followed, BMI, and time spent in vigorous physical activities. In these models, the RR was computed as the risk of infertility in a specific group compared with the risk in the reference group. Tests for linear trend were conducted by using the median values in each category as a continuous variable. Separate models were also fit in subgroups defined according to women’s age, parity, and BMI. All models were initially adjusted for age and calendar time. We subsequently added parity, smoking

history, history of oral contraceptive use, alcohol intake, and coffee intake to the models. The results of the age and calendar time–adjusted models and the multivariable-adjusted models were nearly identical, and only the latter are presented. Values of the dietary and nondietary variables were updated as new data became available from follow-up questionnaires.

The population attributable risk and its 95% confidence interval (CI)²⁵ were used to estimate the proportion of ovulatory disorder infertility cases within this cohort that could have been avoided had all women adhered to specific combinations of low-risk dietary and lifestyle practices, assuming that the associations between these factors and ovulatory disorder infertility are causal. Analyses were performed in SAS 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

During 8 years of follow-up, 25,217 pregnancies and pregnancy attempts were accrued among 17,544 women. Of these, 3,209 were incident reports of infertility (all causes), of which 2,032 were of women who reported undergoing diagnosis for infertility and 416 were of women reporting ovulatory disorder infertility. As expected, a high “fertility diet” score was characterized by a lower intake of trans fat with a simultaneous greater intake of monounsaturated fat; a lower intake of animal protein with greater vegetable protein intake; a higher intake of high-fiber, low-glycemic carbohydrates; greater preference for high-fat dairy products; higher nonheme iron intake; and higher frequency of multivitamin use (Table 2). In addition, women with a high “fertility diet” score were more likely to consume coffee and alcohol and to be physically active. They were also less likely to be smokers, have long menstrual cycles, and be recent users of hormonal contraception.

Table 2. Baseline Characteristics by Quintile of the “Fertility Diet” Score

Characteristic	Quintile of “Fertility Diet” Score				
	1 (lowest)	2	3	4	5 (highest)
Total No. of women	3512	3512	3512	3512	3512
Age (years)	27.1	27.1	27.1	27.1	27.1
Parity (No. of children)	0.1	0.1	0.1	0.1	0.1
Smoking status	15.2	15.2	15.2	15.2	15.2
Alcohol intake (g/day)	10.1	10.1	10.1	10.1	10.1
Coffee intake (cups/day)	1.1	1.1	1.1	1.1	1.1
Physical activity (hours/week)	1.1	1.1	1.1	1.1	1.1
Body mass index (BMI)	24.1	24.1	24.1	24.1	24.1
Menstrual cycle length (days)	28.1	28.1	28.1	28.1	28.1
Use of hormonal contraception	15.2	15.2	15.2	15.2	15.2
Use of oral contraceptives	15.2	15.2	15.2	15.2	15.2
Use of injectable contraceptives	15.2	15.2	15.2	15.2	15.2
Use of intrauterine devices	15.2	15.2	15.2	15.2	15.2
Use of barrier methods	15.2	15.2	15.2	15.2	15.2
Use of fertility awareness methods	15.2	15.2	15.2	15.2	15.2
Use of other methods	15.2	15.2	15.2	15.2	15.2
Use of any method	15.2	15.2	15.2	15.2	15.2
Use of no method	15.2	15.2	15.2	15.2	15.2
Use of unknown method	15.2	15.2	15.2	15.2	15.2
Use of any method except unknown	15.2	15.2	15.2	15.2	15.2
Use of any method except unknown and no method	15.2	15.2	15.2	15.2	15.2
Use of any method except unknown, no method, and oral contraceptives	15.2	15.2	15.2	15.2	15.2
Use of any method except unknown, no method, oral contraceptives, and injectable contraceptives	15.2	15.2	15.2	15.2	15.2
Use of any method except unknown, no method, oral contraceptives, injectable contraceptives, and intrauterine devices	15.2	15.2	15.2	15.2	15.2
Use of any method except unknown, no method, oral contraceptives, injectable contraceptives, intrauterine devices, and barrier methods	15.2	15.2	15.2	15.2	15.2
Use of any method except unknown, no method, oral contraceptives, injectable contraceptives, intrauterine devices, barrier methods, and fertility awareness methods	15.2	15.2	15.2	15.2	15.2
Use of any method except unknown, no method, oral contraceptives, injectable contraceptives, intrauterine devices, barrier methods, fertility awareness methods, and other methods	15.2	15.2	15.2	15.2	15.2

Table 2

Increasing adherence to the “fertility diet” was associated with a lower risk of ovulatory disorder infertility (P for trend $< .001$) and, to a lesser extent, to infertility due to other causes (Table 3). Compared with women in the lowest quintile of the “fertility diet” score, women in the highest quintile had a 66% (95% CI 52–77%) lower risk of ovulatory disorder infertility and a 27% (95% CI 5–43%) lower risk of infertility due to other causes. There was a J-shaped relationship between BMI and ovulatory disorder infertility. Compared with women with a BMI between 20 and 24.9, overweight women (BMI 25–29.9) and women with a BMI below 20 had a similarly higher risk of ovulatory disorder infertility, whereas obese women (BMI of 30 or more) had more than twofold greater risk. This pattern was not present when all infertility cases were considered; women with a BMI below 20 had the highest risk of infertility, and there were no important differences in the risk of infertility at higher levels of BMI. Time spent in vigorous physical activities was unrelated to infertility overall and due to ovulatory disorders. However, when BMI (which is partly determined

by physical activity) was removed from the model, women who engaged in vigorous physical activities for 30 minutes or more each day had a slightly lower risk of infertility due to problems with ovulation (RR 0.78, 95% CI 0.58–1.05).

Table 3. Multivariable Adjusted Relative Risks and 95% Confidence Intervals for Overall and Ovulatory Disorder Infertility According to History and Lifestyle Characteristics

History and Lifestyle Characteristics	Ovulatory Disorder Infertility		All Other Causes of Infertility	
	Case	RR (95% CI)	Case	RR (95% CI)
History of ovulation				
Never	102	1.00	102	1.00
Once	10	0.68 (0.32-1.44)	10	0.68 (0.32-1.44)
Two or more	10	0.68 (0.32-1.44)	10	0.68 (0.32-1.44)
Parity				
Nulliparous	102	1.00	102	1.00
Parous	10	0.68 (0.32-1.44)	10	0.68 (0.32-1.44)
Body mass index (BMI)				
< 25	102	1.00	102	1.00
25-30	10	0.68 (0.32-1.44)	10	0.68 (0.32-1.44)
> 30	10	0.68 (0.32-1.44)	10	0.68 (0.32-1.44)

Table 3

We then considered the association between these factors and ovulatory disorder infertility in subgroups of women according to their age, parity, and BMI (Table 4). The association between the “fertility diet” score and ovulatory infertility was not modified by levels of age, parity, or BMI. Similarly, the relation between BMI and this outcome did not change significantly by age or parity. The association of time spent in vigorous physical activities and ovulatory infertility, however, seemed to be modified by parity (*P* for interaction=.03). Although physical activity was unrelated to ovulatory infertility in parous women, there was a suggestion of an inverse association among nulliparous women, especially when BMI was excluded from the multivariable model (*P* for trend=.06). The RR of ovulatory disorder infertility comparing nulliparous women with at least 30 daily minutes of vigorous physical activity with other nulliparous women was 0.68 (95% CI 0.44–1.04).

Table 4. Multivariable Adjusted Relative Risks and 95% Confidence Intervals for Ovulatory Disorder Infertility According to History and Lifestyle Characteristics by Levels of Age, Parity, and Body Mass Index

Characteristics	Age		Parity		BMI	
	18-24	25-34	Nulliparous	Parous	< 25	≥ 25
History of ovulation						
Never	102	102	102	102	102	102
Once	10	10	10	10	10	10
Two or more	10	10	10	10	10	10
Parity						
Nulliparous	102	102	102	102	102	102
Parous	10	10	10	10	10	10
Body mass index (BMI)						
< 25	102	102	102	102	102	102
25-30	10	10	10	10	10	10
> 30	10	10	10	10	10	10

Table 4

The risk of ovulatory disorder infertility decreased with increasing number of low-risk lifestyle habits followed (*P* for trend<.001) (Fig. 1). Compared with women who did not follow any of these habits, women following one habit had a 30% lower risk of infertility due to ovulatory problems (*P*=.02). The risk of ovulatory disorder infertility was lower for each additional low-risk lifestyle habit followed, up to an 84% lower risk among women following five or more of the habits.

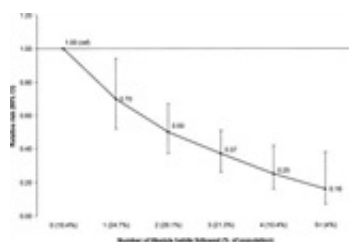


Fig. 1

Last, we calculated the population attributable risk associated with specific combinations of dietary and lifestyle factors to estimate the proportion of cases that may have been avoided had all the women in this cohort adhered to these habits ([Table 5](#)). Diet composition had a greater apparent impact on fertility than either BMI or vigorous physical activity alone. Following a combination of any five lifestyle factors, including diet, BMI between 20 and 24.9, and vigorous physical activity, was associated with a 69% (95% CI 30–86%) lower risk of ovulatory disorder infertility, which translated into a population attributable risk of 66%.

Habit and Lifestyle Characteristics	Number of Women	% of Cohort	OR (95% CI)	Population Attributable Risk (%)
None	10	10	1.0	0
1	10	10	1.0	0
2	10	10	1.0	0
3	10	10	1.0	0
4	10	10	1.0	0
5 or more	10	10	0.31 (0.10–0.96)	69

Table 5

DISCUSSION

We examined the relation between a “fertility diet” pattern and the incidence of infertility and found that increased adherence to this pattern was associated with a substantially lower risk of infertility due to disordered ovulation. Similarly, we found a sixfold difference in ovulatory infertility risk between women following five or more low-risk dietary and lifestyle habits and those following none. Our results suggest that the majority of infertility cases due to ovulation disorders are preventable through modifications of diet and lifestyle. The proportion of cases potentially preventable by following this strategy could be even higher in the general population, because the prevalence of obesity is lower in this cohort (10%) than among comparable women in the general U.S. population (29%).²⁶

Studies regarding the role of diet composition in fertility are scarce. However, our results are consistent with reports by others regarding specific components of this “fertility diet,” including the use of multivitamins,^{27,28} the intake of vegetable protein,²⁹ and the amount and quality of carbohydrates.^{30,31} Because this dietary pattern favors low-glycemic foods while limiting the intake of nutrients that may increase insulin resistance such as trans fatty acids,³² our results are also consistent with the overall hypothesis that glucose homeostasis and insulin sensitivity are important determinants of ovulatory function and fertility in otherwise healthy women, as supported by previous studies.^{33–35} The apparent benefit of consuming moderate amounts of whole-fat dairy products and low amounts of low-fat dairy products on fertility does not have an obvious explanation.

We also found, consistent with earlier reports from this cohort,^{8,9} that increased body weight is related to a higher risk of infertility due to ovulation disorders. Two small randomized trials among women with polycystic ovarian syndrome suggest that weight loss is more important than diet composition in improving reproductive function in these predominantly overweight women,^{36,37} with minor changes attributable to diet composition itself.³⁶ Our results are compatible with those of these trials: the “fertility diet” pattern seemed to be more strongly related to lower ovulatory disorder infertility risk among women with a “healthy” body weight than among overweight and obese women.

We observed a statistically nonsignificant inverse association between time spent in vigorous physical activities and risk of infertility due to ovulatory disorders, which was stronger among nulliparous women. This is in agreement with our previous report⁹ of a lower risk of ovulatory infertility with increasing physical activity levels because that report included many more cases than the current analysis and thus had greater statistical power. Although several studies suggest that intense physical activity may affect ovulation and impair fertility,^{38–40} it is difficult to differentiate between the effect of physical activity and the effect of weight loss associated with strenuous physical activity levels. It is possible that increasing physical activity while maintaining an adequate body weight may improve ovulation and fertility by increasing insulin sensitivity. More importantly, although our data suggest that increased physical activity may be more beneficial in terms of fertility for some women, it also shows that increasing physical activity does not harm the fertility of most women.

There are some important limitations in our study. First, it is not a cohort of women known to be planning to become pregnant. Although cases of infertility were obviously trying to conceive, some of the pregnancy noncases may have conceived accidentally. Nevertheless, we simulated a cohort of pregnancy planners by restricting the study to married women, whose pregnancies are more likely to be intentional,¹⁴ and by considering as noncases reports of infertility due to other causes. This makes it less likely that pregnancy intention affected our results. Second, although assigning points to the different factors of “fertility diet” score is an easy and intuitive method to generate a summary score, the roles that individual factors play becomes obscured. However, since we had previously examined in detail the relation of each factor with ovulatory infertility, this may only be a minor issue in our case. Third, imperfect measurement of diet, physical activity, and other lifestyle factors might have influenced our findings. However, in the case of diet and physical activity, measurement error, mostly due to normal day-to-day variation not captured by the questionnaires, will tend to attenuate the observed associations. In addition, being an observational study, we cannot completely exclude the possibility that our results are due to confounding factors. Nevertheless, adjusting our results for a number of risk factors for infertility had no influence on our results, making it unlikely that unidentified risk factors for infertility could account for these results. Last, because multiple statistical comparisons were performed, it is possible that the statistical significance of some results is overestimated. However, the nominal statistical significance of the observed associations ($<.001$) makes it unlikely that this was a major issue.

Strengths of our study include its prospective design, where information on dietary and lifestyle characteristics was collected at least 2 years before the report of infertility, making it unlikely that subsequent diagnosis or treatment of infertility influenced the results. The use of previously validated questionnaires to assess ovulatory disorder infertility, as well as diet, physical activity, and body weight, adds to the strengths of this study.

In summary, our results suggest that a “fertility diet” pattern may have favorable effects on the fertility of otherwise healthy women and that combining this dietary strategy with body weight control and increased physical activity may help prevent the majority of infertility cases due to problems with ovulation. Because data on the potential role of specific dietary patterns on fertility are scarce, it is important that these findings are reproduced, preferably in large randomized trials. In the meantime, women trying to become pregnant could consider following these lifestyle

practices because they are consistent with an overall healthy lifestyle and may also help them become pregnant.

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