ALINEA

NUTRITION

JULY 2021

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Assaf-Balut C, García de la Torre N, Durán A, et al. A Mediterranean diet with additional extra virgin olive oil and pistachios reduces the incidence of gestational diabetes mellitus (GDM): A randomized controlled trial: The St. Carlos GDM prevention study. *PLoS* One. 2017;12(10):e0185873.

What We Know, Think We Know, or Are Starting to Know

Gestational diabetes mellitus [GDM] affects up to 18% of pregnancies, and is one of the most common disorders during pregnancy [(1)]. GDM is diagnosed if one of the following criteria are present [(2)]:

- Fasting glucose level of >5.1 - 6.9mmol/L [92 - 125mg/dL]
- A 2-hr glucose level of >8.5 - 11.0mmol/l [153 - 199mg/dL] following a 75g oral glucose tolerance test [OGTT]

Typically, the OGTT is conducted between 24-28 weeks gestation [(2)]. The glucose ranges for diagnosing GDM are lower than the diagnostic criteria for type-2 diabetes [(2)]. This is because the diagnostic criteria are based off the risk of adverse pregnancy outcomes associated with blood glucose ranges during pregnancy, in particular pre-eclampsia in the mother and high birthweight and neonatal low blood glucose levels in the offspring [(3)].

As maternal glycaemic control deteriorates, the risk of adverse pregnancy outcomes increases [(3)]. There is a significant overlap between incidence of GDM and obesity, with up to 46% of cases related to adiposity levels [(4)]. However, both GDM and obesity are independently associated with such adverse outcomes [(4)].

Currently, first-line intervention for treating GMD is medical nutrition therapy, with the potential addition of pharmacotherapy if diet and exercise do not bring glucose levels into normal ranges. However, there is relatively scant quality evidence for nutritional approaches to GDM, and to date most of the evidence has examined carbohydrate control, particular of simple sugars [(5)]. Given that diet may influence GDM development during pregancy, there is scope for potential prevention.

The present study investigated a Mediterranean Diet compared to a control diet on GDM incidence at 24-28 weeks gestation.

The Study

The St. Carlos GDM prevention study was a randomised controlled trial in women over 18yrs old with a single gestation pregnancy [i.e., one foetus], and normal glucose tolerance assessed at 8-12 weeks gestation. Randomisation was stratified* according to age, gestational BMI, previous pregnancies, and ethnicity.

There were two parallel arms [i.e., run at the same time]. Both diet groups were provided with the same background Mediterranean diet recommendations for servings of vegetables, fruits, skimmed milk dairy, wholegrains, legumes, fish, red meat, and avoidance of refined and processed foods. The two diet groups were as follows:

- Intervention Group [IG]: Consumed 40ml extra-virgin olive oil and 25-30g pistachio nuts daily.
- Control Group [CG]: Restricted total dietary fat consumption and continued with standard care.

Both groups were recommended to walk for ~30mins each day. Participants were followed-up at routine clinical visits: first ultrasound, 24-28 weeks, 36-38 weeks, and delivery.

The primary outcome was incidence of GDM at 24-28 weeks gestation. Secondary outcomes included required insulin use in diagnosed mothers, gestational weight gain, gestational birth weight [>90th percentile and <10th percentile], perineal trauma, pre-term delivery [<37 weeks gestation], and biochemical outcomes like insulin resistance [HOMA-IR].

*Geek Box: Block Randomisation & Stratified Randomisation

Randomisation provides a means of minimizing the risk of bias, and is most effective particularly where there are unknown factors which could influence the results: randomisation then balances the distribution of these unknown factors between groups. There are a number of type of randomisation: simple, block, and stratified, being common randomisation methods. Simple randomisation involves dividing subjects at random to allocation of either treatment group or control, either using computer generated or numbered tables. The essential characteristic of simple randomisation is that all subjects have an equal chance of allocation to either group. A potential disadvantage may be observed in trials with small sample sizes, where simple randomisation may result in unequal numbers between groups. To address this, block randomisation divides subjects into multiple, smaller groups of equal subjects based on a predetermined group size, allowing for control of balance across similar-sized groups. A potential disadvantage to block randomisation is that the process of randomisation may lead to different covariates between block groups. To address this potential, stratified randomisation is used to achieve balance of characteristics between block groups. Stratification allows for covariate baseline characteristics, for example age, cholesterol, hypertension, and/or sex, to be balanced by grouping together particular characteristics which could influence the outcome. Subjects would then be randomised to blocks, within that particular stratum identified by the covariate characteristic, i.e., similar numbers of subjects with the same level of blood cholesterol. Disadvantages to stratified randomisation arise where there are multiple covariates in small sample sizes, or where subjects are enrolled on an ongoing basis, and baseline characteristics of all subjects are not available prior to randomisation.

Results: 874 women completed the study; 440 in the CG and 434 in the IG. Mean age was 33yrs, and mean BMI was 23. Med diet scores and healthy diet scores were similar between groups at baseline.

- ***GDM:*** 74 participants in the IG were diagnosed with GDM at 24-28 weeks gestation, compared to 103 from the CG [23.4% vs. 17.1%]. The IG was associated with a 25% [RR 0.75, 95% CI 0.57 - 0.98] lower risk of GDM.
- ***Metabolic Outcomes:*** There were statistically significant differences between groups for 2-hr blood glucose levels [110mg/dL CG vs. 106.3mg/dL IG], HbA1c [5.1% CG vs. 4.9% IG], and HOMA-IR [2.2 CG vs. 2.0 IG].

Table 3. Maternal pregnancy and neonatal outcomes.

	CONTROL Group (N = 440)	INTERVENTION Group (n = 434)	p
MATERNAL OUTCOMES			
GDM	103 (23.4)	74 (17.1)	0.012
75g-OGTT 24–28 GW			
Fasting Blood Glucose (mg/dL)	85.7 ± 6.6	84.1 ± 6.6	0.001
1 h Blood Glucose (mg/dL)	123.7 ± 32.0	123.5 ± 30.2	0.912
2 h Blood Glucose (mg/dL)	110.0 ± 26.3	106.3 ± 23.8	0.042
HbA1c (%) 24–28 GW	5.1 ± 0.3	4.9 ± 0.3	0.001
HbA1c (%) 36–38 GW	5.3 ± 0.3	5.2 ± 0.2	0.001
Fasting Blood Glucose 36–38 GW (mg/dL)	77.1 ± 7.4	74 ± 7.7	0.003
Fasting Serum Insulin (mcUI/mL)			
24–28 GW	9.4 ± 5.7	9.1 ± 6.8	0.061
36–38 GW	10.5 ± 9.6	10.0 ± 9.9	0.085
HOMA-IR			
24–28 GW	2.2 ± 2.6	2.0 ± 1.4	0.045
36–38 GW	2.3 ± 2.7	2.0 ± 2.3	0.055

Table *from the paper with the statistically significant metabolic findings highlighted in yellow. This is an excellent example of the difference between statistical significance, and clinical meaningfulness. As you can see from the the actual mean and standard deviation differences between the control and intervention groups, there is negligible difference in these outcomes between the two groups.*

- ***Insulin Therapy:*** Of the women in both groups diagnosed with GDM, 19% [14/74] required insulin therapy in the IG compared to 32% [33/103] in the CG.
- ***Neonatal Outcomes:*** 18 offspring from the CG were >90th percentile birth weight vs. 4 from the IG. For the <10th percentile, 25 were offspring from the CG vs. 5 from the IG. Further, 17 offspring from the CG were born premature [<37 weeks gestation] vs. 5 from the IG group.

The Critical Breakdown

Pros: This was the first RCT assessing the effects of a Med diet on incidence of GDM. The prospective design of the study meant that the diets were allocated before testing for GDM. Randomisation method was appropriate, and block stratification would be expected to equal any potential influence on results due to such variables as age, BMI, etc. The study statistician remained blinded to participant group allocation. Both groups received the same number of visits and practitioner contacts. All statistical analysis were conducted using intention-to-treat, which is a form of analysis that includes all participants that were randomised in the study, irrespective of whether they dropped out or not. All participants with a GDM screening recorded were thus included. The groups were well balanced for completing numbers: 440 and 434 in the CG and IG, respectively. The study was adequately powered [estimate of n = 315] for the primary outcome of GDM incidence. The study was preregistered on the ISRCTN registry, and there are no apparent discrepancies between the registration details and the published paper.

Cons: The study was unblinded, with the exception of statistician and research assistance. While blinding participants and research assistants [dietitians, midwives] would simply have not been possible, it remains open to blind investigators to allocation to boost the perceived methodological rigour of the trial*. Although both groups received the same number of contacts, the IG were counselled by a dietitian, while the CG were counselled by the midwives. While this was to reflect standard care, the difference in delivery of nutrition recommendations may have differentially influenced diets in both groups. For example, it is possible that the CG were aware they were in a comparative trial, given that their olive oil intake, Med diet score and nutrition scores increased over the course of the study. Indeed, at 34-38 weeks gestation there was little difference in Med diet score between groups. The diet advice provided had some very poorly defined recommendations, e.g., “moderate to high” fish consumption or “low” consumption of red/processed meat; it is unclear what any of these opaque terms could mean for weekly servings. Dietary intake was presented as composite scores, but no comparison between nutrient intakes and total diet was analysed.

*Geek Box: Control of Bias in the Lyon Diet-Heart Study

The Lyon Diet-Heart Study was a secondary prevention trial of a Med diet in subjects whom had already experienced a first cardiovascular event, specifically a myocardial infarction [MI]. The intervention group had a 73% reduction in risk of cardiovascular mortality or a non-fatal second MI. The trial was designed as randomised and single blind. In recruitment, the investigators used a two-step process where participants signed an original consent form to take part but without knowing that they were signing up to a dietary intervention, and following the consent to participate were then randomised to the intervention or control diet. At this point, subjects in the intervention group only signed a second consent form agreeing to change their diet to the intervention Med diet. This meant that the participants were unaware that they were taking part in a comparative trial. Further, the physicians assigned to the intervention group were also unaware that their patients were taking part in a comparative trial. This was to avoid 'physician bias', whereby the physician may alter the treatment for their patients if they knew they were participating in a comparative intervention study. Regarding the control group, they did not have any dietary evaluation performed until the final year of the 5-year follow-up period in order not to influence their behaviour, as a potential limitation to nutrition intervention studies where the control group are aware they are participating in a trial is that they change/improve their diets. They LDHS is an example that, notwithstanding methodological issues for nutrition interventions to comply with biomedical standards of double-blinding and placebo control, steps can be taken in the context of free-living, single-blind interventions to minimise the potential for bias toward the intervention group, or to prevent dramatic changes in the control group that undermine the intervention.

Key Characteristic

The logistical regression analysis provides us with more insight than the simple between-group head-to-head comparisons. In a logistic regression, the outcome variable [in this case, GDM] is categorised dichotomously [Yes/No]. The analysis examines the probability of being in one of the two outcome categories [i.e., has GDM/does not have GDM], based on one [or more] independent variables, in this case the intervention Med diet. This analysis also adjusted for variables like age, BMI, ethnicity, number of prior pregnancies, family history of GDM, and smoking status.

In this analysis, the Med diet was associated with a 25% [RR 0.75, 95% CI 0.57 - 0.98] lower risk of GDM. Before we wrap this section up, if you haven' t checked out the Research Lecture on confidence intervals, give it a watch! In the present study, there is a lack of precision in the estimate of effect, although the direction of effect suggests an overall lower risk in the Med diet group. The question we are left is with, is whether this effect would hold up in future research [6].

Interesting Finding

The significant differences in numbers of offspring that were >90th percentile for gestational and <10% percentile for gestational weight in the control group is, unlike the metabolic outcomes, more striking.

Are these findings attributable to differences in diet? This is where the lack of full dietary data presented becomes a major limitation. Bear in mind the background base diet recommendations were similar between groups, only the CG was counselled to restrict dietary fat intake. How low did their dietary fat intake go, and did it lead to restriction of important fat types, like omega-3 fatty acids? We know that maternal DHA supplementation at ~500-600mg/d is associated with longer gestation duration [(7)], and both EPA/DHA are associated with lower risk of pre-term delivery [(8)].

The authors suggest in their discussion that improved glycaemic control may have been responsible for lower rates of large gestational weight. However, they overplay their hand on this as we have seen: the findings may be statistically significant, but the differences were negligible. The paucity of more rigorous dietary data and analysis makes it impossible to tease out further why there may have been such stark differences in rates of these neonatal outcomes between groups.

Relevance

As the first RCT to investigate a Med diet prospectively, the primary outcome in the present study was that a Med diet enriched with extra-virgin olive oil and pistachio nuts reduced the incidence of GDM, compared to a fat-restricted Med diet undergoing usual care. Of particular note, substantially less women from the IG who were diagnosed with GDM required insulin therapy.

There was a 25% lower probability of GDM in the intervention group, however, as discussed under ***Key Characteristic*** above, this is not a particularly precise estimate and caution is warranted in interpreting the finding. This caution is particularly warranted when we consider the lack of any clinically meaningful difference in the metabolic findings that were statistically significant.

The neonatal outcomes provide the starkest contrast between the intervention and control groups, however, we are left with more questions than answers at this point about the role of diet per se in influencing these outcomes, given the lack of thorough dietary analysis in the study, and the fact that differences in olive oil intake, pistachio intakes, and Med diet scores, were not particularly drastic between groups by the 3rd trimester visit [36-38 weeks gestation].

Application to Practice

Evidence from better quality intervention studies and diet comparisons for GDM remains scattered, and there is no particular diet that can be recommended at this point [5]. There is more positive evidence for low glycaemic carbohydrates and high fibre content [5,9]. The exact role of dietary fat remains to be teased out, and the present study remains the first to suggest that enrichment of a background Mediterranean diet with monounsaturated fat food sources may result in lower GDM risk, and potentially more favourable neonatal outcomes.

References

1. Metzger B, Gabbe S, Persson B, Lowe L, Dyer A, Oats J et al. International Association of Diabetes and Pregnancy Study Groups Recommendations on the Diagnosis and Classification of Hyperglycemia in Pregnancy. Diabetes Care. 2010;33(7):676–82.
2. World Health Organisation. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: A World Health Organization Guideline. Diabetes Research and Clinical Practice. 2014;103(3):341-363.
3. Metzger B, Coustan D, Trimble E. Hyperglycemia and Adverse Pregnancy Outcomes. Clinical Chemistry. 2019;65(7):937-938.
4. Catalano P, McIntyre H, Cruickshank J, McCance D, Dyer A, Metzger B et al. The Hyperglycemia and Adverse Pregnancy Outcome Study: Associations of GDM and obesity with pregnancy outcomes. Diabetes Care. 2012;35(4):780-786.
5. Mahajan A, Donovan L, Vallee R, Yamamoto J. Evidenced-Based Nutrition for Gestational Diabetes Mellitus. Current Diabetes Reports. 2019;19(10).
6. Poole C. Low P-Values or Narrow Confidence Intervals: Which Are More Durable?. Epidemiology. 2001;12(3):291-294.
7. Carlson S. Docosahexaenoic acid supplementation in pregnancy and lactation. The American Journal of Clinical Nutrition. 2008;89(2):678S-684S.
8. Kar S, Wong M, Rogozinska E, Thangaratinam S. Effects of Omega-3 Fatty Acids in Prevention of Early Preterm Delivery. Obstetrical & Gynecological Survey. 2016;71(7):394-395.
9. Hernandez T, Mande A, Barbour L. Nutrition therapy within and beyond gestational diabetes. Diabetes Research and Clinical Practice. 2018;145:39-50.