

## Review Article

### **The Mediterranean diet, but not metformin, is effective in the prevention of gestational diabetes: A review of randomized controlled trials**

#### **Abstract:**

Gestational diabetes (GD) is a common and deadly disorder with deleterious effects on both the mother and fetus. The current review assessed the role of the Mediterranean diet and metformin in the prevention of GD. The PubMed, Medline, and Google Scholar databases were searched for relevant articles, and the keywords metformin, Mediterranean diet, and gestational diabetes prevention were used with the proteans AND and OR. Out of the 252 articles retrieved, 48 full texts were assessed, and only nine articles fulfilled the inclusion and exclusion criteria. A data extraction sheet was used to collect the author's name, year of publication, country, methods of the study, risk reduction, odds ratio, relative risk, 95% *CI*, and P values. Three (33.3%) articles assessed the effectiveness of metformin on GD, and another six (66.7%) investigated the effects of the MedDiet on GD. The studies on metformin showed no reduction in GD (odds ratio, 1.07, 0.79–1.44, P value for overall effect=0.65,  $I^2$  for heterogeneity=3%, P value=0.36. Chi-square=2.07, and the mean difference=2), while studies on the MedDiet showed a reduction in gestational diabetes risk (odds ratio, 0.78, -0.67–0.89), P value for heterogeneity <0.00001), heterogeneity, 85%, P value for overall effect=0.0004. Chi-square=34.11 and mean difference=5. The Mediterranean diet was effective in the prevention of GD; however, metformin showed no significant risk reduction for GD.

**Keywords:** Metformin, Mediterranean diet, Gestational diabetes, Prevention

#### **Introduction:**

The debate regarding the detection and treatment of gestational diabetes mellitus (GDM) continues in the twenty-first century. Although women with GDM are at risk of subsequent diabetes mellitus in the years following diagnosis, there is strong controversy regarding the long-term benefits of treatment [1].

GDM is increasing with high economic burden and severe pregnancy-related complications. Effective prevention strategies are lacking; in addition, the recommendations for lifestyles, oral hypoglycemic drugs, and healthy weight are contradictory and not uniform [2].

Metformin is the first-line oral hypoglycemic drug, and was shown to have anticancer and anti-inflammatory effects. In the prevention of the progression of prediabetes to

diabetes mellitus, lifestyle modification is essential [3]. Metformin is an effective alternative to insulin for the treatment of gestational diabetes mellitus [4, 5].

The Mediterranean diet (MD) is characterized by high consumption of fruits and vegetables, legumes, olive oil, fish, and unrefined cereals and avoidance of red meat; together with a moderate amount of alcohol and dairy products, the Mediterranean diet is one of the healthiest diets in the world. The American Diabetes Association recommended the MD for use among patients with diabetes mellitus [6, 7].

Gestational diabetes mellitus is associated with various adverse effects to both the mother and fetus, and the level is increasing worldwide [8]. The prevention of GDM to prevent both short- and long-term effects of the mother and child is of paramount importance [9]. The literature on this important health issue is scarce. The current review aimed to assess the benefits of metformin and the Mediterranean diet in the prevention of GDM.

## **Subjects and Methods:**

### **Eligibility Criteria according to PICOS:**

Randomized controlled studies (RCTs) published in English and that contained information on metformin and the Mediterranean diet either in singleton pregnancy, prior to or during pregnancy were included. Studies assessing other pregnancy outcomes, cohort studies, case-control studies, case reports, animal studies, or studies published in a language other than English were not included.

### **Outcome measures:**

The primary outcome was the prevention of GD.

### **Information sources and literature search:**

A systematic literature search was performed by two researchers, and the search was conducted in PubMed, Medline, and Google Scholar with an interest in articles (RCTs) reporting the relationship between metformin, the MedDiet, and GD risk. In addition, the reference lists were searched for additional studies. The search engine was limited to the period from 2010 to September 2020.

A predetermined table was used to collect study information, including the author's name, year of publication, patient number, study duration, criteria for patient selection, GDM diagnostic criteria and results and how the results were deduced. Data were cross-checked by the two authors for any errors and discrepancies. Any discrepancies were solved by consensus.

**Data analysis:** The RevMan system for meta-analysis was used, and the data were all dichotomized. The fixed effect model was used because no significant heterogeneity

was found. Funnel plots were used to assess lateralization. A P value of  $<0.05$  was considered significant.

**Figure 1. Metformin and the Mediterranean diet in the prevention of gestational diabetes**



**Table 1. Metformin and gestational diabetes prevention**

Author	Year	Country	Duration	Methods	Intervention	Control	Results
Alroda et al. [12]	2015	USA	3.2 years	RCT	67/464	69/487	Not significant
Sales et al. [13]	2018	Brazil	20w	RCT	13/82	16/82	Not significant
Valdes E et al. [14]	2018	Chile	24w	RCT	25/68	19/73	Not significant

**Table 2. The Mediterranean diet and gestational diabetes prevention**

Author	Year	Country	Duration	Method	Intervention	Control	95% CI	P value
Assaf-Balut et al. [15]	2017	Spain	20w	RCT	74/434	103/440	0.57–0.98	0.039
Assaf-Balut et al. [16]	2018	Spain	1year	RCT	41/136	15/115	0.18–0.67	0.003
de la Torre et al. [17]	2019	Spain	24w	RCT	130/936	103/440	0.73–0.93	0.001
H AI Alwattar et al. [18]	2019	UK	17m	RCT	84/477	124/497	0.47–0.91	0.01
Melero et al. [19]	2020	Spain	24w	RCT	19/128	34/132	0.50–0.97	0.037
Olmedo-Requena et al. [20]	2019	Spain	16w	Case-control	102/291	377/1175	0.39, 0.94)	0.028

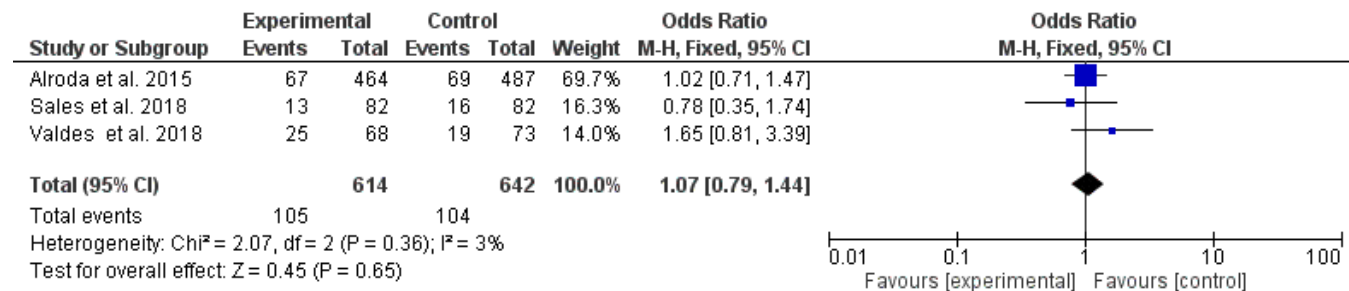
**Table 3. Risk of bias of the included randomized controlled trials**

Study	Year	Selection	Performance	Attrition	Reporting	Other
Assaf-Balut et al. [15]	2017	High	High	Low	Low	Unclear
Assaf-Balut et al. [16]	2018	High	High	Low	Low	Unclear
de la Torre et al. [17]	2019	High	High	Low	Low	Low
H AI Alwattar et al. [18]	2019	High	Low	Low	Low	Low
Melero et al. [19]	2020	High	Unclear	Low	Low	Low
Alroda et al. [12]	2015	High	High	Low	Low	Low
Sales et al. [13]	2018	High	Unclear	Unclear	Low	Low
Valdes E et al. [14]	2018	Low	Unclear	Low	Low	Low

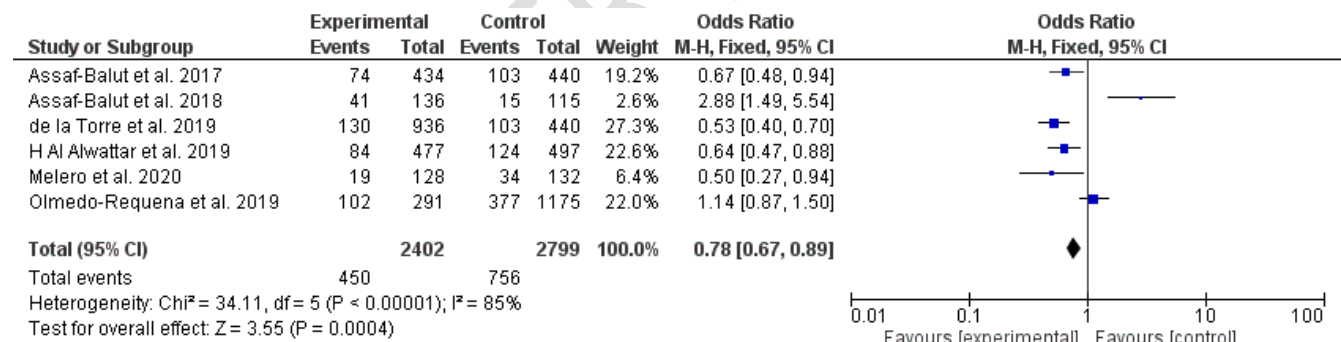
## Results:

Out of the 252 articles identified (132 after the removal of duplicates), 48 full texts were assessed, and only nine articles met the inclusion and exclusion criteria. Three (33.3%) articles assessed the effectiveness of metformin on GD, and another six (66.7%) investigated the effects of the MedDiet on GD. Six articles were from Europe, one was published in the USA, and two were from South America. The studies assessing metformin included 1256 patients and 209 events, while studies on the MedDiet reported 1206 events and 5201 patients. The duration of the studies was (16 weeks to 3.2 years), and the studies on metformin showed no reduction in GD [12–14], while studies on the MedDiet showed a reduction in gestational diabetes risk [15–20] (Tables 1& 2). In the current review, out of the three studies that were included, one showed no effects of metformin on GDM prevention, one study was neutral, and one study showed a positive effect (odds ratio, 1.07, 0.79–1.44, P value for overall effect=0.65,  $I^2$  for heterogeneity=3%, P value=0.36, Chi-square=2.07, and the mean difference=2, Figure 2). Regarding the effects of the Mediterranean diet, out of the six studies included in the meta-analysis, four showed positive effects on GDM prevention (odds ratio, 0.78, -0.67–0.89, P value for heterogeneity <0.00001, heterogeneity,  $I^2$ =85%, P value for overall effect=0.0004, Chi-square=34.11 and mean difference=5, Figure 3).

**Figure 2. Metformin effects on GDM prevention**



**Figure 3. Mediterranean diet effects on GDM prevention**



## **Discussion:**

The present meta-analysis showed that metformin is not effective in the prevention of gestational diabetes mellitus (1.07, 0.79–1.44, P value for overall effect=0.65,  $I^2$  for heterogeneity=3%, P value=0.36), similar to a previous meta-analysis [21]. Another meta-analysis assessing a wide variety of diets and pharmaceutical interventions found a possible benefit of metformin on gestational diabetes prevention in obese women [22]. Metformin was found to be associated with an increased weight in offspring when they were exposed prenatally to the drug [23].

Nutritional intervention, as a cost-effective intervention, is a first-line treatment in the prevention of short- and long-term cardiometabolic risks in both the mother and child [24, 25]. The Mediterranean diet (MD) is characterized by high consumption of fruits and vegetables, legumes, olive oil, fish, and unrefined cereals and avoidance of red meat; together with a moderate amount of alcohol and dairy products the MD is one of the healthiest diets in the world. The American Diabetes Association recommended the MD for use among patients with diabetes mellitus [4, 5]. The current meta-analysis showed that the MedDiet is effective in the prevention of GDM (odds ratio, 0.78, -0.67–0.89, P value for heterogeneity <0.00001, heterogeneity,  $I^2=85%$ , P value for overall effect=0.0004). Our findings were similar to those of Mijatovic-Vukas et al. [26], and the effects might be due to weight reduction [27], low red meat consumption, or the use of virgin olive oil [28–29]. A review conducted in the UK observed the beneficial effects of the MedDiet on GDM [30]. The protectiveness of the MedDiet on GDM ranged from 15%–38% depending on the patient's compliance and the guidelines used for the diagnosis [31].

**A limitation of the study** was the strict selection criteria that was adopted and the small number of randomized controlled trials that was included.

**Conclusion:** The Mediterranean diet was effective in gestational diabetes prevention when recommended at the first visit during pregnancy. Prescribing the MedDiet for women in the reproductive age group is a simple and effective measure to prevent GDM. Metformin is not effective in the prevention of GDM; physicians may need to limit their prescription of this drug to prevent women at risk of GDM, due to lack of a long-term safety profile.

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