Title: Gestational Diabetes Mellitus (GDM) and Diet: A systematic review and meta-analysis of randomized controlled trials examining the impact of modified dietary interventions on maternal glucose control and neonatal birthweight

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Abstract

Background: Medical nutrition therapy is a mainstay of GDM treatment. However, data are limited regarding the optimal diet for achieving euglycemia and improved perinatal outcomes.
Purpose: To investigate whether modified dietary interventions are associated with improved glycemia and/or improved birthweight outcomes in women with GDM when compared to control dietary interventions.
Data Sources: Twelve databases.
Study Selection: Published randomized controlled trials (RCTs) that reported on dietary components, maternal glycemia and birthweight.
Data Extraction: Data were extracted in duplicate using pre-specified forms.
Data Synthesis: From 2269 records screened, eighteen RCTs involving 1151 women were included. Pooled analysis demonstrated that for modified dietary interventions when compared to control, there was a larger decrease in fasting and postprandial glucose (-4.07 mg/dL [95% CI -7.58, -0.57]; p=0.02 and -7.78 mg/dL [95% CI -12.27, -3.29]; p=0.0007 respectively) and a lower need for medication treatment (RR 0.65 [95% CI 0.47, 0.88]; p=0.006). For neonatal outcomes, analysis of 16 RCTs including 841 participants showed that modified dietary interventions were associated with lower infant birthweight (-170.62 g [95% CI -333.64, -7.60]; p=0.04) and less macrosomia (RR 0.49 [95% CI 0.27, 0.88]; p=0.02). The quality of evidence for these outcomes was low to very low.
Limitations: Baseline differences between groups in postprandial glucose may have influenced glucose-related outcomes. As well, relatively small numbers of study participants limit between-diet comparison.
Conclusions: Modified dietary interventions favorably influenced outcomes related to maternal glycemia and birthweight. This indicates that there is room for improvement in usual dietary advice for women with GDM.

Gestational diabetes is one of the most common medical complications in pregnancy and affects an estimated 14% of pregnancies, or one in every seven births globally (1). Women with gestational diabetes and their offspring are at increased risk of both short and of longer-term complications including, for mothers, later development of type 2 diabetes, and for offspring, increased lifelong risks of developing obesity, type 2 diabetes, and metabolic syndrome (2-6). The adverse intrauterine environment causes epigenetic changes in the fetus that may contribute to metabolic disorders, the so-called "vicious cycle" of diabetes (7).

The mainstay of gestational diabetes treatment is dietary and lifestyle advice, which includes medical nutrition therapy, weight management and physical activity (8). Women monitor their fasting and post-meal glucose levels and adjust their individual diet and lifestyle to meet their glycemic targets. This pragmatic approach achieves the glycemic targets in approximately two thirds of women with gestational diabetes (8). However, despite the importance of medical nutrition therapy and its widespread recommendation in clinical practice, there are limited data regarding the optimal diet for achieving maternal euglycemia (8-11). It is also unknown whether the dietary interventions for achieving maternal glycemia are also effective for reducing excessive fetal growth and adiposity (12).

Different dietary strategies have been reported including low glycemic index, energy restriction, increasing or decreasing carbohydrates, or those that modify fat or protein quality or quantity (12-14). Three recent systematic reviews have been performed examining specific diets and pregnancy outcomes (15-17). Viana et al (16) and Wei et al. (15) concluded that low glycemic index diets were associated with a decreased risk of infant macrosomia. However, the most

recent systematic review from Cochrane included 19 trials randomizing 1398 women found no clear difference in large for gestational age or other primary neonatal outcomes with low glycemic index diet (17). The primary maternal outcomes were hypertension (gestational and/or preeclampsia), delivery by cesarean section and type 2 diabetes, outcomes for which most trials lacked statistical power, even when dietary subgroups were combined. Remarkably, no systematic reviews examined the impact of modified dietary interventions on the detailed maternal glycemic parameters including change in glucose-related variables, the outcomes which are most directly influenced by diet.

To address this knowledge gap, we performed a systematic review and meta-analysis of randomized controlled trials to investigate whether in women with gestational diabetes, modified dietary interventions (defined as a dietary intervention different from the usual one used in the control group) offer improved glycemic control and/or improved neonatal outcomes when compared to standard diets.

Methods

In accordance with a published protocol (PROSPERO CRD42016042391), we performed a systematic review and meta-analysis. Reporting is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. An international panel of experts was formed by the International Life Sciences Institute, Europe. This panel determined the review protocol and carried out all aspects of the review.

Data Sources and Search Strategy

The following databases were searched for all available dates using the search terms detailed in Table S1: PubMed, Medline, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, CINAHL, Web of Science Core Collection, Applied Social Sciences Index & Abstracts (ASSIA) ProQuest, ProQuest Dissertations & Theses: A&I and UK & Ireland, NICE evidence search, Scopus, UK Clinical Trials Gateway, ISRCTN, and ClinicalTrials.gov. The initial search was performed in July, 2016. An updated search of Medline, Embase, Cochrane Central Register of Controlled Trials and CINAHL was performed on October 3rd, 2017 using the same search terms.

A hand-search of relevant reviews and all included articles was conducted to identify studies for potential inclusion. As well, experts on the panel were consulted for the inclusion of additional articles. Reference management was carried out using EndNote.

Study Selection

All titles and abstracts were assessed independently and in duplicate to identify articles requiring full text review. Published studies fulfilling the following criteria were included: randomized controlled trials, evaluated modified dietary interventions on women with gestational diabetes, glucose intolerance or hyperglycemia during pregnancy, reported on primary maternal and neonatal outcomes, included women aged 18-45 years, had a duration of two weeks or more and were published in English, French, Spanish, Portuguese, Italian, Dutch, German or Chinese. We excluded studies which included participants with type 1 or type 2 diabetes if data for participants with gestational diabetes were not presented independently, if dietary characteristics

were not available, if the study was in animals, or did not report outcomes of interest. We did not include studies of nutritional supplements such as vitamin D or probiotics as recent reviews have addressed these topics (18; 19).

All citations identified after title and abstract assessment were full text reviewed in duplicate. Reasons for exclusion at the full text review stage were recorded. Any disagreements between reviewers were resolved by consensus and with consultation with the expert group when required.

Data Extraction

Data from included studies were extracted in duplicate using pre-specified data extraction forms. Extracted data elements included study and participant demographics, study design, diagnostic criteria for gestational diabetes, glucose intolerance or hyperglycemia, funding source, description of modified dietary intervention and comparator, maternal and neonatal outcomes. For studies with missing data, inconsistencies or other queries, authors were contacted. Record management was carried out using Microsoft Excel and RevMan.

For articles providing information on maternal weight, fasting glucose, postprandial glucose, HbA1c or HOMA-IR at baseline and post-intervention but not their change, change was calculated as the difference between post-intervention and baseline. Standard deviations were imputed using the correlation coefficient observed in articles reporting full information on the variable at baseline, post-intervention and its change or a correlation coefficient of 0.5 when this information was not available (11). As studies differed in postprandial glucose at baseline,

glycemic control at study entry was not considered to be equivalent in both arms and thus continuous glucose-related variables at follow-up are reported as change from baseline.

Data Synthesis

The primary outcomes were maternal glycemic outcomes (mean glucose, fasting glucose, postprandial glucose [post-breakfast, lunch, dinner and combined], hemoglobin A1c [HbA1c], assessment of insulin sensitivity by homeostasis model assessment of insulin resistance index [HOMA-IR], and change in these parameters from baseline to assessment; medication treatment [defined as oral diabetes medications or insulin]), and neonatal birthweight outcomes (birthweight, macrosomia, and large for gestational age).

Data were pooled into relative risks or mean differences with 95% confidence intervals (95% CI) for dichotomous outcomes and continuous outcomes respectively. Meta-analysis was performed using random effect models. A pre-specified analysis stratified by type of diet and quality assessment was performed to explore potential reasons for inter-study variation. Heterogeneity was assessed using I^2 statistics. Small study effects were examined for using funnel plots. Analyses were conducted using RevMan version 5.3. Pooled estimation of birthweight in the study and control arms, both overall and according to the specific diet intervention was performed using Stata 14.0.

Quality Assessment

Methodological quality and bias assessment was completed by two reviewers. Risk of bias was assessed using the Cochrane Collaboration tool, which rates seven items as being high, low or

unclear risk of bias (20). These items included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other potential sources of bias (20). A sensitivity analysis was performed excluding articles with relevant weaknesses in trial design or execution.

The overall quality of the evidence was also assessed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) working group guidelines (11). GRADE was assessed for all primary and secondary, both maternal and neonatal, but without subgroup analysis per different dietary intervention for each outcome measure.

Results

We screened 2269 records for potential inclusion and 126 articles were reviewed in full (Figure S1). Eighteen studies (12-14; 21-35) were included in the meta-analysis with a total of 1151 pregnant women with gestational diabetes.

Study Characteristics

The types of modified dietary intervention included low glycemic index (n=4), DASH (n=3), low carbohydrate (n=3), fat modification (n=2), soy protein enrichment (n=2), energy restriction (n=1), high fiber (n=1), ethnic diet (i.e. foods commonly consumed according to participant's ethnicity) (n=1) and behavioral intervention (n=1). Details of the study characteristics are included in Table 1. Most trials were single centered and had small sample sizes (range 12-150). Only two trials (one each from Spain and Australia) included over 100 participants, nine had 50-100 participants and seven studies had fewer than 50 participants. They were performed in North

America, Europe, or Australasia and all had a duration of at least two weeks. The ethnicity of participants was reported in seven studies (12; 13; 25; 28; 30; 31; 33).

Most studies assessed individual dietary adherence using food diaries (13; 22-36). While most studies did report an overall difference in dietary composition between the intervention diet and control diet, few studies reported a detailed assessment of dietary adherence. Only five studies used of a formal measure of adherence (23; 24; 28; 32; 33) and four of them reported data (24; 28; 32; 33). Adherence ranged from 20 to 76% in the control group and 60 to 80% in the intervention groups.

Participant Characteristics

When baseline characteristic data were pooled, women in the intervention group were older than women in the control group (pooled mean difference 0.60 years [95% CI 0.06, 1.14]) and had higher postprandial glucose (pooled mean difference 5.47 [95% CI 0.86, 10.08]) most influenced by the DASH and ethnic studies. There was no overall significant difference between the intervention and control groups for body mass index (BMI), gestational age at enrolment, fasting glucose, HbA1c, or HOMA-IR.

Maternal Glycemic Outcomes for all Modified Dietary Interventions

Pooled risk-ratios in 15 studies involving 1023 women demonstrated a lower need for medication (RR 0.65 [95% CI 0.47, 0.88; I^2=55]) (Table 2). Thirteen studies (n= 662 women) reported fasting glucose levels, nine (n=475) reported combined post-prandial glucose measures

and three (n=175) reported post-breakfast glucose measures. Pooled analysis demonstrated a larger decrease in fasting, combined postprandial and post-breakfast glucose levels in modified dietary interventions (-4.07 mg/dL [95% CI -7.58, -0.57; I^2=86; p=0.02], -7.78 mg/dL [95% CI -12.27, -3.29; I^2=63; p=0.0007] and -4.76 mg/dl [95% CI -9.13, -0.38]; I^2=34; p=0.03] respectively) compared to control group. There were no significant differences in change in HbA1c (7 studies), HOMA-IR (4 studies), or in post-lunch or -dinner glucose levels (2 studies).

Neonatal Birthweight Outcomes for All Diets

Pooled mean birthweight was 3266.65g (95% CI 3172.15, 3361.16) in the modified dietary intervention versus 3449.88 g (95% CI 3304.34, 3595.42) in the control group. Pooled analysis of all 16 modified dietary interventions including 841 participants demonstrated lower birthweight (-170.62 g [95% CI -333.64, -7.60; I^2=88]; p=0.04) and less macrosomia (RR 0.49 [95% CI 0.27,0.88; I^2=11]; p=0.02) compared to conventional dietary advice (Table 2 and Figure 1). There was no significant difference in the risk of large for gestational age newborns in modified dietary interventions as compared to control diets (RR 0.96 [95% CI 0.63,1.46; I^2=0]; p=0.85).

Subgroup Meta-Analysis by Types of Dietary Interventions

Pooled analysis of low glycemic index diets showed a larger decrease in fasting glucose (25; 29; 37), postprandial and post-breakfast glucose compared to control diets (25; 29) (Table 2). Whereas pooled analysis of the DASH diet, showed significant favorable modifications in several outcomes, including change in fasting (21; 35) and postprandial glucose (21), HOMA-IR (35), HbA1c (21) medication need (21; 22; 35), infant birthweight (22; 35) and macrosomia (22;

35) (Table 2 and 3). Lastly, pooled analysis of soya protein-enriched diet demonstrated a significant decrease in medication use and birthweight (14; 26) (Table 2 and 3). One soya protein intervention (n=68 participants) described significantly lower HOMA-IR (35) (Table 2).

One study for each of behavioral and ethnic specific modified dietary interventions was included. The behavioral change dietary intervention reported significant differences in change in postprandial glucose, and in HbA1c (Table 2) (23). Ethnic diet demonstrated a significantly larger decrease in fasting and in postprandial glucose (Table 2) (33). Fat modification, low carbohydrate, and energy restriction diets were not associated with a significant difference in our primary outcomes in the stratified analysis.

Secondary Outcomes

Weight gain from inclusion was lower for low carbohydrate diets and cesarean birth for DASH diets (Table S2). Specific diet interventions did not show significant between-group differences in maternal gestational weight gain throughout pregnancy, preeclampsia/eclampsia, neonatal hypoglycemia as defined by the authors, preterm birth, neonatal intensive care unit admission or small for gestational age newborns (Table S2 and S3).

Sensitivity Analysis of Primary Outcomes

Sensitivity analysis was performed to explore reasons for heterogeneity and to assess outcomes when studies with methodological concerns were removed. We were unable to include four studies (21; 22; 33; 35), including all the DASH diet studies where clarification of certain aspects of the results could not be obtained, even after a direct approach to the authors. The authors of

the ethnic diet study authors responded to queries but did not provide the required information regarding gestational age at randomization (33). After these studies are removed, the changes in postprandial (-5.90 mg/dL [95% CI -7.93, -3.88]; I^2=0; p=0.0001), and in post-breakfast glucose levels (-4.76 mg/dl [95% CI -9.13, -0.38]; I^2=34; p=0.03) and birthweight (-74.88 g [95% CI -144.86, -4.90]; I^2=1; p=0.04) remained significant when all diets were combined (Tables 3). Furthermore, the heterogeneity in most primary outcomes decreased after removal of these four studies.

When dietary subgroups were assessed, low glycemic index diets had significant differences in changes in fasting (-5.33 mg/dl [95% CI -6.91, -3.76]) (25; 28; 29), postprandial (-7.08 mg/dl [95% CI -12.07, -2.08]) (25; 29) and post-breakfast glucose (-8.6 mg/dl [95% CI -14.11, -3.09]) (25; 29). The soya protein diet had differences in change of HOMA-IR (-2.00 [95% CI -3.17, -0.83]) (26), required less medication use (RR 0.44 [95% CI 0.21, 0.91]) and had a lower birthweight (-184.67 g [95% CI -319.35, -49.98]) (14; 26). The behavior modification diet had significant differences in change in postprandial glucose (-6.90 mg/dl [95% CI -9.35, -3.95]) and in HbA1c (-0.19 % [95%CI -0.26, -0.12]) (23).

Assessment of Bias and Quality of the Evidence

None of the included studies were assessed as having a low risk of bias in all seven items of the Cochrane Collaboration Tool (Figure S2). Most studies were high risk for blinding of participants and personal and for other sources of bias (Figure S3). Studies scored high risk for other sources of bias for concerns such as baseline differences and industry funding. Most

studies had an “unclear risk of bias” for selective outcome reporting and very few had registered protocols (Figure S3).

GRADE assessment for the outcomes of interest reveals overall low to very low quality of evidence (Table S4). Considerations to downgrade quality of evidence involved the entire spectrum, including limitations in the study design, inconsistency in study results, indirectness and imprecision in effect estimates.

Evaluation for Small Study Effect

Funnel plots of means and relative risks of the primary outcomes for the main analysis are shown in Figures S4 and S5 and for the sensitivity analysis in Figures S6 and S7. Overall, funnel plot asymmetry improves with the sensitivity analysis compared to the main analysis for neonatal birthweight outcomes.

Discussion

In this meta-analysis, we pooled results from 18 studies including 1151 women with a variety of modified dietary interventions. Remarkably, this is the first meta-analysis with a comprehensive analysis on maternal glucose parameters. Despite the heterogeneity between studies, we found a moderate effect of dietary interventions on maternal glycemic outcomes including changes in fasting, post-breakfast and postprandial glucose levels, need for medication treatment and on neonatal birthweight. After removal of four studies with methodologic concerns, we saw an attenuation of the treatment effect. Nonetheless, the change in post-breakfast and postprandial glucose levels as well as lowering of infant birthweight remained significant. Given the

inconsistencies between the main and sensitivity analysis, we consider that conclusions should be drawn after the last one. These data suggest that dietary interventions modified above and beyond usual dietary advice for gestational diabetes have potential to offer better maternal glycemic control and infant birthweight outcomes. However, the quality of evidence, was judged as low to very low due to the limitations in the design of included studies, the inconsistency between their results and the imprecision in their effect estimates.

Previous systematic reviews have focused on the easier to quantify outcomes like the decision to start additional pharmacotherapy, glucose-related variables at follow-up not addressing change from baseline, birthweight, and pregnancy outcome (16-18). The most recently published Cochrane systematic review by Han et al. did not find any clear evidence of benefit other than a possible reduction in caesarean section associated with DASH diet (17). The very high carbohydrate intake (~400g/day), and 12 servings of fruit and vegetables in the DASH diet (23; 24), limit its clinical applicability and generalizability to women from lower socio-economic, inner city backgrounds in western countries. The Cochrane review shared one of our primary outcomes, large for gestational age (17). Neither meta-analysis detected a significant difference in risk of large for gestational age because the trials with a larger effect on birthweight (the three DASH studies) did not report on large for gestational age.

Our findings regarding pooled analysis of low glycemic index dietary interventions are broadly consistent with those of Viana et al (16) and Wei et al. (15). Viana et al. noted decreased birthweight and insulin use based on four studies of low glycemic index diet among 257 women (mean difference -161.9g [95% CI -246.4, -77.4] and RR 0.767 [95% CI 0.597, 0.986],

respectively) (16). Wei et al. also reported decreased risk of macrosomia with a low glycemic index diet in five studies of 302 women (RR 0.27 [95% CI 0.10, 0.71]) (18). In our analyses of four studies in a comparable number of participants (n= 276), we found the same direction of these effect estimates, without significant between-group differences. This is most likely due to the different studies included. For example, we were unable to obtain effect estimates stratified by type of diabetes in the study by Perichart-Perera et al. (which included women with type 2 diabetes) and therefore did not include this study (40). An important difference between our analyses and that of Wei et al. is that they included DASH diet as a low glycemic index dietary subtype (18). We also included a recent study by Ma et al. not included by the previous reviews (31).

Our sensitivity analyses highlighted concerns regarding some studies included in previous reviews. Notably, after removal of the studies with the most substantial methodologic concerns in the sensitivity analysis, differences in the change in fasting plasma glucose were no longer significant. While differences in the change in postprandial glucose and birthweight persisted, they were attenuated.

This review highlights limitations of the current literature examining dietary interventions in gestational diabetes. Most studies are too small to demonstrate significant differences in our primary outcomes. Seven studies had fewer than 50 participants and only two had more than 100 participants (n=125 and 150 respectively). The short duration of many dietary interventions, and the late gestational age at which they were started (38) may also have limited their impact on glycemic and birthweight outcomes. Furthermore, we cannot conclude if the improvements in

maternal glycemia and infant birthweight are due to reduced energy intake, improved nutrient quality or specific changes in types of carbohydrate and/or protein.

We have not addressed the indirect modifications of nutrients. For example, reducing intake of dietary carbohydrates to decrease postprandial glucose may be compensated by a higher consumption of fat potentially leading to adverse effects on maternal insulin resistance and fetal body composition. Beneficial or adverse effects of other nutrients such as n-3 LCPUFA, vitamin D, iron, and selenium cannot be ruled out.

Our study has important strengths and weakness. To our knowledge, ours is the first systematic review of dietary interventions in gestational diabetes comprehensively examining the impact of diet on maternal glycemic outcomes assessing the change in fasting, postprandial glucose, HbA1c and HOMA-IR from baseline. This is especially important taking into account that groups were not well-balanced at baseline. Our review also benefits from the rigorous methodology used as well as the scientific, nutritional and clinical expertise from an international interdisciplinary panel. However, it also has limitations. Baseline differences between groups in postprandial glucose may have influenced glucose-related outcomes. Furthermore, three of the included trials were pilot studies and therefore not designed to find between group differences (12; 25; 33). The low number of studies reporting on adherence clearly illustrates that the quality of the evidence is far from ideal. The heterogeneity of the dietary interventions even within a specific type (varied macronutrient ratios, unknown micronutrient intake, short length of some dietary interventions) as well as baseline characteristics of women included (such as prepregnancy body mass index, or ethnicity) may have also affected our pooled results. It should

also be noted that the relatively small numbers of study participants limit between-diet comparisons. Lastly, we were unable to resolve queries regarding potential concerns for sources of bias because of lack of author response to our queries. We have addressed this by excluding these studies in the sensitivity analysis.

Conclusions

Modified dietary interventions favorably influenced outcomes related to maternal glycemia and birthweight. This indicates that there is room for improvement in usual dietary advice for women with gestational diabetes. Although the quality of the evidence in the scientific literature is low, our review highlights the key role of nutrition in the management of gestational diabetes and the potential for improvement if better recommendations based on adequately powered high-quality studies were developed. Taking into account the prevalence of gestational diabetes, new studies designed to evaluate potential dietary interventions for these women should be based in larger study groups with appropriate statistical power. As most women with gestational diabetes are entering pregnancy with a high BMI, evidence-based recommendations regarding both dietary components and total energy intake are particularly important for overweight and obese women. The evaluation of nutrient quality, in addition to their quantity, as well as dietary patterns such as Mediterranean diet (39) would also be relevant. In particular, there is an urgent need for well-designed dietary intervention studies in the low and middle-income countries where the global health consequences of gestational diabetes are greatest.

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Contributors: JY– data extraction, statistical analyses, wrote first draft manuscript; JK - data extraction, wrote first draft summary tables; MB - literature extraction, statistics, manuscript revision; AGP - literature extraction, statistics, manuscript revision; IS - statistics, manuscript

revision; IG - statistics, manuscript revision ; EH – data extraction, GRADE assessments; EMvdB – concept and design, data extraction, manuscript review; ECG – concept and design, data extraction, manuscript review; SH – concept and design, data extraction, manuscript review; MH - concept and design, draft manuscript evaluation; KL – concept and design, data extraction, critical review for intellectual content; SFO – concept and design, data extraction, manuscript review; LP – concept and design, manuscript review; RR – concept and design, data extractions, revised draft manuscript; PR – concept and design, data extraction, revised draft manuscript; LvL – data extraction, contribution to draft summary tables; BS – data extraction, critical review for intellectual content, HM – concept and design, data extraction, revised draft manuscripts; RC – literature extraction, statistical analyses, revised draft manuscript, RC is the guarantor of these data.

Figure Legends

Figure 1: Forest plot of birthweight for modified dietary interventions compared to control diets in women with gestational diabetes

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Table 1: Characteristics of studies included

Author, year	Country	n	Estimated sample size	Definition of Gestational Diabetes	Duration of dietary intervention	Gestational age in weeks at enrollment (mean±SD)	Baseline Body Mass Index in kg/m^2 (mean±SD)	Mean Maternal Age in years (mean±SD)	Dietary Intervention	Diet Composition*
Low Glycemic Index (GI) Diet										
Grant, 2011 (25)	Canada	47	50 to detect a 0.6 mmol/L difference in capillary glucose; n not achieved	Canadian Diabetes Association, 2008 (40)	28 weeks until delivery	**Control**: 29±2.35 **Intervention**†: 29±3.21	**Control**: 26±4.69 **Intervention**: 27±4.58 (Pre-pregnancy)	**Control**: 34±0.46 **Intervention**: 34±5.16	Low GI: Women were provided with a list of starch choices specific to either intervention (low GI) or control	**Control**: GI: 125.0±0.8.8 **Intervention**: GI: 49.0±0.8
Louie, 2011 (28)	Australia	99	120 to detect a 260g difference in birth weight (stopped early because of smaller than expected SD)	Australasian Diabetes in Pregnancy Society criteria (41)	Randomization until delivery	**Control**: 29.7±3.5 **Intervention**: 29±4.0	**Control**: 24.1±5.7 **Intervention**: 23.9±4.4 (Pre-pregnancy)	**Control**: 32.4±4.5 **Intervention**: 34±4.1	Low GI: Target GI ≤50 but otherwise similar composition to the control diet	**Control**: Energy 1934±465; Carb 40.3±8.3; Protein 22.2±7.5; Fat 35.1±16.9; GI 105.0±25.92 **Intervention**: Energy 1836±403; Carb 38.7±8.3; Protein 23.4±5.8; Fat 34.9±11.0; GI 47.0±6.5
Ma, 2015 (29)	China	95	Not reported	Chinese Medical Association and American Diabetes Association (42)	24-26 weeks until delivery	**Control**: 27.9±1.1 **Intervention**: 27.5±1.1	**Control**: 21.15±2.75 **Intervention**: 21.90 ± 3.14 (Pre-pregnancy)	**Control**: 30.0±3.5 **Intervention**: 30.1±3.8	Low GI: Women provided with an exchange list for starch choices specific to either intervention (low GI) or control	**Control**: Energy 2030±215; Carb 49.8±6.8; Protein 18.8±2.5; Fat 31.8±3.8;GI 135.9±19.0 **Intervention**: Energy 2006±215; Carb 48.56±7.; Protein 18.9±2.9; Fat 32.1±4.1; GI 50.1±2.2

Moses, 2009 (13)	Australia	63	Not reported	Australasian Diabetes in Pregnancy Society (41)	28-32 weeks until delivery	**Control**: 29.9±1.11 **Intervention**: 30.3±1.11	**Control**: 32.8±7.92 **Intervention**: 32.0±6.68 (At enrolment)	**Control**: 31.3±4.52 **Intervention**: 30.8±3.90	Low GI: Women asked to avoid specific high GI foods and were provided with a booklet outlining carb choices	**Control**: Energy 1656±433; Carb 36.2±8.2; Protein 24.0±4.4; Fat 34.3±9.9 **Intervention**: Energy 1713±368; Carb 36.7±6.1; Protein 23.9±3.9; Fat 33.4±6.12; GI 48.0±5.0
DASH (Dietary Approaches to Stop Hypertension) Diet										
Asemi, 2013 (21)	Iran	34	32 for "key variable serum HDL"	50g glucose challenge >140 mg/dl → 100g OGTT; GDM if 2+ fasting >95 mg/dl, 1 hr 180 mg/dl, 2 hr 155 mg/dl, 3hr 140 mg/dl	4 weeks	Not reported	**Control**: 31.4±5.7 **Intervention**: 29.0±3.2 (At enrolment)	**Control**: 29.4±6.2 **Intervention**: 30.7±6.7	DASH diet: diet rich in in fruit, vegetables, whole grains and low-fat dairy; low in saturated fats, cholesterol, refined grains and sweets	**Control**: Energy 2392±161; Carb 54.0±6.9; Protein 17.6±2.8; Fat 29.3±5.6 **Intervention**: Energy 2400±25; Carb 66.8±2.2; Protein 16.8±1.2; Fat 17.6±0.9
Asemi, 2014 (22)	Iran	52	42 to detect a 75g difference in birth weight	As above	4 weeks	**Control**: 25.9±1.4 **Intervention**: 25.8±1.4	**Control**: 31±4.9 **Intervention**: 29.2±3.5 (At enrolment)	**Control**: 30.7±6.3 **Intervention**: 31.9±6.1	DASH diet (same as above)	**Control**: Energy 2352±163; Carb 54.2±37.1; Protein 18.2±3.4; Fat 28.5±5.6 **Intervention**: Energy 2407±30; Carb 66.4±2.04; Protein 17.0±1.3; Fat 17.4±1.0
Yao, 2015 (35)	China	33	42 to detect a 75g difference in birth weight; not achieved	50g glucose challenge → 100g OGTT results with 2^+ of: fasting >95 mg/dL, 1-hour ≥180	4 weeks	**Control**: 25.7±1.3 **Intervention**: 26.9±1.4	**Control**: 30.9±3.6 **Intervention**: 30.2±4.1 (At enrolment)	**Control**: 28.3±5.1 **Intervention**: 30.7±5.6	DASH diet (same as above)	**Control**: Energy 2386±174; Carb 52.3±7.2; Protein 18.0±3.3; Fat 28.3±5.1 **Intervention**: Energy 2408±54; Carb

				mg/dL, 2-hour ≥155 mg/dL and 3-hour ≥140 mg/dL						66.7±2.3; Protein 16.9±1.2; Fat 17.17±1.16
Low Carbohydrate Diets										
Cypryk, 2007 (24)	Poland	30	Not reported	WHO criteria	2 weeks	29.2±5.4	Not reported	28.7±3.7	Low (intervention) vs high carb (45% vs 60% of total energy, respectively)	‡**Control**: Carb 60%; Protein 25%; Fat 15% ‡**Intervention**: Carb 45%; Protein 25%; Fat 30%
Hernández, 2016 (12)	USA	12	Pilot study to estimate SD	Carpenter and Coustan Criteria (43)	30-31 weeks until delivery	**Control**§: 31.7±2.45 **Intervention**: 31.2±0.98	**Control**: 34.3±3.92 **Intervention**: 33.4±3.43 (At enrolment)	**Control**: 30±2.45 **Intervention**: 28±4.90	Low carb (intervention) vs higher-complex carbohydrate/ lower fat	‡**Control**: Carb 60%; Protein 15%; Fat 25% ‡**Intervention**: Carb 40%; Protein 15%; Fat 45%
Moreno-Castilla, 2013 (30)	Spain	152	152 to detect a 22% difference in need for insulin	2006 National Diabetes and Pregnancy Clinical Guidelines (44; 45)	≤35 weeks until delivery	**Control**: 30.1±3.5 **Intervention**: 30.4±3.0	**Control**: 26.6±5.5 **Intervention**: 25.4±5.7 (Pre-pregnancy)	**Control**: 32.1±4.4 **Intervention**: 30.4±3.0	Low carbohydrate (intervention) vs control (40% vs 55% of total diet energy as carbohydrate)	‡**Control**: Energy 1800 minimum; Carb 55%; Protein 20%; Fat 25% ‡**Intervention**: Energy 1800 minimum; Carb 40%; Protein 20%; Fat 40%
Soy Protein Enrichment Diets										
Jamilian, 2015 (26)	Iran	68	56 (minimum clinical difference not reported)	One-step 75g OGTT, American Diabetes Association (46)	6 weeks	Not reported	**Control**: 28.4±3.4 **Intervention**: 28.9±5.0	**Control**: 29.3±4.2 **Intervention**: 28.2±4.6	Soya protein diet had the same amount of protein as control diet but the protein portion was made up of 35% animal protein, 35% soy protein, 30% other plant proteins	**Control**: Energy 2426±191; Carb 54.6±7.1; Protein 14.4±1.7; Fat 32.1±5.4 **Intervention**: Energy 2308±194; Carb 54.6±7.3; Protein 15.0±2.6; Fat 30.3±4.7
Sarathi, 2016 (14)	India	62	Not reported	IADPSG criteria (47)	From diagnosis until delivery	**Control**: 25.56±1.69 **Intervention**: 25.19±1.92	Not reported	**Control**: 29.17±3.38 **Intervention**: 29.43±2.98	Soya based protein diet: 25% of cereal part of high fiber complex	‡**Control**: Energy 1600-2000; minimum carb 175g; ‡**Intervention**:

									carbohydrates replaced with soya	Energy 1600-2000; minimum carb 175g;
Fat Modification Diets										
Lauszus, 2001 (27)	Denmark	27	20 to detect a difference in cholesterol of 0.65 mmol/l	3-h 75 grams OGTT, GDM if 2^{+} glucose > 3 SD above the mean	34 weeks until delivery	Not reported	**Control**: 32.2±5.61 **Intervention**: 35.3±8.65 (At enrolment)	**Control**: 29±3.74 **Intervention**: 31±3.61	High MUFA (monounsaturated fatty acids): source was hybrid sunflower oil with high content oleic acid and snacks of almonds and hazelnuts	**Control**: Energy 1727; Carb 50.0±3.6; Protein 19.0±3.6; Fat 30.0±7.2 **Intervention**: Energy 1982; Carb 46±3.5; Protein 16±3.5; Fat 37±3.5
Wang, 2015 (34)	China	84	Not reported	IADPSG criteria (47)	~27 weeks until delivery	**Control**: 27.3±1.96 **Intervention**: 27.4±1.52	**Control**: 22.2±3.6 **Intervention**: 21.4±3.0 (Pre-pregnancy)	**Control**: 29.7±4.64 **Intervention**: 30.3±4.17	Polyunsaturated fatty acid meals (50-54% carbohydrate, 31-35% fat with 45-40g sunflower oil)	**Control**: Energy 1978±107; Carb 55.4±2.0; Protein 17.9±1.0; Fat 26.7±1.3 **Intervention**: Energy 1960±90; Carb 47.7±0.7; Protein 18.0±0.7; Fat 34.3±0.2
Other Diets										
Bo, 2014 (23)	Italy	99 in diet study) (total n=200)	200 to detect a 10% difference in fasting glucose (based on exercise portion of trial)	75g OGTT	24-26 weeks until delivery	Not reported	**Control**: 26.8±4.1 **Intervention**: 26.9±4.6	**Control**: 33.9±5.3 **Intervention**: 35.1±4.4	Behavioral dietary recommendations: individual recommendations for helping dietary choices	**Control**: Energy 2116±383; Carb 46.9±5.9; Protein 15.6±2.6; Fat 37.4±4.2 **Intervention**: Energy 2156±286; Carb 47.8±4.9; Protein 15.5±2.4; Fat 36.7±3.9
Rae, 2000 (31)	Australia	124	120 to detect a decrease in insulin use from 40 to 15% and a decrease in macrosomia from 25 to 5%	OGTT fasting glucose >5.4mmol/L and/or 2 hour glucose >7.9mmol/L (48)	<36 weeks until delivery	**Control**: 28.3±4.6 **Intervention**: 28.1±5.8	**Control**: 38.0±0.7 **Intervention**: 37.9±0.7 (At diagnosis)	**Control**: 30.6 **Intervention**: 30.2 (SD not reported)	Moderate energy restriction (1590-1776kcal/day) vs control (2010-2220kcal/day)	**Control**: Energy 1630±339; Carb 41.0±5.6; Protein 24.0±2.3; Fat 34.0±5.3 **Intervention**: Energy 1566±289; Carb 42.0±5.7; Protein

										25.0±2.4; Fat 31.0±5.7
Reece, 1995 (32)	USA	50	Post-hoc calculation	Not reported	24-29 weeks until delivery	Not reported	Not reported	Not reported	Fiber-enriched diet: Fiber taken as fiber-rich foods (40g/day) and a high fiber drink (40g/day)	‡**Control**: Carb 50%; Fat 30%; Fiber 20g/d ‡**Intervention**: Carb 60%; Fat 20% with 80g fiber/day
Valentini, 2012 (33)	Italy	20	Not reported (pilot study)	4th International Workshop Conference on GDM (49)	From diagnosis (screening at 24-28 weeks) until delivery	**Control** 27.1±5.9 **Intervention**: 21.3±6.8	**Control**: 24.1±4.7 **Intervention**: 25.7±3.6 (Pre-pregnancy)	**Control**: 30.2±4.7 **Intervention**: 28.9±3.3	Ethnic meal plan: foods commonly consumed per participant's ethnicity with the same kcal and nutrient composition as the control diet	‡**Control**: Carb 55%; Protein 17%; Fat 28%; fiber 21g ‡**Intervention**: Carb 55%; Protein 17%; Fat 28%; fiber 21g

* Reported actual dietary intake. When not reported, prescribed dietary intake is reported.; † Intervention is defined as dietary intervention different from the usual dietary intervention used in the control group; ‡ Indicates prescribed diet; § The control and intervention groups were reversed for the purpose of meta-analysis so it could be included in the low carbohydrate group.

Table 2: Pooled analyses of primary maternal glycemic and infant birthweight outcomes

Outcome	Diet Subgroup	No. of Studies	No. of Women	Effect estimate	I^2 (%)
Maternal Glycemic Outcomes					
				Mean [95% CI]	
Change in fasting glucose (mg/dl)	All diets	13	662	-4.07 [-7.58, -0.57]	86
	Low GI (25; 28; 29)	3	195	-5.28[-6.83, -3.73]	0
	DASH (21; 35)	2	67	-11.55 [-14.00, -9.09]	0
	Low carbohydrate (12; 24)	2	42	3.81 [-4.29, 11.92]	69
	Fat modification (27; 34)	2	109	4.87 [-0.44, 10.18]	0
	Soya protein (14; 26)	2	130	-7.47 [-20.28, 5.34]	91
	Behavior (23)	1	99	-1.50 [-5.66, 2.66]	-
	Ethnic (33)	1	20	-25.34 (-37.57, -13.11)	-
Change in postprandial glucose (mg/dl)	All diets	9	475	-7.78 [-12.27, -3.29]	63
	Low GI (25; 29)	2	121	-7.08 [-12.07, -2.08]	4
	DASH (21)	1	34	-45.22 [-68.97, -21.47]	-
	Low carbohydrate (24)	1	30	-3.00 [-10.06, 4.06]	-
	Fat modification (27; 34)	2	109	-6.43 [-13.08, 0.22]	0
	Soya protein (14)	1	62	-1.05 [-11.03, 8.93]	-
	Behavior (23)	1	99	-6.90 [-11.68, -2.12]	-
	Ethnic (33)	1	20	-16.28 [-22.83, -9.73]	-
Change in post-breakfast glucose (mg/dl)	All	3	175	-4.76 [-9.13, -0.38]	34
	Low GI (29)	1	83	-8.6 [-14.11, -3.09]	-
	Low carbohydrate (24)	1	30	-3.00 [-8.15, 2.15]	-

	Soya protein (14)	1	62	-1.05 [-9.73, 7.63]	-
Change in post-lunch glucose (mg/dl)	All	2	92	4.50 [-1.90, 10.90]	0
	Low carbohydrate (24)	1	30	4.00 [-4.56, 12.56]	-
	Soya protein (14)	1	62	5.14 [-4.51, 14.79]	-
Change in post-dinner glucose (mg/dl)	All	2	92	1.81 [-5.28, 8.90]	13
	Low carbohydrate (24)	1	30	1.00 [-8.14, 10.14]	-
	Soya protein (14)	1	62	3.03 [-8.20, 14.26]	-
Change in HOMA-IR (uUI/ml x mmol/L)	All	4	212	-1.10 [-2.26, 0.07]	90
	DASH (35)	1	33	-1.90 [-2.36, -1.44]	-
	Low carbohydrate (12)	1	12	0.60 [-1.90, 3.10]	-
	Soya protein (26)	1	68	-2.00 [-3.17, -0.83]	-
	Behavior (23)	1	99	-0.30 [-0.71, 0.11]	-
Change in HbA1c (%)	All	7	407	-0.05 [-0.13, 0.02]	84
	Low GI (28; 29)	2	167	0.01 [-0.02, 0.03]	0
	DASH (21)	1	34	-0.25 [-0.42, -0.08]	-
	Fat modification (27)	1	25	0.10 [-0.14, 0.34]	-
	Soya protein (14)	1	62	-0.01 [-0.07, 0.05]	-
	Behavior (23)	1	99	-0.19 [-0.26, -0.12]	-
	Ethnic diet (33)	1	20	-0.05 (-0.27, 0.17)	-
				Relative Risk [95% CI]	
Medication treatment	All	15	1023	0.65 [0.47, 0.88]	55
	Low GI (13; 25; 28; 29)	4	293	0.80 [0.55, 1.14]	34
	DASH (21; 22; 35)	3	119	0.29 [0.17, 0.50]	0
	Low carbohydrate (30)	1	150	1.00 [0.75, 1.34]	-
	Energy restriction (31)	1	117	1.05 [0.47, 2.34]	-

	Fat modification (34)	1	84	Not estimable	-
	Soya protein (14; 26)	2	130	0.44 [0.21, 0.91]	0
	Behavior (23)	1	99	0.61 [0.15, 2.42]	-
	Ethnic (33)	1	20	2.00 [0.21, 18.69]	-
	Fiber (32)	1	11	Not estimable	-
Infant Birthweight Outcomes					
				Mean [95% CI]	
Birthweight (g)	All	16	841	-170.62 [-333.64, -7.60]	88
	Low GI (13; 25; 28; 29)	4	276	-54.25 [-178.98, 70.47]	0
	DASH (21; 22; 35)	3	119	-598.19 [-663.09, -533.30]	0
	Low carbohydrate (12; 24)	2	42	57.73 [-164.93, 280.39]	0
	Energy restriction (31)	1	122	194.00 [-42.58, 430.58]	-
	Fat modification (27; 34)	2	109	-139.61 [-294.80, 15.58]	0
	Soya protein (14; 26)	2	131	-184.67 [-319.35, -49.98]	0
	Ethnic diet (33)	1	20	-370.00 [-928.87, 188.87]	-
	Fiber (32)	1	22	-94.00 [-446.68, 258.68]	-
				Relative Risk [95% CI]	
Large for gestational age	All (33)	8	647	0.96 [0.63, 1.46]	0
	Low GI (13; 25; 28)	3	193	1.33 [0.54, 3.31]	0
	Low carbohydrate (30)	1	149	0.51 [0.13, 1.95]	-
	Energy restriction (31)	1	123	1.17 [0.65, 2.12]	-
	Soya protein (14)	1	63	0.45 [0.04, 4.76]	-
	Behavior (23)	1	99	0.73 [0.25, 2.14]	-
	Ethnic diet (33)	1	20	0.14 [0.01, 2.45]	-
Macrosomia	All	12	834	0.49 [0.27, 0.88]	11
	Low GI (13; 25; 28; 29)	4	276	0.46 [0.15, 1.46]	0

	DASH (22; 35)	2	85	0.12 [0.03, 0.51]	0
	Low carbohydrate (24; 30)	2	179	0.20 [0.02, 1.69]	-
	Energy restriction (31)	1	122	1.56 [0.61, 3.94]	-
	Fat modification (34)	1	84	0.35 [0.04, 3.23]	-
	Soya protein (26)	1	68	0.60 [0.16, 2.31]	-
	Ethnic diet (33)	1	20	0.20 [0.01, 3.70]	-

Table 3: Sensitivity analysis of primary maternal glycemic and infant birthweight outcomes

Outcome	Diet Subgroup	No. of Studies	No. of Women	Effect estimate	I^2 (%)
Maternal Glycemic Outcomes					
				Mean [95% CI]	
Change in fasting glucose (mg/dl)	All diets	10	575	-1.98 [-5.41, 1.45]	74
	Low GI (25; 28; 29)	3	195	-5.33 [-6.91, -3.76]	0
	DASH	0	0	Not estimable	-
	Low carbohydrate (12; 24)	2	42	3.66 [-4.42, 11.73]	57
	Fat modification (27; 34)	2	109	4.88 [-1.45, 11.21]	0
	Soya protein (14; 26)	2	130	-7.51 [-20.31, 5.30]	90
	Behavior (23)	1	99	-1.50 [-6.47, 3.47]	-
	Ethnic	0	0	Not estimable	-
Change in postprandial glucose (mg/dl)	All diets	7	421	-5.90 [-7.93, -3.88]	0
	Low GI (25; 29)	2	121	-7.08 [-12.07, -2.08]	4
	DASH	0	0	Not estimable	-
	Low carbohydrate (24)	1	30	-3.00 [-8.15, 2.15]	-
	Fat modification (27; 34)	2	109	-4.85 [-13.32, 3.62]	40
	Soya protein (14)	1	62	-1.05 [-9.73, 7.63]	-
	Behavior (23)	1	99	-6.90 [-9.85, -3.95]	-
	Ethnic	0	0	Not estimable	-
Change in post-breakfast glucose (mg/dl)	All diets	3	175	-4.76 [-9.13, -0.38]	34
	Low GI (29)	1	83	-8.6 [-14.11, -3.09]	-

	Low carbohydrate (24)	1	30	-3.00 [-8.15, 2.15]	-
	Soya protein (14)	1	62	-1.05 [-9.73, 7.63]	-
Change in post-lunch glucose (mg/dl)	All diets	2	92	4.50 [-1.90, 10.90]	0
	Low carbohydrate (24)	1	30	4.00 [-4.56, 12.56]	-
	Soya protein (14)	1	62	5.14 [-4.51, 14.79]	-
Change in post-dinner glucose (mg/dl)		2	92	1.81 [-5.28, 8.90]	0
	Low carbohydrate (24)	1	30	1.00 [-8.14, 10.14]	-
	Soya protein (14)	1	62	3.03 [-8.20, 14.26]	-
Change in HOMA-IR (uUI/ml x mmol/l)	All	3	179	-0.74 [-2.09, 0.61]	75
	DASH	0	0	Not estimable	-
	Low carbohydrate (12)	1	12	0.60 [-1.90, 3.10]	-
	Soya protein (26)	1	68	-2.00 [-3.17, -0.83]	-
	Behavior (23)	1	99	-0.30 [-0.71, 0.11]	-
Change in HbA1c (%)	All	5	353	-0.03 [-0.11, 0.05]	87
	Low GI (28; 29)	2	167	0.01 [-0.02, 0.03]	0
	DASH	0	0	Not estimable	-
	Fat modification (27)	1	25	0.10 [-0.14, 0.34]	-
	Soya protein (14)	1	62	-0.01 [-0.07, 0.05]	-
	Behavior (23)	1	99	-0.19 [-0.26, -0.12]	-
	Ethnic diet	0	0	Not estimable	-

				Relative Risk [95% CI]	
Medication treatment	All	11	884	0.82 [0.65, 1.04]	24
	Low GI (13; 25; 28; 29)	4	293	0.80 [0.55, 1.14]	34
	DASH	0	0	Not estimable	-
	Low carbohydrate (30)	1	150	1.00 [0.75, 1.34]	-
	Energy restriction (31)	1	117	1.05 [0.47, 2.34]	-
	Fat modification (34)	1	84	Not estimable	-
	Soya protein (14; 26)	2	130	0.44 [0.21, 0.91]	0
	Behavior (23)	1	99	0.61 [0.15, 2.42]	-
	Ethnic	0	0	Not estimable	-
	Fiber (32)	1	11	Not estimable	-
Infant Birthweight Outcomes					
				Mean [95% CI]	
Birthweight (g)	All	12	702	-74.88 [-144.86, -4.90]	1
	Low GI (13; 25; 28; 29)	4	276	-54.25 [-178.98, 70.47]	0
	DASH	0	0	Not estimable	-
	Low carbohydrate (12; 24)	2	42	57.73 [-164.93, 280.39]	0
	Energy restriction (31)	1	122	194.00 [-42.58, 430.58]	-
	Fat modification (27; 34)	2	109	-139.61 [-294.80, 15.58]	0
	Soya protein (14; 26)	2	131	-184.67 [-319.35, -49.98]	0
	Ethnic diet	0	0	Not estimable	-
	Fiber (32)	1	22	-94.00 [-446.68, 258.68]	-
				Relative Risk [95% CI]	
Large for gestational age	All	7	627	1.00 [0.66, 1.53]	0
	Low GI (13; 25; 28)	3	193	1.33 [0.54, 3.31]	0

	Low carbohydrate (30)	1	149	0.51 [0.13, 1.95]	-
	Energy restriction (31)	1	123	1.17 [0.65, 2.12]	-
	Soya protein (14)	1	63	0.45 [0.04, 4.76]	-
	Behavior (23)	1	99	0.73 [0.25, 2.14]	-
	Ethnic diet	0	0	Not estimable	-
Macrosomia	All	9	729	0.73 [0.40, 1.31]	0
	Low GI (13; 25; 28; 29)	4	276	0.46 [0.15, 1.46]	0
	DASH	0	0	Not estimable	0
	Low carbohydrate (24; 30)	2	179	0.20 [0.02, 1.69]	-
	Energy restriction (31)	1	122	1.56 [0.61, 3.94]	-
	Fat modification (34)	1	84	0.35 [0.04, 3.23]	-
	Soya protein (26)	1	68	0.60 [0.16, 2.31]	-
	Ethnic diet	0	0	Not estimable	-