

Mindfulness-Based Stress Reduction, Mediterranean Diet, and Fetal Growth

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Failure of the fetus to attain its biologically determined growth potential is associated with an increased risk of perinatal mortality and morbidity, as well as adverse neurodevelopment in childhood and long-term risk of cardiovascular, respiratory, and neurological morbidity.¹⁻³ Although terminology and diagnostic criteria are inconsistent,



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in general, fetal intrauterine growth restriction refers to a fetus with biometry below a given percentile for gestational age, while small for gestational age (SGA) refers to newborns with birth weight less than the 10th percentile for gestational age.⁴ These definitions have limitations because larger fetuses that do not meet these criteria may not have achieved their growth potential and may be at risk of adverse outcomes and constitutionally small fetuses or newborns (ie, size appropriately small for inherent factors such as maternal height and weight with no increased risk of perinatal mortality and morbidity) may be misdiagnosed with intrauterine growth restriction or SGA. By definition, SGA is diagnosed in approximately 10% of newborns. A variety of maternal, fetal, and placental risk factors increase the risk of SGA through various mechanisms that may culminate in a final common pathway of reduced uterine-placental perfusion and decreased transfer of fetal oxygen and nutrition.⁴ To date, there are no evidence-based prevention strategies for SGA.

In this issue of *JAMA*, Crovetto and colleagues⁵ report findings from their randomized clinical trial that investigated whether interventions targeting maternal stress and nutrition could reduce risk for SGA. The study team enrolled pregnant individuals at high risk for SGA based on risk factors for SGA published by the Royal College of Obstetricians and Gynaecologists.⁶ Participants (n = 1221) were randomized at 19 weeks 0 days' gestation through 23 weeks 6 days' gestation to receive a Mediterranean diet intervention (n = 407), a mindfulness-based stress reduction intervention (n = 407), or usual prenatal care (n = 407). The 2 interventions were selected based on previous evidence that each intervention may modify the pathophysiology of SGA, including inflammation and oxidative stress.^{7,8} Participants randomized to the Mediterranean diet group received monthly individual and group dietary education and were encouraged to increase intake of whole grains, vegetables, fruit, dairy, legumes, nuts, fish, white meat, and olive oil. They were also provided free olive oil (2 L every month) and walnuts (15 g daily). Participants randomized to the mindfulness-based stress reduction group completed 8 weekly 2.5-hour group sessions of a mindfulness-based stress reduction program adapted for pregnancy that included guided meditation and prenatal yoga practices. Participants randomized to the usual care group received usual pregnancy care according to local institutional protocols. The primary outcome

was SGA, defined as birth weight less than the 10th percentile on a customized local birth weight standard.

Among 1184 pregnant individuals who completed the trial, the rate of SGA was significantly lower in participants randomized to either intervention, compared with those receiving usual prenatal care (14% in the Mediterranean diet group and 15.6% in the mindfulness-based stress reduction group vs 21.9% in the usual care group). Results of a preplanned subgroup analysis showed no differential effect of the interventions on the primary outcome in any subgroup, with the possible exception of smoking status, whereby Mediterranean diet appeared to be more effective in preventing SGA among participants who smoked during pregnancy. In addition, the intervention groups had lower rates of a composite adverse perinatal outcome, defined as preterm birth, preeclampsia, perinatal mortality, severe SGA (birth weight less than the third percentile), neonatal acidosis, 5-minute Apgar score below 7, or any major neonatal morbidity (18.6% in the Mediterranean diet group and 19.5% in the mindfulness-based stress reduction group vs 26.2% in the usual care group). Neither intervention appeared more effective than the other in reducing SGA or adverse perinatal outcomes. Results of biomarker analyses in a subset of participants showed the expected biological effects of the interventions: urinary levels of α -linolenic acid and hydroxytyrosol (biomarkers of extra-virgin olive oil and walnut intake) were significantly increased in the Mediterranean diet group and 24-hour urinary cortisone/cortisol ratio (estimating 11 β -hydroxysteroid dehydrogenase type 2—an enzyme that converts cortisol into its inactive form cortisone) was significantly increased in the mindfulness-based stress reduction group.

The results of this study are novel in demonstrating that nutritional and psychological interventions may have a clinically important effect on fetal growth beyond usual prenatal care. These results are biologically plausible. The link between maternal mental illness and adverse birth outcomes is well established.⁹ The American College of Obstetricians and Gynecologists currently recommends screening all patients for depression in pregnancy and the postpartum periods, although access to specialty perinatal mental health professionals is challenging.¹⁰ In this study, mindfulness-based stress reduction reduced maternal stress and risk for SGA. However, mindfulness interventions are time- and resource-intensive, and traditionally delivered mindfulness-based interventions may not be feasible for medically high-risk patients, including high-risk pregnant individuals. Provision of mindfulness-based stress reduction programs via telehealth, as has been done for patients with cardiovascular disease, may improve access for perinatal patients.¹¹

Studies of women who became pregnant and gave birth during famine confirmed an association between maternal

malnutrition and SGA, although high-quality studies do not support additional nutrient intake to increase fetal growth in the absence of maternal malnutrition.^{12,13} Prenatal nutrition guidelines in the US primarily focus on addressing deficiencies (eg, iron, folic acid, iodine), promoting appropriate maternal gestational weight gain, and avoiding fetotoxic substances, such as mercury, alcohol, and tobacco.¹⁴ Nutrition counseling beyond these recommendations is not routinely imbedded in prenatal care, and most pregnant people do not receive adequate nutrition education during pregnancy.¹⁵ Moreover, pregnant women who are food insecure or live in “food deserts” may have limited access to nutritious food and are at an increased risk for adverse obstetric outcomes.¹⁶ In this study, Mediterranean diet (including provision of olive oil and walnuts at no cost) appears to be associated with a meaningful decrease in SGA newborns.

The randomized study design is an important strength because it reduced selection bias and confounding that adversely affect studies linking nutrition to adverse pregnancy outcomes. Analysis followed the intention-to-treat principle with missing data imputed using the conservative worst-case scenario. Testing 2 interventions in a single trial was an efficient approach, and the assessment of biomarkers provided assurance that the interventions effectively modified the anticipated targets.

Nonetheless, the study has several limitations, many of which are acknowledged by the authors. The study was con-

ducted at a single center in a high-resource setting and enrolled a homogeneous predominantly White patient cohort with normal body mass index and medium-to-high socioeconomic status; these factors substantially limit generalizability of the findings. With only short-term outcomes reported, it is unknown if these interventions have lasting effects for mother or child. The composite adverse perinatal outcome included a heterogeneous group of outcome measures, some of which are not causally related to SGA. Moreover, even though the study showed benefit, it is notable that adherence to the interventions was relatively low (60% for Mediterranean diet and 50% for mindfulness-based stress reduction). In addition, the investigators did not test the effect of a combination of the 2 interventions to assess for a possible additive or synergistic effect.

The single-site randomized trial among pregnant women at high risk for SGA reported by Crovetto et al⁵ in this issue of *JAMA* demonstrated that Mediterranean diet or mindfulness-based stress reduction significantly reduced the risk of SGA. These results represent important novel findings, given that there is no proven intervention for prevention of SGA. The important limitations, including the homogeneous study population, high-resource setting, and evaluation of only short-term outcomes, limit the generalizability of the findings. Accordingly, implementation of these interventions into clinical practice should await results of the neurodevelopmental assessment and other outcomes among the offspring at 2 years of age and replication of the study results in other populations.

ARTICLE INFORMATION

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