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Review

Dietary *trans* fatty acids in early life: a review

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Abstract

Trans fatty acids are unsaturated fatty acids with at least a double *trans* configuration, resulting in a more rigid molecule close to a saturated fatty acid. These appear in dairy fat because of ruminal activity, and in hydrogenated oils; margarines, shortenings and baked goods contain relatively high levels of *trans* fatty acids. These fatty acids can be incorporated into both fetal and adult tissues, although the transfer rate through the placenta continues to be a contradictory subject. In preterm infants and healthy term babies, *trans* isomers have been inversely correlated to infantile birth weight. However, in multigenerational studies using animals, there is no correlation between birth weight, growth, and dietary *trans* fatty acids. Maternal milk reflects precisely the daily dietary intake of *trans* fatty acids, from 2% to 5% of the total fatty acids in human milk. The level of linoleic acid in human milk is increased by a high *trans* diet, but long-chain polyunsaturated fatty acids remain mostly unaffected. Likewise, infant tissues incorporate *trans* fatty acids from maternal milk, raising the level of linoleic acid and relatively decreasing arachidonic and docosahexaenoic acids. This suggests an inhibitory effect of *trans* fatty acid on liver Δ-6 fatty-acid desaturase activity. As opposed to blood and liver, the brain appears to be protected from the *trans* fatty-acid accumulation in experimental animals, but no data have yet been reported for human newborns. Further investigations in humans are needed to definitively establish the potential physiological consequences of *trans* fatty-acid intake during the neonatal period.

Keywords: *Trans* fatty acids; Neonate; Human milk; Tissue composition; Conjugated linoleic acid

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1. Introduction

Trans fatty acids are unsaturated fatty acids with at least a double bond in *trans* configuration or geometry, i.e., the two hydrogen atoms of the carbons adjacent to the double bond point to opposite directions which is different from the double bond of *cis* configuration in the fatty acids of mammals, and hence of human cells [1]. In addition, the double bond can be located anywhere along the molecule, so that many positional isomers may exist. The double-bond angle of the *trans* fatty acids is smaller than the *cis* isomeric configuration and the acyl chain is more linear, resulting in a more rigid molecule with different physical properties such as a higher melting point and greater thermodynamic stability [2].

The official International Union of Pure and Applied Chemistry (IUPAC) nomenclature for fatty acids is commonly used [3]. The carbon length of the fatty acid chain is indicated by the number before the colon, and the number of the double bond is indicated by the number after the colon. The *trans* configuration is designated by a *t*-; the number preceding the *t*- indicates the position of the *trans* bond acids counted from the carboxyl end of the molecule, and *c*- designates the *cis* isomers. Thus, the abbreviation 18:1 9*t* correspond to the *trans*-Δ-9-octadecenoic acid (elaidic acid), and 18:1 9*c*, to the *cis* configuration (oleic acid).

Owing to the complexity of the possible fat mixtures, there is not a simple and definitive method for the simultaneous determination of both the total *trans* content (sum of all *trans* fatty acids) and the fatty-acid composition. Traditionally, total *trans* content was determined by infrared (IR) spectroscopic techniques, which do not quantify individual fatty acids. Currently, a complete analysis can be achieved using capillary gas chromatography (GC) in combination with other techniques, particularly silver thin layer chromatography (Ag-TLC), IR spectroscopy and mass spectrometry (MS) [4].

2. Dietary sources and intakes of *trans* fatty acids

Trans-isomeric fatty acids occur naturally in dairy and other animal fats by biological hydrogenation in the stomach of ruminants, but they originate mainly from the industrial process of catalytic hydrogenation of fats; 80–90% of dietary *trans* fatty acids are derived from this latter source, whereas 2–8% are provided by dairy products [5,6]. The major *trans* isomers in the diet are the C18 *trans*-monounsaturated fatty acids found in partially hydrogenated vegetable oil and ruminant fats, and *trans*-polyunsaturated fatty acids appear only in trace amounts. Hardened marine oils contain a mixture of geometrical and positional isomers of C20-22 monounsaturated fatty acids and di- and tri-unsaturated fatty acids. The most prevalent *trans* fatty acid in partially hydrogenated vegetable oils is 18:1 10*t* [7], and the major *trans* isomer in milk is 18:1 11*t* (vaccenic acid) [8].

The *trans* fatty-acid content of food products containing partially hydrogenated vegetable oils varies widely within a product category and among categories. Foods with major contributions to *trans* fatty acid intake are baked goods such as doughnuts and Danish pastry (37% *trans* fatty acids), imitation cheese (38%), margarines (11–49%), confectionary fats (27%), and deep-fried foods such as fried chicken, french-fried potatoes,

and snack chips, which may contain up to 36% *trans* fatty acids when high *trans* oils are used in the frying process [9]. The *trans* fatty-acid content of dairy fat varies between seasons and regions due to the different feeding practices of the animals, but usually range from about 2% to 7% [10].

Estimated rates of *trans* fatty-acid intakes have been controversial, since calculations vary depending on the method used: food-questionnaire, food availability or food disappearance data, and extrapolations from adipose or milk data through theoretical equations described in the literature. Estimates of *trans* fatty-acid intake based on availability or disappearance data give the highest values, while based on food-questionnaire data gives the lowest. In summary, means for estimated dietary *trans* fatty-acid intake as a percentage of total fatty acids based on food-questionnaire data are 6–8% for diets in the USA, about 6–4% for diets in Great Britain, about 2–4% for diets in Germany, and 1.7% for diets in Spain [11–13]. In general, *trans* fatty acids are consumed in rather large amounts in industrialized countries, averaging 2–8 g/day, which equals about 2.5% of total energy or 6–8% of the total intake [12–14]. Nevertheless, the amounts of *trans* fatty acids in the diet have remained relatively constant over the past few decades, in part because the increased use of partially hydrogenated vegetable fat has been counterbalanced with a concomitant decrease in the intake of animal fat (butter, lard and tallow), and a lower *trans* fatty-acid content in processed edible fats and oils.

3. Exposure of fetus to *trans* fatty acids

Trans fatty acids are not excluded from metabolically active body tissues. Dietary *trans* fatty acids are incorporated into body tissues and fluids of humans and experimental animals, namely brain, liver, adipose tissue, spleen, plasma and milk. The amounts incorporated are considerable [15,16], except in the brain [17], and the accumulation generally reflects the *trans* fatty-acid content and profile in the diet, although these acids are incorporated into tissues in a lower proportion than they occur in the diet. Incorporation in tissues occurs preferentially in the sn-1 position of membrane phospholipids deplacing saturated fatty acids and only minor *trans* isomers such as the 18:2*t* may be incorporated at the sn-2 position, competing with PUFA in cell membranes [18,19].

The placental transfer of *trans* fatty acids was demonstrated years ago by injecting labeled 18:1 9*t* [1-^{14}C], 18:2 9*t*,12*t* [1-^{14}C] and their *cis* isomers into the jugular vein of pregnant rats [20]. However, studies considering the transfer of *trans* isomers across the placenta have reported contradictory results. For example, Pettersen and Opstvedt [21] did not find significant percentages of *trans* fatty acids in tissue lipids of newborn pigs whose mothers were fed with high *trans* diets, and Johnston et al. [22] found similar results in body lipids of newborn rats (0.5% in the extracted lipids fat) from mothers fed with hydrogenated margarine stock containing about 40.7% *trans* fatty acids. In humans, an early study of the latter authors [23] showed, in human fetal liver lipids or in total body lipids of newborn babies, $<0.5\%$ total *trans* fatty acids to about 1.5–6.8% in the depot fats of their mothers, suggesting that *trans* fatty acids do not efficiently cross the placental unit. The Federal Drug Administration report of 1985 prepared for the Center for Food Safety and Applied Nutrition concluded that the human placenta acts as a barrier for *trans*

fatty acids and excluded a significant exposure of untoward effects for the fetus [24]. Nevertheless, Koletzko and Müller [25] later rejected this thesis because they detected *trans* fatty acids at similar levels in cord blood of term infants and maternal plasma lipids. In addition, Houwelingen and Hornstra [26] found a direct correlation between 18:1 9*t* in maternal plasma of the mothers and in fetal tissues, after natural abortion, although the values found on *trans* fatty acids were low. Based on these reports, the International Life Sciences Institute Expert Panel on *Trans*-fatty acids and early development [27] have concluded initially in 1997 that "*trans* fatty acids are transferred by the placenta to the fetus and incorporated into fetal tissues".

The *trans* fatty-acid content of tissue lipids decreased in the following order: maternal plasma > placenta > fetus. However, despite that the myelinogenesis process is not finished in fetus, the amount of *trans* isomers transferred to fetal brain was negligible in all studies, suggesting a low transference of *trans* isomers to the central nervous system during early development [21].

In human fetal tissues from abortions performed at 5–15 weeks of gestational age, *trans* fatty acids were inversely correlated with the rate $n-6$ long-chain polyunsaturated fatty acids (LC-PUFA)/18:2 $n-6$ [26]. Our results for pregnant rats fed with three experimental diets, containing about 0%, 15% and 30% *trans* fatty acids, showed that the placenta incorporated high amounts of *trans* isomers into its structure, although this barrier did not prove completely impermeable, since a number of *trans* fatty acids crossed the organ and were accumulated in the liver and total body lipids of the fetus, but not the brain, showing a clear exposure of the fetal tissues to *trans* maternal dietary fatty acids.

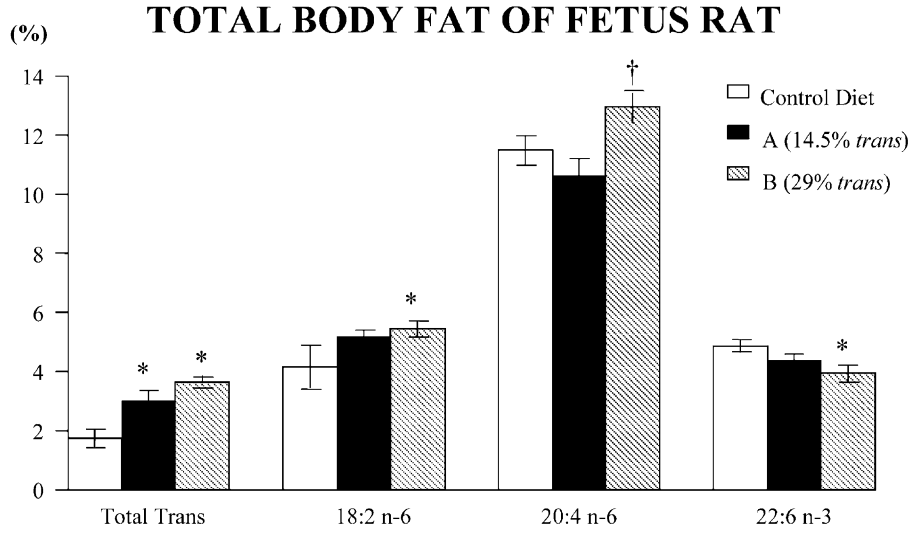

Fig. 1. Percentages of total *trans* fatty acids, linoleic acid (18:2 $n-6$), arachidonic acid (20:4 $n-6$) and docosahexaenoic acid (22:6 $n-3$) in total body fat of fetus rats fed their own mothers for 10 weeks on 0%, 14.5% and 29% *trans* fatty acid diets. Results are mean ± S.E.M.; $n=6$ for each group. Significant differences are indicated by: * $p<0.05$ vs. control, † $p<0.05$ vs. A group.

Tissue levels of other fatty acids such as of linoleic and docosahexaenoic acids were also affected (Fig. 1).

4. Milk *trans* fatty acids

The *trans* fatty-acid content of human milk varies, reflecting daily *trans* dietary intake. Marked variations appear in different populations and different dietary habits, varying from 7.2% in Canada [28], with a pattern of *trans* fatty acids similar to that of partially hydrogenated oils used in the mother's diet, to 1.9% in France [29], 18:1 11*t* being the predominant isomer, suggesting the influence of cow's milk fat in the diet. Also, the individual diet can alter the milk fatty-acid profile and different diets could be consumed even in a geographically small area, hampering general conclusions to be drawn about the *trans* fatty-acid content in maternal milk [30]. In general, *trans* fatty acids comprise 2–5% of all fatty acids in human milk [31], and 2–11% in bovine milkfat [32]. Infant formulas generally contain lower amounts of *trans* fatty acids, with reported values of 0.1–2% of total fatty acids [33]. However, in Spain, due to the Mediterranean diet, the average content of *trans* fatty acids in mature human milk represents 0.95% [34] which is lower than the 0.6–4.5% detected in commercial infant formulas in the same country [35].

Craig-Schmidt et al. [31] developed an equation to correlate the percentages of 18:1*t* in human milk [y] and maternal diet [x] [$y = 1.49 + 0.42x$], which is also used to make estimates of intake of dietary *trans* fatty acids in populations. This equation predicts human milk 18:1*t* percentages close to the value found in a study performed by our group in rat milk [$y = 0.33 + 0.46x$], demonstrating a direct dosage–response relationship between the intake of *trans* fatty acids and their incorporation into maternal milk [36].

Ratnayake and Chen [37], conducting an epidemiological study, reported a negative correlation between milk contents of 18:1 *trans* and linoleic and α-linolenic fatty acids in Canadian human milk, suggesting that the rise in *trans* fatty acids might occur at the expense of essential fatty acids, since high *trans* dietary products usually contain less of these last fatty acids. However, another study in animals [38] has shown an increase in 18:2 $n-6$ in milk fat of sows fed with partially hydrogenated soybean oil. Our results agree with this last study [36], and one hypothesis to explain the increase of 18:2 $n-6$ in the milk of rats fed with high *trans* fatty acid diets could be that the mammary gland might regulate the acylation of milk triglycerides and phospholipids in order to maintain the physico-chemical properties of the fat globules. Our data support this hypothesis, given that both LC-PUFA and the unsaturation index remained nearly constant in milk regardless of the dietary *trans* fatty-acid content. There is no evidence for changes in the LC-PUFA content of maternal milk derived from the intake of *trans* fatty acids. Pettersen and Opstvedt [38] found a reduction in the level of PUFA $n-6$ and PUFA $n-3$ in colostrum, but not in the milk of sows fed high *trans* diets. These researchers concluded that changes in the fatty-acid composition of colostrum and milk in sows were moderate to minor and that no consistent effects on the levels of polienoic acids were evident.

Trans fatty acids have been shown to depress milk fat when fed or infused to lactating dairy cows and mice [39–41], although there was not a dosage-dependent milk-fat response to dietary *trans* fatty acids, and differences in the inhibitory effects between

isomers of octadecenoic fatty acids have been reported [42]. Nevertheless, in sow's milk, no significant difference in fat content has been shown [38], nor is there any evidence of milk-fat reduction in lactating women, although more data are needed.

5. Neonatal tissue accretion

It is still uncertain whether the exposure to *trans* fatty acids has negative consequences in early life. Few studies treat the incorporation of *trans* fatty acids in human tissues during the neonatal period. Levels of about 1–2% of *trans* fatty acids have been reported in blood lipid fractions of preterm babies [43] and infants at birth and between 1 and 12 months [44], as well as low amounts of 18:1*t* in adipose tissue of preterm babies (0.1–0.9%) [45].

Animal studies have fewer variables and provide more possibilities for tissue sampling to ascertain the incorporation and biological consequences of dietary *trans* fatty acids during the neonatal and lactating periods. Newborn animals from mothers fed with *trans* fatty acids have markedly lower levels of these acids ($< 1–2\%$), despite high *trans* content in the maternal diet [21]; *trans* isomers might cross the placenta in low amounts, but they could also be catabolized in fetal tissues rather than stored, or they might also be diluted within the novo-synthesized fatty acids.

During lactation, *trans* fatty acids present in maternal milk in high amounts depending on their dietary content are absorbed by lactating animals and stored in various tissues and organs in different amounts, the adipose tissue showing the highest content [46], whereas the brain has shown the lowest or negligible incorporation [46,47]. The levels of *trans* isomers rise quickly in all neonatal tissues during the first weeks of suckling, and at the end of lactation, reach levels similar to those found in milk in the mature tissues except for the brain [21] where none of these isomers have been detected either in the fetal or the adult state [17]. This reflects a clear protective mechanism to limit the incorporation of these fatty acids in the central nervous system.

Dietary *trans* fatty-acid incorporation have minor but consistent effects on the profile of essential fatty acids in suckling tissues, causing a rise in the proportion of linoleic acid and a minor drop in the content of the long-chain and higher desaturated homologues, namely arachidonic and docosahexaenoic acids [46]. Thus, an inverse correlation have been reported between *trans* fatty acids and the contents of long-chain polyunsaturated fatty acids (LC-PUFA) in blood lipid classes in preterm babies of 4 days of life [43], fetal tissues and umbilical arterial walls from full-term neonates [26], and in plasma phospholipids from healthy children aged 1–15 years [48], suggesting an impairment of the elongation and the desaturation systems of essential fatty acids (EFA).

Some studies have investigated the effects of *trans* fatty acids on Δ-6 fatty-acid desaturase activity in liver microsomes of adult rats, pointing out an inhibitory effect. However, many of the results refer to the systems deficient in essential fatty acids (EFA) [49] or the use of specific *trans* fatty acids in amounts far from the real composition of commercial fats [50]. On determining this enzymatic activity in the liver microsomes of pregnant rats fed with three experimental diets (about 0%, 15%, and 30% of *trans* fatty acids), we found a partially inhibitory effect in the *trans* diets [51]. Experiments with animals have shown the need of higher linoleic acid intake to avoid potential competition

when diets contain partially hydrogenated oils [52], especially during pregnancy and lactation as stated by the FAO [53]. It has been suggested that marginal EFA deficiency develops in mothers during pregnancy and lactation [54,55], but it is difficult to determine from blood–lipid data whether a mother's stores of EFA are sufficient for fetal development. Despite that the inhibition of Δ-6 desaturation is probably one of several mechanisms that prevent excess production and accumulation of LC-PUFA $n-6$ and $n-3$ in cell membranes, there is still much that is not understood about the regulation of these enzymatic systems and there are no studies available on Δ-6 fatty-acid desaturase activity in the different stages of development which are drawing definitive conclusions. Moreover, studies with rodents have shown that *trans* fatty acids may be further desaturated and elongated to unusual C18 and C20 polyunsaturated fatty acids with unknown physiological consequences [56,57].

Trans isomers have also been inversely correlated with infantile birth weight in preterm and healthy term babies [43,48]. The conversion of essential fatty acids (EFA) into LC-PUFA may be critical especially for the fetus and preterm babies which depend on the maternal supply of these fatty acids not only for fetal growth but also for the development and maturation of the brain, to maintain the vascular system and for the synthesis of eicosanoids [58]. Diets deficient in PUFA have also been related to retarded intrauterine growth [59] and to visual and intellectual disorders [60]. However, determining whether *trans* fatty acids affect human fetal and infant growth and development is a complex issue and many factors are difficult to control (e.g., nutritional status, genetic background, lifestyle, and general health of the mother) that may influence fetal growth, neurodevelopment, and maturity [27]. Furthermore, adverse effects of *trans* fatty acids on growth, reproduction, and longevity were not detected in studies using several animal species and multigenerational experiments [61,62], with few exceptions [63]. Nevertheless, these models may not have been appropriate for addressing all the subtle effects that influence development of human infant retinal, neural, or brain function.

6. Conjugated linoleic acids (CLA)

Conjugated linoleic acids (CLA) are a group of linoleic (18:2)-derived isomers with conjugated double bonds, mostly at carbon atoms 9 and 11 or 10 and 12, with all possible *cis* and *trans* combinations. CLA have been recently receiving growing attention because they have exhibited potent chemoprotective properties to inhibit carcinogen-induced neoplasias in mice, rats and human cultured mammary cells (0.1–1% in the diet) [64,65]; they have also shown the ability to reduce body fat accumulation in some experimental models [66,67]. However, the biochemical mechanisms for those functions are still largely unknown.

CLA occur naturally in several foods but they are found in highest concentrations in milk fat and body fat of ruminants (2.9–11.3 mg/g fat); the predominant fatty acid isomer is the 18:2 9*c*,11*t*. CLA are also present in plant oils and partially hydrogenated oils but in very low amounts [68].

There are not studies about the effects of CLA on neonatal fatty acid metabolism in humans. It is known that CLA may moderately modify body weight, fat and lean mass of

growing animals. Chin et al. [69] found that feeding diets supplemented 0.5% CLA to rat dams during gestation and lactation enhanced pup growth while producing no observed evidence of harm. However, other authors did not detect any change in body weight [70], or even a lowering in rate growth, not only in young animals but also in adults [67,71]. This opposite effect could be explained by the fact that CLA have been reported to decrease body fat mass and this effect is more prone than an effect of increasing in lean mass. CLA supplementation has been associated with an increase in the activity of the enzymes related to fatty acid β-oxidation in mice but also with changes in body fat mobilisation; animals fed with CLA in several studies presented a higher accumulation of fat in liver [67,71]. So that, dietary CLA may alter fatty acid metabolism and there are more studies needed to evaluate the possible effects of the intake of CLA on infant growth.

CLA are incorporated into fetal and neonatal tissues. The most of the CLA detectable in human tissues is of dietary origin, eventhough there can be endogenous synthesis through Δ-9 desaturation of 18:1 11*t* [72]. Jiang et al. [73] found a good correlation between the intake of milk fat and the occurrence of CLA in human adipose tissue. Dietary CLA has been associated with a lowering in linoleic acid in hepatic phospholipids and triglycerides of mice, whereas arachidonic acid only decreased significantly in these last neutral lipids, associated with a rising to 18:1 and CLA levels [74]. Dietary CLA may be desaturated to a similar extension by Δ-6 fatty-acid desaturase than linoleic acid, and it has been suggested that they might compete with it for this enzymatic acitivity [74]. There is no known position in which CLA are incorporated into membrane phospholipids.

Intake of CLA during lactation results in an increase in the concentration of CLA in maternal milk. A concentration of 18:2 9*c*,11*t* in human milk of about 5.8 mg/100 g fat in Australian women and 3.64 mg/g fat in USA women has been reported [30]. In experimental animals, a transfer efficiency of dietary CLA isomers of 55–69% for sow mature milk has been estimated [75]. Dietary CLA supplementation of sows during gestation and lactation increased saturated fatty acids and decreased monounsaturated fatty acid levels in milk fat. As we have described above for *trans* fatty acids, CLA have been shown to depress milk fat when fed or infused to lactating dairy cows [76]. Nevertheless, there is no evidence of milk-fat reduction in lactating women.

Further investigations are needed to establish whether dietary amounts of *trans* fatty acids transferred from the mother during fetal development and suckling of the newborn, or from formula and other dietary sources during early infant growth, are likely to influence normal metabolism, growth and development specifically during the early stages of life.

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