WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 4, 143-159. Research Article ISSN 2277– 7105

DIET AND LIFESTYLE IN THE PREVENTION OF OVULATORY DISORDER INFERTILITY

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Article Received on
21 Jan. 2019,

Revised on 11 Feb. 2019,
Accepted on 04 March 2019

DOI: 10.20959/wjpr20194-14458

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ABSTRACT

Diet, exercise, and energy expenditure (physical activity) define the "energy balance" which modulates body habitus. These modifiable lifestyle factors provide an opportunity for therapeutic intervention in the subfertile. The evidence evaluating dietary and physical activity habits are largely observationally based, with multiple groups providing conflicting results. However, the preponderance of evidence appears to support an approach of moderation, with avoidance of high saturated fat diets, low pesticide residue fruits/vegetables, and maintenance of a low to moderate intensity exercise routine. Body habitus, especially in regard to morbidly obese patients, is more difficult to adjust to a meaningful degree. Obesity itself appears to be a risk factor for infertility, although traditional semen parameters do not tend to reflect reproductive impairment. Aggressive low-calorie diets, and the immediate post-operative period for bariatric surgery, tend to decrease fertility potential. Ultimately, better studies are needed to further our understanding of these lifestyle factors and to inform reproductive urologists to better serve and counsel the subfertile.

KEYWORDS: Diet, Lifestyle, Disorder Infertility.

INTRODUCTION

Infertility is a common condition affecting one of six couples during their reproductive lifetime. Among these couples, problems with ovulation can be identified in 18–30% of the cases.[1]

Although treatment options for infertility are available, their large cost and frequency of adverse events have motivated the identification of potentially modifiable risk factors. We

have previously found that body weight, physical activity, and dietary factors, such as intakes of specific fatty acids, 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.[2]

A prospective study of dietary carbohydrate quantity and quality in relation to the risk of ovulatory infertility. Eur J Clin Nutr. In press), dairy foods iron, and multivitamins, 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.[3]

BACKGROUND

The Role of Nutrition in Fertility Problems

Currently, 1 in 6 women in the US struggles with a fertility problem. Ovulatory infertility accounts for as many as 30% of all cases of infertility[4]. Many women prefer to avoid the expense and potential adverse effects[3] of medical infertility treatment. Nutrition not only plays an important role in achieving pregnancy, but the mother's nutritional status at the time of conception can determine the health of her pregnancy as well as affect embryonic and fetal growth and development. In fact, placental and embryonic development is most vulnerable at the time of conception and can be influenced by maternal nutritional status[5]. For most women, making simple dietary modifications is more affordable; relatively easy compared with the effort involved in conventional fertility treatments; and, for a subset of women preferring natural options, may be more consistent with their personal beliefs about health[6].

Weight and Fertility

Women who are either underweight or overweight are at increased risk for infertility, particularly ovulatory infertility.[7] While PCOS is typically associated with women who are overweight, it can in fact occur at any weight, as can its underlying pathophysiology, insulin

resistance. The relationship between weight loss and resolution of fertility challenges in women with PCOS is well established in the medical literature. Maintaining a BMI between 18.4 and 24.4 appears to be optimal for promoting fertility and preventing or reducing insulin resistance.[8]

Glycemic Load and the Insulin Resistance Connection

The role of insulin resistance is well established in PCOS, which is one of the primary causes of ovulatory infertility problems, and improvement in insulin resistance with weight loss in overweight women with PCOS is known to improve fertility. In the NHS, women whose diets were high in glycemic load had nearly double the risk of ovulatory infertility. Glucose homeostasis and insulin sensitivity appear to be central to healthy ovulatory function and fertility.[9]

Micronutrient Deficiencies: Folic Acid and Anemia in Fertility Challenges

Adequate intake of iron supplements and sources of non-heme iron (i.e., plant-based sources) reduces the risk of ovulatory infertility, whereas this association is not seen with supplementation of heme iron (i.e., from animal sources) Folate is important for oocyte maturation, while zinc is important for healthy ovulation and normal menstruation. Reactive oxygen species have a negative impact on oocyte maturation and ovulation, suggesting the important role for antioxidants in fertility. Poor folate status and elevated levels of homocysteine have been associated with an increased risk of fertility problems, miscarriage, and pregnancy complications, including preeclampsia.[10]

Protein and Ovulatory Infertility:

According to Chavarro et al., a high intake of animal protein leads to a 39% greaterlikelihood of ovulatory infertility than does a diet primarily based on plant protein sources. Further, women with higher protein intake from plant sources (beans, legumes, nuts, seeds) were 22% less likely to experience infertility than women with lower plant protein intake.[11]

Trans Fats and Fertility

The quality of energy and sources of fats appears to be important in ovulatory infertility. Pharmacologic activation of the peroxisome proliferator–activated receptor g (PPAR-g) improves ovulatory function in women with polycystic ovary syndrome, and specific dietary fatty acids can affect PPAR-g activity. According to Chavarro et al., for every 2% increase in the intake of energy from transfats rather than from carbohydrates or omega-6

polyunsaturated fats, there was a 73% increase. Also, obtaining 2% of energy from *trans* fats rather than from monounsaturated fats was associated with a more than doubled risk of ovulatory infertility. Unsaturated fats may increase the risk of ovulatory infertility when consumed instead of carbohydrates or unsaturated fats found in nonhydrogenated vegetable oils.[12]

Dairy and Ovulatory Infertility

Two or more servings per day (versus 1 or less per week) of low-fat dairy products were associated with an 85% increase in ovulatory infertility risk. It appears that a protein component of dairy causes the problem, as the effects were only observed with low-fat dairy, and in fact higher intake of high-fat dairy may decrease risk.[13]

Diet

Multiple investigators have examined the link between diet and male fertility potential. The majority of these studies utilize validated food frequency questionnaires to ascertain the exposures of interest. Many of these studies relied upon healthy volunteers with unknown fertility status. Relatively few investigations have been based upon cohorts characterized by subfertility, and even fewer delve into couple-based fertility outcomes (i.e., live birth rates as opposed to sperm quality assessments). Nevertheless, the literature offers a broad framework to allow physicians to provide informed recommendations regarding a given patient's dietary habits.[14]

Natural fatty acids can be distributed amongst three broad categories dependent upon the number of double bonds along the hydrocarbon backbone: saturated, monounsaturated, and polyunsaturated. Additionally, double bonds allow for cis versus trans configuration, the latter of which occurs rarely in nature.[15]

Several groups have examined semen parameters in relation to fat intake, serving as the one dietary factor with the broadest and most robust set of primary literature. A significant proportion of saturated fats in the western diet are derived from meat intake. Attaman and colleagues examined 99 men who had presented to a single infertility clinic for treatment[16]. Similar to other studies, the investigators used a detailed food frequency questionnaire. However, they also correlated questionnaire responses to fatty acid levels in spermatozoa and seminal plasma. They found a dose-dependent relationship between total fat intake and sperm concentration. Subjects in the highest third of fat intake, compared to the lowest third, had a

38% decrease in sperm concentration (CI 10–58%). The majority of this effect was driven by consumption of saturated fatty acids. In their subanalysis of sperm fatty acid content, no association could be drawn between reported fat intake and levels within the semen. In contrast, they did demonstrate a reliable trend of sperm saturated fatty acid content and sperm concentration ($r = -0.53$).

In a subsequent study, Jensen et al. specifically examined saturated fat intake amongst healthy young men presenting for a military service physical[17]. Their cohort consisted of 701 men with unknown fertility status. Again, they demonstrated a dose-response relationship with the consumption of saturated fats. Comparing the highest quartile against the lowest, they demonstrated a 41% decrease in total sperm count (CI 4– 64%). No correlation was found when comparing other types of fat intake against semen quality. A more contemporary study by Xia et al. further stratified types of meat intake and compared these dietary habits to assisted reproductive technology (ART) outcomes[18]. They prospectively followed 141 couples that underwent a total of 246 ART cycles using in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) as clinically indicated. They demonstrated that poultry intake correlated to higher fertilization rates (78 versus 65%, highest to the lowest quartile, respectively). Pertinent to saturated fat consumption, they examined the rates of processed meat intake. Fertilization rates dropped progressively as processed meat intake increased, with lowest to highest quartiles obtaining a fertilization rate of 82, 67, 70, and 54%, respectively. The decrement in fertilization rate was ameliorated by the use of ICSI, possibly indicating deficient capacitation or an ineffective acrosomal reaction. Ultimately, live birth rates did not correlate with total meat intake, which may reflect ICSI serving as an effective rescue treatment[19].

Beverages The primary literature contains considerably fewer studies examining the reproductive effects of non-alcoholic beverages, most of which investigated the role of caffeinated products. However, over the last century, our fluid intake has shifted markedly from traditional norms. The high consumption of milk, as well as sweetened beverages, now characterizes the western die.[20] A substantial focus on diary consumption and perceived harm to reproductive potential has been fueled by the concept of endocrine disruptors and endocrine active substances.[21] These substances are theorized to affect development, reproductive health, and some cancer risks through ingestions of small amounts via either food, drinking water, or other environmental exposure. In terms of dairy products, a relevant

point is that commonly consumed milk is derived from cows of differing stages of pregnancy. It has been estimated that 60 to 80% of estrogens consumed in our diets are derived from such milk.[22] These dietary estrogens have been suggested as a possible cause of impaired spermatogenesis.[23] Clinical studies, however, have had mixed results in regard to the harmful effects of milk consumption. An early study by Vujkovic et al. utilized a cohort of 161 men recruited from a fertility clinic.[24] They examined a multitude of dietary factors and serum biomarkers, including dairy intake. Their results showed no statistical difference in semen analysis or DNA fragmentation based upon dairy consumption. A subsequent study concentrated specifically on a broader array of dairy products, including non-milk products such as cheese. Afeiche et al. utilized the Rochester Young Men's Study cohort, which consists of a study population of 189 healthy men with ages ranging from 18 to 22 years. Their findings demonstrated an inverse relationship to full fat dairy products and sperm morphology and progressive motility. However, the results did not reach statistical significance when examining low-fat dairy products. It is unclear how much saturated fat intake confounded these results. In a follow-up study by the same group, 155 men recruited from a fertility clinic were stratified based upon low- or high-fat diary consumption.

In this case, low-fat dairy intake correlated with high sperm concentration and progressive motility. Men in the highest quartile of low-fat dairy consumption, compared to the lowest quartile, had 33% (CI 1–55) higher sperm concentration. This result was primarily driven by the ingestion of low-fat milk, whereas cheese intake trended toward worse semen parameters. Given the conflicting and small effect sizes of these studies, it is doubtful that the estrogens consumed via this route contribute appreciably to male subfertility.[25]

Coffee and Caffeine Intake Similar to the inconsistent results of trials associating dairy to reduced semen parameters, the effects of caffeine upon spermatogenesis remain unclear. Caffeine is an adenosine receptor antagonist, which results in a multitude of short-term physiologic effects. Dias and colleagues attempted to characterize these physiologic effects within the male reproductive tract by culturing human Sertoli cells in a variety of caffeine concentrations. Their results demonstrated different metabolic responses based on caffeine dosage. At low to moderate concentrations, Sertoli cells were stimulated to produce lactate, which can improve germ cell survival. However, at high concentrations of caffeine, the antioxidant capacity of Sertoli cells dropped dramatically, which may result in excessive

oxidative stress. The non-linear response to caffeine exposure in vitro may explain some of the variability observed in clinical studies of both male and female partners.[26]

Jensen et al. examined their cohort of Dutch military recruits for risks of caffeine consumption, the same group of 2554 men analyzed for sweetened beverage intake.[27] They found that high intake of daily caffeine (> 800 mg/day) trended toward impaired semen concentrations, although the effect did not reach statistical significance. A follow-up meta-analysis, which spanned 28 studies and 19,967 subjects, concluded that caffeine intake did not affect semen parameters overall[28]. The authors were cautious to mention that increased caffeine consumption may increase the rates of sperm aneuploidy, a finding primarily supported by a study by Jurewicz et al.[29] However, the effects of caffeine on the genetic material have also been conflicting, as caffeine exposure did not appreciably change the results of the sperm chromatin structure assay in men presenting to an infertility clinic[30]. Two recent studies have documented reduced fecundity in couples where men consume significant amounts of caffeine. Wesselink and colleagues prospectively followed 662 couples trying to conceive over a 12-month duration[31] They found that caffeine intake was significant only in the male partner, where men consuming more than 300 mg/day had a fecundity ratio of 0.72 (CI 0.54–0.96) compared against men drinking less than 100 mg/day. The investigators caution that this result was not monotonic, as moderate drinkers tended to conceive more often, although statistical significance was not reached. In a similar study, the EARTH cohort was utilized to relate caffeine intake to ART outcomes[32]. A total of 171 couples, subjected to 205 ART cycles, were analyzed. Their results demonstrated no significant correlation between caffeine intake and semen parameters. However, when comparing the lowest and highest quartiles of male caffeine intake, higher caffeine exposure in the male partner resulted in fewer live births (19 as opposed to 55, $p < 0.01$). These latter studies illustrate the poor surrogacy of semen parameters upon reproductive potential, suggesting that pregnancy and live.

Physical Activity

Several investigators have attempted to quantify the effects of physical activity and exercise upon semen parameters. Similar to the studies examining diet, the literature involving male subfertility and physical activity relies heavily on self-reported exposures. However, a handful of groups have attempted to control for physical activity by either randomized trial or through small cohorts designed to invasively assess the physiology of exercise response.

Exercise Early studies characterizing a link between exercise habits and male reproductive potential provided discordant results. In one of the earliest investigations, Vaamonde et al. categorized 45 healthy volunteers as either "physically active", "competitive athlete," or "triathlete" based upon self-reported exercise routines[33].

Their results demonstrated a negative impact of increasing exercise intensity upon semen parameters, with morphology carrying the strongest trend. A concomitant observational study that followed, assessing endurance athletes, provided similar results, although statistical significance was never achieved[34]. In an alternative strategy, several groups examined the putative impact of exercise on the hypothalamic-pituitarygonadal axis. Steinacker and colleagues followed ten competitive rowers preparing for a world championship.[35] Serial blood draws demonstrated a progressive and dosedependent drop in FSH, LH, and total testosterone. In contrast, differing results were obtained when men were subjected to moderate exertion. Grandys et al. followed 15 healthy volunteers during a pre-set 5-week cycling program[36]. In this cohort, total testosterone actually increased from a mean of 543 to 635 ng/dL ($p < 0.01$), whereas sex hormone-binding globulin decreased. It would be reasonable to infer that intratesticular testosterone increased in this population, perhaps promoting spermatogenesis. Excessive cycling, although, appears to be counterproductive for sperm production as evidenced by a study by Wise et al.[37] In this prospective study, 2261 men provided semen samples and completed a physical activity questionnaire. Cycling greater than 5 h per week was associated with lower sperm concentration (OR 1.92, CI 1.03–3.56) and lower total motile sperm counts (OR 2.05, CI 1.19–3.56). The above work appeared to demonstrate that excessive exercise is detrimental to male fertility. To better study the "overtraining syndrome," Safarinejad et al. randomized 286 healthy volunteers to either moderate intensity or heavy intensity exercise programs[38]. This well-designed trial tracked several parameters, including gonadotropins and semen analyses. Men in the heavy-intensity arm dropped their sperm concentrations from a mean baseline of 66.2 to 35.4 million/ mL ($p = 0.01$). Similarly, statistically significant and meaningful decrements were noted in sperm motility, strict morphology, LH, FSH, and total testosterone. Downward trends were realized in the moderate intensity program as well, although only sperm concentration obtained marginal statistical significance ($p = 0.042$). These results were bolstered by a recent analysis of semen quality in men undergoing an extreme training program, where a relationship was observed with worsening DNA fragmentation. Based on the presented data, exercise excess should be avoided amongst men that are pursuing fertility.

Body Habitus

Body weight is a function of genetics, environmental factors, and the concept of energy balance defined as the relation of caloric intake and expenditure. It is clear that population trends of body habitus are skewing toward the overweight (BMI > 25) and obese (BMI > 30) categories. It is now estimated that 2 billion of the world's population is overweight and that one third of these individuals are obese[39]. These population-based changes are driven in part by diet, through the consumption of industrialized foods, and by a progressively sedentary lifestyle. The consequences of this epidemic are highly relevant to reproductive medicine. In this section, we will review the data analyzing the link between subfertility and elevated BMI. The hormonal consequences of being underweight (i.e., BMI < 20) have been clearly delineated in terms of reproductive health. In contrast, studies addressing elevated BMI and fertility potential have produced conflicting results. Additionally, a multitude of confounders exists that may bias data, including risk factors for weight gain, mainly poor dietary habits and low physical activity, as addressed in the prior sections of this review. There is also high concordance of BMI between partners and spouses, thereby further complicating couple-based fertility outcomes since obese men are more likely to be paired with obese women.

Much of the initial concern regarding elevated BMI and male subfertility was based upon known hormonal dysregulation that accompanies increased adiposity. Hausman et al. comment "that adipose tissue is the largest endocrine and paracrine organ in the body producing, in addition to adipokines, a wider variety of factors than ever expected." The most relevant and treatable example involves peripheral aromatization within the adipocyte of androgens into estrogen[40]. An aberrant T/E ratio negatively effects spermatogenesis, which is amenable to aromatase inhibitors[41]. More contemporary investigations have concentrated on leptin, a hormone produced by fat cells and responsible for various processes that include satiety, energy balance, and modulation of the hypothalamic-pituitary-gonadal axis. Obesity induces leptin resistance in target tissues, including the hypothalamus, resulting in dysregulation of sex hormones (obesity related hypogonadotropic hypogonadism) and providing one link between obesity and male infertility.[42]

However, the role of leptin is continually reinterpreted as new evidence emerges. Martins et al. recently reported the presence of leptin receptors in cultured human Sertoli cells, providing an independent molecular mechanism beyond diminished intratesticular testosterone. A subsequent animal study by Borges et al. found that leptin receptors were

downregulated in testes of obese mice, implying leptin resistance. They also demonstrated downregulation of LH receptors, which further muted any response from pituitary 56 Page 6 of 10 Curr Urol Rep (2018) 19:56 signaling. The putative mechanisms for obesity induced subfertility have spawned a multitude of studies aiming to correlate BMI with reproductive predictors[43].

Tips for Optimizing Ovulation and Fertility with Diet and Nutrition

1. Maintaining a normal weight reduces the risk of ovulatory infertility.
2. Maintain glucose homeostasis and insulin sensitivity with a low-glycemic diet.
3. Address micronutrient deficiencies, particularly folic acid, and iron deficiency anemia.
4. Emphasize plant-based proteins over animal sources of protein.
5. Adequate intake of iron from plant sources and supplements, as well as optimal micronutrient intake, reduces the risk of ovulatory infertility.
6. Reduce trans-fat intake to decrease the risk of ovulatory infertility.
7. Choose whole-fat dairy, which appears to decrease the risk of ovulatory infertility, whereas low-fat daily appears to increase the risk[44].

These dietary strategies form the basis of what is often referred to as a Mediterranean diet, are easily implemented by most individuals, and not only prevent ovulatory infertility but also promote long-term cardiovascular health and reduce diabetes risk.

RESULTS AND DISCUSSION

The aims of study whether dietary plans and other lifestyle practices have an impact on the risk of infertility due to ovarian disorders, a condition that the Mayo Clinic says affects about 25% of infertile couples.

Table1.

	Intervention (*N* = 92)	Control (*N* = 100)	*P*-value
Age (mean; SD)	30.4 (4.1)	29.9 (4.5)	0.43
Caucasian (%; N)	93.5 (86)	95.0 (95)	0.65
Body Mass Index (kg/m^2; mean; SD)[b]	35.9 (3.3)	35.8 (3.1)	0.73
Education level (%; N)			
No education or primary school (4–12 years)	4.5 (4)	1.0 (1)	0.52
Secondary education	20.2 (18)	21.4 (21)	
Intermediate Vocational Education	51.7 (46)	55.1 (54)	
Higher Vocational Education and University	23.6 (21)	22.4 (22)	
Smoking (yes; %; N)	22.0 (20)	17.2 (17)	0.40
Nulliparous (yes; %; N)	75.0 (69)	73.0 (73)	0.75
Anovulatory (yes; %; N)	46.7 (43)	53.0 (53)	0.39
PCOS (yes; %; N)	35.9 (33)	42.0 (42)	0.38
Duration infertility (months; median; IQR)	22.0 (15.0; 37.0)	17.0 (13.0; 25.8)	0.02
Pregnant after randomisation (yes; %; N)[c]	68.5 (63)	76.0 (76)	0.24

At follow-up, the intervention group reported a statistically significantly lower energy intake compared to the control group (− 216 kcal [95%C.I. − 417; − 16]; P = 0.04), while there were no differences in macronutrient intake as a percentage of total energy, diet quality measured with the DHD15-index, and physical activity. Excluding underreporters did not affect the results for energy intake. Despite the difference in reported energy intake at follow-up, we did not observe a difference in BMI 5.5 years after randomisation between the intervention and the control group. In line with the lower reported energy intake, the intervention group had a significantly lower absolute intake of all macronutrients at follow-up, with exception of protein and saturated fat.

Reported energy intake and BMI at follow up differed significantly among women in the intervention group who successfully lost weight during the intervention, women in the intervention group who did not lose weight successfully, and the control group. Post-hoc analysis showed no difference in reported energy intake between women allocated to the

intervention group who successfully lost weight during the intervention compared to women allocated to the intervention group who did not lose weight successfully.

All the women included in the study did not have a history of infertility, and their pregnancy attempts were followed over a span of 8 years. Each woman was assigned a fertility score based on several factors that have been associated with lower risks of ovarian disorder infertility. These factors include:

- Higher consumption of mono-saturated fats over trans fats
- A higher percentage of protein consumed from vegetable over meat sources
- Low glycemic carbohydrate consumption with emphasis on fiber intake
- Consumption of high fat dairy over low or non-fat dairy
- Taking multivitamins
- Adequate Iron consumption
- Healthy BMI
- Regular physical activity

The more of these lifestyle factors a woman participated in, the higher the score she was assigned and the more she was considered to be following a "fertility diet". Over the next 8 years, the researchers recorded pregnancy successes to see if there was a significant difference between women with higher scores compared to women with lower scores. After reviewing the numbers, they found that the women that followed the fertility diet saw a lower risk of infertility due to an ovulation disorder compared to women who didn't follow the diet. In addition, they found that for each additional lifestyle factor that women incorporated into her lifestyle the risk for infertility dropped. According to their results: "The risk of ovulatory disorder infertility decreased with increasing the number of low-risk lifestyle habits followe. 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…The risk of ovulatiory disorder infertility was lower for each additional low-risk lifestyle followed, up to an 84% lower risk among women following five or more of the habits[45].

Overall, the researchers concluded that changes in a women's diet and lifestyle can impact her risk for infertility. "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[46].”

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 popu- lation, because the prevalence of obesity is lower in this cohort (10%) than among comparable women in the general U.S. population (29%).[47]

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, the intake of vegetable protein, and the amount and quality of carbohydrates. Because this dietary pattern favors low-glycemic foods while limiting the intake of nutrients that may increase insulin resistance such as trans fatty acids, 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.

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