APPRAISALS IN META-JOURNAL HOUR 8

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The paper:
Effects of a lifestyle intervention to prevent deterioration in glycemic status among South Asian women with recent gestational diabetes: A randomized clinical trial. Full article: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2789570

Why was this study conducted?

Women with gestational diabetes mellitus (GDM) are at increased risk of developing type 2 diabetes mellitus (T2DM). The Lifestyle Intervention in Gestational Diabetes (LIVING) study is a randomized implementation trial of a pragmatic lifestyle intervention program among South Asian women with a recent GDM-affected pregnancy. The aim was to investigate whether a resource-appropriate and context-appropriate lifestyle intervention focused on diet and physical activity could prevent glycemic deterioration among women with recent GDM in South Asia.

How was it done?

Study design and participants

The LIVING study is a participant-unblinded, parallel-group individual randomized clinical trial. The 12-month lifestyle intervention versus usual care was conducted at 19 urban hospitals in India, Sri Lanka, and Bangladesh. Participants included women diagnosed with GDM within the previous 18 months with an oral glucose tolerance test (OGTT) from 24 to 34 weeks gestation and who did not have T2DM. They were enrolled from November 2017 to January 2020, and follow-up ended in January 2021. Randomisation was conducted through a central, computer-based randomization service, and was stratified by country, centre, and use of insulin during pregnancy. The site investigators and participants were unblinded to allocation (intervention vs. usual care). However, all central study staff, statisticians, and outcome adjudicators remained blinded until the final database lock. There were several exclusion criteria including the confirmed case of T2DM, travel time to hospital more than 2 hours (unless individual circumstances impeded hospital attendance for study visits), lack of access to a mobile telephone, use of steroids during pregnancy other than for lung maturation of the baby and likelihood of moving residence in the next 3 years.

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Sampling method and sample size calculation

Hospitals were selected from study sites using a purposive sampling method. Women with prior or current GDM were purposively sampled from hospital records. A sample size of 1414 women with GDM was estimated to provide 90% power (2-sided $\alpha = 0.05$) to detect a 35% relative decrease in worsening glycemic status, assuming a 20% cumulative incidence in the control group at 24 months (conservative assumptions projected from the Diabetes Prevention Program)[2] and 20% missing outcome data. However, as the recruitment process was longer than expected, the median follow up became shorter where a survival analysis using a log-rank test with 14 months of median effective follow-up had approximately 80% power with the original assumption's constant.

Interventions

A 12-month lifestyle intervention focused on diet and physical activity involving group and individual sessions, as well as remote engagement, adapted to local context and resources. This was compared with usual care. The lifestyle intervention was based on prior approaches associated with preventing weight gain in post-GDM populations and modified through mixed-methods formative research in each country[3,4]. The planned program included four 90-minute face-to-face group sessions over 6 months followed by two face-to-face individual sessions for individuals who were persistently overweight or had gained more than 2% of baseline body weight. At group sessions, trained facilitators aimed to provide core messages and lead activities with a focus on diet and physical activity. Intervention group participants were planned to receive a detailed written program content, a total of 84 prerecorded voice or text messages over a 42-week period and monthly follow-up calls after completion of group sessions. No attempt was made to influence the treatment of participants receiving usual care.

Study procedures

Follow-up visits were conducted every 6 months after baseline assessment. An OGTT was performed at each annual visit and at the end of follow-up using local laboratories. Glycosylated hemoglobin (HbA1c) was measured at interim 6-month visits, followed by an OGTT if the HbA1c was 6.5% (48 mmol HbA1c/mol Hb) or greater and at the end of follow-up. Data on blood pressure, anthropometry, diet, and physical activity were collected at each visit. Blood pressure was measured using an automated sphygmomanometer (Omron JPN1), with a mean of 2 readings after 5 minutes of rest recorded. Body weight was properly measured using a digital scale (Omron HN286) and waist circumference was also properly measured. Dietary intake information was collected using local adaptations of the Intake 24 dietary recall system (Food Standards Scotland, Newcastle University, and the University of Cambridge), and physical activity levels were assessed using the Modified Global Physical Activity Questionnaire (GPAQ). Planned termination of follow-up occurred with a verified non-study diagnosis of T2DM or if a participant became pregnant.

Outcomes

Primary Outcome	**Proportion of women with a change of glycaemic category, at or prior to final visit:** 1. Normal glucose tolerance to prediabetes (impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)) or T2DM. 2. Prediabetes (IFG or IGT) to T2DM.
Prespecified Secondary Outcome	**Progression to T2DM and mean changes in:** 1. Fasting plasma glucose 2. Systolic blood pressure 3. Body weight 4. Waist circumference 5. Physical activity level 6. Calorie intake
Other Prespecified Outcome	1. Heart rate 2. Diastolic blood pressure 3. Hip circumference 4. Daily moderate activity 5. Daily sedentary activity 6. Sleep duration 7. Intake of specific dietary components

Statistical Analysis

All analyses were based on the intention-to-treat (ITT) principle, with the exclusion of participants subsequently found to be ineligible. A sensitivity analysis for the primary outcome included these participants. The primary analysis consisted of a survival analysis of time to change in glycemic status at or prior to the final patient visit, which occurred at varying times after 12 months for each patient. The Poisson models were used for sensitivity analysis. The effectiveness of the study intervention on the primary outcome was estimated using Cox proportional hazard model, with the randomized group and use of insulin during index pregnancy as fixed effects and the study center as a random effect. A similar approach was taken for the secondary outcome of T2DM. For other secondary outcomes (continuous variables), repeated-measure linear mixed models were used to assess differences between groups over time. Prespecified sensitivity analyses included using HbA1cor fasting plasma glucose when OGTT results were not available. Additionally, Poisson regression was used in place of Cox models. No imputation for missing data was done. Statistical significance is based on a 2-sided type I error rate of 5%. A Holm-Bonferroni adjustment was used to control the family-wise error rate across secondary outcomes.

What was the finding?

Study participants

Of 3389 registered patients with GDM, 1823 individuals had an OGTT at a median (IQR) of 6.5 (4.8-8.2) months postpartum. Of these, 160 individuals (8.8%) had T2DM and 51 individuals were excluded for other reasons. Additionally, of 1823 individuals with an OGTT, 621 individuals (34.1%) had prediabetes. 11 randomized participants were subsequently identified as ineligible and excluded from the primary analysis, leaving 1601 women (800 women in the intervention group and 801 women in the usual care group). Baseline characteristics were similar between randomized groups, with some variation by country. The mean (SD) age was 30.9 (4.9) years, and the mean (SD) BMI was 26.6 (4.6); 234 participants (14.6%) required insulin during index pregnancy. At baseline, 1001 women (62.5%) had normoglycemia and 600 women (37.5%) had prediabetes (including 240 women with IFG [15.0%], 188 women with IGT [11.7%], and 172 women with IFG and IGT [10.7%]).

Intervention Fidelity

A total of **1601** women were randomized to the **intervention group** (**N=800**) and **usual care** (**N=801**):

- **1001** (**62.5%**) women with **normoglycemia.**
- **600** (**37.5%**) women with **prediabetes**.

Among participants randomized to the **intervention** (N=800), **717 (89.6%)** women received at least some content and **644 women (80.5%)** received **all program content,** delivered as originally planned or through an alternate mode. Intervention fidelity was affected by slow initial recruitment and subsequently by COVID-19 lockdowns. Consequently, among **644 women**:

- **476** (**73.9%**) women received some or all content through **individual engagement.**
- **315** (**48.9%**) women received some or all content **remotely**.

Prior to Covid-19 lockdowns, 139 intervention group participants who had completed group sessions (42.3%) were offered intensification sessions owing to nonachievement of weight goals and 129 of these individuals (92.8%) received at least 1 such session.

After lockdowns, because of difficulty in reliably assessing body weight, intensification session were offered to all intervention group participants and 311 individuals (98.4%) received at least 1 such session.

Primary Outcome

Median (IQR) follow-up was 14.0 (11.4-19.8) months for the intervention group and 14.3 (11.5-20.3) months for the usual care group. A total of 1308 participants (81.7%) had an end-of-study follow-up OGTT or at least 1 follow-up OGTT, which increased to 1438 individuals (89.8%) when HbA1c or fasting plasma glucose were also considered. Worsening of glycemic status occurred in 421 participants: 204 individuals (25.5%) in the lifestyle intervention group and 217 individuals (27.1%) in the usual care group, and there was no statistically significant difference in risk (HR, 0.92 [95%CI, 0.76-1.12]; *P* = .42). In sensitivity analyses using Poisson models, including all randomized participants, and using alternate measures of glycemia among individuals without an OGTT, there was still no statistically significant difference in risk.

Outcome	Glycemic deterioration	
Median of 14.1 months of follow-up	Intervention	Usual Care
	N (%)	N (%)
	204 (25.5)	217 (27.1)

Secondary Outcomes

There were no statistically significant differences between randomized groups in any secondary outcomes. T2DM developed in 154 individuals (74 participants [9.3%] in the intervention group and 80 individuals [10.0%] in the usual care group; hazard ratio, 0.89 [95%CI, 0.69-1.23]; *P* = .48). T2DM developed among 122 of 600 individuals with prediabetes at baseline (20.3%) and 32 of 1001 individuals with baseline normoglycemia (3.2%). Body weight increased in both groups by 0.4 kg despite a decrease in caloric intake. There were small decreases overall in moderate physical activity levels and sedentary behavior, with no statistically significant between-group differences. Sleep duration, fasting plasma glucose, and blood pressure increased in both groups, without any statistically significant between-group differences. There were no statistically significant between group differences for other prespecified outcomes. Ultimately, given that *P* values for all outcomes were nonsignificant, no adjustment for multiple comparisons was made.

How much can we take out from this research/paper?

This community-based 2-arm lifestyle intervention trial was necessary for the high-risk women. Firstly, if it is shown effective then the quantity and scope of the effectiveness could be delineated where those did not benefit from it could be further examined. Secondly, if it is not effective as what was reported in this paper, it is indicative of shortcoming of the interventional program itself and not the scientific content of the diets and physical activity unless there is real reason to re-examine these proven health interventions. Another related lesson would be do not assume proven intervention works without assessing it actually does in the setting where it is applied. This study has in its plan a process evaluation that will reveal why it did not work out as expected. This is very crucial and potentially very educational and informative to everyone involved especially to all the stakeholders in those countries. Also, this is urgent and imperative because of the high incidence of dysglycaemia in the high-risk women.

In general, the study was well planned and well reported although some typos were present in the paper. However, as usual in all clinical research, it faced on-the-ground challenges when rolled out. The recruitment period was longer than expected mostly was > 2 months after randomisation that intervention began. This has caused a change in the primary outcome analysis and potentially a loss in power (from 90% at 24 months to 80% at 14 months). Calculation of required number of individuals for survival analysis heavily dependent on the outcome of interest or can be denoted as hazard rate. The length of the study is determined by the accrual period (recruitment period) and the follow up period. If the follow up period after recruitment is shorten, then correspondently the number of individual needs to recruited is higher in order to achieve the estimated outcome.

Other challenges were due to the COVID-19 and the related lockdown, and many socioeconomic effect and impact on many families. This has caused lost of physical contact in the delivery of the intervention and outcome measurements as well as psychosocial impact to the deliverers (not reported). The intervention is long and complex and it is very much relied on the deliverers to 'make it work'. We hope this will be assessed and reported after the process evaluation is completed.

Other explanations that could explain ineffectiveness of the intervention include factors that were not sufficiently dealt with such as affordability of the participants to implement healthier diets and physical activity as suggested in the intervention content even more so during the pandemic. Healthier diets are usually more costly, and physical activity is tied to occupation in the lower income groups of the population not social living environment. Psychological wellbeing is another domain that could confound health effects of dietary and physical behaviours[5].

Statistical analysis was well planned and appropriate. Author did a very good job in pre-specifying the variables for analysis and divided it into random and fixed effect and ran the analysis accordingly. Mixed effect model was applied for both survival and linear analysis which has much advantage when the data set was not normally distributed. In addition, mixed effect model was able to analysis hierarchical data of different country, and repeated measure measurement as per in this paper compared to the general linear model.

The study has applied sensitivity analyses and showed the results were essentially the same. This raises another theoretical argument of how much an exposure is considered adequate before its health effect could be observed. This study's complex intervention was not perfectly completed among all the participants, but majority were exposed to some sessions and personal contacts. Are diets and physical activity education and coaching combined when given in some forms and level not sufficient to change the health (body weight and glycaemia status) of the people who received them? Perhaps, it is equally true that knowledge ('faith') without action is as good as 'dead'. Again, the actual reason for the ineffectiveness will be explained by the report from the process evaluation to the trial.

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