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Gestational Weight Gain: Now and the Future

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Since shortly before the release of the 2009 Institute of Medicine report, *Weight Gain During Pregnancy: Reexamining the Guidelines*,¹ there has been an explosion of research around the amount of weight a woman gains during her pregnancy. For the mother herself, the more weight she gains during pregnancy, the harder it is to return to her pre-pregnancy weight. Retaining more weight postpartum, especially among women who are already overweight or obese, can lead to lifelong obesity and its cardiovascular consequences. Excessive weight gain in subsequent pregnancies can accentuate this pattern. Furthermore, a higher body mass index (BMI) at the start of a subsequent pregnancy is associated with increased risk of adverse health outcomes for the baby in both short and long term.

Higher amounts of gestational weight gain can also lead to adverse health consequences in the child. It has long been known that the more the mother gains, the larger the newborn baby. With the advent of the obesity epidemic, epidemiologic studies have recently turned to the question of the extent to which gestational weight gain predicts longer-term weight-related outcomes. Given that most cohorts do not have decades of followup, the bulk of the research to date has examined outcomes in childhood and adolescence. Most of these studies have shown what we expected—the more the weight gain during pregnancy, the higher the BMI or risk for obesity in the offspring.^{2–6} In addition to the scarcity of long-term followup, few studies have measured cardio-metabolic outcomes, and only one previous study had done so in adulthood. Among 21-year-old Australian men and women, Mamun et al.⁷ found that higher weight gain in their mothers' pregnancies predicted higher BMI and (non-significantly) higher systolic blood pressure. In this issue of *Circulation*, Hochner et al.⁸ extend these findings with data on a range of cardiovascular risk factors among a subset of men and women in their early 30s from the Jerusalem Perinatal Study begun in the 1970s. More gestational weight gain was associated with more overall and central adiposity, higher

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blood pressure, and higher plasma triglyceride level, but not with concentrations of glucose, insulin, LDL-cholesterol, or HDL-cholesterol.

The study of Hochner et al.⁸ calls attention to several issues with implications for current practice and future research, of which I highlight three. First, adjusting for adult BMI nullified the observed associations. In addition to suggesting a mediating effect by adiposity, which tracks from childhood to adulthood, this finding also suggests that children who are able to shed obesity by the time of early adulthood might largely avoid cardiovascular complications of obesogenic factors during early development. This implication is supported by recent observations from a combined analysis of four cohorts, in which the small proportion of overweight or obese children who attained normal weight status at 23–46 years had similar levels of cardiovascular risk factors to those who had been lean throughout.⁹ Attaining future leanness among already obese children, however, is a formidable challenge.

A second set of issues relates to the complex role of pre-pregnancy BMI. The higher the BMI entering pregnancy, the less the weight a woman gains during pregnancy. Thus to isolate the offspring cardiovascular disease-related effects of gestational weight gain, it is imperative to adjust for (or to examine effect modification by) maternal BMI, which most but not all published studies have done. However, it does not follow that one can compare the impact of pre-pregnancy BMI with that of gestational weight gain in these adjusted models. Some studies fall prey to comparing the magnitude of effects, or even p-values, of the two predictors on a continuous scale. But one is measured in kg/m² and the other in kg. Hochner et al.⁸ avoid this trap by expressing both in quartiles. More importantly, these two predictors have different etiologic meanings and therefore different implications for intervention. Gestational weight gain occurs by definition after pregnancy starts, exerts whatever causal effects it has on child health through intrauterine mechanisms, and appears to be modifiable once pregnancy starts, an assertion now being tested by numerous randomized controlled trials.¹⁰ The effects of pre-pregnancy BMI on offspring health, however, can represent not only the *in utero* environment but also inherited genes and all of the post-natal environmental factors that mothers and children share. Distinguishing these possibilities requires clever study designs. Recently, two types of studies have cast doubt on whether maternal obesity causes offspring obesity and cardiovascular disease through intrauterine mechanisms. One type exploits within-family comparisons. In two recent analyses, maternal-offspring BMI associations were weaker (or non-existent) in sibling pairs compared with between-sibling associations.^{11, 12} The other design relies on an instrumental variable approach based on the concept of mendelian randomization. One such study found no association of the mother's *FTO* polymorphism, an "instrument" for maternal obesity, with childhood fat mass after adjusting for the child's *FTO*.¹³ Even supposing we can identify and quantify causal prenatal effects of maternal obesity, however, pre-pregnancy BMI and weight gain still differ in clinical implications. Avoiding adverse effects of elevated BMI entering pregnancy could be tantamount to solving the entire obesity epidemic in girls and young women.

An additional question is why some studies fail to uncover associations between gestational weight gain and offspring obesity. Besides failure to adjust for maternal BMI in some

studies, another possibility is that the different components of weight gain during pregnancy exert different effects. What we measure as total weight gain actually consists of 4 components: maternal tissue, fluid accumulation, the placenta, and the fetus. Several studies that either adjust for fetal size at birth or measure net weight gain, i.e., total weight gain minus weight at birth, do not show associations with offspring adiposity, suggesting primacy of the fetal component.^{4, 5, 12, 14} Preliminary data on the 4 components from the US Collaborative Perinatal Project indeed indicate that fetal weight gain is the primary predictor of child BMI, whereas a mother's tissue gain is the only predictor of her own postpartum weight retention.¹⁵ Future studies of gestational weight gain may have to take such distinctions into account to further our understanding of mechanisms, help to tailor interventions, and perhaps inform revision of guidelines.

Ultimately, there may come a time when we no longer rely on measuring weight gain at all. Weight is easy to measure and is accurate even in clinical settings. Nevertheless, when we analyze effects of weight gain, implicitly or explicitly we are usually more interested in metabolic process for which weight gain is a proxy, rather than the weights themselves. For a given BMI or even fat mass or amount of visceral fat, one person's degree of dysmetabolism may be different from another's.¹⁶ At least one current randomized controlled trial in pregnancy focuses on lifestyle changes that could improve glucose-insulin homeostasis irrespective of weight.¹⁷ Should this trial and other studies find that measuring metabolic changes during pregnancy substantially improves risk prognostication over weight alone, a number of thorny questions would arise. For example, when will there be inexpensive and non-invasive tests for dysmetabolism in pregnant women (and perhaps even in the fetus)? How often would clinicians need to deploy them? Regarding interventions, how "personalized" would they need to be? What is the balance between "one-size-fits-all" and truly individualized interventions? If adopting individualized approaches appears effective and cost-effective, where does that lead development of guidelines for pregnant women, which are most helpful with only a few variations on a common theme? Addressing these and related questions is crucial for understanding how to interrupt the intergenerational cycles of obesity and cardiovascular disease—from mother to child to (in the growing female) mother—by intervening during early, plastic periods of human development.

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