—Review—

Associations of Nutrients and Dietary Preferences with Recurrent Pregnancy Loss and Infertility

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This review examines associations of nutrients and dietary preferences with recurrent pregnancy loss (RPL), miscarriage, and infertility. Research articles, reviews, and meta-analyses of RPL and infertility that focused on nutrition, meals, and lifestyle were reviewed, and associations of nutrients and dietary preferences with pregnancy are discussed in relation to recent research findings. Studies related to RPL were given the highest priority, followed by those dealing with miscarriage and infertility. Multivitamin supplements—even when lacking folic acid or vitamin A—reduced total fetal loss. High-dose folic acid supplementation before conception reduced the risk of miscarriage and stillbirth. A meta-analysis revealed a strong association of vitamin D deficiency/insufficiency with miscarriage. Another meta-analysis revealed that seafood and dairy products reduced the risk of miscarriage, whereas a caffeine intake of 300 mg/day or more was associated with miscarriage. A balanced diet that included nutrients with antioxidant properties helped prevent miscarriage, whereas a diet that included processed foods and nutrients with proinflammatory effects increased the risk of miscarriage. Associations of nutrients with RPL warrant further research. (J Nippon Med Sch 2024; 91: 254–260)

Key words: infertility, miscarriage, nutrient, review recurrent pregnancy loss

Introduction

The estimated incidence of recurrent pregnancy loss (RPL), defined as the loss of two or more pregnancies, is 0.4-0.8%[1]. Causes of RPL include antiphospholipid antibody syndrome, uterine morphological abnormalities, maternal chromosomal abnormalities, and fetal chromosomal abnormalities. However, approximately 50% of RPL cases are idiopathic[2]. Some unexplained cases of pregnancy loss are reportedly associated with immune disorders[3,4], and a link between immunity and certain nutrients has been reported[5–7]. Additionally, unexplained infertility, including endometriosis, may be associated with abnormal immunocompetence[8].

To improve pregnancy outcomes in patients with idiopathic RPL and infertility, we review the literature regarding the relationship between feeding habits and pregnancy. A clear understanding of the relationship between nutrition and pregnancy will help women with RPL or infertility to improve their diet and pregnancy outcomes. Specifically, we hypothesize that individualized nutritional management will significantly improve pregnancy outcomes.

Vitamins

Vitamins A and C, Multivitamins, and Folic Acid

According to the Cochrane Database of Systematic Reviews 2016, vitamins A (relative risk [RR]: 1.05, 95% confidence interval [CI]: 0.61-1.23) and C (RR[9]: 1.14, 95% CI: 0.92-1) are not associated with total fetal loss[10]. However, multivitamin supplements without folic acid (RR: 0.49,

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95% CI: 0.34-0.70, 1 trial, 907 women), with or without vitamin A, reduced total fetal loss (RR: 0.60, 95% CI: 0.39-0.92, 1 trial, 1,074 women), as compared with placebo or no multivitamin supplement treatment groups[10]. Although no data on folic acid monotherapy is available, folic acid taken in combination with other vitamins did not reduce the fetal loss rate[10]. Nonetheless, Gaskins et al.[11] reported that an average folic-acid intake ≥1,161 μg/day resulted in a lower stillbirth rate at 20 weeks of gestation, as compared with an average intake of 241 μg/day. This suggests that a high folic acid intake (average 1,000 μg/day) at 8-19 weeks of gestation as preconception care reduces miscarriage risk (the recommended preconception dose to avoid neural tube defects is 400-800 μg)[11]. Indeed, the risk of miscarriage was reportedly 10% lower when folic acid supplementation was started at least 3 months before conception (adjusted risk ratio [aRR]: 0.46, 95% CI: 0.42-0.50) than when it was started 1-2 months before (aRR: 0.56, 95% CI: 0.50-0.62), or after, conception (aRR: 0.56, 95% CI: 0.51-0.61)[12]. Although some studies reported that vitamin C supplementation did not affect pregnancy rates[13], some researchers believe that it may increase the live birth rate[13]. Vitamin A deficiency is known to cause implantation failure[14].

Vitamin D

Numerous studies suggest an association between recurrent miscarriage and vitamin D deficiency; however, others dispute this. A recent review found that vitamin D insufficiency (50-75 nmol/L) and deficiency (<50 nmol/L) were associated with increased incidence of miscarriage, as compared with normal levels of vitamin D (>75 nmol/L) (odds ratio [OR]: 1.6, 95% CI: 1.11-2.30)[15]. Chen et al. found that 64.6% of individuals with RPL also had vitamin D insufficiency or deficiency and suggested that supplementation with 1,25 (OH)2D may have a regulatory effect[16]. Further, persons with serum vitamin D levels ≤30 nmol/L had significant elevations in antibody titers, namely, antiphospholipid antibodies (OR: 2.22, 95% CI: 1.0-4.7, P<0.05), antinuclear antibodies (OR: 2.81, 95% CI: 1.1-7.4, P<0.05), anti-single stand DNA antibodies (OR: 3.76, 95% CI: 1.1-12.4, P<0.05), and thyroid peroxidase antibodies (OR: 2.68, 95% CI: 1.2-6.1, P<0.05)[17]. Additionally, peripheral blood levels of CD19+ B cells, CD56+ natural killer cells, and NK cytotoxicity at an effector to target cell ratio of 25:1 were significantly higher in patients with low vitamin D levels (P<0.05)[17]. Although there were no detectable differences in vitamin D receptor and CYP27B1 (vitamin D activating enzyme) levels in the endometrium of women with RPL, expression of both was diminished in villi and decidua[18]. A study of the effect of vitamin D3 and the balance of Th17 and Treg cells[19] found that when lymphocyte immunotherapy plus vitamin D_3 (n=22) was compared with lymphocyte immunotherapy alone (control) (n=22) Th17, Treg, and Th1 decreased after lymphocyte immunotherapy. However, the frequency of Th17 cells and the Th17/Treg ratio were significantly lower in the experimental than in the control group[19]. Overall, the Cochrane Database of Systematic Reviews 2019 indicates that there are no available data on the association between vitamin D and miscarriage[20] and, to date, there are no reports of adverse effects of vitamin D supplementation[20,21]. For more information on the relationship between vitamin D and infertility, please see the review by Gaskins and Chavarro[13].

Antioxidants

The Cochrane Database of Systematic Reviews 2017 includes N-acetyl-cysteine, melatonin, L-arginine, myoinositol, D-chiro-inositol, carnitine, selenium, vitamin E, vitamin C, vitamin D plus calcium, coenzyme Q10, pentoxifylline, and omega-3 polyunsaturated fatty acids. None of these antioxidants was associated with miscarriage occurrence (OR: 0.79, 95% CI: 0.58-1.08)[22]. As for individual antioxidants and their effects on pregnancy, CoQ10 supplementation was not associated with miscarriage incidence in patients with polycystic ovary syndrome, as compared with patients without the syndrome (OR: 0.61, 95% CI: 0.14-2.76)[23]. Melatonin reportedly increased biochemical pregnancy (OR: 1.65, 95% CI: 1.14-2.38) but did not reduce miscarriage (OR: 1.28, 95% CI: 0.65-2.51)[24]. N-acetyl-cysteine reduced miscarriage incidence (OR: 0.76, 95% CI: 0.37-1.53), but not significantly[25]. For more information on the associations between antioxidants and infertility, please see the review by Gaskins and Chavarro[13].

Dietary Fats

Lipids are fats, oils, fatty acids, glycerin, and cholesterol, and fatty acids are the major component of lipids. There is no clear evidence to suggest a relationship between RPL and fatty acids. A study on the association between pre-pregnancy blood fatty-acid levels and pregnancy outcomes showed that total saturated fatty acids was not significantly associated with pregnancy loss (RR: 0.98, 95% CI: 0.89-1.07)[26], whereas polyunsaturated fatty acids increased the risk (RR: 1.10, 95% CI: 1.00-1.20)[26].

The two main types of unsaturated fatty acids are omega-3 fatty acids and omega-6 fatty acids. Omega-3 fatty acids reduce inflammation and may prevent premature labor[9]. Relative to EPA and DHA, omega-6 fatty acids have been reported to decrease atherosclerosis[27]. The three most important dietary omega-3 fatty acids are eicosapentaenoic acid, docosahexaenoic acid, and alpha-linolenic acid[28].

Omega-3 fatty acids were not associated with pregnancy loss[26], although they improved vascular endothelial function of the endometrium in patients with primary antiphospholipid syndrome[29], and uterine blood-flow velocity was reduced in women with a history of recurrent miscarriage[30]. Mean omega-3, omega-6, and omega-6 to omega-3 ratio did not differ between women with RPL and infertile women[31].

Protein

Animal Protein

Meat

There is no clear evidence to suggest a relationship between RPL and meat. Certain high-protein foods increase the risk of ovulation disorders and subsequent poor pregnancy outcome[32]. Multivariable-adjusted analysis (RR: 1.32, 95% CI: 1.08-1.62) revealed that animal protein sources varied in the extent to which they increased the risk of ovulatory failure[32]. Meat is a source of protein that contains other nutrients, such as saturated fatty acids, hormones, antibiotics, and polybrominated biphenyls[33,34]. Further, a study of clinical pregnancy rates in patients treated with assisted reproductive technology (ART) found no effect of fish or chicken consumption on pregnancy outcome; however, red meat consumption had a significant negative effect (OR: 0.68, 95% CI: 0.48-0.89)[35]. According to a review on pre-pregnancy intake of meat and other protein-rich foods and its relationship with the outcome of infertility treatment with ART, total meat intake as a protein source was not associated with ART outcome[36]. The relationship between miscarriage and consumption of meat, including red and white meat, is not yet fully understood[37].

Seafood

There is no clear evidence to suggest a relationship between RPL and seafood. Fish is a source of protein and omega-3 fatty acids[13]; however, it may also contain organochlorines and mercury[38]. A meta-analysis showed that consumption of a large amount of fish caused a 19% reduction in miscarriage events, as compared with low fish intake[39]. Further, in patients treated with ART, the ORs for live birth per two servings/week of fish were 1.54 (95% CI: 1.14-2.07), 1.50 (95% CI: 1.13-1.98), an 1.64 (95% CI: 1.14-2.35) when fish substituted for any other meat, any other protein-rich food, or processed meat, respectively[36]. Nonetheless, it is possible that consumption of fish contaminated with polychlorinated biphenyls or persistent chlorinated pesticides might adversely affect pregnancy.

Vegetable Protein

Soy (phytoestrogens)

There is currently no research on the relationship between vegetable protein and RPL. Soy consumption neither helps nor harms couples trying to conceive. Analysis of soy food intake and age-corrected ART births showed that the group with a soy food intake of 0.34-1.02 servings/day had a significantly higher birth rate than a group with no isoflavone intake (OR: 1.85, 95% CI: 1.10-3.20)[40]. Similarly, the birth rate increased with a higher intake (7.56-27.89 mg/day) of soy-derived isoflavones (OR: 1.77, 95% CI: 1.03-3.03)[40]. The results of a prospective, controlled, randomized trial showed significantly higher rates of implantation, clinical pregnancy, and ongoing pregnancy/delivery in patients who received progesterone plus phytoestrogens for luteal-phase support while undergoing *in vitro* fertilization embryo transfer, as compared with patients who received progesterone plus placebo[41]. A randomized trial of the effect of phytoestrogens in women with unexplained infertility who were on clomiphene therapy found no significant difference in miscarriage rates between the two groups (4% vs. 4%, P: not significant). However, pregnancy rates significantly differed between the groups (26% vs. 12%, $P<0.01$)[42]. In that study, the phytoestrogen-treated group had significantly thicker endometrium (8.9 ± 1.4 vs. 7.5 ± 1.3, $P<0.001$) and significantly higher luteal phase plasma progesterone (13.3 ± 3.1 vs. 9.3 ± 2.0, $P<0.01$) than did the control group, suggesting that a diet rich in estrogenic components may improve pregnancy rates in patients undergoing clomiphene therapy[42].

Dairy Products

The relationship between RPL and dairy products is not yet fully understood. A meta-analysis reported a 37% reduction in miscarriage events at high versus low intake levels of dairy products[37]. The risk of miscarriage for a group drinking milk ≥8 times per week was 0.6 times (OR: 0.6, 95% CI: 0.5-0.8) that of a group drinking milk ≤3 times per week[43]. Similarly, the risk in a group eating cheese ≤5 times per week was 0.5 times (OR: 0.5, 95% CI: 0.4-0.6) that of a group eating cheese ≤2 times per week[43]. A case-control study compared dairy product consump-

Table 1 Associations of nutrients with recurrent pregnancy loss, miscarriage, stillbirth, and fertility

	Recurrent pregnancy loss	Miscarriage	Stillbirth	Infertility
Vitamins				
Vitamin A		→[10]	→[10]	↓[14]
Vitamin C		→[10]	→[10]	→[13]
Multivitamin without folic acid with/ without vitamin A		↓[10]	↓[10]	
Folic acid		Recommended: ≥1,000 mg/day ↓[11], ↓[12]	Recommended: ≥1,000 mg/day ↓[11]	↓[13]
Vitamin D	↓[16]	↓[15], →[20]		↓[13]
Antioxidants		→[22-24], ↓?[25]		→[13]
Lipids				
Saturated fatty acid		→[26]		
Unsaturated fatty acid				
Polyunsaturated fatty acid		↑[26]		
Omega-6 fatty acid	→[31]			→[31]
Omega-3 fatty acid	→[31]	→[26]		→[31]
Protein				
Animal protein				↑[32], →[36]
Red meat		→[37]		↑[35]
Total meat		→[37]		↓[36]
Seafood		↓[39]		↓[36]
Vegetable protein				
Soy (isoflavone)		→[42]		↓[40,41,42]
Dairy products				
All dairy products		↓[37]		→[13]
Milk, Cheese		↓[43,44]		
Grains (cereal)		↓[37], →[45]		↑[46]
Sugar Substitute	↑[47, 48]	↑[41]		↑[45]
Preference				
Caffeine	↑ more than three cups of coffee/day (300 mg/day)[50], ↑[48]	↑ more than three cups of coffee/day (300 mg/day)[39]	↑[51]	→[13]
Dietary pattern				
Alternative Mediterranean style variation		→[49,50]		↓[49,50]
Fertility diet		→[49,50]		↓[49,50]
Dietary Inflammatory Index	↑[52]			
Dietary Antioxidant Index	↓[53]			

↑ : increase, → : no obvious impact, ↓ ?: possibly decrease, and ↓ : decrease. The numbers on the upper right corner of arrows indicate the reference number.

tion of women who had and had not experienced a spontaneous miscarriage and found significant differences between groups in servings per day of dairy products (P<0.001)[44]. Regarding the relationship between infertility and dairy products, the review by Gaskins and Chavarro[13] suggests that there is currently no clear evidence to support a strong association.

Grains (Cereal)

Results of meta-analysis indicated an association between high consumption of cereal and a lower rate of miscarriage (OR: 0.57, 95% CI: 0.41-0.79)[37]. However, Amini et al.[45] reported no significant difference in cereal intake levels between a group of women with successful childbirth and another group with miscarriage incidence. Several studies have suggested that a low glycemic load and high intake of whole grains may be beneficial for conception[46].

Sweeteners

While there is no direct evidence linking sugar intake to RPL, excessive sugar consumption may lead to insulin resistance, which has been associated with RPL[47]. Inflammation and oxidative stress associated with metabolic syndrome were reported to contribute to RPL[48]. A meta-analysis reported a 37% reduction in miscarriage events when comparing high and low dairy product intake (OR: 7.50, 95% CI: 1.31-43.10). In a meta-analysis, high sugar intake increased miscarriage in middle-income individuals (OR: 7.50, 95% CI: 1.31-42.86)[37]. Refined sugar and artificial sweetener consumption were negatively correlated with ovarian stimulation and embryo development[49].

Preferences

Caffeine

A retrospective case-control study showed an increased RPL risk when daily caffeine intake was 151-300 mg (OR: 3.045, 95% CI: 1.237-7.287), as compared with ≤150 mg; RPL risk was further increased when daily caffeine intake was ≥301 mg (OR: 16.11, 95% CI: 6.547-39.619). The study considered the caffeine content of one espresso to be approximately 100 mg per cup[50]. The risk of miscarriage increased in a dose-dependent manner, with caffeine intake of 300 mg caffeine/day, i.e., three cups of coffee (RR: 1.37, 95% CI: 1.19-1.57) or 600 mg/day, i.e., six cups of coffee (RR 2.32, 95% CI: 1.62-3.31)[39]. Additionally, caffeine consumption within 4 weeks before pregnancy, during the first trimester of pregnancy, and at a dose ≥300 mg/day during the first 4 weeks of pregnancy increased the risk of late miscarriage and stillbirth[51]. *CYP 1A2* is the primary gene responsible for caffeine metabolism, and the OR of RPL risk increased in proportion to caffeine intake when homozygous *CYP1A2* gene polymorphisms were observed[52]. The review by Gaskins and Chavarro[13] suggests that there is no clear evidence to support a strong association between infertility and coffee. For more information on the relationship between infertility and coffee, please refer to the review by Gaskins and Chavarro[13].

Dietary Patterns

Gaskins et al.[53,54] proposed that although Mediterranean-style and fertility diets are effective for infertility they do not reduce the risk of miscarriage. In turn, Yan et al.[55] reported that a balanced diet reduced the frequency of miscarriage events (OR: 0.73, 95% CI: 0.36-0.89), whereas processed foods were associated with an OR of 1.97 (95% CI: 1.36-3.34). Vahid et al.[56,57] evaluated the Dietary Inflammatory Index (DII) and Dietary Antioxidant Index (DAI) in patients with RPL. DII is used to evaluate inflammation related to diet and, generally, higher inflammation is associated with a high DII score, indicating an increased risk of miscarriage (OR: 2.12, 95% CI: 1.02-4.43)[56]. DAI indicates the relationship between antioxidants and diet. Specifically, the higher the DAI value, the stronger the antioxidant effect; it is now well-established that consuming an antioxidant-rich diet reduces miscarriage events among patients with RPL[57].

The content of all studies included in this review is summarized in **Table 1**.

Conclusion

Our review of the literature, including clinical and experimental data on the effects of foods on the incidence of RPL, miscarriage, and infertility, strongly suggests a direct relationship between feeding habits and the risk of miscarriage during pregnancy. We conclude that a balanced diet that includes nutrients with antioxidant properties helps prevent miscarriage, whereas a diet that includes processed foods and nutrients with proinflammatory effects poses a severe threat of miscarriage, and possibly RPL and/or infertility, although the latter warrants further research.

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