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Review

Emerging Trends in Research on Food Compounds and Women's Fertility: A Systematic Review

Aleksandra Bykowska-Derda [1], Ezgi Kolay [1], Malgorzata Kaluzna [2] and Magdalena Czlapka-Matyasik [1,*]

[1] Institute of Human Nutrition and Dietetics, Poznan University of Life Sciences, 31 Wojska Polskiego St., 60-624 Poznań, Poland; aleksandra.derda@up.poznan.pl (A.B.-D.); ezgi.kolay@up.poznan.pl (E.K.)
[2] Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences, 49 Przybyszewskiego St., 60-355 Poznan, Poland; mkaluzna@ump.edu.pl
* Correspondence: magdalena.matyasik@up.poznan.pl; Tel.: +48-61-846-62-04

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Featured Application: The application of this systematic review is a comprehensive study of food compounds, nutrition, food production, health and environmental sciences in improving female fertility.

Abstract: Pro-healthy behaviours, including the diet, are significant factors in maintaining women's fertility health. However, to improve the patient's nutrition management, it is important to seek food-derived bioactive compounds to support fertility treatment. This review analysed recent studies of food compounds related to fertility, using databases including PubMed, Web of Science and Science Direct as well as PRISMA (preferred reporting items for systematic reviews) to ensure complete and transparent reporting of systematic reviews. This review lists foods associated with a higher birth rate, using original papers from the last five years (2015). The analysis included the impact of food compounds such as caffeine, fatty acids, folates and vitamin D, as well as the intake of fish, whole grains, dairy and soya. In addition, dietary patterns and total diet composition supporting women's fertility were also analysed. The results will encourage further research on the relationship between food components and fertility.

Keywords: female infertility; nutrient; vitamin D; folates; soy; antioxidants; minerals; vitamins; food research trends; environmental impact

1. Introduction

Fertility, known as the ability to establish a clinical pregnancy, is dependent on multiple factors, including female age, environmental pollution, diet, tobacco use, alcohol intake, as well as diseases affecting endocrine function and the anatomy of the reproduction system [1,2]. In turn, infertility is medically defined as a failure to establish a clinical pregnancy after 12 months of regular and unprotected sexual intercourse. It is estimated that infertility in women of child-bearing age is 1 in 7 couples in developed countries and 1 in 4 couples in developing countries, which is increasing significantly [1]. The demand for infertility services is still growing and can be improved thanks to technological advances and the development of medicine.

Factors influencing fertility may be unmodifiable, such as age and environment, or could be medically treated, such as health status—including endocrine disorders. Furthermore, some factors could be modifiable, such as health behaviours, dietary patterns and micronutrient intake.

It has been confirmed that in-vitro fertilisation success rate seems to be highest during the summer months when the pollution of particulate matter (PM) is at its lowest [3]. Phthalates, which may negatively influence the fertility health of women [4], were found to affect the occupational health of hairdressers [5]. Some primary factors, such as excess body weight or underweight, also decrease the rate of fertility [6,7]. Body saturation with vitamin D was suggested to have a beneficial influence on fertility [8–12].

The recommendations by the Committee of the American Society for Reproductive Medicine in collaboration with the Society for Reproductive Endocrinology and Infertility American Society for Reproductive Medicine, advise females to follow a healthy diet, avoid alcohol and decrease caffeine intake to a moderate level [13]. It is also advisable for women to supplement folate (400 µg/day) to decrease the chance of neural tube defects [13]. However, there is some evidence showing that some food ingredients and specific dietary patterns in women may be positively associated with pregnancy and live birth rates [14–16].

One of the food ingredients widely discussed in the context of fertility is sugar. It was shown that its presence in the diet reduces nutritional density and worsens its nutritional quality [17]. The possible mechanism between sugar-sweetened beverages and fertility was explained by increased insulin resistance, leading to oxidative stress. This relation may deleteriously affect semen quality and ovulatory function. Such a mechanism was hypothesised by Hatz, et al. [18], who studied a group of nearly five thousand women and found that fertility and the amount of sugar consumed in sugar-sweetened beverages (particularly sodas and energy drinks) was associated with lower fecundability [18].

A large group of compounds that are still being studied are bioactive compounds in food. Their roles in oxidative stress and fertility have been presented in many studies [19–22], including several studies on female animal models and bioactive food compounds [23–25]. Their role is hypothesised to diminish the effect on the endocrine system of disruptive chemicals. For example, there is some evidence that animals treated with BPA (Bisphenol A), after maternal supplementation of folate and a high phytoestrogen diet, influence oocyte growth and foetal methylation of DNA [26,27]. Other studies have highlighted that a low dose (but not a high dose) of ginger powder, improved the follicle counts of rats [23]. Therefore, it is not clear what dose will be as effective on humans. Additionally, human fertility is affected by complex and multiple factors which could be difficult to expose animals to.

The time of preconception may motivate couples to adopt healthier behaviours and to seek information on factors improving fertility. Even though medical consultation is still the most common source for seeking advice for fertility, social media and the internet also play significant roles [28]. The choice of supplement options is vast, as the fertility supplement market is continuously growing and it has been estimated to be worth USD 1.45 billion globally in 2018 [29]. The use of supplements is not always recommended by healthcare professionals, and their misuse may even pose a threat to health.

The literature related to food compounds and fertility has not been extensively collected, and there is no consensus on what the trends are in these studies or what groups of food ingredients should be considered as supportive or detrimental to fertility. In light of this evidence, an analysis of diet ingredients, food research (e.g., ginger, BPA) and fertility could lead to new supporting therapy strategies that affect the birth rate through the modulation of eating habits. Accordingly, this review provides an analysis of new food compound research influencing fertility and revises recent studies involving the impact of food bioactive compounds on women's fertility.

2. Materials and Methods

2.1. Search Strategy

A systematic search of literature published before December 2019 was performed in PubMed (National Institiute of Health, USA)(https://www.ncbi.nlm.nih.gov/pubmed), Web of Science (Clarivate Analytics, USA) (https://www.webofknowledge.com), Scopus (Elsevier, RELX Group plc), (https://www.scopus.com) and Science Direct (Elsevier, RELX Group plc) (https://www.sciencedirect.

com/) to identify studies describing the association between bioactive food compound intake and women's fertility. The search strategy was restricted to English language original articles. The following types of documents were excluded: review, book and book chapters.

The search was based upon the following index terms, titles or abstracts listed below: ((bioactive OR nutrient OR food OR ingredient OR vitamin OR mineral OR antioxidant OR phytonutrient) AND (fertility)). The protocol was registered in the "PROSPERO International prospective register of systematic reviews" PROSPERO 2020: CRD42020160223 and is available on https://www.crd.york.ac.uk/prospero/display_record.php?ID = CRD42020160223.

2.2. Inclusion and Exclusion Criteria

Studies on the influence of food compounds on infertility, signs and symptom changes in patients affected by infertility were included. Studies using different food components concerning changes in the concentration of biomarkers for the assessment of infertility and changes in symptoms were analysed. The systematic search included a population of women in the reproductive age 21–50 with diagnosed infertility or healthy women trying to conceive. All studies conducted on animals and case reports were excluded. The studies included were both qualitative and quantitative. A quality assessment of questionable articles was performed with a checklist described by Kmet et al. [30]. Articles written in a language other than English were excluded. Since the search included new trends in food research, it only included articles within the last five years (2015).

2.3. Study Extraction Process

The study selection process includes an assessment of articles based upon titles, abstracts and full text, which were performed by two independent researchers in parallel in each database. At each step of the assessment, all disagreements between the researchers were resolved after consultation with the review coordinator. Only in the case of disagreement during the title assessment process was the paper included in the next step. Full-texts of all records that were selected in the abstract review phase were searched for through the library of Poznan University of Life Sciences.

3. Results

A total of 4609 studies were screened for inclusion in this systematic review. After the elimination process (Figure 1), a total of 25 qualitative studies and 4 quantitative studies were included. The studies were performed internationally and included the following countries USA (n = 20) [15,31–45], Australia (n = 1) [46], New Zealand (n = 1) [46], Ireland (n = 1) [46], United Kingdom (n = 2) [46,47], China (n = 1) [48], Denmark (n = 4) [41,43,49,50], Greece (n = 1) [14], Iran (n = 2) [51,52], Brazil (n = 2) [53,54], Canada (n = 1) [43], Russia (n = 1) [55], Italy (n = 2) [56,57], Spain (n = 1) [58]. The articles concerned female fertility and the intake of a Mediterranean dietary pattern (n = 2) [51,57], fruit, vegetables and whole grain intake (n = 3) [38,46,53], fish (n = 1) [42], dairy (n = 3) [15,43,44], types of fatty acids (n = 4) [39–41], soy (n = 2) [32,33], caffeine (n = 3) [45,50,54], folate and B12 (n = 4) [34,35,59,60], melatonin (n = 1) [58], CoQ10 (n = 1) [48] as well as a combination of different compounds (n = 4) [37,47,52,55]. The women who participated in the studies were either planning pregnancy (n = 6) [36,40,41,45,46,55], infertile (n = 3) [49,51,55], undergoing or subjected to assistive reproductive technology (ART) therapy (n = 16) [14,15,31,34,35,39,42,44,50,52–54,57,58]. The main results of the studies have been summarized in Table 1 (qualitative studies) and Table 2 (quantitative studies).

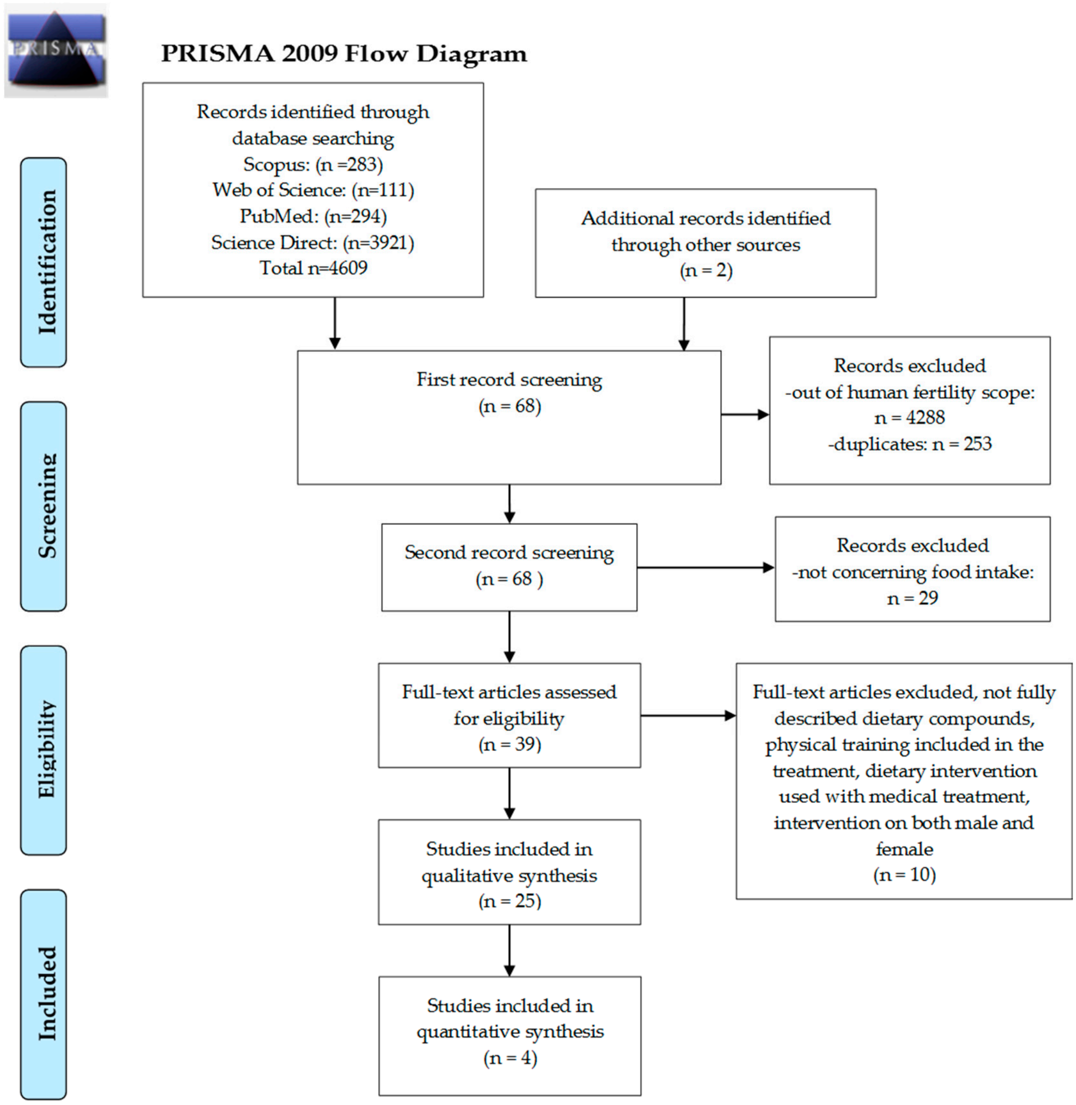

Figure 1. Preferred reporting items for systematic reviews (PRISMA) Study selection process diagram.

Table 1. Qualitative studies on bioactive food components and women's fertility included in the review process.

Study	Sample	Assessment Tool	Results
		Dietary Patterns	
Ricci et al. 2019 [57], Italy	n = 474 ART	FFQ	There were no consistent associations between adherence to a Mediterranean diet and successful obstetrics outcomes. There was an effect of the average adherence score on a Mediterranean diet on oocyte number and clinical pregnancy in women >35 years old but no effect on live birth.
Jahangirifar et al. 2019 [51], Iran	n = 140 infertile	FFQ	High adherence to the healthy dietary pattern was associated with a high average number of oocytes when compared with low adherence.
Karayiannis et al. 2018 [14], Greece	n = 244 non-obese ART	FFQ	Mediterranean diet score was positively related to clinical pregnancy and live birth among women <35 years old but not among women ≥35 years
Gaskins et al. 2019 [31], USA	n = 357 ART	FFQ	Pro-fertility dietary pattern (supplemental intake of folate, B12, low-pesticide residue produce, high intake of whole grains, seafood, dairy, soy foods) has a higher likelihood of live birth.

Table 1. *Cont.*

Study	Sample	Assessment Tool	Results
		Fruits, Vegetables and Wholegrains	
Grieger et al. 2018 [46] Australia, New Zealand, Ireland, UK	n = 5628 nulliparous with low-risk singleton pregnancies	FFQ	Low intake of fruit and high intake of fast food was associated with an increase in time to pregnancy and infertility
Braga et al. 2015 [53], Brazil	n = 269 ART	FFQ	The intake of cereals, vegetables and fruits positively influenced the embryo quality at the cleavage stage. The intake of fruits influenced the likelihood of blastocyst formation. The intake of red meat had a negative effect on the implantation rate and the likelihood of pregnancy.
Gaskins et al. 2016 [38], USA	n = 273 ART	FFQ	High whole grain intake was related to a high probability of live birth.
		Fatty Acids	
Eskew et al. 2017 [39], USA	n = 60 ART	Serum fatty acid index	Trans FA and elaidic FA had a negative correlation with IVF outcomes, other FA did not have any consistent correlations
Mumford et al. 2016 [40], USA	n = 259 regularly menstruating women	24h dietary record Serum reproductive hormones	Dietary docosapentaenoic acid (DPA) intake was associated with a reduced risk of anovulation
Wise et al. 2018 [41], USA, Denmark	n = 1290 (USA), n = 1126 (Denmark) attempting pregnancy	FFQ	High trans FA and low ω-3 FA intake was associated with reduced fecundity
Fish			
Nassan et al. 2018 [42], USA	n = 351 ART	FFQ	Fish intake was positively related to the proportion of cycles resulting in a live birth.
		Dairy	
Wise et al. 2017 [43], USA, Denmark	n = 2426 attempting pregnancy	FFQ	High phosphorus and lactose intake was associated with high fecundability
Afeiche et al. 2015, [15], USA	n = 232 ART	FFQ	High dairy intake was associated with high chances of live birth
Souter et al. 2017 [44], USA	n = 265 ART	FFQ Antral follicle count (AFC)	High dairy protein intake was associated with lower AFC
		Caffeine	
Setti et al. 2018 [54], Brazil	n = 524 ART	FFQ	≥3 servings of regular or diet soft drinks were associated with oocyte dysmorphism, lower embryo quality on 2–3 days of culture, and had a mild effect on blastocyst formation, implantation and pregnancy rate. Consumption of sweetened coffee was negatively associated with embryo quality.
Wesselink et al. 2016 [45], USA and Canada	n = 2135 pregnancy planner	FFQ	Preconception caffeine intake was not appreciably associated with pregnancy. Caffeinated coffee intake showed little association with pregnancy. Black tea, but not green tea, was associated with a slight decrease in pregnancy
Lyngsø et al. 2019 [50], Denmark	n = 1708 ART	FFQ	Intake of 1–5 cups of coffee versus none had a higher probability of achieving a pregnancy or a live birth when receiving IUI. No associations were found, between coffee consumption and achieving a pregnancy or a live birth from IVF/ICSI.
		Soya	
Chavarro et al. 2016 [32], USA	n = 239 ART	FFQ Urinary BPA	BPA was inversely associated with live birth rate unless women had a high intake of soy.
Vanegas et al. 2015 [33], USA	n = 315 ART	FFQ	Dietary soy intake was positively related to the probability of live birth.

Table 1. *Cont.*

Study	Sample	Assessment Tool	Results
		Folate	
Gaskins et al. 2019 [34], USA	n = 304 ART	FFQ residence-based daily nitrogen dioxide (NO_2), ozone, fine particulate, and black carbon concentrations	Supplemental folate intake modified the association of NO_2 exposure and livebirth
Mínguez-Alarcón et al. 2016 [35], USA	n = 178 ART	FFQ Urinary BPA	High BPA was associated with a lower probability of implantation among women with <400 µg/day intake of folate, but not among women with ≥400 µg/day
		Vitamin D	
Fung et al. 2017 [36], USA	n = 132 healthy attempting pregnancy	Serum 25(OH)D, 24h diet recalls every 3 months	Women with vit. D intake below EAR and serum 25(OH)D at risk for inadequacy had a lower pregnancy rate
Jensen et al. 2019 [49], Denmark	n = 16212 infertile	Vitamin D fortification in margarine (mandatory in the nation since 1985)	Exposition to fortified margarine was associated with an increased chance of live birth.
		Antioxidants	
Skalnaya et al. 2019 [55], Russia	n = 150 healthy n = 169 pregnant n = 75 miscarriage n = 91 primary infertility	Serum metal levels Iron, copper, manganese	Serum Cu levels in women with miscarriage and infertility were 30 and 35% lower than those in pregnant women. Serum Cu levels were significantly associated both with and reproductive health problems
Li et al. 2019 [37], USA	n = 349 ART	FFQ	There were inverse associations of β-carotene intake from foods and of lutein and zeaxanthin intake with live birth rates. Total consumption of vitamins A, C, and E before infertility treatment was not associated with live birth rates.

25(OH)D-*25-hydroxyvitamin D, ART—Assistive Reproductive Technologies*, AMH—Anti-Mullerian Hormone, FSH—Follicle-stimulating Hormone, FFQ—Food Frequency Questionnaire, EAR—Estimated Average Requirement, BPA—Bisphenol A, FA—fatty acid, IVF—In Vitro Fertilization, ICSI—Intracytoplasmic Sperm Injection.

Table 2. Quantitative studies concerning bioactive food components and female fertility qualified for the review.

Study	Treatment	Sample	Clinical Pregnancy Rate [%]	Embryo Quality	Fertilisation Rate [%]	Live Birth Rate [%]
Yangying et al. 2018 [48], China	Coenzyme Q10 600mg/day 60 days preceding IVF	Control group n = 93 Study group n = 76	25	0 (0,1.75)	45	22
		poor ovarian response	32	1 (0;2)	67	32
Espino et al. 2019 [58], Spain	Melatonin 3mg/day and 6mg/day for 40 days	healthy control n = 10	50	2.3 (0.5;4.0)	51.1	50
		subjected to 2nd IVF:	20	2.0 (0.4;3.6)	47.9	20
		no melatonin n = 10 3mg/day n = 10	30	5.1 (2.8;7.4)	67.4	30
		6mg/day n = 10	30	4.6 (2.8;6.3)	63.7	30
Agrawal et al. 2012 [47], UK	Multiple micronutrient supplement or folic acid alone 3-6 months	Micronutrients n = 29 Folic Acid n = 27	66.7 39.3	N/A	N/A	N/A
Fatemi et al. [52], Iran	Vitamin E, 400 mg/day and vitamin D3, 50,000 IU/one in two weeks, placebo 8 weeks	Intervention group n = 52	62.1	71.20%	73.3	20
		Placebo n = 53 Women scheduled for ICSI	22.6	67.50%	70.9	7

IVF—In Vitro Fertilization, ICSI—Intracytoplasmic Sperm Injection.

4. Discussion

This systematic review aimed to identify emergent trends in food compounds studies which influence women's fertility. We qualified a total of 29 studies from the past five years among women planning to conceive either naturally or with assisted reproductive technologies.

4.1. Dietary Patterns, Intake of Fruits, Vegetables and Whole Grains

The modern diet and nutrition analysis based on dietary patterns also assessed the nutrition behaviours as a whole, rather than looking at a single nutrient. Dietary patterns are defined as the quantity, variety, or combination of different foods and beverages in a diet and the frequency in which they are habitually consumed. The frequency reflects food compounds consumed in the diet directly. The most common dietary patterns are pro-healthy, Mediterranean, western and dairy-related [61,62]. The results of this systematic review (presented in Table 1) showed that a high intake of fruits and vegetables and adherence to a pro-healthy dietary pattern is associated with a higher average number of oocytes [51] and embryo quality [53]. The Mediterranean dietary pattern has been associated with supporting fertility health in women. Karayannis et al. found that this dietary pattern is only related to the live birth rate in women under the age of 35 [14]. Another study showed that it was related only to higher oocyte number and clinical pregnancy in women over 35 [57]. The Mediterranean diet is characterised by a high intake of extra virgin olive oil, vegetables, fruits, cereals, nuts and legumes, a moderate intake of fish and other meat, dairy products and red wine and low intakes of eggs and sweets [63]. Another dietary pattern used in the studies was a fertility diet dietary pattern characterised by the intake of supplemental folate and B12, low-pesticide residue produce, high intake of whole grains, seafood, dairy and soy foods. This dietary pattern was positively related to the likelihood of live birth [31].

4.2. Fatty Acids and Fish Intake

The current review has shown that there is no conclusive evidence about the impact of polyunsaturated fatty acids, including the intake of omega-3 on human fertility [13]. The results of the review are inconclusive: two studies found an association between omega-3 fatty acids and fertility [40,41], while another study found no impact of these fatty acids on fertility [39]. However, all of the studies analysing fatty acid intake found that the amount of trans fatty acid consumed is negatively related to the live birth ratio [39,41]. These results also support Grieger et al., who found that a high consumption of fast foods (a rich source of trans fatty acids) influences fertility [46].

4.3. Dairy

For many years, the topic of high dairy intake has been controversial and linked with both a positive and negative impact on the health of women [16,64,65]. Nevertheless, to date, most of the studies concerning female reproductive health have been skewed towards a positive association. Moreover, all of the studies in this systematic search, including the period 2015–2019 concerning dairy intake and fertility, have found at least a small positive relationship between these variables [15,43,44]. It should be noted that dairy foods are generally perceived as a pro-healthy dietary attribute. We studied this group of foods previously and found that a more significant effect on dairy consumption by women was the family environment than health-related protective factors [66].

4.4. Caffeine

Decreasing the caffeine intake to moderate during the time of preconception has been recommended to couples who plan pregnancy [13]. A high intake of caffeine, especially black tea [45] and coffee with added sugar and diet soft drinks [54] has been related to a lower live birth rate. However, coffee intake of 1–5 cups daily has been associated with higher chances of a live birth than none [50]. The intake of caffeine and coffee may be associated with more favourable dietary patterns and health behaviours which could influence fertility [67]. This could be the reason why different types of caffeinated beverages bring contrasting results.

4.5. Soy

The use of nutrients as factor diminishing adverse health effects of environmental pollutants was found in research concerning soy. Soy, as the food product containing phytosterols, could alleviate the effect of endocrine disruptor bisphenol A. This hypothesis is supported by a study concerning women undergoing ART, urinary bisphenol A and soy intake and their influence on live birth rate [32]. Intake of soya, regardless of environmental pollutants, was also related to a higher probability of life birth [33]. High soy intake has also been related to weight loss in women with polycystic ovary syndrome (PCOS), which may improve health and disease results [68]. The results of the above studies show that food ingredients may not always have a direct impact on fertility and their indirect impact is equally important. However, more studies concerning soy intake on fertility and women's health are needed. Many studies suggest that high soy intake may cause interference with ovarian function because of its high phytoestrogen content [69,70]. More studies are needed to determine the appropriate intake of soy of women trying to conceive, since an excessive intake of soy may not be safe.

4.6. Folate

The Center for Disease Control and Prevention (CDC) in the United States, recommends that healthy women with a low risk of birth defects should supplement 400 μg a day of folic acid at least 12 weeks before conception and early pregnancy to avoid neural tube defects [71]. However, it is unknown whether folate intake is related to female fertility. Recent studies have turned to methylenetetrahydrofolate reductase (MTHFR) gene mutations as the cause of recurrent miscarriages [72]. It seems that supplementation of vitamins B6, B12 and supraphysiologic methylfolate could help women with MTHFR gene mutations to conceive [73]. A high intake of folate and B12 was associated with an increased birth rate in women undergoing ART [59]. A high folate-to-homocysteine ratio was related to a lower risk of anovulation in regularly menstruating females [60]. Interesting retrospective studies were also conducted on supplemental folate intake and pollutant exposure among women undergoing ART. The subjects with high pollutant exposure had a lower rate of live birth [35] or implantation ratio [34]; however, folate supplementation positively modified these results in both studies. These results agree with the animal studies mentioned previously [26,27].

4.7. Vitamin D

During the current study, a number of studies were found which analysed the effect of vitamin D [8–11,36,49,74–78]. Nine of them showed a positive, statistically significant association with female fertility [8,9,11,36,49,74,76–78]. However, since only possible interactions with food compounds were searched for, and vitamin D is mostly formed under sun exposure, two of them concerning vitamin D dietary intake were included in the review. Summing up the issues of vitamin D and fertility, it should be emphasised that food products fortified with vitamin D could be advisable [49] for some populations, not only because of the fertility support but also overall health [79].

4.8. Antioxidants

The search also resulted in study findings involved in other single micronutrients. In a Russian study concerning serum metal concentration in the blood of women, it was found that females with infertility and miscarriage had a lower concentration of copper than pregnant women [55]. Moreover, there was no difference between the copper levels of pregnant women and a healthy control group, which supports the hypothesis that copper may play a role in female fertility.

A diet rich in antioxidants, such as the Mediterranean dietary pattern could improve fertility, although the only recent study concerning the intake of antioxidants did not support this hypothesis. Moreover, the intake of foods with a high concentration of β-carotene, lutein and zeaxanthin was inversely associated with live birth rates [37]. The reasoning of these results may be variable, starting from the accuracy of the food frequency questionnaire used in the study to the dietary pattern which leads to these results. The most important is the fact that supplementing antioxidants as fertility support or for other health conditions could be dangerous and should not be advised to the patients.

4.9. Other Food Compounds

Most of the studies found in the systematic search were qualitative and retrospective, although four prospective randomised trials published between 2015 and 2019 were also included in the review (Table 2). The studies concerned coenzyme Q10 [48], melatonin [58] and multiple nutrient supplementation of vitamin E and D [52] as well as numerous micronutrient or only folate supplement [47]. All of the included study interventions had a positive effect on the pregnancy rate and should be further studied to support fertility treatment nutritionally.

5. Conclusions

In conclusion, it should be noted that reproductive performance is influenced by food and type of nutrition. The findings of the current study suggest that the importance of food production. In particular, the availability and intake of pro-healthy food compounds is a significant factor supporting fertility in females. Women planning pregnancy should especially ensure an intake of fruits and vegetables, folate and vitamin D. A high intake of sweetened beverages and trans-fatty acids appears to decrease the chance of pregnancy and live birth rate. Soy food intake needs to be further analysed because of its endocrine-disruptive properties. Environmental pollution influences fertility around the world, and the appropriate intake of bioactive food compounds could diminish this effect. However, the excessive intake of specific micronutrients, such as antioxidants, may decrease fertility. More randomised prospective studies are needed to analyse the impact of micronutrients on fertility, taking into consideration the patient environment and environmental pollution.

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