Preventing metabolic disease may start in the womb... of your grandmother

March 2 2015

No one wants to have child who is born underweight, but for numerous reasons, this may be unavoidable. An intriguing research report involving rats suggests that helping fetuses achieve optimal weight before birth is of even greater importance than currently believed: Underweight infants may eventually become the grandparents of children at a higher risk for metabolic problems like high cholesterol, diabetes, and obesity. This report appears in the March 2015 issue of *The FASEB Journal*.

"It is our hope that these findings will spur on studies in humans to study the impact of essential nutrients not just for their impact on infant birthweight and health, but longer term health across the lifespan. Our data suggests that in rats, low birthweight can be passed down from both the mom and the dad, and that this cannot be altered by essential nutrient supplementation in the mom or dads diet," said Kjersti Aagaard, M.D., Ph.D., FACOG, a researcher involved in the work from the Division of Maternal-Fetal Medicine at Baylor College of Medicine in Houston, Texas. "However, we can change the adult health and risk of obesity, diabetes and high cholesterol and bad lipids later in life. These findings further underscore the importance of long-term follow up studies in our patients, and notably interventions in pregnancy which may have long-term impacts which we cannot easily or reliably measure at birth."

To make this discovery, Aagaard and colleagues started with two groups of rats. One of these groups had their blood vessels to the womb tied off toward the end of pregnancy, leading to low birthweight pups; the second group underwent a "sham" surgery but did not have their blood

vessels to the womb tied. All of the rats delivered naturally, giving rise to the first generation of low birthweight and normal rats. These rats were later allocated to the nutrient-supplemented diet after weaning, or kept on a regular diet. When they reached early adult life, they were bred to produce pups of their own (grandpups) and were maintained on their allocated diets. These pregnancies were not surgically manipulated, but the grandpups were low birthweight if either of their parents were low birthweight. These grandpups were kept on the same diet as their parents and followed up to 1 year of age (well into rat adulthood). They were then tested for obesity with clinical DEXA scans, for diabetes with clinical glucose tests and special "clamp" studies, and fasting lipid levels were measured. In some of the animals, liver and other tissues were collected to study the epigenetic changes to the DNA.

"Studies like these really change how we perceive things like 'healthy' and 'wellness,'" said Gerald Weissmann, M.D., Editor-in-Chief of *The FASEB Journal*. "Our health and wellness is far more than just our DNA, diet, environment and exercise. It's also that of our parents and grandparents. Studies like this can help inform health policy to focus on repairable, epigenomic disease risks, rather than on risk factors faced by any one person at any one time."

More information: Danielle Goodspeed, Maxim D. Seferovic, William Holland, Robert A. Mcknight, Scott A. Summers, D. Ware Branch, Robert H. Lane, and Kjersti M. Aagaard. Essential nutrient supplementation prevents heritable metabolic disease in multigenerational intrauterine growth-restricted rats. FASEB J. March 2015 29:807-819; DOI: 10.1096/fj.14-259614

Provided by Federation of American Societies for Experimental Biology