Long-term effects of trans fatty acid intake during pregnancy and lactation: does it have deleterious consequences?

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By feeding rats a diet enriched with partially hydrogenated vegetable oil rich in trans fatty acids (TFAs) during gestation and lactation and exposed to the same diet after weaning, Pisani et al. recently concluded that TFAs intake during the perinatal period could promote deleterious consequences in the adult offspring [1]. In this article, we comment on this study. There is increasing interest in the effects of early nutrition on the predisposition to glucose intolerance and Type 2 diabetes in adulthood. Human studies have demonstrated that women exposed during pregnancy to the nutritional limitation imposed by severe famine have offspring with reduced size at birth [2], an increased risk of glucose intolerance [3] and obesity in adult life [4,5]. Chronic ingestion of hydrogenated vegetable fat rich in TFAs is known to modify the circulating lipid profile, to increase the risk of cardiovascular diseases, and to reduce insulin sensitivity, leading to Type 2 diabetes [6-8] by modifying the expression of genes associated with insulin sensitivity [9] and increasing inflammatory markers [10]. However, few studies have described the effects of TFAs during gestation and lactation on the metabolism of offspring in adulthood.

Maternal nutrition & fetal programming
Nutrition during intrauterine life influences fetal development and may cause adaptive and permanent changes in the structure, physiology and metabolism of the newborn with long-term consequences [11]. Epidemiological studies have linked low birthweight with the risk of a number of chronic diseases in adulthood (e.g., Type 2 diabetes, obesity, hypertension and coronary heart disease) [12-15]. Furthermore, it has been proposed that the metabolic syndrome X, which includes glucose intolerance, insulin resistance, obesity, hypertriglyceridemia, low HDL-C, hypertension and atherosclerosis, is initiated in the perinatal period as a low-grade systemic inflammatory condition [16].

The availability of nutrients to the fetus depends on those crossing the placenta, which at the same time are influenced by maternal nutrition [17,18]. Despite these antecedents, the real impact of maternal nutrition on fetal development is not completely understood [19]. However, studies in sheep and rats have demonstrated that alterations in the quantity or quality of food intake may affect intrauterine development and have negative long-term effects affecting glucose tolerance in adults [20,21].

Although lipogenesis [22] and cholesterolgenesis [23,24] occur in the fetus and placental transfer of maternal lipid moieties is relatively low when compared with other nutrients [25,26], alterations of lipid components at the maternal site, such as those caused by hypercholesterolemia in pregnant women [27] or high intake of saturated fat during pregnancy in rats [28,29], may have negative long-term consequences. Moreover, in rats, while adult offspring of dams
fed a high-fat diet derived from polyunsaturated fatty acids (PUFAs) during pregnancy and lactation have normal glucose tolerance [30], there are also studies in which enhanced intake of fish oil rich in n-3 long-chain PUFAs during the perinatal period resulted in impaired pancreatic insulin release and/or enhanced insulin sensitivity [31]. Furthermore, an increase in the proportional intake of n-6 PUFAs during the perinatal period has been associated with an enhanced prevalence of obesity in adults [32].

Thus, these reported findings allow us to conclude that both the amount and quality of fat in the diet during pregnancy and lactation may have major implications in the health of the adult, but as yet we do not understand the mechanism(s) involved.

Trans fatty acids during pregnancy & lactation

Industrial hydrogenation of edible oils, the process that leads to the formation of trans isomers of unsaturated fatty acids (TFAs), is used to improve their technological qualities. Another dietary source of these fatty acids is the milk and meat of ruminants, where they are formed during the biohydrogenation of fatty acids by rumen microorganisms. These TFAs are known to interfere in the conversion of parent essential fatty acids of the n-6 and n-3 families, linoleic acid (LA, 18:2 n6) and α-linolenic acid (ALA, 18:3 n3), respectively, into their long-chain PUFA (LCPUFA) derivatives [33]. Among these LCPUFAs, arachidonic acid (ARA, 20:4 n6) and docosahexaenoic acid (DHA, 22:6 n3) are critical in pre- and postnatal development, and are synthesized primarily in the liver from the dietary essential fatty acids, through Δ6 and Δ5 desaturation reactions. It has also been shown in pregnant rats that TFAs decrease the activity of Δ6-desaturase [34], and therefore alter the maternal profile of LCPUFAs, affecting their availability to the fetus. Furthermore, it has been suggested that a defect in the activity of Δ6 and Δ5 desaturases may be a factor that predisposes to the development of the insulin resistance syndrome [35].

It is known that TFAs can cross the placenta [36], as a correlation between the relative amounts of the main dietary TFA (18:1 n9t) in maternal plasma and fetal tissues exists [37]. Moreover, high concentrations of TFAs in the presence of altered LCPUFA status during pregnancy have been associated with low birthweight [38,39]. In addition, it has been found that dietary TFA intake during human pregnancy is associated with increased fetal loss, although the mechanisms are not understood [40]. Some effects of TFA intake during lactation, which may negatively affect newborn nutrition, have also been reported. Maternal consumption of TFAs during lactation favors an impairment of lipid metabolism in the mammary gland, with a decreased lipogenesis rate [41], increased TFA incorporation in mammary gland and a decreased percentage of essential fatty acids in the milk [42].

Trans fatty acid & programming of obesity-related insulin resistance

Since intrauterine nutrition that would cause a decreased birthweight may influence the adult risk for chronic diseases [12], it is suggested that an adequate supply of essential fatty acids and their LCPUFA derivatives is of pivotal importance during pregnancy, lactation and infancy. Although the consumption of TFAs is decreasing in most Western countries, the negative association between the intake of these fatty acids and the essential PUFAs still persists at low maternal intake [43]. Thus, although the negative effects of TFAs on fetal development cannot yet be ascertained, it is advised that their maternal intake should be reduced as much as possible.

Any efforts to determine the mechanism by which the ingestion of TFAs during gestation and lactation has negative effects on fetal programming with long-term consequences, are highly desirable. The paper of Pisani et al. represents an attempt to shed light on the role of TFAs in the metabolic programming of insulin resistance and cardiovascular disease [1]. It is now well established that adipocytes share with immune cells certain properties such as complement activation [44] and proinflammatory cytokine production, such as TNF-α [45] or plasminogen activator inhibitor (PAI)-1 [46,47]. Thus, a body of evidence suggests that obesity-related insulin resistance is a chronic inflammatory disease initiated in adipose tissue [48] with the inappropriate secretion of adipokines. In addition, a high intake of TFAs has been shown to promote inflammatory markers [10] and insulin resistance [9] and to alter blood lipid profile and adiposity [49]. In keeping with this scenario, Pisani et al. evaluate whether feeding rats during pregnancy and lactation with a TFA-rich diet has effects on adiposity and on inflammatory markers in the adult offspring [1]. They fed
pregnant and lactating rats with either a control diet or with a hydrogenated vegetable fat diet rich in TFAs. Upon weaning, some pups were kept on the TFA diet. Then, the authors analyzed the adiposity and PAI-1 and adiponectin expression in adipose tissue in the 90-day-old offsprings. They found increased levels of insulin, adiponectin and epididymal adipose tissue PAI-1 mRNA levels in the offspring continuously kept on the TFAs. The offspring of mothers fed the TFA diet during pregnancy and lactation but exposed to the control diet after weaning, also exhibited an increase in adiponectin serum concentration and PAI-1 mRNA levels in epididymal adipose tissue. In a previous study, the authors also found an increase in PAI-1 mRNA and a decrease in adiponectin mRNA in the adipose tissue of 21-day-old offspring of rats fed a diet containing hydrogenated vegetable fat during gestation and lactation [50]. These results suggest that early exposure to hydrogenated vegetable fat causes a long-term alteration in adipose tissue PAI-1 gene expression.

The results are of potential interest as PAI-1 is the main inhibitor of the fibrinolytic system, and its plasma levels are an independent predictor of coronary artery disease [51]. Moreover, it has been proposed that PAI-1 is a real component of the metabolic syndrome [52]. Thus, any effort to determine the mechanism by which the ingestion of TFAs during gestation and lactation has negative effects on fetal programming of insulin resistance is valuable. Pisani et al. attempt to do this, although the experimental design used does not allow reaching definite conclusions to be reached [1]. They compare the effects of a diet containing not only TFAs but one also having a higher proportion of saturated fatty acids and a lower proportion of PUFA than the control diet. In addition, food intake of the experimental animals was decreased compared with the controls, and it is well known that any of these dietary conditions applied during pregnancy and/or lactation may have long-term effects on any of the measured variables (i.e., body weight, body fat content and insulin sensitivity). This includes the increased carcass fat content that they found in offspring rats receiving the hydrogenated vegetable fat rich in TFAs during gestation and lactation, followed by the continuous exposure of the offspring to this diet until the 90th day of life, since it is known that adipose tissue mass enlarges to a greater extent in response to dietary saturated fats than polyunsaturated fats even without the intervention of TFAs [53]. Furthermore, it has been shown that LCPUFA deficiency induced by an energy-dense diet increases the production of inflammation markers such as TNF-α and IL-6. This effect in turn decreases the production of endothelial nitric oxide and adiponectin, inducing insulin resistance in maternal and fetal tissues [54]. In addition, it has been hypothesized that supplementation with essential fatty acids and LCPUFAs during the perinatal period can reduce the burden of low grade inflammatory diseases [55,56]. Thus, from the study discussed, it is not possible to discern if the TFAs, the increase in saturated fat, or the decrease in essential fatty acids or LCPUFA, or even the under-nutrition present in the experimental model used, is the starting point of the programming events that result in the inflammatory state found in the pups when adults.

Conclusion & future perspective

By emphasizing the deleterious consequences of the intake of dietary components rich in TFAs during pregnancy and lactation, Pisani et al. [1] have positively contributed to the public awareness for reducing the consumption of baked and processed foods containing partially hydrogenated fats and oils by industry [101,102], as TFA intake during the perinatal period may have negative effects on progeny in favoring an inflammatory condition. However, owing to the different uncontrolled variables present in the study, the experimental design used in this paper does not allow the mechanism(s) involved to be established. It is therefore mandatory to perform programming studies with pregnant animals that are pair fed on diets with differences in their TFA content but containing balanced proportions of the other fatty acids, in particular those that are essential during the perinatal period, in order to attain a clear understanding of the mechanism(s) involved in their long-term negative effects.

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Executive summary

Background

- Women exposed to severe famine during pregnancy have offspring with reduced birthweight and an increased risk of glucose intolerance and obesity as adults.
- Chronic ingestion of hydrogenated vegetable fat rich in trans fatty acids (TFAs) modifies the expression of genes associated with insulin sensitivity and inflammatory markers.
- A diet rich in TFAs during gestation and lactation appears to promote deleterious consequences in the adult offspring.

Maternal nutrition & fetal programming

- Nutrition during intrauterine life influences fetal development and may cause adaptive and permanent changes with long-term consequences.
- The availability of nutrients to the fetus depends on those crossing the placenta, which is influenced by maternal nutrition.
- Placental transfer of lipid moieties is relatively lower than other nutrients, but alterations in the amount and quality of lipids in the diet during pregnancy and lactation may have major implications in the health of the adult.

Trans fatty acids during pregnancy & lactation

- TFA interfere in the conversion of parent essential fatty acids into their long-chain polyunsaturated derivatives, which are critical in pre- and postnatal development.
- TFA can cross the placenta, and their intake during pregnancy has been associated with increased fetal loss. Their consumption during lactation impair lipid metabolism in mammary gland, altering milk composition.

Trans fatty acids & programming of obesity-related insulin resistance

- A high intake of TFA favors an increase of inflammatory markers and insulin resistance, as well as the alteration of blood lipid profiles and adiposity.
- Offspring of rats fed a TFA-rich diet during pregnancy and lactation, and exposed to the same diet after weaning, exhibited an increase in circulating adiponectin and insulin, body fat and plasminogen activator inhibitor (PAI)-1 mRNA in white adipose tissue.

Conclusion & future perspective

- The recognition of the deleterious consequences of the intake of TFA during pregnancy and lactation has positively contributed to the public awareness for reducing the consumption of foods containing these lipids.
- Nonetheless, it is mandatory to develop appropriate experimental designs to firmly establish the underlying mechanism(s).

Bibliography

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56. Das NU: Can essential fatty acids reduce the burden of disease(s)? *Lipids Health Dis.* 7, 9 (2008).

**Websites**


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