

A comprehensive survey: prevention of female infertility by nutrition

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ABSTRACT

There is an important relationship between nutrition and infertility in women. Most diseases that cause infertility in women can be prevented and treated with proper nutrition. The present study aims to determine the role of nutrition in women's fertility. Samples of this study are all articles published in magazines, books, and theses from the Web Of Sciences, PubMed, Medline, Elsevier, and Google Scholar search engines with the keywords of "female infertility," "nutrition," "diet," "fertility outcomes," "folate," "iron," "omega-3 fatty acids", and "Vitamin." In the beginning, 1052 articles were found, and after reviewing the STROBE checklist, 38 articles were selected. After reviewing the inclusion and exclusion criteria and evaluation, 23 articles were included in the study. Various studies showed that proper nutrition improves women's ovulation parameters and pregnancy outcomes. The reviewed studies suggested a balance between protein and carbohydrates, consuming foods with a low glycemic index, high fiber diet, eating five meals a day, daily consumption of essential fatty acids such as omega 3 and 6, use of organic materials, low-fat proteins, complex carbohydrates, folic acid, antioxidants, vitamins, and foods that cause regular ovulation such as cod liver oil, licorice plant, five-finger plant, thistle, and cinnamon. The results of this comprehensive study indicate that proper nutrition through adequate consumption of micronutrients can positively impact women's fertility. These findings highlight the potential contribution of diet interventions to clinical practice for infertility prevention and management.

Keywords: Infertility, nutrition, women, survey

INTRODUCTION

Infertility is an increasing problem. According to the World Health Organization (WHO) statistics, 15% of couples suffer from this problem, and 30% of these infertility problems are caused by women.¹ Infertility is defined as the inability to conceive a child after one year of sexual intercourse without the use of contraceptive methods. Infertility may have symptoms in women, such as irregular periods and hormonal changes.² Several factors affect women's fertility, including diet and consumption of micronutrients. Micronutrients include vitamins and minerals required in small amounts as dietary components.³ Most diseases that cause infertility in women can be prevented and even treated with proper nutrition. In order to have proper nutrition for infertility, it is necessary to have a proper diet and also to know the effects of food in preventing infertility. Although these micronutrients do not contain energy, they are necessary for the catabolic and anabolic processes of the body. Therefore, investigating the relationship between nutrition and infertility is important for preventing and treating this condition.

The causes of infertility include various diseases such as polycystic ovary syndrome (PCOS), thyroid disorders, and endometriosis. Also, lifestyle, exercising, smoking, alcohol consumption, and stress are factors affecting infertility.^{4,5} Age is also a significant factor in female infertility, and with age, the quality and number of eggs decrease.⁶ Considering these factors can be effective in choosing treatment strategies and preventing infertility.

Nutrients play a significant role in preventing pregnancy, and a balanced diet with a variety of proteins, healthy fats, vegetables, fruits, and whole grains can improve the nutrients necessary for the optimal functioning of the reproductive system. Proper nutrition through adequate intake of micronutrients is important for optimal reproductive health.^{4,6} Studies have shown that certain nutrients such as iron, omega-3 fatty acids, and folate positively affect pregnancy outcomes.^{7,8} Also, not being overweight through proper nutrition and regular exercise can improve pregnancy outcomes and reduce risks during pregnancy.^{9,10} Therefore, with proper nutrition,

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women can play an important role in pregnancy health and preventing diseases leading to infertility.

Considering that much research has been conducted on treating infertility, the factors affecting it, and the effect of nutrition on the progress of fertility in women, the present study aims to determine the role of nutrition in women's fertility. This article aims to provide a comprehensive survey of articles on preventing infertility in women through proper nutrition. By examining the relationship between nutrition and infertility, this article tries to help raise awareness about nutrition and a healthy diet in preventing and treating infertility. We hope this information can be useful to women seeking to conceive and infertility professionals.

METHODS

This survey study was conducted to determine the role of micronutrients in women's fertility. Samples of this study are all articles published in magazines, books, and theses. Articles were extracted from the Web Of Sciences, PubMed, Medline, Elsevier, and Google Scholar search engines. To find all the desired articles, the keywords "female infertility," "nutrition," "diet," "fertility outcomes," "folate," "iron," "omega-3 fatty acids", and "Vitamin" were used.

These keywords were searched in the mentioned databases published from 2012 to 2022. Database search was done with high sensitivity by a researcher familiar with a database search. In the beginning, the titles of the articles that were searched by the research team with the mentioned keywords were 1052 titles. To avoid bias, the search was conducted by two experts independently, then similar and repeated searches were excluded from the study. A checklist was designed based on the objectives, and by studying other available sources, the abstracts of the collected articles were studied, and the articles that did not have the required information according to the checklist were excluded from the study. A list of all available articles reviewed in the mentioned databases was prepared based on the search strategy and keywords. The searched articles' titles were reviewed, and those with duplicate titles were removed.

In the next step, the full text of the remaining articles was examined using the STORBE checklist, and finally, the articles that received the quorum of the qualitative evaluation score were included in the present study. All the mentioned steps were performed by two independent experts in order to avoid bias. If there was a difference of opinion between the two researchers, the article was reviewed by a third person. The purpose of the STORBE checklist was to provide recommendations to clarify the design of the implementation method and the findings

of observational studies. This checklist has six general sections, title and abstract, introduction, methods, results, discussion, and other information. This checklist evaluates different aspects of the methodology, including sampling methods, variable measurement, statistical analysis to adjust for confounders, and the validity and reliability of the used tools and study objectives. Each part of the checklist was given a score, and at the end, two researchers compared the total scores obtained from the articles. The minimum obtainable score was 15.5. The articles that received the quorum of the quality evaluation score were included in the study. The criteria for the inclusion of articles in the study were articles published in English, their content was to investigate the effect of nutrition on women's fertility, and the original research article was refereed. Figure 1 shown the process of searching and selecting articles.

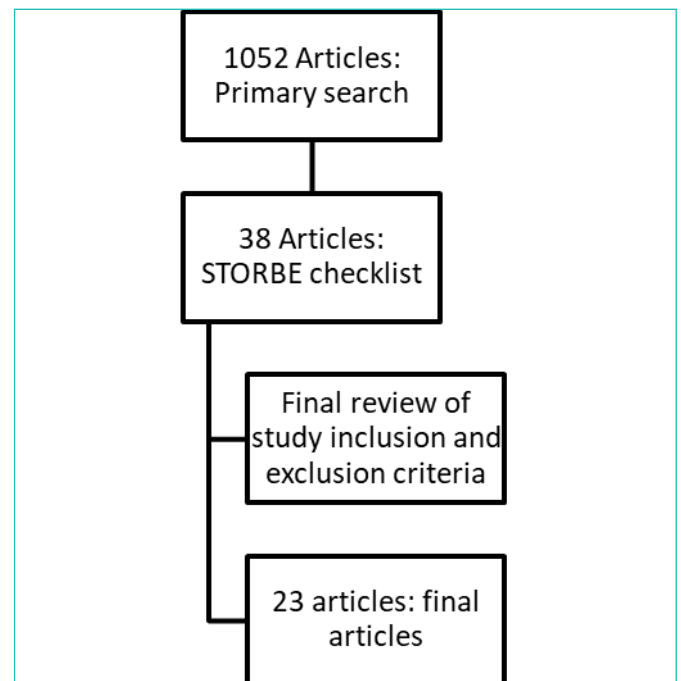


Figure 1. The process of searching and selecting articles

In the beginning, 1052 articles were found, and after reviewing the STORBE checklist, 38 articles were selected. After reviewing the inclusion and exclusion criteria and evaluation, 23 related articles were included in the study.

RESULTS

The results of the reviewed studies are summarized in **Table 1**.

Table 1 lists the results of 23 studies on the relationship between nutrition and infertility in women. The information in this table includes the author(s) of the study, the purpose of the study, the type of study, the sample and location of the study, the method of the study, and the key findings of the studies that examine the relationship between nutrition and infertility.

Table 1. Summary of reviewed studies

Author(s)	Purpose of research	Sample number - location	Method	Results
Mills et al. ¹¹	Pregnancy loss and iodine levels	347 women - Texas and Michigan	Lab experiment	Low iodine levels associated with highest rate of pregnancy loss
Agrawal et al. ¹²	Micronutrient intake in infertile women	104 infertile women - London	Examination of fertility and blood nutrients	Micronutrients during ovulation stimulation can increase ovulation rate
Buhling et al. ¹³	Micronutrient intake and female fertility	Germany	Review studies	Micronutrient supplements can increase fertility in infertile women
Paffoni et al. ¹⁴	Vitamin D deficiency and infertility	803 women - Italy	Lab experiment	No negative consequences in surrogate mother's children, regardless of using or not using her eggs
Henmi et al. ¹⁵	Ascorbic acid on serum progesterone levels in women with luteal phase defects	122 women - Japan	Examination of serum progesterone levels	Ascorbic acid and antioxidants can have positive effects on serum progesterone levels
Mills et al. ¹⁶	Fertility delay in women with urinary iodine deficiency	501 Women - United States	FFQ oral frequency questionnaire, lab investigation	Lower urinary iodine-to-creatinine ratio associated with lower likelihood of pregnancy
Lerchbaum et al. ¹⁷	Vitamin D and female fertility	Germany	Review of studies	Vitamin D administration to women with polycystic ovaries increases endometrial lining thickness
Youssef et al. ¹⁸	Oral antioxidants in infertile women with unknown cause	218 women - Egypt	Hormonal examination, ultrasound laparoscopy	Antioxidant intake did not enhance fertility in women without a known cause
Wise et al. ¹⁹	Omega-3 consumption and fertility	1290 women - USA / 1126 women - Denmark	Lab investigation, FFQ oral frequency questionnaire	Decreased omega-3 consumption associated with decreased fertility
Górna et al. ²⁰	Protein intake and infertility	100 women - Poland	Examination of nutrition and anthropometry	Infertile women had higher intake of calories and protein compared to fertile women
Afeiche et al. ²¹	Dairy consumption and in vitro fertilization outcomes	232 women - United States	Questionnaire on eating frequency and examination of ovary and fetus	Increased dairy consumption linked with greater likelihood of achieving live birth
Shishehgar et al. ²²	High protein diet vs standard diet in managing polycystic ovary syndrome	Iran	Review studies	High-protein diet led to improvement of metabolic variables
Phy et al. ²³	Low-starch, low-dairy diet on weight loss among obese individuals	24 women - United States	Measurement of BMI, blood sugar, HbA1, testosterone	Weight loss and testosterone reduction seen with the intervention
Nikokavoura et al. ²⁴	Very low-calorie diet in promoting weight loss among women	1016 women - England	600 kcal per day with a multivitamin	No significant difference in weight loss outcomes between the two groups
Sadeghi et al. ²⁵	Differences in food intake, physical activity, and weight between infertile and fertile women	288 women - Iran	Questionnaire and anthropometry	Infertile women had lower physical activity levels and higher intake of certain nutrients compared to healthy women
Ruder et al. ²⁶	Antioxidant consumption in infertile women with unknown cause	273 women - United States	Food frequency questionnaire	Vitamin E consumption linked with reduction in pregnancy duration in women over 30 years of age. Increased intake of beta-carotene and vitamin C associated with shorter time to conceive in women under 35
Gaskins et al. ²⁷	Folate intake and fertility in women affected by assisted reproductive treatment	232 women - United States	Food frequency questionnaire	Increased folate intake linked with greater egg replacement and higher chance of achieving live birth
McGrievy et al. ²⁸	Dietary patterns and nutrient intake of women with polycystic ovary syndrome	46 women - United States	Quality of life, EBI questionnaire, and physical activity questionnaire	Overweight women with polycystic ovary syndrome who were experiencing infertility had a diet lacking in whole grains, fiber, and iron
Rajaeieh et al. ²⁹	Dairy consumption and polycystic ovary syndrome	400 women - Iran	Food frequency questionnaire	No association between milk consumption and polycystic ovaries
Kazemi et al. ³⁰	Fat intake and egg quality	236 women - Iran	Food frequency questionnaire	High fat consumption had adverse effect on fetal growth. Eggs low in antioxidants had reduced likelihood of fertilization and egg replacement
Tsai et al. ³¹	Dietary habits and nutrient intake in women with polycystic ovary syndrome	206 women - Taiwan	Anthropometry and food consumption questionnaire	Women with polycystic ovary syndrome had lower intake of carbohydrates compared to control group
Twigt et al. ³²	Pre-pregnancy diet and successful continuation of pregnancy in women undergoing IVF/ICSI treatment	199 women - Netherlands	Diet questionnaire	Correlation observed between diet score and probability of achieving pregnancy following IVF/ICSI treatment
Mahoney ³³	Lifestyle modification in overweight and obese women with polycystic ovary syndrome	12 women - United States	Food frequency questionnaire, physical activity survey	Changes in diet and physical activity resulted in regular menstruation

Our results showed that proper nutrition improves women's ovulation parameters and pregnancy outcomes. In general, **Table 2** shows the reviewed studies suggestion for diets for women's fertility.

Diet	Description
Balance between protein and carbohydrates	A diet that balances protein and carbohydrates can improve fertility.
Low glycemic index foods	Consuming foods with low glycemic index can improve fertility
High fiber diet	A high fiber diet can improve fertility
Eating five meals a day	Eating five meals a day can improve fertility
Daily consumption of essential fatty acids (omega 3 and 6)	Daily consumption of essential fatty acids, such as omega 3 and 6, can improve fertility
Use of organic materials	Using organic materials can improve fertility
Low-fat proteins	Consuming low-fat proteins can improve fertility
Complex carbohydrates	Consuming complex carbohydrates can improve fertility
Folic acid	Consuming folic acid can improve fertility
Antioxidants and vitamins E, C, and D	Consuming antioxidants and vitamins E, C, and D can improve fertility
Foods that cause regular ovulation	Consuming foods that cause regular ovulation, such as cod liver oil, licorice plant, five-finger plant, thistle, and cinnamon, can improve fertility

DISCUSSION

This study aims to provide a comprehensive survey of articles on preventing infertility in women through proper nutrition. Most of the reviewed studies showed that polycystic ovary is one of the causes of female infertility. Overweight, infertile women with PCOS, who had a diet low in whole grains with fiber and iron,^{28,34} and high sugar consumption, along with a low amount of legumes and vegetables,³⁵ and low consumption of starch and low dairy products were successfully treated for their obesity.²³ Also, weight loss significantly affects the recovery of polycystic ovaries,²² so moderate weight loss causes recovery in 50% of affected people.³³

One of the effective foods in treating female infertility is antioxidants and vitamins.³⁰ Vitamin D was one of the main micronutrients in the studied studies. Vitamin D, also considered a steroid hormone, is received through food in the form of vitamin D₂ (ergocalciferol) or vitamin D₃ (cholecalciferol) or made in the skin after contact with sunlight. The active form of vitamin D, 1 and 25 dihydroxy vitamin D₃ binds to its receptor in different tissues and affects the expression of more than 200 genes, and in this way, it exerts various effects on organs such as parathyroid, pituitary, pancreas, ovary, colon, immune system, and skin.³⁶

Vitamin D is present in tissues such as decidua, placenta, ovarian cells, endometrium, and pituitary gland and affects the function of ovarian granulosa cells. It also plays a role in influencing steroidogenesis, fertility, and regulation of the immune system.³⁷ Recently, the role of vitamin D in the anti-müllerian hormone (AMH) gene expression has been proven in the laboratory environment.³⁸ In human ovarian tissue, cholecalciferol stimulates the production of progesterone,¹³ estradiol,¹⁷ and estrone.¹⁶ Vitamin D is essential in estrogen biosynthesis in female and male gonads.³⁹⁻⁴¹

In this regard, the study of Paffoni et al.¹⁴ which aimed to determine vitamin D deficiency and infertility, showed that vitamin D is an influential factor in women's fertility and the outcome of IVF. However, Aleyasin et al.⁴² reported no significant relationship between vitamin D levels and IVF outcomes. The study of Anifandis et al.⁴³ also showed that people with sufficient vitamin D levels are less likely to get pregnant than people with vitamin D deficiency.

German women who had polycystic ovaries and were administered with vitamin D exhibited an increase in their endometrial thickness. Additionally, research has shown that vitamin D has the potential to enhance the ovarian reserve of women in the later stages of their reproductive age.⁴⁴ While Rajaeieh et al.²⁹ found no association between milk consumption and PCOS, other studies,^{24,27} have suggested that increased dairy consumption may lead to a greater chance of achieving live birth. The discrepancy between these findings could be due to the differences in the types of low-fat and high-fat dairy products consumed, which were not taken into account during the studies.

Vitamin E was also one of the effective micronutrients in women's fertility in the reviewed studies. Tocopherols, the major forms of vitamin E, protect cell membrane components against oxidation, act as an anti-inflammatory in immunocompromised people, and are neuroprotective. They are fat-soluble, and their deficiency becomes apparent months after the onset of deficiency.⁴⁵ In a study, vitamin E supplementation was associated with a shorter time to get pregnant in women over 30 years old, and women under 35 years old had a shorter time to get pregnant with beta-carotene and vitamin C intake.²⁶

On the other hand, vitamin C prevents the peroxidation of lipids, revives vitamin E, and protects against DNA damage by H₂O₂ radicals.⁴⁶ Ascorbic acid is a crucial component in the biosynthesis of collagen, which is especially important for the growth of ovarian follicles during ovulation and the luteal phase.⁴⁷ In ovarian tissue, the concentration of vitamin C is very high.³⁷ As the study

of Murray et al.⁴⁷ showed, the consumption of high doses of ascorbic acid causes a significant increase in tissue-inhibiting metalloproteinases and, as a result, increases the survival of follicles.

According to the results of the Henmi et al.¹⁵ study, which examined the impact of ascorbic acid supplementation on serum progesterone levels in individuals with luteal phase defects, it was observed that the use of ascorbic acid supplements could increase serum progesterone levels among patients with luteal phase defects. Although various micronutrients and antioxidants positively affect infertility treatment.²⁰ Youssef et al.¹⁸ found that using antioxidants does not increase fertility in infertile women of unknown cause, which may be due to the use of Octatron capsules.

Folate was also another micronutrient of interest in the reviewed studies. Folate, also known as folic acid, is a water-soluble vitamin found in green vegetables, grains, and potatoes. When taken alongside vitamins B6 and B12, folate has been shown to effectively lower blood homocysteine levels.⁴⁴ Homocysteine is an amino acid that is indirectly required for protein metabolism. According to studies, low levels of folate and increased levels of homocysteine cause frequent miscarriages. On the other hand, synthetic folic acid folate is oxidized and thus has more stability than folate, which has a bioavailability of nearly 90%.¹³ Folic acid is one of the essential and important vitamins for women of childbearing age.⁴⁸

Among the problems associated with folic acid deficiency, we can mention infertility, megaloblastic anemia, increased plasma homocysteine, cancer, and neuropsychiatric disorders.⁴⁹ If there is a lack of folic acid during pregnancy, problems such as spontaneous abortion, premature birth, decollement, preeclampsia, and neural tube defects may occur.⁵⁰⁻⁵² Higher folate levels are associated with higher implantation and live birth.²⁷

Iodine was another significant micronutrient in the reviewed studies. Iodine is a rare element that is necessary for the synthesis of thyroid hormones. Iodine exists in various forms of sodium iodide and potassium salts in nature. Any change in thyroid function can reduce sexual activity and fertility.⁵³ The effect of hypothyroidism on the hypothalamus, pituitary axis, gonads, peripheral metabolism, and sex hormones is undeniable.⁵⁴ A prospective cohort study by Mills et al.¹¹ aimed at pregnancy loss and iodine levels showed that urinary iodine levels were associated with pregnancy loss, and the lower the urinary iodine level, the higher the pregnancy loss rate. Also, the results of a population-based prospective study by Mills et al.¹⁶

which was conducted to examine delaying pregnancy in women with low urinary iodine concentration, showed that improving urinary iodine concentration can increase the fertility of women.

Omega-3 fatty acids were also one of the significant micronutrients in the studies. The three main omega-3 fatty acids are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Because these fatty acids are vital and necessary for the body's regular metabolism, they are considered essential fatty acids.⁵⁵ Unsaturated fatty acids are needed as a dietary supplement throughout a person's life, especially during pregnancy, breastfeeding, and old age. Many recommendations exist to include these two fatty acids EPA and especially DHA, in the human diet.⁴⁴ Polyunsaturated fatty acids (PUFAs) have been found to possess anti-inflammatory properties that can be attributed to a range of mechanisms, such as eicosanoid metabolites, thromboxane, prostaglandins, leukotrienes, and prostacyclin. Wise et al.¹⁹ study, which aimed to determine dietary fat intake and fertility in two Danish and American women groups, showed a positive and significant relationship between omega-3 fatty acid consumption and fertility. Nevertheless, in the study of Stanhiser et al.⁵⁶ the average ratio of omega-3 to omega-6 and omega-6 to omega-3 was not significantly different between fertile and infertile groups. Moreover, there was no relationship between pregnancy and the concentration of but-3 fatty acids, including alpha-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid, or omega-6 fatty acids linoleic acid (LA). Also, there was no significant relationship between the individual's serum concentration of omega fatty acids and the chance of miscarriage adjusted for age.

While physical activity and a healthy diet have been shown to enhance fertility outcomes, it is crucial to identify an appropriate dietary regimen for the management of fertility-related issues.¹⁶ Certain foods have been recommended to improve women's fertility, indicating that infertile women should incorporate a proper diet into their treatment plans.

Our study contributes to the literature by comprehensively reviewing the evidence regarding the role of nutrition in women's fertility. The findings indicate that diet interventions focused on adequate intake of key micronutrients can benefit clinical practice for infertility prevention and management. The limitation of the present study is that due to the simultaneous consumption of food, it was not possible to investigate the effect of individual foods on women's fertility.

CONCLUSION

Many studies reported a positive effect of micronutrients on women's fertility and stated that insufficient micronutrients could affect women's fertility adversely. Also, it seems that correct nutritional planning effectively supports and provides nutritional needs and has favorable effects on women's reproductive health in the short and long term. On the other hand, providing education and training on proper nutrition and providing advisory programs and nutritional counseling for women of childbearing age could be effective in preventing women's infertility. For this reason, since infertility treatments are costly and many people are not covered by insurance for this type of treatment, it seems that preventing fertility problems and achieving reproductive health with a correct diet and the use of complementary medicines containing micronutrients can have a positive and beneficial effect on women's reproductive health. More controlled clinical trial studies in this regard are recommended to achieve more robust and reliable results.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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