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Maternal Nutrition Influences Angiogenesis in the Placenta Through Peroxisome Proliferator Activated Receptors: A Novel Hypothesis

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ABSTRACT

Placental angiogenesis is critical to maintain adequate blood flow during gestation, and any alterations in this process can result in an adverse pregnancy. Growing evidence indicates that suboptimal maternal nutrition can alter placental development. Although the underlying mechanisms are not clear, maternal nutrition likely influences the expression of genes involved in placental development through regulation of various transcription factors such as peroxisome proliferator-activated receptors (PPARs), which can be activated by ligands including long-chain polyunsaturated fatty acids. Indeed, several studies demonstrated a role for PPAR in implantation, trophoblast differentiation, and angiogenesis. Alterations in maternal nutrition during pregnancy can affect the expression of PPARs via epigenetic mechanisms or through homocysteine, which is known to compete for PPARs. This review discusses the role of maternal nutrition particularly micronutrients like folate, vitamin B₁₂, and omega-3 fatty acids in modulating the activity of PPARs during placentation and angiogenesis, which affects placental and fetal growth. Additional animal and human studies need to be undertaken to elucidate the molecular mechanisms through which maternal nutrition regulates PPARs, specifically to determine whether PPARs affect placental angiogenesis directly through angiogenic factors or indirectly by modulating trophoblast differentiation.
Differential Regulation of Hepatic Transcription Factors in the Wistar Rat Offspring Born to Dams Fed Folic Acid, Vitamin B\textsubscript{12} Deficient Diets and Supplemented with Omega-3 Fatty Acids

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ABSTRACT
Nutritional status of the mother is known to influence various metabolic adaptations required for optimal fetal development. These may be mediated by transcription factors like peroxisome proliferator activated receptors (PPARs), which are activated by long chain polyunsaturated fatty acids. The objective of the current study was to examine the expression of different hepatic transcription factors and the levels of global methylation in the liver of offspring born to dams fed micronutrient deficient (folic acid and vitamin B\textsubscript{12}) diets and supplemented with omega-3 fatty acids. Female rats were divided into five groups (n = 8/group) as follows; control, folic acid deficient (FD), vitamin B\textsubscript{12} deficient (BD) and omega-3 fatty acid supplemented groups (FDO and BDO). Diets were given starting from pre-conception and continued throughout pregnancy and lactation. Pups were dissected at the end of lactation. Liver tissues were removed; snap frozen and stored at -80°C. Maternal micronutrients deficiency resulted in lower (p<0.05) levels of pup liver docosahexaenoic acid (DHA) and arachidonic acid (ARA) as compared to the control group. Pup liver PPAR\textalpha{} and PPAR\textgamma{} expression was lower (p<0.05) in the BD group although there were no differences in the expression of SREBP-1c, LXR\textalpha{} and RXR\textalpha{} expression. Omega-3 fatty acids supplementation to this group normalized (p<0.05) levels of both PPAR\textalpha{} and PPAR\textgamma{} but reduced (p<0.05) SREBP-1c, LXR\textalpha{} and RXR\textalpha{} expression. There was no change in any of the transcription factors in the pup liver in the FD group. Omega-3 fatty acids supplementation to this group reduced (p<0.05) PPAR\textalpha{}, SREBP-1c and RXR\textalpha{} expression. Pup liver global methylation levels were higher (p<0.01) in both the micronutrients deficient groups and could be normalized (p<0.05) by omega-3 fatty acid supplementation. Our novel findings suggest a role for omega-3 fatty acids in the one carbon cycle in influencing the hepatic expression of transcription factors in the offspring.
Maternal Micronutrients, Omega-3 Fatty Acids, and Placental PPARγ Expression

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ABSTRACT

An altered one-carbon cycle is known to influence placental and fetal development. We hypothesize that deficiency of maternal micronutrients such as folic acid and vitamin B₁₂ will lead to increased oxidative stress, reduced long-chain polyunsaturated fatty acids, and altered expression of peroxisome proliferator activated receptor (PPARγ) in the placenta, and omega-3 fatty acid supplementation to these diets will increase the expression of PPARγ. Female rats were divided into 5 groups: control, folic acid deficient, vitamin B₁₂ deficient, folic acid deficient + omega-3 fatty acid supplemented, and vitamin B₁₂ deficient + omega-3 fatty acid supplemented. Dams were dissected on gestational day 20. Maternal micronutrient deficiency leads to lower (p<0.05) levels of placental docosahexaenoic acid, arachidonic acid, PPARγ expression and higher (p<0.05) levels of plasma malondialdehyde, placental IL-6, and TNF-α. Omega-3 fatty acid supplementation to a vitamin B₁₂ deficient diet normalized the expression of PPARγ and lowered the levels of placental TNF-α. In the case of supplementation to a folic acid deficient diet it lowered the levels of malondialdehyde and placental IL-6 and TNF-α. This study has implications for fetal growth as oxidative stress, inflammation, and PPARγ are known to play a key role in the placental development.
Preconceptional Omega-3 Fatty Acid Supplementation on a Micronutrient-Deficient Diet Improves the Reproductive Cycle in Wistar Rats

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ABSTRACT

Folic acid and vitamin B_{12} deficiencies are associated with high reproductive risks ranging from infertility to fetal structural defects. The aim of the present study was to examine the effects of preconceptional omega-3 fatty acid supplementation (eicosapentaenoic acid and docosahexaenoic acid) to a micronutrient-deficient diet on the reproductive cycle in Wistar rats. Female rats were divided into five groups from birth and throughout pregnancy: a control group, a folic acid-deficient (FD) group, a vitamin B_{12}-deficient (BD) group, a folic acid-deficient + omega-3 fatty acid-supplemented (FDO) group and a vitamin B_{12} deficient + omega-3 fatty acid-supplemented (BDO) group. Dams were killed on gestation Day 20 and their ovaries and mammary glands were dissected out and subjected to histological examination. Maternal micronutrient deficiency (FD and BD groups) resulted in an abnormal oestrous cycle (p<0.001), whereas omega-3 fatty acid supplementation (FDO and BDO groups) restored the oestrous cycle to normal. There were fewer corpora lutea in the ovaries of FD rats compared with controls. In addition, rats in both the FD and BD groups exhibited an absence of lactating ducts in their mammary glands compared with controls. The findings of the present study indicate, for the first time, that maternal micronutrient deficiency affects the oestrous cycle and morphology of the ovary and mammary glands. Omega-3 fatty acid supplementation ameliorated these effects. This may have implications for infertility and pregnancy outcomes.
Role of Maternal Long-Chain Polyunsaturated Fatty Acids in Placental Development and Function

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ABSTRACT

During pregnancy, maternal long-chain polyunsaturated fatty acids (LCPUFAs) are preferentially transferred by the placenta to meet the requirements of the developing fetus. These LCPUFAs are essentially required by the trophoblast cells right from early gestation for several physiological processes involved in optimum placental growth and activity. They are structural constituents of the cell membrane, stimulate angiogenesis, and are metabolized into various eicosanoids, which modulate inflammation in the placenta. LCPUFAs and their metabolites also act as ligands for transcription factors like peroxisome proliferator-activated receptors, which regulate the expression of various physiologically important genes. Several pregnancy complications like preeclampsia are associated with increased placental inflammation and oxidative stress, and omega-3 LCPUFAs are known to reduce excess inflammation and oxidative damage in the trophoblast cells. This chapter describes the multiple roles of maternal LCPUFAs in placental development and function, reducing the risk of adverse pregnancy outcomes.
AWARDS
AWARDS

Total Number - 4

1. “Travel Award of 2000 SGD” from the “8th World Congress on Developmental Origins of Health and Disease” for the paper “Preconceptional Omega-3 Fatty Acid Supplementation on a Micronutrient Deficient Diet Alters Hepatic Transcription Factors Expression in Wistar Rats” held at SUNTEC Singapore on Nov 26-29, 2013.

2. “Best Oral Presentation Award” at “International Conference on Food and Nutrition Technology for Public Health Care” held at New Delhi for the paper “Effect of Pre-Conceptional Maternal Micronutrients and Omega-3 Fatty Acids on Dam Placental Fatty Acid Profile in Wistar Rats” on May 4-5, 2012; pg-89.

3. “Best Oral Presentation Award” at “43rd National Conference of Nutrition Society of India” held at Hyderabad for the paper “Preconception Maternal Micronutrient Deficiency: Reproductive Cycles and Breast Development in Wistar Rats” on Nov 11-12, 2011; pg-73.

4. “Junior and Senior Research Fellowship” for pursuing PhD by “Department of Science and Technology (DST)” under the “INSPIRE” programme.
INTERNATIONAL CONFERENCES
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Total Number - 5

1. Mini Oral presentation at “8th World Congress on Developmental Origins of Health and Disease” held at SUNTEC Singapore of the paper “Preconceptional Omega-3 Fatty Acid Supplementation on a Micronutrient Deficient Diet Alters Hepatic Transcription Factors Expression in Wistar Rats” on Nov 17-20, 2013; Pg- S239.

2. Oral presentation at “First International and Third National Conference on Biotechnology, Bioinformatics and Bioengineering” held at Tirupati, Andhra Pradesh of the paper “Effect of Omega-3 Fatty Acid Supplementation to a Micronutrient Deficient Diet on the Placental PPARγ Expression in Wistar Rats” on June 28-29, 2013; Pg- 121.

3. Poster presentation at 17th Society of Natal effects on health in adults meeting held at Mysore of the paper “Omega-3 Fatty Acids, Folic Acid, Vitamin B₁₂ and Placental PPARγ Expression” on Feb 1-3, 2013; pg-39.

4. Oral presentation at “International Conference on Food and Nutrition Technology for Public Health Care” held at New Delhi for the paper “Effect of Pre-Conceptional Maternal Micronutrients and Omega -3 Fatty Acids on Dam Placental Fatty Acid Profile in Wistar Rats” on May 4-5, 2012; pg-89.

5. Poster presentation at 16th Society of Natal effects on health in adults meeting held at CCMB Hyderabad of the paper “Preconceptional Micronutrient Deficiency Leads to Abnormal Estrous Cyclicity while Omega-3 Fatty Acid Supplementation Results in Normalcy in Wistar Rats” on Feb 3-5, 2012; pg-25.
NATIONAL CONFERENCES

Total Number - 3


2. Oral presentation at “44th National Conference of Nutrition Society of India” held at Tirupati for the paper “Preconception Omega-3 Fatty Acid Supplementation to a Micronutrient Deficient Diet Improves Placental PPARγ Expression” on Nov 16-17, 2012; pg-69.

3. Oral presentation at “43rd National Conference of Nutrition Society of India” held at Hyderabad for the paper “Preconception Maternal Micronutrient Deficiency: Reproductive Cycles and Breast Development in Wistar Rats” on Nov 11-12, 2011; pg-73.