Efficacy trials comparing dosages of vitamin D and calcium co-supplementation in gestational diabetes mellitus patients require a methodological revamp

To the Editor,

In this letter, I want to discuss a recently (2021) published clinical trial report by Gunasegaran et al. (1) in the Journal of Obstetrics and Gynaecology Research on the efficacy of prenatal vitamin D and calcium co-supplementation in gestational diabetes mellitus (GDM) patients. The report suggests that co-supplementation with vitamin D 1,000 IU and calcium 1,000 mg is relatively beneficial compared to co-supplementation with vitamin D 250 IU and calcium 500 mg in achieving blood glucose and lipid homeostasis in GDM patients on medical nutrition therapy (1). The co-supplements were given daily for six weeks (1).

The study is important as antenatal glycemic control yields better perinatal outcomes in GDM patients and their neonates. Hyperglycemia in GDM occurs in late pregnancy, due to inadequate insulin secretion and consequent failure to counteract the physiological insulin resistance. Furthermore, homeostasis of the blood lipid profile in GDM patients is also critical as its derangement is related to diabetes and cardiovascular risk in the long term. Several nutritional supplements have been tested to see their effect on these markers, including vitamin D, probiotics, omega-3 fatty acids, and so on. Vitamin D is crucial among these, as an association between its deficiency and GDM has been reported in observational studies. However, the physiologic role of vitamin D in pregnancy remains poorly understood. Since regular supplementation of vitamin D and calcium in pregnancy is not yet established, it's a hot topic in obstetric medicine, making the trial by Gunasegaran et al. (1) relevant in this milieu. It is perhaps the first trial from the Indian subcontinent in this context and important addition to the existing literature, predominantly sourced from Iran (2,3). The absence of participant attrition from the trial added merit to it (1). Regarding its limitations, the authors have highlighted its lack of blinding of study participants and personnel and heterogeneity across the participants' baseline vitamin D status (1).

Given the importance of the trial, its scientific appraisal is critical, and I have two viewpoints to share in this regard. First, regarding the statistically significant outcomes, the risk of type 1 error plausibly remains high due to the relatively small sample size of the trial (70 participants data analyzed) (1,4). Second, although the trial (1) depicted statistically how changes in different outcomes post-intervention varied between the compared intervention groups, the inclusion of a placebo arm would have reasonably enhanced its methodological rigor (5). A placebo arm-based juxtaposition is critical before ascertaining comparative efficacy between high and low doses of vitamin D and calcium co-supplementation to investigate if these respective interventions are better than placebo.

To conclude, since every piece of evidence sourced from different clinical trials contributes to the obstetric medicine evidence pool, future trialists may consider the strengths and limitations of this trial while preparing their trial protocol. Therefore, double-blinded, adequately powered trials of factorial design may be the methodological foundation to disentangle the metabolic effects of prenatal vitamin D, calcium, their co-supplemented form, and their different dosages in GDM patients.

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