Invited Commentary

Invited Commentary: How Early in Life Does the Risk of Obesity Originate?

Jennifer L. Baker*

* Correspondence to Dr. Jennifer L. Baker, Institute of Preventive Medicine, Copenhagen University Hospital, Øster Søgade 18, 1st Floor, 1357 Copenhagen K, Denmark (e-mail: jba@ipm.regionh.dk).

Initially submitted October 29, 2011; accepted for publication December 2, 2011.

Mothers and fathers influence the risk of obesity in their children through genetic, environmental, and behavioral factors. Unique to the mother, however, is the intrauterine environment in which the fetus develops, and it is during this time in the uterus that the risk of later obesity in the child may develop. In this issue of the Journal, Fleten et al. (Am J Epidemiol. 2012;176(2):83–92) investigate whether the intrauterine environment plays a role in the development of adiposity by comparing the association between maternal prepregnancy body mass index (BMI; measured as weight in kilograms divided by height in meters squared) and offspring BMI at 3 years of age with the paternal-offspring association at the same age in the Norwegian Mother and Child Cohort Study. In that large study of stable, relatively healthy and well-educated families, significant differences in maternal-offspring and paternal-offspring BMI associations were not identified. These findings are interpreted as indicating that the influence on the child’s BMI of the intrauterine environment is less important than that of genetics and shared environment. Results from that study suggest that further consideration should be given to the specificity of the fetal overnutrition hypothesis in terms of which aspects of the intrauterine environment may influence offspring adiposity and when across the life course these effects may manifest themselves.

body mass index; child; fathers; fetal programming; infant; mothers; obesity; pregnancy

Abbreviation: BMI, body mass index.

In the ongoing search into when the risk of developing obesity originates, much focus has been directed toward the critical role of the intrauterine environment. According to the fetal overnutrition hypothesis, maternal prepregnancy obesity negatively affects the whole hormonal environment in which the fetus develops (1, 2), as evidenced by the higher rates of gestational diabetes mellitus experienced by obese women (3). Exposure to this adverse environment leads to adverse alterations in the transfer of glucose, free fatty acids, and amino acids to the developing fetus (1, 2). As a result, there are permanent alterations in metabolic and appetite control systems that increase the risk that the offspring will develop obesity throughout life. It has even been postulated that these alterations can be transmitted across generations, thus making maternal prepregnancy obesity a potential contributor to the worldwide increase in the prevalence of obesity that has been observed over the last several decades (4).

In this issue of the Journal, Fleten et al. (5) investigated the role of the intrauterine environment on childhood adiposity by comparing associations between maternal and paternal prepregnancy body mass index (BMI; measured as weight in kilograms divided by height in meters squared) and offspring BMI at 3 years of age. These comparisons were based on the assertion that maternal and paternal prepregnancy BMI are markers of genetic, behavioral, and environmental factors but only maternal prepregnancy BMI reflects the intrauterine environment. In this population of more than 29,000 trios of mothers, fathers, and children from the contemporary Norwegian Mother and Child Cohort Study, it was found that maternal and paternal BMI z scores were positively associated with offspring BMI at 3 years of age. The difference between the maternal-offspring and paternal-offspring associations was not, however, significantly different. The associations were little changed by
adjustment for several prenatal and postnatal factors. The only exception occurred when Fleten et al. adjusted for intrauterine factors as the maternal-offspring association strengthened. In these adjusted analyses, however, the maternal-offspring and paternal-offspring BMI associations were not significantly different. The authors interpreted these results to mean that the association between maternal prepregnancy BMI and offspring BMI at 3 years of age was likely attributable to shared familial risk factors rather than to the intrauterine environment.

The fetal overnutrition hypothesis focuses on how negative effects of maternal adiposity on the developing fetus may predispose the child to developing obesity later in life. Supporting this hypothesis is a study on Pima Indians in which comparisons were made between sibling groups, in which one sibling was born before the mother developed type 2 diabetes mellitus and the other was born after (6). The mean BMI of the exposed siblings was significantly higher than that of the unexposed siblings, thus supporting the role of the intrauterine environment in transmitting a risk of obesity beyond that of genetics. Additionally, children born to women who have experienced dramatic weight loss after bariatric surgery are less likely to develop obesity than siblings who were born before the surgery (7). In a large study that compared the impact of maternal weight gain in pregnancy on offspring BMI in young adulthood using a sibling study design, differential effects were found by maternal prepregnancy BMI (8). In normal-weight women (BMI < 24.9), the associations were largely explained by genetic and environmental factors. In contrast, among overweight and obese women (BMI ≥ 25.0), there seemed to be an additional effect of the weight gain on offspring BMI, thus suggesting that the intrauterine environment in these heavier women has an effect on offspring (8). Clearly, there is evidence to support the fetal overnutrition hypothesis, but how relevant it is to the current levels of obesity among children remains unknown.

A woman’s BMI reflects many facets of her health and well-being. It is a summative indicator of her genetic endowment, as well as of environmental and behavioral factors that have contributed to her current body habitus. At the same time, it is also predictive of her future health and health-related behaviors. Similarly, a man’s BMI reflects these same factors. In the case of pregnancy and childbearing, a woman’s BMI is predictive of the success of her pregnancy and her child’s health through biologic and behavioral pathways. For example, obese pregnant women are more likely to develop gestational diabetes and to deliver macrosomic infants (>4,500 g) than are nonobese women (3). In the postnatal period, women who were obese before pregnancy are less likely to initiate (9) and continue (10) breastfeeding. Each of these factors is, in turn, a risk factor for obesity in the offspring. Layered upon these factors are the lifestyle behaviors and characteristics that allowed for the development of obesity in the parents. It is not surprising that the children of obese parents are more likely to become obese themselves (11). Parental BMI reflects a continuity of circumstances to which the fetus, infant, and child are exposed. As a result, it is challenging to disentangle the relative importance of these several factors, as well as their timing, on childhood adiposity.

In the study by Fleten et al. (5), differences between the maternal-offspring and paternal-offspring BMI associations when the offspring were 3 years of age were not detected. There are several possibilities as to why an impact was not detected that should be explored. Even though maternal BMI is associated with offspring BMI, it may not be a sensitive enough indicator of disturbances in the intrauterine environment that have associations with adiposity in children. BMI is a reasonable, albeit imperfect, measure of adiposity, but it does not describe the distribution of the fat mass (12). Because central adiposity is strongly associated with metabolic disorders (12), it is possible that a measure such as prepregnancy waist circumference could be a better indicator of the intrauterine environment, and this remains to be investigated. Similarly, assessing adiposity in children using BMI alone may not be an accurate enough method of estimating fat mass for investigating these types of associations, as again it is an imperfect indicator of adiposity. Indeed, when associations between maternal and paternal BMI and offspring fat mass assessed using dual energy x-ray absorptiometry at the ages of 9–11 years were investigated, maternal BMI had a significantly stronger association than did paternal BMI (13). However, the relevance of the difference for demonstrating an effect of the intrauterine environment was questioned by the researchers (13). Another issue is that of age. There is evidence to suggest that parental BMI and offspring BMI associations strengthen with the age of the offspring (14), so it is possible that although differences were not detected at 3 years of age in the study by Fleten et al. (5), they could emerge as these children grow older.

Many negative obesity-related health outcomes are an upper tail of the distribution phenomenon; that is, the risk of these outcomes notably increases only at the highest BMI values. For example, significantly elevated risks for overall mortality from 25 to 69 years of age were found among American adults with a BMI of 35 or higher, with weaker evidence of increased risks for those who were overweight or obese, with a BMI from 30 to 34.9 (15). Therefore, it is worthwhile to consider whether the potential effects of the fetal overnutrition hypothesis are expected to operate across the entire spectrum of maternal BMI values or if they are likely to occur only among women with extremely high BMI values. The population of Norwegian families in the study by Fleten et al. was relatively thin compared with that of other Western countries. Twenty-two percent of women and 45% of men were classified as overweight, and 9% of women and 10% of men were classified as obese according to World Health Organization criteria (5). As a result of their large sample size, if these associations operated in a graded manner across the normal and overweight range of BMI values, it is likely that the current study would have detected this (5). If, however, the differential associations are only evident at the extremes of maternal obesity, despite the more than 2,600 obese women in the study (5), there may have been too few to detect an effect given the heterogeneity of BMI values in this category. Understanding how these associations operate in heavier populations is relevant. For
example, in the United States, 34% of women of reproductive age (20–39 years) are obese (BMI ≥ 30), of whom nearly 8% are classified as severely obese (BMI ≥ 40) (16). Thus, it would be interesting to see how these associations look in this population or in another with a similarly high prevalence of obesity.

In addition to parental BMI, numerous other prenatal and postnatal factors are likely to influence the development of adiposity in the child. It is a real strength of the Norwegian Mother and Child Cohort Study that extensive information is available on numerous factors of interest that operate during these different periods. The associations reported by Fleten et al. (5) changed little with adjustment for a wide variety of factors, such as breastfeeding, smoking, day care attendance, outdoor activity time, television and video watching, and even the child’s diet, among others. When intrauterine nutritional factors (gestational weight change, maternal diabetic status, and maternal diet during pregnancy) were adjusted for, however, the maternal-offspring BMI association strengthened, whereas the paternal-offspring association remained virtually unchanged. The strengthening of the maternal association was attributed to the effect of gestational weight change (5), which is suggestive of an impact of intrauterine environment on offspring BMI. As the difference in the maternal-offspring and paternal-offspring associations in these adjusted analyses only approached statistical significance, however, the finding was not interpreted as supporting a potential intrauterine effect on later offspring BMI (5).

Because the role of the postnatal environment is continuously increasing and changing over time, it is challenging to detect an effect of the intrauterine environment on childhood adiposity. The study by Fleten et al. (5) lends support to the idea that shared family genetic, environmental, and behavioral factors may be of greater importance for childhood adiposity than is the intrauterine environment, at least in this population of stable, relatively healthy and well-educated Norwegian families. Nonetheless, these findings do not refute the fetal overnutrition hypothesis, as there are some methodological limitations to the study. Instead, these findings serve to highlight that the specificity of the hypothesis warrants further investigation. For example, are effects of fetal overnutrition expected to appear across the spectrum of factors such as maternal BMI, or do they only appear in cases of extreme metabolic disturbances, such as pregnancies complicated by diabetes or severe obesity? Similarly, in the case of more modest intrauterine disturbances, are single factors, such as gestational weight gain, enough, or are interactions among these types of prenatal factors, as well as with postnatal factors, required before the effects manifest themselves? Further research is also needed to investigate whether potential intrauterine effects on offspring adiposity differ with age or if they remain constant. Additionally, further investigations are needed to examine whether it is the absolute level of adiposity or the resulting pattern of growth that matters. Testing the effect of the intrauterine environment is undoubtedly challenging, yet going forward the use of analytic methods such as path analysis may make it possible to disentangle the complex pathways through which prenatal and postnatal factors operate and thus lead to a better understanding of how the intrauterine environment influences the later risk of offspring adiposity.

ACKNOWLEDGMENTS

Author affiliation: Institute of Preventive Medicine, Copenhagen University Hospital, Copenhagen, Denmark.

The author thanks Dr. Kathleen M. Rasmussen for her constructive comments on an earlier version of this commentary.

Conflict of interest: none declared.

REFERENCES


