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# Prepregnancy Nutrition and Early Pregnancy Outcomes

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## Abstract

Implantation failure and pregnancy loss are estimated to affect up to 75% of fertilized ova; however as of yet there is limited empirical evidence, particularly at the population level, for understanding the environmental determinants of these losses. The purpose of this review is to summarize the current knowledge on prepregnancy nutrition and early pregnancy outcomes with particular focus on the outcome of spontaneous abortion among pregnancies conceived naturally and early pregnancy end points among pregnancies conceived through *in vitro* fertilization. To date, there is limited evidence to support associations of prepregnancy vitamin D and caffeine intake with pregnancy loss. There is suggestive data supporting a link between a healthy diet and lower risk of pregnancy loss. High folate and minimal to no alcohol intake prior to conception have the most consistent evidence supporting an association with lower risk of pregnancy loss.

### Keywords

nutrition; diet; spontaneous abortion; miscarriage; pregnancy loss; early pregnancy; in vitro fertilization; reproductive health

## Introduction

Human reproduction is a highly inefficient process compared to other mammals. Although uncertain, up to 75% of all fertilized ova may be lost [1, 2]. A large percentage (~45%) of lost pregnancies are a result of implantation failure and therefore are never recognized as

**Conflict of Interest**

Audrey J. Gaskins, Thomas L. Toth, and Jorge E. Chavarro declare that they have no conflict of interest.

**Compliance with Ethics Guidelines**

**Human and Animal Rights and Informed Consent**

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pregnancies [3]. These early losses many times manifest clinically as female infertility. The remaining 30% of lost pregnancies occur after implantation and are termed spontaneous abortions (loss prior to 20 weeks) or still births (loss at ≥ 20 weeks) [4]. While many of these early losses are still missed, clinically recognized losses account for ~15% of recognized pregnancies, making it the most frequent adverse pregnancy outcome [5]. Chromosomal abnormalities are implicated in the case of about 50% of all clinical pregnancy losses; however, the remaining 50% of the causes are not well understood and may be preventable and related to environmental factors such as diet [6].

Nutritional exposures offer promise as potential modifiable risk factors for early pregnancy outcomes as numerous studies underline their impact on fertility, gametogenesis, embryonic development, and fetal loss [7]. At present, there is little research on the association between diet and early pregnancy outcomes, specifically pregnancy loss, because of the challenges associated with studying them, particularly in naturally conceived pregnancies. For instance, unlike many later reproductive outcomes, most miscarriages occur at home and are not reported to a clinician. This makes conducting large scale prospective studies difficult as disease registries rarely capture pregnancy loss, fewer still document early miscarriages, and even less include individual-level pre-conceptional data on modifiable lifestyle factors like diet.

Very early pregnancy endpoints such as fertilization and implantation failure are practically impossible to study in naturally conceived pregnancies. Thus, studying women undergoing *in virto* fertilization (IVF) provides a unique opportunity to observe of many early developmental measures including oocyte production and maturation, oocyte fertilization, pre-implantation embryo development, implantation, and early pregnancy losses that cannot be observed in couples conceiving naturally. As these early clinical endpoints represent the majority of pregnancy failures even detecting associations of small magnitude may have large population effects.

The purpose of this paper is to review the current literature on prepregnancy nutrition and early pregnancy endpoints. While the majority of research will focus on studies evaluating the link between dietary factors and pregnancy loss among naturally conceived pregnancies, studies among IVF populations will be utilized to highlight the potential for diet to impact very early reproductive outcomes and lend insight into potential biological mechanisms. Only dietary factors with sufficient human literature to review are summarized here. These include dietary patterns, folate, vitamin D, caffeine, and alcohol.

## Dietary Patterns

To date, three studies have assessed the relationship between overall diet and risk of pregnancy loss. The largest study came from the Nurses' Health Study II where pre-conception diet and pregnancy outcomes were assessed among 11,072 women contributing 15,959 pregnancies over 18 years of follow-up [8]. The authors found that adherence to the Alternate Healthy Eating Index 2010, Alternate Mediterranean Diet, or Fertility Diet patterns prior to pregnancy were not associated with risk of pregnancy loss. In analyses restricted to pregnancies within a year of diet assessment (aimed at minimizing the effect of

exposure misclassification over follow-up), the Fertility Diet (characterized by high intake of monounsaturated fats, vegetable protein, high-fat dairy, iron, and multivitamins and low intake of trans fat, animal protein, glycemic load, and low-fat dairy) was inversely associated with fetal loss; however the association was modest (RR=0.82, 95% CI 0.69, 0.96 comparing women in the highest quartile of adherence with women in the lowest quartile of adherence). These findings are not entirely consistent with two other studies on dietary habits and risk of pregnancy loss. A case-control study from Italy found a higher risk of spontaneous early miscarriage with lower intake of green vegetables, fruit, and dairy products coupled with a higher intake of fat [9]. Similarly, a population-based case-control study from the UK found that lower intake of fresh fruit and vegetables, dairy, and chocolate was associated with increased odds of spontaneous abortion [10].

While the case-control studies provide seemingly congruent evidence in support of a healthy diet rich in fruits, vegetables, and dairy some limitations are worth noting. First, both case-control studies assessed diet after the outcome was recorded using a non-validated dietary questionnaire with 13 or fewer food groups. In that setting, recall bias and unmeasured confounding by other dietary variables are potential concerns. Both studies also asked about diet in the first trimester of pregnancy which tends to suffer from strong confounding by pregnancy symptoms. Pregnancy symptoms like nausea (and aversions to tastes or smells) can influence dietary behavior [11] and these symptoms are more frequent and/or severe in pregnancies that are eventually carried to term than in those that miscarry [12].

Two studies from *in vitro* fertilization cohorts further suggest that healthy dietary patterns might have a positive impact on chances of implantation and clinical pregnancy. The first study found that increasing adherence to Dutch dietary recommendations (characterized by high intake of whole grains, monounsaturated or polyunsaturated oils, vegetables, fruit, meat or meat replacers, and fish) in women undergoing IVF increased the chance of ongoing pregnancy [13]. Similarly, a separate cohort study of Dutch women undergoing IVF found that high adherence to a “Mediterranean” diet (characterized by high intake of vegetable oil, fish, legumes, and vegetables and low intake of snacks) was associated with increased probability of pregnancy after IVF (OR= 1.4, 95% CI: 1.0–1.9) [14]. When intermediate endpoints were evaluated in this latter study, there were no associations with fertilization or embryo quality measures, suggesting that the beneficial effects of the “Mediterranean” diet were more likely on the endometrium (as opposed to early embryo development or quality).

While there is suggestive evidence from both natural and IVF conceived pregnancies that a diet rich in fruits, vegetables, whole grains, vegetable oils, and fish may be protective of pregnancy loss, future prospective cohort studies that enroll couples pre-conceptionally and measure diet immediately prior to conception are needed to further elucidate the relationship between dietary patterns and risk of pregnancy loss.

## Folate

The importance of folate intake prior to conception has been recognized since the early 1990s when the U.S. Preventive Services Task Force and Centers for Disease Control and Prevention recommended that all women planning or capable of pregnancy take 400 μg of

folic acid daily to prevent neural tube defects [15]. While the impact of folate deficiency and defects in folate and homocysteine metabolism on incidence of pregnancy loss are generally well accepted [16–19][20–25], the evidence on the preventive effects of folic acid supplementation on miscarriage has been more controversial. In the mid 1990's the safety of folic acid supplementation was called into question on the basis of three papers [26–28], which suggested folic acid supplementation increased the risk of miscarriage. However, these findings were later challenged due to methodological errors [29, 30] and two follow-up studies on folate supplementation during pregnancy from China [31] and Brazil [32] provided strong evidence that periconceptional folic acid use did not increase miscarriage rates. Three recent cohort studies also found encouraging results suggesting that the use of folic acid prior to or during early pregnancy was associated with a reduced risk of miscarriage [33–35]. The most recent study reported that consuming >730μg/day of supplemental folate, compared to none, was associated with a 20% reduced risk of spontaneous abortion [35]. Moreover, the authors calculated that for every 42 women that go from taking 400 μg/day of supplemental folate (the current recommendation) to 730 μg/day, one spontaneous abortion could be prevented.

Studies among couples undergoing infertility treatment suggest that folate may exert many of its beneficial effects very early on in pregnancy. Among Polish women, those who received a folic acid supplement had better quality oocytes and a higher degree of mature oocytes compared to women who did not receive folic acid [36]. Moreover, a recent cohort study of US women undergoing IVF found that pre-treatment intake of supplemental folate >800 μg/day was associated with higher fertilization rates, lower probability of cycle failure prior to embryo transfer, improved embryo survival manifested in higher implantation rates, and an overall higher live birth rate [37]. While three other cohort studies of folate and clinical outcomes of IVF from European populations did not show this benefit [38–40], they excluded women failing prior to embryo transfer. If higher levels of folate prevent early adverse outcomes prior to embryo transfer, then excluding these women would attenuate the results, and could be one explanation for their null findings.

Overall, the vast literature on folate and early pregnancy outcomes suggest that higher intake of supplemental folate may be an effective strategy to prevent early adverse pregnancy outcomes such as failed fertilization, implantation failure, and clinical pregnancy loss. While the literature from IVF cohorts and basic science suggest that most of folate's beneficial effects may be on supporting the exponential increase in DNA synthesis that occurs during early embryo development, corroborating evidence from natural pregnancies which focused on later pregnancy losses suggest that folate's beneficial effects could extend throughout gestation.

## Vitamin D

Researchers worldwide have consistently demonstrated a seasonal distribution in conception and birth rates among human pregnancies [41–43]. Similar seasonal changes in pregnancy rates have also been reported from several in vitro fertilization programs [44–48]. While many factors have been implicated as drivers of these trends, seasonal variation in vitamin D levels has been one of specific interest since the majority of evidence points to reduced

ovulation rates and endometrial receptivity during long, dark winters (when vitamin D levels are low) and peaked rates of conception and multiple pregnancy rates during summer (when vitamin D levels are highest).

The majority of literature on vitamin D and pregnancy loss among naturally conceived pregnancies comes from studies that measured 25-hydroxyvitamin D, 25(OH)D, in blood samples taken at the first prenatal visit. To date, three studies found no association between early pregnancy concentrations of serum 25(OH)D and risk of miscarriage [49–51]. One study found that women who had a miscarriage after gestational week 10 had lower plasma 25(OH)D concentrations at their first trimester visit compared with those who did not have a miscarriage [52]; however, these findings were based on a small number of cases (n=3). Only one study was able to assess 25(OH)D concentrations prior to pregnancy in relation to pregnancy loss and found that levels did not differ between the women who had a miscarriage (54 nmol/l) and those who did not (62 nmol/l) (p-value=0.14) [52].

In 2010, a potential role of vitamin D in IVF started to gain interest when a study reported that pregnancy rates after IVF were almost four fold higher in women who were vitamin D sufficient than in those who were vitamin D deficient [53]. Since then the number of publications on this topic has grown with heterogeneous results [54]. The second study published on this association actually observed a negative effect of increasing follicular fluid vitamin D levels on IVF outcomes [55]. Specifically, women with higher 25(OH)D levels had decreased embryo quality scores and reduced clinical pregnancy rates compared to patients with intermediate or low 25(OH)D levels. Conflicting results were also produced from a later study by Rudick et al. in which serum vitamin D was positively associated with clinical pregnancy rate in non-Hispanic and Hispanic whites but an inverse relationship was observed among women of Asian ethnicity [56]. A study among Iranian woman undergoing IVF found that fertilization rates were higher among women who had sufficient levels of vitamin D, but no correlation was seen between the vitamin D levels and pregnancy rate [57]. Two studies have investigated the association between vitamin D levels and IVF outcomes among egg donor recipients and while one found a significant increase in clinical pregnancy rates with increasing vitamin D levels [58], suggesting a specific effect of 25(OH)D on endometrial receptivity, the second study could not confirm this association [59].

At present, very little can be conclusively drawn from the findings of vitamin D and early pregnancy outcome studies given the heterogeneity of findings. While vitamin D deficiency appears to be detrimental, it is unclear whether high levels of vitamin D confer additional benefit once sufficiency has been achieved. A randomized trial testing the effects of high (1000 IU) and low (500 IU) dose vitamin D supplementation on 1000 women initiating IVF treatment in Sweden is currently ongoing. Results from this study should lend considerable additional insight on the effects of vitamin D on early pregnancy outcomes.

## Caffeine

Studies on maternal caffeine consumption and risk of spontaneous abortion have been conducted since the 1980s and to-date it stands as the most researched dietary factor in

regards to pregnancy outcomes. The association between early pregnancy consumption of caffeine and risk of spontaneous abortion was recently summarized in a meta-analysis of 26 studies encompassing approximately 15,000 cases of miscarriage from over 180,000 women [60]. The authors found that for every 100 mg/day increase in caffeine intake in early pregnancy, the risk of spontaneous abortion increased by 14% (RR=1.14 95% CI 1.10, 1.19) in a relatively linear fashion. The evidence on prepregnancy consumption of caffeine and risk of pregnancy loss, however, is less conclusive most likely due to differences in study design, populations, outcome ascertainment, and exposure classification. Most previous studies on prepregnany caffeine intake and pregnancy loss have enrolled women early in pregnancy and asked about caffeine intake retrospectively prior to the interview, raising concerns about possible selection and recall biases. Thus, for the purposes of this review, we will focus on the few studies that have enrolled participants before pregnancy [61–64]. Overall, while most of these studies were small, the majority showed that pre-pregnancy consumption of caffeine was not associated with increased risk of spontaneous abortion. In the largest study to date (n=5,132 women), Hahn and colleagues found that the multivariable hazard ratio of miscarriage (95% CI) for preconception caffeine consumption of 100–299 mg/day, 200–299 mg/day, and ≥ 300 mg/day compared with <100 mg/day were 1.00 (0.81, 1.23), 1.19 (0.96, 1.49), and 1.09 (0.89, 1.33) [63]. Moreover, when specific sources of caffeine intake were assessed (e.g. coffee, tea, soda), none were consistently associated with risk of spontaneous abortion. The one study that did find a link between prepregnancy consumption of caffeine and SAB only reported associations at the very highest level of intake (e.g. >900 mg/day) [64]. Taken together, these prospective cohort studies provide reassuring evidence that while early pregnancy consumption of caffeine might modestly increase the risk of pregnancy loss intake prior to conception seems to have little to no impact on miscarriage risk.

The first study on caffeine intake and outcomes of IVF found no association between caffeine intake prior to treatment and oocyte retrieval, fertilization, embryo transfer, or implantation rates [65]. However, they found that usual caffeine intake of 3–50 and >50 mg/day compared with <2 mg/day yielded an odds ratio for miscarriage of 19.8 (95% CI 1.3, 300.9) and 10.5 (95% CI 0.9, 125.3) respectively. Caution should be taken when interpreting these results due to the small sample size (n=221) and low levels of caffeine intake. The second study that evaluated this association did so in a much larger population of women (n=2,474 women and 4,716 cycles) [66]. These authors found that caffeine consumption by women prior to IVF treatment was associated with lower peak estradiol level but was not associated with number of oocytes retrieved, fertilization rate, implantation rate, or live birth rate. Moreover, the range of intake compared in this population (e.g. none vs. 0–800, 801–1400, and >1401 mg/week) was more relevant given the average caffeine consumption of reproductive aged women is around 161 mg/day (1127 mg/week) [67].

Taken together, the evidence on prepregnancy caffeine consumption and early pregnancy outcomes suggests that moderate caffeine intake is not associated with pregnancy loss. While there is ample evidence suggesting that caffeine intake during early pregnancy is associated with increase miscarriage rates, prepregnancy intake does not appear to be detrimental. Therefore, while women should still be counseled to limit caffeine intake to less

than 200 mg during pregnancy, this advice does not seem warranted to extend to prepregnancy intake.

## Alcohol

Alcohol intake has received much attention in the context of early adverse pregnancy outcomes, specifically miscarriage, due to its proposed role as a reproductive toxicant. Numerous studies have documented the adverse consequences of maternal alcohol consumption during pregnancy on risk of spontaneous abortion [68–74] yet there is conflicting evidence on the impact of pre-pregnancy alcohol intake on pregnancy loss. While two studies found that pre-pregnancy alcohol intake was directly [75, 76] associated with pregnancy loss, many more reported no association [64, 73, 77, 78]. Of note, however, is that the majority of these previous studies relied on retrospective report of pre-pregnancy alcohol consumption with the potential for recall bias [73, 76–78], were unable to include early pregnancy losses [73, 75–78], had limited control for other lifestyle factors [64, 73, 75, 76, 78], and relied on small sample sizes (e.g. <60 cases) [75–77] which has limited the conclusions that can be made from the findings. The best evidence to date comes from a nested case-control study which used prospective data from a population-based cohort comprising of 11,088 Danish women [64]. In this study, the multivariable odds ratio (95% CI) for miscarriage (defined as a pregnancy loss at <28 weeks gestation) was 0.92 (0.64, 1.32) for 1–3 drinks per week, 0.98 (0.67, 1.45) for 7–13 drinks per week, and 1.28 (0.71, 2.32) for 14+ drinks per week compared to women consuming <1 drink per week. This data suggests that moderate alcohol intake even at levels up to 2 servings per day prior to pregnancy is not associated with excess risk of miscarriage.

Studies on alcohol intake and pregnancy outcomes from IVF populations paint a much more severe situation and point to adverse effects of alcohol both prior to and after embryo fertilization. A cohort study of women undergoing IVF from California reported that maternal alcohol consumption during the year prior to IVF was negatively associated with oocyte retrieval [79]. Furthermore, compared to women who drank less than 1 drink per day, those who drank 1 drink per day or more had a more than two-fold increase in miscarriage rates (OR: 2.21 95% CI 1.09–4.49). This effect estimate increased when the authors assessed the same association according to alcohol intake in the week prior to IVF initiation. Similar findings were reported in a cohort study of women undergoing IVF from Boston [80]. Women who consumed > 50 grams of alcohol per week had significantly lower peak estradiol levels and greater odds of failed fertilization. Women consuming 1 to 7 drinks per week had 18% greater odds of failed implantation. Moreover, a smaller study among Polish women undergoing IVF found that alcohol consumption prior to treatment was associated with the development of poorer quality embryos [81].

At present, the literature from naturally and IVF conceived pregnancies seem at odds-prepregnancy alcohol consumption does not appear detrimental among naturally conceived pregnancies but appears very unfavorable for early and intermediate endpoints of IVF. One reason for this discrepancy could be that the studies among naturally conceived pregnancies are unable to observe early reproductive failures. As mentioned in the introduction, these early failures many times manifest as female infertility. As alcohol intake has been

associated with longer waiting time to pregnancy [82] and higher risk of infertility [83], it could be that the studies concerned with fetal loss after pregnancy recognition could be looking too late to observe alcohol's particularly detrimental effects. It could also be that the IVF population represents a more susceptible subgroup of women and therefore the effects of suspected reproductive toxicant, such as alcohol, many be amplified. Given this uncertainty, the best available evidence suggests that minimal to no alcohol intake prior to conception is the safest advice to minimize early adverse pregnancy outcomes.

## Conclusions

Evidence on using nutritional exposures as modifiable risk factors to prevent early adverse pregnancy outcomes continues to grow. At present, there is substantial evidence to support the use of preconception folic acid supplements not only to prevent birth defects but also to prevent pregnancy loss, particularly at early stages of embryo development. There is suggestive evidence linking moderate to high alcohol intake to early pregnancy failures; however this is largely derived from studies among IVF pregnancies. Thus, the safest advice for women trying to get pregnant would be to lower or stop their intake of alcohol. While the limited data on dietary patterns and pregnancy loss seems to suggest benefit, few rigorous studies have been conducted on this relationship. There is ample evidence suggesting that caffeine intake during early pregnancy is associated with increase miscarriage rates; however prepregnancy caffeine intake does not appear to be detrimental within recommended levels of intake. The relationship between vitamin D and early pregnancy outcomes still remains to be determined and at present seems null. Future studies are needed, particularly in the areas of preconception dietary patterns and vitamin D status, and ideally in the form of prospective cohort studies or randomized trials to further elucidate the potential impact of dietary exposures on early pregnancy outcomes.

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•• Of major importance

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