

## Systematic Literature Review of the Impact of Dietary Factors on Female Fertility

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### Abstract

**Background:** Infertility is a common problem that affects a significant portion of the population causing stress and concern. Clinical intervention is possible but modification of lifestyle factors, including dietary factors is a more cost-effective and simpler alternative. Improved comprehension of the preventive and curative properties of dietary factors is essential is vital to improving chances of fertility.

**Aim:** Review of published research articles to determine the impact of dietary factors on female infertility.

**Methodology:** A systematic review was carried out using selected keywords and a detailed search of the relevant databases. Stringent inclusion and exclusion criteria were employed to screen the identified papers and the final selected 8 papers were reviewed to determine the impact of studied dietary factors.

**Results:** A general consensus among 7 out of the 8 selected papers indicated the importance of consumption of micronutrients in their supplemental form in order to increase the likelihood of pregnancy. Several of the papers affirmed that the respondents were unable to obtain sufficient nutrition from their regular dietary intake and required supplements to meet the daily requirements.

**Conclusion:** Consistent administration of micronutrients, specifically in the form of supplements, appears to have widespread benefits aimed at improving the chances of successful conception and live births, highlighting their positive effect on infertility.

**Keywords:** *Infertility; Diet; Dietary Factors; Female; Vitamins*

### Key Messages

- Infertility is a surprisingly common concern affecting a significant portion of the population and evidence suggests that modifying lifestyle factors can improve fertility outcomes.
- Diet is important part to fertility, with the current review indicating that consumption of micronutrients is beneficial to a successful pregnancy and decreased infertility.
- Evidence suggests that several women aiming at conception do not obtain the required nutrient intake from their diet and require supplemental intake instead.

### Introduction

Infertility can be described as the inability to conceive after 12 months of consistent intercourse without contraceptives [1]. Research indicates that roughly 12% of women between the ages of 15 and 44 years have sought medical intervention for fertility-related concerns

[2]. Examination of couples reporting difficulties in conception reveal that at least 33.33% of cases are attributable to the woman and female fertility rates have been shown to decrease significantly with age [3,4]. Although couples opt for assisted reproductive technology, such techniques are expensive and inaccessible [5]. Modifying lifestyle habits, including body weight and diet can affect fertility rates [6]. Vitamins and supplements also play a role in improving fertility but comprehensive reviews of their effects are limited. Macronutrients can be easily obtained from dietary sources, but it is difficult to obtain suggested levels of micronutrients. The present systematic review aims at providing an improved understanding of the role that micronutrients play in female fertility.

### Methodology

The present review involved an examination of relevant databases using selected keywords. Identified articles were screened using outlined inclusion and exclusion criteria and necessary data was extricated from the chosen studies.

### Information sources

The current systematic review involved the methodical searching through pertinent electronic databases for the collection of appropriate source material. The researcher examined PubMed, Cochrane, Medline, POPLINE, Science Direct and Nature for pertinent research information on dietary components that had an effect on female infertility. The search strings that were used included 'female infertility diet', 'female infertility dietary factors', 'infertility women diet factors', 'infertility in women diet' and 'female infertility "diet"'. Corresponding research articles that were published between 2007 and 2018 were selected for further analysis. Abstracts from the preliminary articles were screened to ensure the relevance of the study before further assessment was conducted. PRISMA guidelines were strictly adhered to during the course of the review. Based on the information gathered from the collected papers, the researcher narrowed the scope of the systematic review to a discussion on the impact of supplements.

### Criteria for selection

Studies were included in the systematic review based on a set of well-defined inclusion and exclusion criteria.

#### Inclusion criteria

- Only published, English language research studies that involved human participants were considered.
- Research studies needed to have a minimum number of participants (studies containing above 50 participants were considered for the review).
- Dietary factors being studied should be clearly mentioned.
- Studies needed to clearly demonstrate an investigation of the impact of these factors on fertility.
- To narrow down the definitive scope of the review, a final screening step was conducted to include papers discussing the specific impact of supplements.

#### Exclusion criteria

- Studied dietary factors were macronutrients.
- Dietary components were already known or widely believed to be detrimental to female fertility.
- Systematic reviews and meta-analyses.
- Research studies that did not explicitly focus on female fertility or infertility as an outcome.
- Papers that contained incomplete or inadequately defined information.

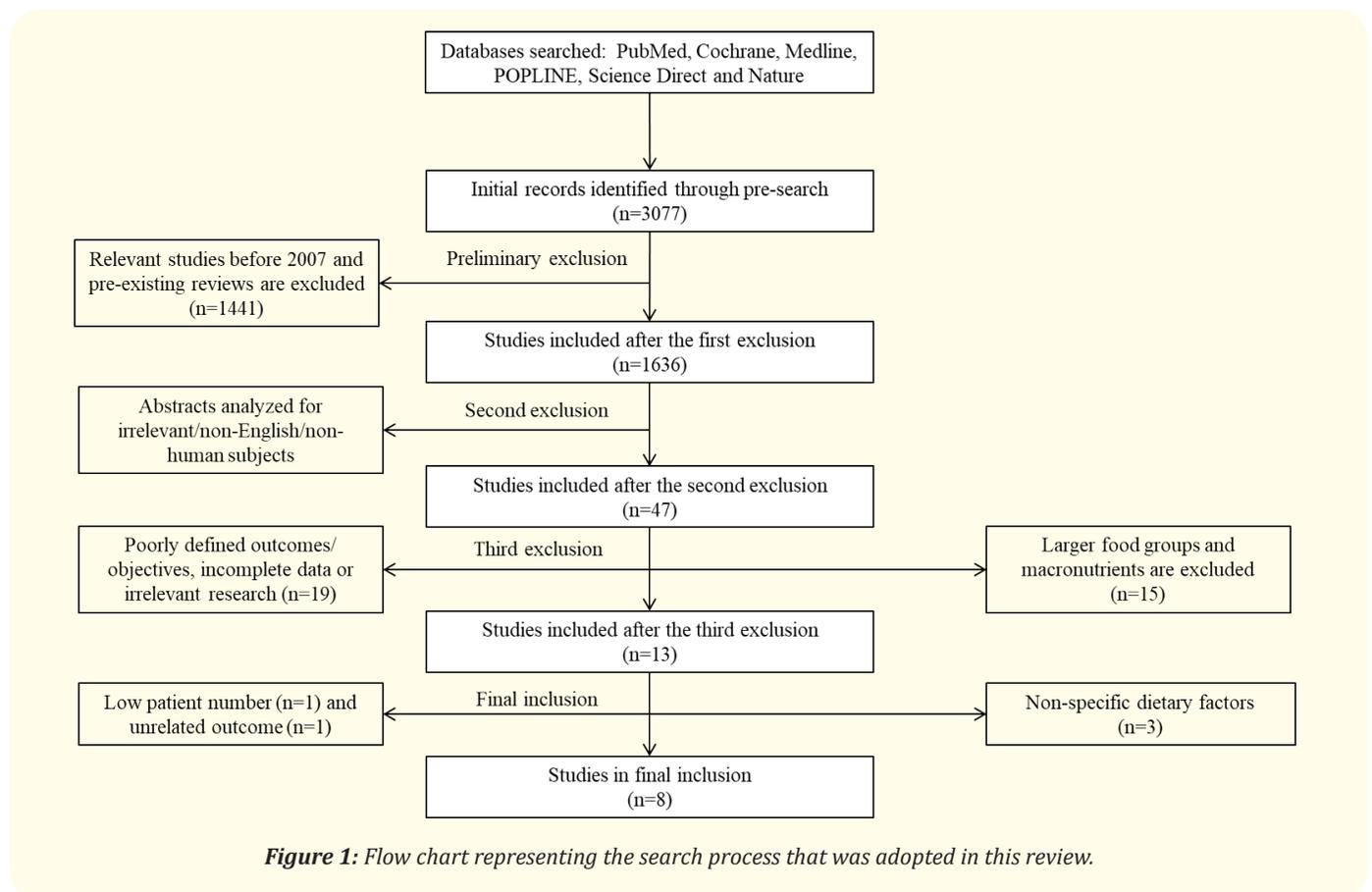
**Data extraction**

Following the selection of studies for inclusion in the review, data was extracted from each study related to the title, authors, year of publication, participants included in the study, factors that were being investigated, outcome and type of study. Additional notes were recorded to allow the researcher to evaluate papers and critically evaluate their inclusion in the systematic review. Extracted information was reviewed and the collected data was assessed. The extracted details are presented in tabular form, provided in Supplemental table 1.

**Results**

A preliminary search of the six databases was conducted using relevant keywords and a total of 3077 articles were obtained. An initial screening of the articles was carried out and any data that fell beyond the stipulated time range or was not a research article was excluded. Based on this categorization, a total of 1441 sources were immediately excluded. The abstracts of the remaining articles were then thoroughly examined and according to the adjudged relevance of the information, a total of 47 studies were considered for inclusion. These studies were further screened using the inclusion and exclusion criteria, along with a brief consultation of the quality of the studies and overall, a total of 8 papers were chosen for inclusion in the systematic review. Quality assessment of the included papers was carried out using the Newcastle Ottawa Scale (NOS) scale for cohort and case control studies. All the cohort studies and both case control studies were found to be of good quality as per the scale. The pilot study assessing the impact of micronutrients on ovulation infertility was treated as a case control study and was found to be of fair quality. However, it was included owing to the relevance of the research material.

A flow chart representing the systematic search that was used is represented in figure 1.



**Figure 1:** Flow chart representing the search process that was adopted in this review.

The findings of these studies have been classified based on the factor that was investigated.

### Antioxidants

Among the incorporated studies, one paper focused on the potential impact of dietary antioxidants and fertility rates, specifically examining the consumption of these supplements by women [7]. Antioxidant intake was assumed to have a positive impact on conception and reduced the oxidative stress in the body. Information collected from a cohort of 437 women participating in the randomized control trial (RCT) was analyzed to ascertain if antioxidants could enhance the rates of successful conception in women. During the study, only female antioxidant intake was measured and data was collected about the subjects' vitamin intake and other related supplements. Women forming the study population were members of the RCT group, who met pre-defined inclusion and exclusion criteria. Relevant dietary data was collected using a structured questionnaire. Collected responses were analyzed using hazard ratios and Cox proportional hazard regression models. The study also accounted for additional covariates that had the potential to impact the final outcome.

Overall, the study concluded that among the cohort, an increase in the consumption of antioxidants appeared to be associated with a decrease in the time required for women to conceive, although the precise effect varied according to the nature of the antioxidant and demographic factors, including age and BMI. For instance, in women having a BMI lower than 25 kg/m<sup>2</sup>, a reduction in the time needed to successfully conceive was only significantly linked to an increase in consumption of vitamin C. Similarly, among women younger than 35 years, it was observed that there was a significant relationship between a conception time and amount of ingested vitamin C and  $\beta$ -carotene. Vitamin E was also found to reduce the conception time in women above the age of 34.

Findings from this study were explained based on previously available information. Vitamin C is known to be responsible for not only decelerating detrimental oxidizing reactions but also is hypothesized to aid in the production of luteal collagen.  $\beta$ -carotene levels were associated with the success of IVF techniques. The antioxidant activity of vitamin E was believed to reduce potential damage to the corpus luteum and the epithelium on the ovarian surface.

While the results from this study point to the benefits of antioxidants, it must be noted that there were some limitations, such as a lack of ethnic variation. Additionally, participants were being treated for unknown infertility, thus potentially limiting the extrapolation of these findings to other populations.

### Folic acid

Three of the included studies focused on the effect that consumption of folic acid and related supplements had on women's fertility [8-10]. Folic acid is one of the most common supplements that women trying to conceive are advised to include in their diet. The three papers included a total study population of 778 women, all of whom were undergoing treatment for infertility. Two studies explicitly examined the impact of folic acid provided as a supplement [8,9], whereas the third paper examined the indirect effect that dietary folate had on the implantation success [10]. The third paper [10] was included owing to the similarity of the study population and the novelty of the study, as well as the relevance of the proposed impact of folic acid on implantation.

A longitudinal cohort study was employed to analyze the effect that dietary folate had on Swedish women seeking clinical assistance for fertilization [8]. A questionnaire was used to gather information from the population and laboratory tests were used to analyze the folate and homocysteine levels in subjects. Findings from the study indicated that infertile women reported higher folate levels than fertile controls and interestingly, reported a relationship between women experiencing miscarriages and higher folate levels. The Swedish cohort investigation, which also included a case control analysis, was unable to detect conclusive evidence of folic acid exhibiting a significant effect on pregnancy and live births. The researcher was thus unable to conclude if increased consumption of supplemental folate would improve chances of conception and pregnancy in women who were infertile.

The second study was conducted in female patients undergoing assisted reproductive technology treatment in the United States [9]. Information from a prospective cohort of 238 women was analyzed to investigate the benefits of dietary and supplemental folate. A combination of a questionnaire and clinical data was used to obtain information about the impact of folate. Findings from this study highlighted that more than half a woman's folate intake originated from supplements. Higher levels of folate were positively associated with various aspects of pregnancy and a substantial increase in the live births in women who consumed more folate. It could thus be concluded that an increased intake of supplemental folic acid was beneficial to a woman's chance of a successful pregnancy in cases of impaired fertility.

The same study population was included in another prospective cohort study to investigate the impact that dietary folate had on successful implantation [10]. Combining a questionnaire to assess dietary intake and clinical techniques to examine biochemical parameters, folate levels were compared with recorded bisphenol A (BPA) concentrations and extrapolated to female fertility. Folate concentrations impacted the effect that BPA had on IVF treatments. Higher folate levels were associated with improved chances of implantation. Researchers in this study predicted that consumed folic acid had an impact on earlier stages of fertility rates than what was earlier assumed.

Although the studies used supporting biochemical assays to provide weightage to their findings, the use of self-reporting measures and take-home questionnaires is a limiting factor as there is no guarantee of their accuracy. The different measures of outcome utilized in these studies introduce the possibility of varied findings. While some research considers the primary outcome measure to be live births, others take into account factors prior to a clinical pregnancy.

### **Vitamin D**

Two studies investigated the effects of vitamin D on female fertility, with a total of 313 women being assessed to determine the overall impact of this micronutrient [11,12]. Both studies affirmed that the fat-soluble vitamin exerted significant influences on female fertility. The prospective cohort study reported an association between insufficient vitamin D and reduced chances of clinical pregnancy [11]. Similarly, the case control study examining the vitamin D and calcium levels in Middle Eastern women found that respondents with fertility issues reported higher vitamin deficiencies [12]. Interestingly, both studies also discussed the relative difficulty that the study population faced in meeting their vitamin requirements, outlining the importance of supplemental intake. These findings highlight the vitality of consuming the stipulated dosage of vitamins and the crucial aspect of relying on supplements to complement dietary intake.

The case control study was limited by its inability to determine if consumption of vitamin D could improve fertility on a prospective basis, but the cohort study addressed this concern. The studies employed comparatively small sample sizes, which had the potential to introduce problems related to identification and analysis of statistical significance. Additionally, the fertility conditions that these papers address are varied, with the case-control study discussing the implications of vitamin D deficiencies among a subfertile population and the cohort study focusing on healthy, nulliparous women.

### **Multiple micronutrients**

A prospective RCT was carried out to compare the efficiency of providing multiple micronutrients (MMN) and solely folic acid to a selected group of subfertile female participants who were preparing to undergo ovulation induction [13]. Findings from the study indicated that providing multiple micronutrients was more efficient than solely administering folic acid. A key distinguishing factor of this paper involved the proposed application of findings to a subfertile female population as opposed to an infertile population. A decision to include the research study in the systematic review was made on the basis of the study population, which consisted of women exhibiting either ovulatory or unexplained infertility. Subjects included in the pilot study were randomly administered either MMN or folic acid supplements. Four weeks after the initiation of the supplementation, ovulation induction was carried out and ultrasound studies were used to affirm the success of the procedure.

Individuals who received the MMN supplements showed significantly higher rates of conception and also took less time to become pregnant when compared to those who only received folic acid supplements. In fact, nearly 70% of MMN-receiving group successfully conceived after 3 treatment cycles, a value that was significantly higher than the approximately 40% success rate recorded among women who only received folic acid. This difference was statistically significant with  $p < 0.01$ . The consumption of MMN also facilitated more rapid conception, with 15 women in the MMN treatment group being able to conceive on their first attempt and only 2 women reporting this result in the folic acid group.

Despite the importance of these findings, a limitation of this pilot study is the reliance on self-recall for dietary habits. This introduced room for error in the comparison of dietary sources of various micronutrients. The comparison of MMNs with folic acid highlights the importance of the combination of micronutrients in improved fertility, but prevents the identification of which micronutrient provided the maximal contribution to fertility.

A prospective cohort study involved the collection of data from 18555 nurses and the subsequent investigation of the impact of multivitamins on ovulatory infertility [14]. A validated questionnaire was used to collate information related to the respondents’ dietary and supplemental intake of multivitamins. Overall, researchers reported that the habitual consumption of multivitamins significantly reduced the chances of ovulatory infertility in the study population ( $p < 0.001$ ). When the specific components of the multivitamin tablet were assessed, the initial positive impact was attributed to various B vitamins, excluding pantothenic acid. However, further multivariate adjustments that were made to account for factors such as iron levels, which were known to contribute to infertility, revealed that only folic acid was able to reduce ovulatory infertility ( $p = 0.04$ ). A distinctive limitation of this investigation was the failure to confirm the self-reports of infertility using medical records or clinical documents, reducing the reliability of the collected data.

**Discussion and Critical Analysis**

An analysis of the studies included in this systematic review highlights the importance of including supplemental micronutrients, primarily vitamins, in the diet of women aiming to conceive. Seven out of the eight included studies found a significant positive correlation between the studied factor and successful conception despite fertility issues [7,9-14]. Fertility issues affect a significant portion of the population, with some studies arguing that reliance on medical assistance has increased in the recent decade [15]. The inability to conceive successfully and carry out a pregnancy to full-term is a stressful event for any couple, highlighting the importance of identifying methods to successfully address these concerns [16]. While an increasing number of couples take advantage of ART and other similar possibilities, these are often expensive and not always viable [5]. Studies have indicated that modifying lifestyle factors, including an improved nutritional intake, can enhance fertility rates and outcome [17]. Several research studies focus on areas such as reduction of weight and obesity in relation to improved chances of conception [18,19], with less comprehensive information available related to the importance of specific dietary factors. Women who are attempting to conceive or who have conceived are prescribed a bevy of vitamins and supplements [20], but the exact nature of these prescriptions can vary and a more comprehensive understanding of the role that individual micronutrients play in humans can help regularize prescriptions and dosages for women, leading to improved outcomes. Table 1 provides a brief overview of some uses of supplements for female fertility.

Folic Acid	Vitamin D	Antioxidants	Multivitamins
<ul style="list-style-type: none"> <li>Improved oocyte quality and maturation</li> <li>Reduced chances of neural tube defects</li> <li>Improved chance of successful clinical pregnancy [8,9]</li> </ul>	<ul style="list-style-type: none"> <li>Deficiency may contribute to PCOS</li> <li>Improved success pregnancy with ART</li> <li>Can improve chances of successful conception [11]</li> </ul>	<ul style="list-style-type: none"> <li>Protects epithelial surface of the ovary</li> <li>Impacts success rate of IVF treatment</li> <li>May reduce impact of oxidative stress [7]</li> </ul>	<ul style="list-style-type: none"> <li>Prevents fetal structural defects</li> <li>Improves blood flow to uterus and ovaries</li> <li>Prevents miscarriages [13]</li> </ul>

*Table 1: Benefits of consumption of reviewed dietary factors on female fertility.*

Findings from the current review indicate that consumption of vitamins appears to be linked to a reduction in the time needed for conception, successful clinical pregnancy and live births, in populations with regular and impaired fertility. Compiled results suggest that adequate consumption of vitamins has the potential to contribute to both preventive and curative aspects in cases of infertility and improves the outcome of clinical methods designed to assist in reproduction. Data collected from the studies also emphasizes the necessity of supplemental intake of vitamins prior to and during pregnancy, as evidence collected from the respondents indicates that women relying on solely dietary intake to meet their vitamin requirements were often nutrient deficient.

The findings from the present review match previous studies. Researchers elucidated on the concept of providing multivitamins in order to reduce the time needed to conceive and improve fertility [21]. The importance of antioxidants in relation to infertility has also previously been discussed [22-24]. The role of folic acid supplements and the benefits that they provided to women aiming for successful conception has also previously been investigated [25,26]. Researchers have also reviewed earlier studies related to the benefits that vitamin D provided to fertility outcomes, with a positive association between fertility and the vitamin being observed [27].

Out of three studies that examined the impact of folic acid, the prospective case control focusing on folic acid supplementation in women undergoing IVF treatment did not record significant benefits associated with the supplement [8]. This finding is in contradiction to common medical advice and previous research results. An included study opined that some research analyzing the impact of folic acid failed to account for chemical pregnancies and earlier stages of conception [10]. However, the folate study with contradictory results [8] had measured urinary HCG levels, which would detect even chemical pregnancies. A potential explanation for this finding is the possibility of alternate genetic pathways and genotypes involved in the utilization of folic acid and folate [28]. A study conducted analyzing these pathways examined the possibility that genetic polymorphisms in the folate pathway could influence the outcome in women with unexplained infertility. Based on their results, it was seen that the infertile study group showed a significant difference in the presence of certain polymorphic genes related to folate metabolism.

A key concern that was formulated from the analysis of these papers is the variation among the studied populations. The case control study investigating the impact of vitamin D on fertility included an analysis of subfertility women [12], the pilot study involving the effects of micronutrients recruited infertile women but applied the results to subfertility [13]. The prospective cohort studies involving the effect of multivitamins and vitamin D included women with no suspected history of infertility [11,14] and the remaining studies included women who were infertile or undergoing infertility treatment [7-10]. While disparity in the study population introduces room for improved comprehension, it also leads to difficulties in accurately comparing the findings. Additionally, among infertile populations, both ovulatory and unexplained infertility were recorded. This reduces the specificity of the impact of consumed vitamins. Many studies relied on the respondent to recall the details of their diet and fertility conditions. Although self-recall data was generally supported by clinical information or medical records, this method of data collection reduced the reliability of the responses that were collated. Another consideration was that women in six out of the eight studies were undergoing some form of medical assistance for conception, which may have had an impact on the monitored outcome. The current systematic review also suffers from a publication bias, as only published studies were included.

## **Conclusion**

Infertility is a common concern that affects several couples. While clinical treatment options exist for such cases, they are often not cost effective or easily available. Preventive measures, including modified lifestyle approaches need to be explored, especially the impacts of dietary factors on infertility. The current systematic review examined data collected from 8 studies related to the consumption of supplements and their impact on female infertility. The majority of the findings indicated that regular administration of supplements was significantly beneficial to fertility, reducing the time needed for conception, increasing the chances of a successful conception and improving the chances of a successful live pregnancy. Findings from the review also indicate that the majority of the respondents failed

to consume the necessary number of micronutrients in their regular diet, necessitating the use of supplements. The variations recorded among the study populations and protocol reveal the necessity for standardization of the tests in the future and increased attention to both the preventive and curative properties of these dietary factors.

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