Exercise during pregnancy reduces the risk of type-2 diabetes in offspring

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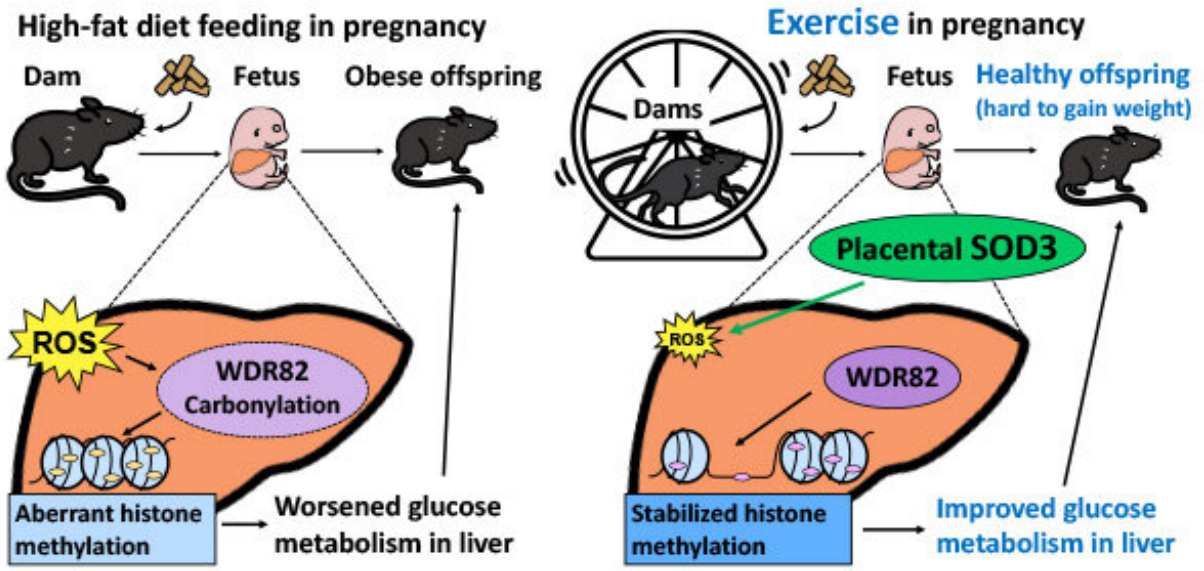

Maternal exercise protects offspring from the detrimental effects on their glucose metabolism when the mother consumes a high-fat diet. Exercise-induced, placenta-derived SOD3 protein plays a fundamental role in improving the levels of reactive oxygen species (ROS), protein carbonylation, and histone modification. Credit: Tohoku University

A new study has demonstrated that maternal exercise during pregnancy improves the metabolic health of offspring, even when the mother is obese or on a high-fat diet. Physical exercise by the mother induces the placenta to secrete the key protein SOD3, resulting in a lowered risk of

diabetes for the offspring. The findings in the paper identified the mechanisms behind this process.

The results were published in the journal *Diabetes* on March 15, 2022.

A worrying trend

Maternal obesity and type 2 diabetes are on the rise. More than 30% of women of childbearing age in Western and Asian countries are classified as obese. Meanwhile, 630 million people are expected to be living with type 2 diabetes by 2045. Children born to obese mothers or mothers with type 2 diabetes have an increased risk of diabetes, even after going on to live healthy lives.

"With the growth of maternal obesity, a worrying cycle is forming where the risks of diabetes gets passed down from generation to generation," says assistant professor Joji Kusuyama from Tohoku University's Interdisciplinary Institute for Frontier Sciences (FRIS), and lead author of the study. "Stopping this cycle is a critical and pressing medical problem."

In the research group with Kusuyama was Laurie Goodyear, Nathan Makarewicz, Brent Albertson, Ana Alves-Wagner, Royce Conlin, Noah Prince, Christiano Alves, Krithika Ramachandran, and Michael Hirshman from the Joslin Diabetes Center; Chisayo Kozuka fromRIKEN's Center for Integrative Medical Sciences; Toshihisa Hatta from Kanazawa's Medical University; Yang Xiudong and Yang Xia from the University of Texas at Houston; and Ryoichi Nagatomi from Tohoku University's Graduate School of Biomedical Engineering.

Previously, the group showed that exercise during pregnancy has tremendous benefits on an offspring's metabolic health, demonstrating that placenta-derived SOD3, which stands for supuroexide dismutase 3,

plays a key role in transmitting the benefits of maternal exercise to the offspring. Building on this, the team set out to understand how SOD3 prevents the negative effects of obesity being passed from mother to child and found that SOD3 inhibited high-fat diet-induced abnormalities in the offspring's glucose metabolism.

The link between maternal and childhood obesity

Histone methylation plays a fundamental role in epigenetic modification—heritable changes to strands of DNA that do not affect the inherited base pairs. Methyl group (-CH3) attaches to an amino acid in the tail of histone proteins that wrap DNA, sometimes activating gene expression, sometimes inhibiting it.

When a mother consumes a diet heavy in fat, the histone H3 trimethylation H3K4me3 gets decreased in the fetal liver and hinders the expression of glucose metabolism genes.

This, the researchers discovered, is caused by two things. Reactive oxygen species (ROS)—oxygen in a reactivated and activated state which aids the body's metabolism and cellular functions—becomes elevated. Meanwhile, WDR82, a key protein that regulates histone methyltransferase, becomes oxidative, impairing protein functions.

The harmful effects of a maternal high-fat diet on an offspring's metabolism are reversed by maternal exercise. Genetic manipulation demonstrated that placental SOD3 is indispensable for the protective effects of maternal exercise on offspring.

The study also highlighted how crucial exercise is for negating this. When the researchers infused N-acetylcysteine (NAC), an antioxidant that boosts performance in the liver, into the fetal liver, it did not reproduce the results of SOD3. This suggests the naturally produced

SOD3 from exercise during pregnancy is pivotal for the offspring's metabolic well-being.

Implications for the future

Given the simplicity and cost-effectiveness of exercise, encouraging mothers to exercise could help reverse the alarming rates of obesity and type-2 diabetes. The merits of SOD3 may not be limited to the metabolism stresses Kusuyama. "There may be wider benefits of this protein on other organs in the child. We are currently looking into the modifications in placenta tissue brought about by SOD3 that may have positive lifelong impacts on children."

The authors caution the study is only at the preclinical stage and its applicability to humans requires further studies. Additionally, certain aspects of the signaling pathway require further investigation.

More information: Joji Kusuyama et al, Maternal Exercise-Induced SOD3 Reverses the Deleterious Effects of Maternal High Fat Diet on Offspring Metabolism Through Stabilization of H3K4me3 and Protection Against WDR82 Carbonylation, *Diabetes* (2022). DOI: 10.2337/db21-0706

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