New insight into why poor diet during pregnancy negatively affects offspring's health

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Poor diet during pregnancy increases offspring's vulnerability to the effects of aging, new research has shown for the first time.

The research, by scientists from the University of Cambridge, provides important insight into why children born to mothers who consumed an unhealthy diet during pregnancy have an increased risk of type 2 diabetes (a significant contributing factor to heart disease and cancer) later in life.

"What is most exciting about these findings is that we are now starting to really understand how nutrition during the first nine months of life spent in the womb shape our long term health by influencing how the cells in our body age," said Dr Susan Ozanne, the senior author on the paper and British Heart Foundation Senior Fellow from the Institute of Metabolic Science at the University of Cambridge.

It is well established that environmental factors interact with genes throughout life, affecting the expression of those genes and, consequently, tissue function and disease risk. Diet during critical periods of development, such as during the nine months in the womb, has been cited as one such environmental factor. Epigenetics, which refers to modifications to the DNA that regulate how much of a gene is produced, has been suggested to underlie these effects.

However, until now, very little was understood about the underlying mechanisms that control the interaction between diet during gestation and gene expression in offspring throughout their adult life. Research, funded by the BBSRC and the British Heart Foundation, has now shown that the gene Hnf4a, which has been linked to type 2 diabetes, is regulated by maternal diet through epigenetic modifications to our DNA. Additionally, they found that poor diet exacerbates the rate at which these key epigenetic modifications accumulate during the aging process.

Previous research has shown that the gene Hnf4a plays an important role both during development of the pancreas and later in the production of insulin. The researchers hypothesised that diet during pregnancy influences the expression of this gene later in life, thereby influencing the risk of diabetes.

To test their theory, the researchers used a well-established rat model where, by altering the protein content of the mother's diet during pregnancy, the offspring develop type 2 diabetes in old age.

First, they studied the RNA from insulin secreting cells in the pancreas from offspring of normally fed as well as malnourished mothers in young adult life and in old age. When they compared the two, they found that there was a significant decrease in the expression of the Hnf4a gene in the offspring prone to type 2 diabetes. The expression of Hnf4a also decreased with age in both groups.

Second, they studied the DNA and found that the decrease of Hnf4a was caused by epigenetic changes. The age associated epigenetic silencing was more pronounced in rats exposed to poor maternal diet. They concluded that the epigenetic changes resulting from maternal diet and aging lead to the reduced expression of the Hnf4a gene, decreasing the function of the pancreas and therefore its ability to make insulin (and thereby increasing the risk of diabetes).

The scientists then studied the DNA from insulin secreting cells from human pancreases to show that expression of this important gene was controlled in the same way in humans.

"It is remarkable that maternal diet can mark our genes so they remember events in very early life," said Dr Miguel Constancia, the senior co-author on the paper from the Department of Obstetrics and Gynaecology and Metabolic Research Laboratories at the University of Cambridge. "Our findings reveal a novel mechanism by which maternal diet and aging interact through epigenetic processes to determine our risk of age-associated diseases."

Professor Jeremy Pearson, Associate Medical Director at the British Heart Foundation, said: "We already know that a healthy pregnancy is important in shaping a child's health, and their risk of heart disease as they grow up. The reasons why are not well understood, but this study in rats adds to the evidence that a mother's diet may sometimes alter the control of certain genes in her unborn child. It's no reason for expectant mothers to be unduly worried. This research doesn't change our advice that pregnant women should try to eat a healthy, balanced diet."

Professor Douglas Kell, Chief Executive, BBSRC said: "Epigenetics is a relatively young field of research with tremendous potential to underpin our understanding of many biological processes in all organisms. The fact that there is a relationship between the biology of a pregnant mother and the long term health of her child has been known for some time but our understanding of the biological processes behind some of the more subtle effects is still at a nascent stage. This study uncovers – through epigenetics and molecular biology research – an important piece of this puzzle and shows us how apparently minor changes within cells at the very earliest stages of development can have a major influence on our health into old age."

More information: The paper 'Maternal diet and aging alter the epigenetic control of a promoter-enhancer interaction at the Hnf4a gene in rat pancreatic islets' will be published in the 07 March edition of *PNAS*.

Provided by University of Cambridge