COMMENTS AND RESPONSES

Comment on: Rowan et al. Metformin in Gestational Diabetes: The Offspring Follow-Up (MiG TOFU): Body Composition at 2 Years of Age. Diabetes Care 2011;34:2279–2284

We applaud Dr. Rowan and the MiG TOFU (Metformin in Gestational diabetes: The Offspring Follow-Up) investigators for their intense efforts at following the 2-year offspring outcomes from the MiG trial (1). Understanding how in utero exposures impact longer-term offspring consequences is critical. However, we feel compelled to caution against overinterpretation of this study's findings.

Of note, 46% of the mothers in the metformin group required insulin to achieve adequate glycemic control (1); therefore, ~50% in this group actually received both. Although 43% of the total infant cohort received anthropometric measures at 2 years, only ~15% received dual-energy X-ray absorptiometry (DEXA) scans, thus potentially biasing the results. The absence of any differences in the primary outcome of central fat by DEXA could be real due to a lack of sensitivity in DEXA's precision to measure central fat or may be confounded by unknown differences in the much smaller cohort. That said, the lack of any difference in waist circumference suggests that there was no difference in central adiposity, arguing against the primary hypothesis of less visceral fat in the metformin-exposed offspring.

Upper arm circumference and subscapular and bicep skinfolds were increased in the offspring exposed to metformin (with or without insulin) despite no detectable differences in any other measure. Of concern is that the investigators interpreted these slight increases in skinfold thickness, in the absence of a difference in total fat, to suggest less visceral fat accretion. None of the offspring measures (central DEXA or waist circumference) suggest a difference in central adiposity. Although data in young children are minimal, in older children, waist circumference is the best anthropometric predictor of visceral fat (2) and is not different between groups. Importantly, visceral fat depots in young children are very small, and we caution against any interpretation of a visceral fat difference based on crude indirect measures (i.e., total fat by DEXA minus subcutaneous fat).

In adults, fat stored in subcutaneous rather than visceral depots for a given total adiposity imparts a more favorable metabolic phenotype. Data in young children are lacking. However, fat cell expansion is likely not infinite, and subcutaneous expansion may lead to spillover into other nonadipose tissue depots with adverse metabolic consequences (3). A recent study of newborns in which intrahepatic lipid and abdominal fat were directly measured by magnetic resonance imaging showed that these variables, as well as total fat, were correlated with maternal BMI (4). Is the relative expansion of subcutaneous fat stores early in life a favorable outcome, as the authors suggest? Studies looking at early expansion of total adiposity (90% of which is subcutaneous fat) suggest that early adipose tissue accretion increases obesity risk later (5). If metformin increases fetal insulin sensitivity and facilitates fat storage, this might not be favorable in early childhood when nutrient excess is the norm.

We simply do not yet understand the potential of diverting cell differentiation toward adipogenesis, the relative importance of fat depot locations, or the implications of excess fat storage early in life on the later development of chronic insulin resistance. In summary, caution should be exercised when interpreting the MiG TOFU data to suggest child health may be improved.

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