The Association Between Maternal Placenta Growth Factor Levels and Small-for-Gestational Age Infants: Findings From the Multi-Country Women First Study

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Objectives: Examine the association between Placenta Growth Factor (PlGF) levels during pregnancy, maternal nutrition supplementation (MNS) and the prevalence of small-for-gestational age (SGA) infants in the Women First (WF) Study.

Methods: WF is a RCT of MNS consisting of a lipid-based micronutrient supplement ± a protein-energy supplement (for low maternal BMI or weight gain), provided to women daily until delivery starting either ≥ 3 months pre-conception (Arm 1), at the end of the first trimester (Arm 2) or not at all (control group, Arm 3). Serum samples were obtained at 12 (Arms 1 and 2) and 34 weeks (Arms 1, 2 and 3) gestation from a subset of women in three of the WF sites (Guatemala [Guat] (n = 257); India [Ind] (n = 171, Arms 1 & 2 only); and Pakistan [Pak](n = 279)). PlGF was measured using an ELISA. An ultrasound late in the 1st trimester determined whether infants were SGA at birth (weight-for-age centile < 10, INTERGROWTH-21st standards). PlGF levels were examined for arm, site and time point differences using ANOVA and post-hoc Tukey testing. The association between SGA and PlGF was analyzed by logistic regression adjusting for maternal height, age and education (STATA software v. 17.0).

Results: In participants with PlGF measurements, the prevalence of SGA infants is 23% in Guat, 44% in Ind and 34% in Pak. PlGF levels increased from 12 to 34 weeks gestation in Arms 1 and 2 in every site (Tukey's adjusted $P < 0.0001$). There are no differences in PlGF among sites at 12 weeks, whereas all sites are different at 34 weeks (Tukey's adjusted $P < 0.0001$). Regarding the association between SGA and PlGF (adjusting for maternal height, age and education), there are no differences by arm within each time point and site (arms were combined in subsequent analyses). PlGF is associated with SGA only in Guat at 34 weeks: odds of an infant being SGA decreases as PlGF increases (OR = 0.9989, 95% CI: 0.9981, 0.9998, unadjusted $p = 0.015$). For a 50 pg/mL increase in PlGF, the odds of the infant being SGA decreased by 0.948 (5.2%; OR 95% CI: 0.909, 0.990).

Conclusions: An association between PlGF and prevalence of SGA was found in Guatemala at 34 weeks: as PlGF increases, the odds of a SGA infant decreases. The MNS did not result in differences among arms.

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