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Proinflammatory State in the Odontogenesis of Fetuses Exposed to Different Types of Fatty Acids during Pregnancy

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Highlights of the Study

- Lipid consumption during pregnancy impairs the development of fetuses.
- A trans-fatty acid diet increases JAK2 expression in the odontogenesis.
- Lipid consumption in the maternal diet remains a topic to be explored in embryonic development.

Keywords
Fatty acid · Diet · Odontogenesis · Rat

Abstract

Objectives: The aim of the present study was to analyze the possible changes caused by the maternal ingestion of different types of fatty acids during pregnancy in the proinflammatory state in the odontogenesis of the fetuses. ***Subject and Methods:*** Twenty-four jaws (n = 6 per group) of Wistar rats were collected on the 20th day of intrauterine life. Mothers were separated on the first day of pregnancy into 4 groups according to diet, as described below: control group (C) – diet with soy oil as a source of fat; saturated fatty acid group (S) – diet with lard in saturated fatty acids; trans-fatty acid group (T) – diet with vegetable fat, rich in trans-saturated fatty acids; and polyunsaturated fatty acid (PUFA) group – diet with fish oil, rich in PUFAs. ***Results:*** Microscopic analysis showed no alterations in tissue development of the teeth between the groups with different lipid diets (T, S, and PUFA) when compared to the control group (C); immunohistochemical analysis for the expression of JAK2, STAT3, P-STAT3, SOCS3, and IL-6 showed no statistically significant difference ($p > 0.05$) compared to the control group. However, there were changes ($p < 0.05$) between the T group and the PUFA group in the expression of JAK2. ***Conclusion:*** Thus, lipid consumption in the maternal diet remains a topic to be explored in embryonic development, despite not causing morphological changes to the tooth germ of rats.

Introduction

Maternal diet during pregnancy directly affects fetal development, and permanent changes may be observed in childhood and adulthood, influencing the propensity of offspring to develop metabolic disorders, such as obesity, type 2 diabetes, and cardiovascular disease [1]. Saturated fatty acids (SFAs) such as lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), and stearic acid (18:0) are composed of linear chains of carbon and hydrogen

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(-CH_2-) that do not have double-chain bonds. At room temperature, they are solid and are found in processed foods, bovine meat, chicken fat, lard, coconut, dairy products, and butter oil [2]. Lauric acid and palmitic acid induce transcription of factor κB (NF-κB), promoting the activation of proinflammatory genes, such as COX-2 (cyclooxygenase-2), resulting from the indirect activation of Toll-like-4 receptors. It has been established that SFAs contribute to increase in total cholesterol levels and cardiovascular diseases [3]. Trans-fatty acids (TFAs) are extremely harmful to health as they affect the development of the fetus through the inhibition of the delta-6 desaturase enzyme [4]. TFAs are geometric isomers of unsaturated fatty acids (FAs). They are obtained from herbivorous mammals (ruminant animals) that have a specific bacterial flora; they can also be artificially generated from the partial hydrogenation of liquid vegetable oils, mainly industrialized products. This process reduces the oxidative characteristic of these fats and allows a better texture, flavor, and longevity to industrialized foods [2]. Dietary TFAs are found in bakery products, such as cakes and pies, in highly processed foods known as "fast foods," cookies, and snacks [5]. The harmful effects of exacerbated ingestion of TFAs, most processed ones, have been evidenced by several scientific reports, linking the consumption of TFAs to greater insulin resistance, metabolic disorders of lipids, and changes in endothelial function, in addition to the imminent risk of cardiovascular diseases. Such conditions are often observed by higher levels of inflammatory markers, such as IL-6, TNF-α, and C-reactive protein; increased oxidative stress; LDL cholesterol; and reduced HDL cholesterol [2].

In contrast, consumption of n-3 polyunsaturated fatty acids (PUFAs) may reduce inflammatory responses, minimizing the risk of obesity, insulin resistance, and cardiovascular disease [6]. Long-chain PUFAs have been highlighted in the literature as essential for fetal development as well as for the proper cellular functioning of different systems in offspring [6]. PUFA families are metabolized by desaturating enzymes (Δ5- and Δ6-desaturase) and elongases with α-linolenic acid being transformed into EPA and DHA and linoleic acid, resulting in arachidonic acid. These FAs are known as essential FAs because, even though they are not produced by the body, they are essential for its functioning and, therefore, must be consumed regularly through the diet [7]. The n-6 and n-3 PUFAs (omega 6 and omega 3) are molecules that are converted in the body into signals called eicosanoids. These have different actions, being proinflammatory if derived from n-6 and anti-inflammatory if derived from n-3. Thus, it is known that n-3 PUFAs (such as EPA and DHA) can be used to regulate the inflammatory process due to the production of IL-10 and reduction in levels of TNF-α, IL-6, and C-reactive protein [7].

JAK/STAT is a signaling pathway of the innate and adaptive immune response process. Janus kinases (JAKs), found in the cytoplasm, are a type of non-receptor tyrosine kinase that promotes the binding of cytokines and hormones to the cell membrane [8]. The cell-surface receptors, also known as transmembrane receptors, are close enough for two JAKs to carry out a process of transphosphorylation, which can continue signaling by signal transducer and activators of transcription (STATs) [9, 10]. The seven STATs available in mammals have a tyrosine residue near their C-terminus, which are phosphorylated by JAKs, and this phosphorylated STAT then migrates towards the cell nucleus to regulate (by activation or suppression) gene transcription [11]. Suppressors of cytokine signaling (SOCS) are a class of suppressors of the pathway, providing a negative feedback, as they come from the activated transcription of STATs. SOCS binds to phosphorylated JAKs by deactivating the pathway by physically blocking (preventing STAT binding) and binding to receptors on JAKs specifically [10].

The participation of the JAK/STAT pathway in oral tissues has been investigated under different specific contexts so far. Recently, some authors have demonstrated that JAK2/STAT3 is activated in periodontal ligament fibroblasts during orthodontic tooth movement [12]. In addition, others have revealed that SOCS1 and SOCS3 play pivotal roles in the inflammatory process following periodontal disease [13]. Literature on the roles of the JAK/STAT pathway in odontogenesis is scarce. STAT has been reported to be expressed in cells directly involved in the formation of dentin and enamel in the molars of 5-day old rats [14], and JAK 1-3 and STAT 1 have been detected in secretory ameloblasts and have been shown to participate in amelogenesis [15]. In contrast, they were detected only in murine odontoblasts [15]. However, there are no studies on the role of the JAK/STAT pathway in odontogenesis together with the factors related to different FAs from diets.

Thus, the purpose of this study was to evaluate the proinflammatory state from the JAK/STAT pathway of the tooth germ of the fetuses from dams treated with normolipidic diets, based on different types of FAs during pregnancy.

Materials and Methods

Animals and Experimental Design

All procedures were carried out according to the International Standards for Research involving Animals. A total of 13 2-month-old virgin Wistar female rats were obtained from the Centro de Desenvolvimento de Modelos Experimentais para Biologia e Medicina, the Federal University of Sao Paulo. The rats were kept under light-cycle conditions (12 h light and 12 h dark) at 24°C ± 1°C with food and water ad libitum. This study was approved by the Animal Ethics Committee under Protocol # 8298100720.

The rats were mated when they were 3 months old. The following day, the presence of spermatozoa in the vaginal lumen was verified with the aid of a microscope. For this, a small amount of saline solution (0.9%) was introduced into the vagina and aspirated using a dropper. Once probable conception was confirmed (1st day of pregnancy), the females were kept in individual plastic cages and distributed sequentially into four different groups, receiving one of the four experimental diets during pregnancy. The groups were control group (C) – diet containing soybean oil as a source of fat (n = 4); SFA group (S) – diet containing lard as a source of fat (n = 3); TFA group (T) – diet containing hydrogenated vegetable fat as a source of fat (n = 3); and PUFA group (n-3 PUFA) – diet containing fish oil as a source of fat (n = 3). The composition of the diets followed the recommendations of the American Institute of Nutrition (AIN-93) [16]. Pregnant rats received a diet containing 20% protein (AIN-93 G) throughout gestation. Regarding lipids, the diets were normolipidic and normocaloric, with similar lipid and energy content. The source of lipids was soybean oil in the control diet (C), lard rich in SFA in the SFA diet (S).

Hydrogenated vegetable fat rich in TFA in the TFA diet (T) and fish oil rich in n-3 PUFA in the diet AG polyunsaturated PUFA (n-3 PUFA). The addition of 10 g of soybean oil to every 1 kg of diet, except for diet C, was made to meet the minimum requirement of essential FAs. The experimental design was established in previous studies conducted by our group [17, 18].

On the 20th day of pregnancy (of a total of 21–22 days), the pregnant rats were submitted to euthanasia to obtain the fetuses. A total of 24 specimens were collected, six fetuses (n = 6) (regardless of sex) from each group. The body weight and food intake were recorded weekly from all animals.

Histological Analysis

At the end of the established experimental period, pregnant rats were anesthetized with isoflurane (Isoflurane®; BioChimico Ltda, Itatiaia, RJ, Brazil) inhalation and euthanized by decapitation after 4 h of fasting. Fetuses were collected via caesarean section and euthanized by decapitation. The jaws of the fetuses were collected for histological analysis. The following parameters were evaluated: the shape of dental germs, evaluation of cell nuclei, the presence of inflammatory infiltrate, and atypical cells. Such changes were comparatively evaluated in relation to animals belonging to the control group.

Immunohistochemical Analysis

Serial 3-μm sections were deparaffinized in xylene, rehydrated in ethanol (99.5%), and pretreated with citric acid buffer (10 nM, pH 6, 0.1M citric acid, Synth®, São Paulo, Brazil; 0.1 M sodium citrate, Synth®, São Paulo, Brazil), in microwave, for three cycles of 5 min each for antigenic recovery. Primary antibodies (Santa Cruz Biotechnology, Inc.®, USA) were used as follows: IL-6 at a dilution of 1:150; JAK2 in the ratio 1:200; STAT3 diluted 1:100; p-STAT3 at 1:200; and SOCS3 at 1:200 were deposited on slides and incubated overnight at 4°C. The specimens were then washed twice with PBS and incubated with the biotinylated secondary antibody for 30 min (Starr Trek Universal HRP Detection Kit, Biocare Medical®), washed with PBS, incubated with streptoavidin, conjugated with hydrogen peroxide for 30 min, and then stained with DAB (3,3-diaminobenzidine, 0.05%-DAKO North America Inc.®, California, USA). Counter-staining was performed with Harris hematoxylin (Sigma®, Missouri, USA). 1,000 cells were evaluated at ×400 magnification by a systematic randomization system, according to the scores, following the guidelines of Galvani et al. [19].

Statistical Analysis

Results were expressed as mean ± standard deviation values. The Kruskal-Wallis test was used, followed by Dunn's test of multiple comparisons, when necessary. Statistical calculations were performed using the GraphPad Prism program, version 5.0, and a significance level of 5% ($p < 0.05$) was adopted.

Results

Clinical Parameters

All rats received food ad libitum throughout pregnancy, and individual consumption was assessed weekly. In this study, no statistically significant differences ($p > 0.05$) were noticed in the maternal body weight, body weight gain, and food intake during the pregnancy period for all groups. The results are presented in Table 1.

Histopathological Analysis

All animals in the control group had tooth germs in the bell stage. In the bell stage (Fig. 1) of this control group, the internal epithelium already differentiating into preameloblasts can be visualized. Still, at this moment, a fourth layer of cells is observed, located between the internal epithelium and the stellate reticulum, called the intermediate extract, and at the junction of the internal and external epithelium, called the cervical loop. The shape of the future tooth is determined by the basement membrane (which separates the preameloblastic cells from the cells of the dental papilla), determining the occlusal (Fig. 1a, b, c) or incisor (Fig. 1d) dental pattern. The tooth germs of all experimental groups (Fig. 1b, c, d) could be morphologically compared to the control group (Fig. 1a) and showed no variation between them in all the structures evaluated. Thus, all groups were morphologically classified as normal, regardless of the diet that was offered during pregnancy.

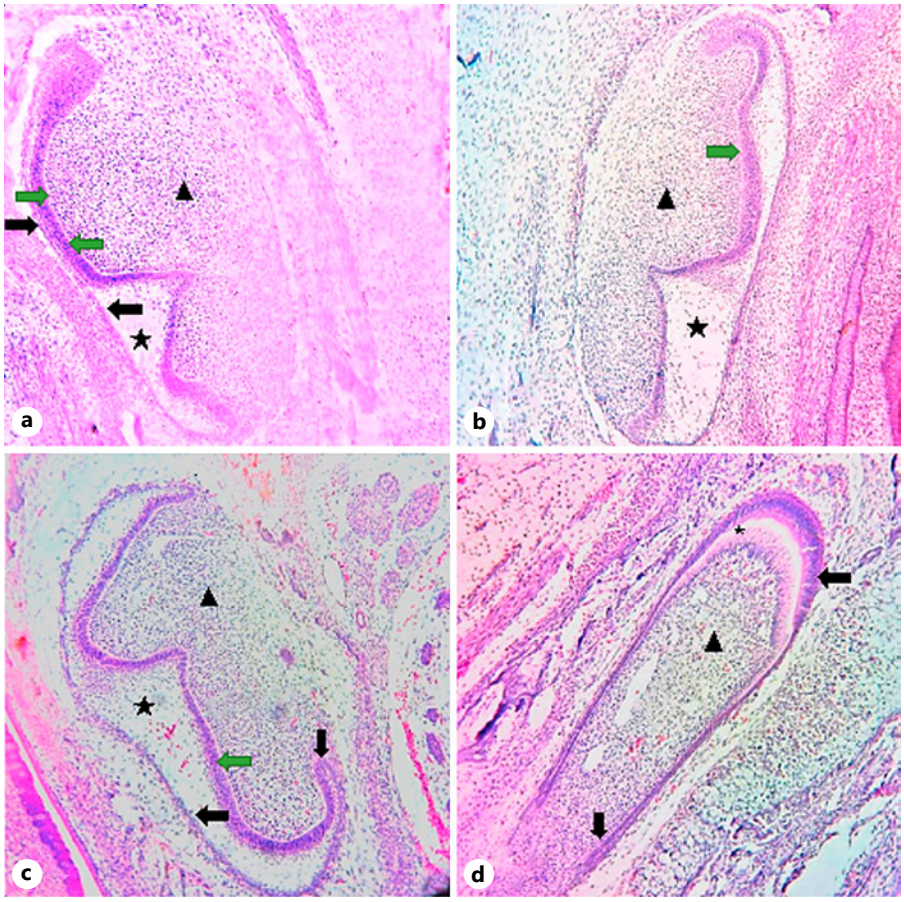

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Fig. 1. Photomicrographs of rat tooth germs stained to H.E. All tooth germs are in bell stage. **a** Control group. **b** SFA group. **c** TFA group. **d** PUFA group. Arrowhead: dental papila; green arrow: inner epithelium; black arrow: outer epithelium; asterisk: stellate reticulum. ×40 magnification.

Table 1. Body weight, weight gain, and food intake of rats during pregnancy

	C	S	T	PUFA
Body weight, g				
Initial (G0)	259.51±20.31	272.67±13.89	268.09±7.20	242.18±4.00
First week (G7)	305.64±18.02	308.20±15.71	308.24±7.99	276.20±3.27
Second week (G14)	343.65±16.14	344.55±17.30	349.66±6.01	314.65±7.31
Third week (G20)	393.77±19.86	387.16±22.51	390.57±14.12	370.52±7.57
Body weight gain, g				
First week (G7)	46.13±5.30	35.53±6.23	40.15±1.27	34.02±7.26
Second week (G14)	38.01±3.41	36.35±8.74	41.42±4.28	38.45±4.43
Third week (G20)	50.12±4.93	42.62±7.12	40.91±9.09	55.87±0.86
Food intake, g				
First week (G7)	276.65±17.62	266.16±30.09	272.05±23.25	253.73±1.28
Second week (G14)	276.44±15.63	271.36±30.00	282.78±15.57	232.08±11.65
Third week (G20)	226.39±14.97	230.99±21.16	227.63±15.36	198.91±13.05

$p > 0.05$. C, control group; S, saturated fatty acid group; T, trans-fatty acid group; PUFA, polyunsaturated fatty acids group.

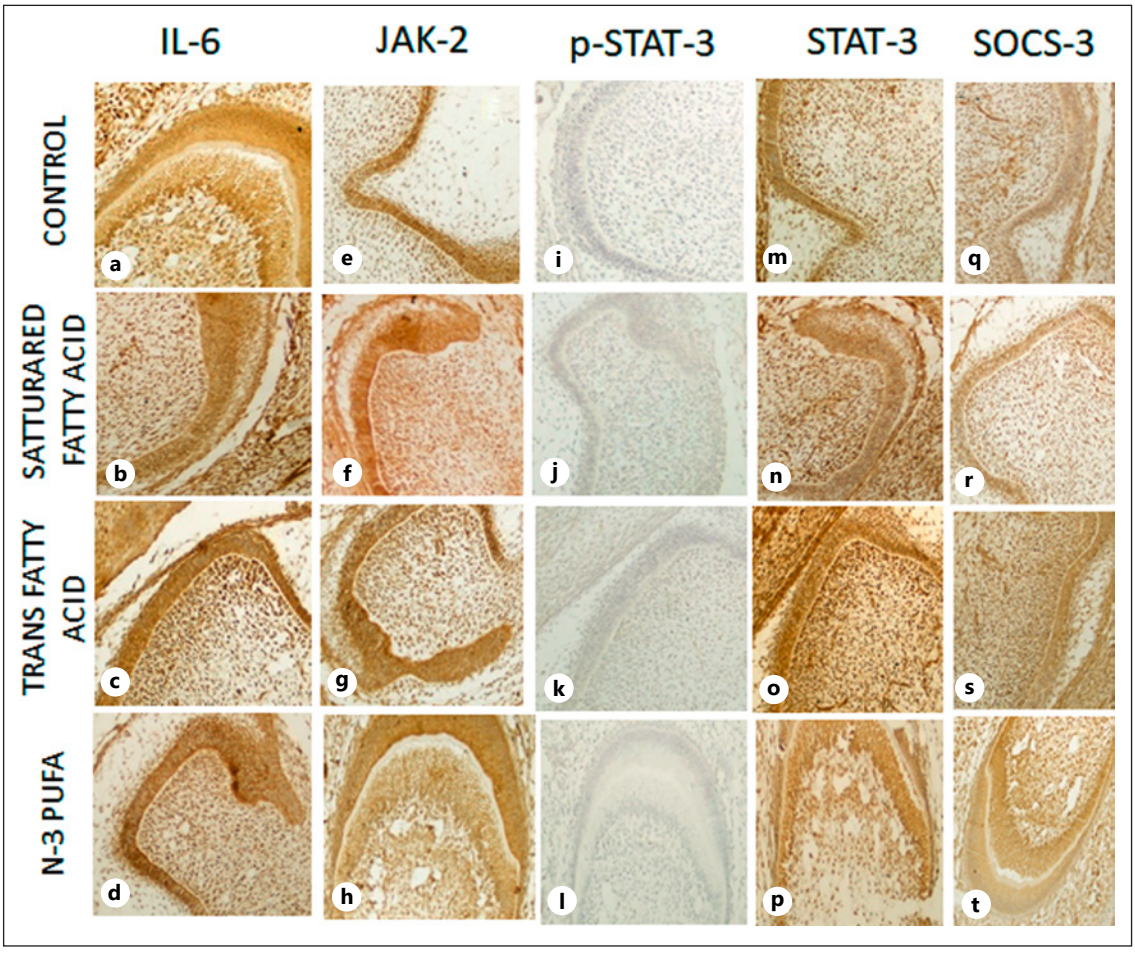

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Fig. 2. Immunohistochemistry for IL-6 (**a–d**), JAK2 (**e–h**), p-STAT3 (**i–l**), STAT3 (**m–p**), and SOCS3 (**q–t**) in rat tooth germs exposed to different types of FAs during pregnancy. ×40 magnification.

Immunohistochemistry

Immunohistochemistry was performed to detect IL-6, JAK2, STAT3, P-STAT3, and SOCS3. The C group showed a strong expression of the proinflammatory cytokine IL-6 throughout the observed tissue (Fig. 2a–d), being categorized mostly as score 3 (Table 2). The experimental groups had results that can be compared to the control group and showed no statistical difference in relation to the control group ($p > 0.05$). The C group showed a strong expression of JAK2 in all the observed tissues (Fig. 2e–h), being categorized mostly as score 3 (Table 1). The experimental groups S and n-3 PUFA showed no statistical relevance when compared to group C. Group T showed reduction in the expression of JAK2 ($p < 0.05$) when compared to the n-3 PUFA group. P-STAT3 was not detected in the tissues of the C group (Fig. 2i–l), being categorized mostly as score 0 (Table 2). The experimental groups showed results similar to the C group with no statistically significant differences ($p > 0.05$). The C group showed a strong expression of STAT3 throughout the observed tissue (Fig. 2m–p), being categorized mostly as score 3 (Table 2). All experimental groups had similar results when compared to the control group ($p > 0.05$). The C group obtained a score of 3 in all tissues observed in terms of expression of SOCS3 (Fig. 2q–t) (Table 2). All experimental groups had results similar to those in the control group with no statistical difference in all analyses performed ($p > 0.05$).

Discussion

Murine dental development is similar to dental development in humans and may involve several changes during this process. Odontogenesis is characterized by the

Table 2. Immunohistochemistry for IL-6, JAK2, p-STAT3, STAT3, and SOCS3 in rat tooth germs exposed to different types of FAs during pregnancy

Groups	*N*	0	1	2	3
IL-6					
C	6	0	1	0	5
S	6	0	0	2	4
T	6	0	0	0	6
PUFA	6	0	0	1	5
JAK2					
C	6	0	0	1	5
S	6	0	0	1	5
T*	6	0	1	2	3
PUFA	6	0	0	0	6
p-STAT3					
C	6	6	0	0	0
S	6	5	1	0	0
T	6	6	0	0	0
PUFA	6	6	0	0	0
STAT3					
C	6	0	0	1	5
S	6	0	0	1	5
T	6	0	0	2	4
PUFA	6	0	0	0	6
SOCS3					
C	6	0	0	1	5
S	6	0	0	0	6
T	6	0	0	1	5
PUFA	6	0	0	1	5

Results are expressed as scores. C, control group; S, saturated fatty acid group; T, trans-fatty acid group; n-3 PUFA, n-3 PUFA group. * $p < 0.05$ when compared to the PUFA group.

following stages: dental lamina, button, cap, bell, crown, and rizinogenesis phases [20]. The harmful effects of maternal consumption of SFAs and TFAs, especially when consumed during pregnancy and/or lactation, are already known [17, 18]. Previous studies have shown that the increased consumption of SFAs can lead to an increase in the levels of glucose, insulin, leptin, TNF-α, MCP-1, IL-6, NF-κB, and activation of TLR4 [21]. Increased production of TNF-α in the vascular endothelium implies an increased risk of cardiovascular diseases and the inflammatory process can compromise the skeletal muscle and the liver [22]. TFAs can also cause an increase in inflammatory cytokines [23]. Additionally, higher levels of TNF-α were shown to be associated with newborns of women with preeclampsia [24]. TFAs can also inhibit Δ5- and Δ6-desaturase enzymes which are responsible for the biosynthesis of essential FAs [4]. TFAs can interfere with the passage of essential FAs through the placenta and through breast milk [7]. On the other hand, PUFAs can cause both an increase in omega-6 intake and a reduction in the inflammatory condition associated with omega-3 intake. The association of omega-3 in the diet of pregnant women, for example, reduces the activation of TLR4 as well as the production of IL-6 and IL-8 by adipose and placental cells [25].

In view of the information mentioned above, our microscopic analysis showed that the fetuses exposed to TFAs, SFAs, or n-3 PUFAs during pregnancy did not show changes in odontogenesis when compared to the fetuses in the control group. We did not detect any changes in the shape of the enamel organ, the presence of degenerations or cells with atypia. Given the absence of similar studies for possible comparisons, it can be concluded that TFAs, SFAs, and n-3 PUFAs in normolipidic maternal diets were not able to trigger any morphological changes in the tooth germs of murine fetuses. Therefore, despite the high inflammatory potential of this food and its direct relationship to the health of the fetus, it can be said that the tooth structure was not affected in the experimental conditions reported here.

It is known that a diet with high lipid consumption causes changes in the intestinal immune response from the impairment of the JAK/STAT pathway, which is involved in the differentiation of T and B cells. This pathway can also be compromised by maternal obesity [26]. In the study performed by Eid et al. [27], it was demonstrated that the high level of IL-6 would be directly related to the increase in JAK2 and STAT3. In fact, maternal obesity results in weight gain in offspring, hyperleptinemia, impairment of the JAK/STAT pathway, and reduced expression of the leptin receptor ORBb [28]. We studied the markers for JAK2, STAT3, p-STAT3, SOCS3, and IL-6 to elucidate the biological behavior of the JAK/STAT pathway against odontogenesis under the action of different types of FAs in a normolipidic diet. Our results show that there was activation of the JAK/STAT pathway in the control group detected by the strong presence of JAK2, STAT3, SOCS3, and IL-6. These results agree with previous studies demonstrating that STAT is expressed in cells directly involved in the formation of dentin and enamel in rat molars [14]. Of particular importance is the expression of JAK 1-3 and STAT 1, as these proteins actively participate in amelogenesis [15]. In contrast, our results are pioneering in demonstrating that maternal consumption of TFAs, SFAs, or n-3 PUFAs in normolipidic diets is not able to alter the expression of JAK2 and STAT3 in the fetuses. Thus, it seems appropriate to conclude that such normocaloric/normolipidic diets do not

alter the expression of some proteins belonging to the JAK/STAT pathway. Considering the absence of phosphorylated STAT in all groups and treatments tested in this study, we affirm that the pathway would no longer be active at the end of tooth development. To support this assumption, there was negative feedback marked by SOCS3 in all groups studied without distinction. Therefore, it can be assumed that the observed inflammatory picture is physiological in nature. There was a statistically significant difference in the T group when compared with the PUFA group, where the T group exhibited a reduction in JAK2 expression. This is a novel finding; we suggest that the isolated reduction of JAK2 may demonstrate a deficiency in cell development by other functions of the JAK/STAT pathway of dental tissue. However, further studies are needed to clarify this further.

Some studies have shown that soybean oil can favor the n-6 FAs cascade, to the detriment of the n-3 derivatives, also generating harmful conditions in different segments of the organism [29]. In this context, it would be interesting to investigate whether, and to what extent, the adoption of the same proportion of n-6 and n-3 FA, but not n-6 FA only in the control group will impact on the results found.

Conclusions

The immunohistochemistry data from JAK2, STAT3, p-STAT3, SOCS3, and IL-6 did not show changes in the inflammatory condition of the fetuses from dams fed normolipidic diets based on different types of FAs during pregnancy. To the best of our knowledge, little information is available within the field. In particular, the role of the JAK/STAT signaling pathway during tooth development associated with continuous exposure to different FAs should be further examined. It appears that FAs and TFAs do not exert harmful outcomes in odontogenesis.

Statement of Ethics

The study was approved by the Ethics Committee on the Use of Animals of the Federal University of Sao Paulo (UNIFESP), No. 8298100720.

Conflict of Interest Statement

All authors declare that there is no conflict of interest.

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Author Contributions

Study design and data search: Isabella Bortoloto Lebeis, Daniel Vitor de Souza, and Lais Vales Mennitti. Data analysis and writing the paper: Isabella Bortoloto Lebeis, Daniel Vitor de Souza, Lais Vales Mennitti, Luciana Pellegrini Pisani, Carla Maximo Prado, and Daniel Araki Ribeiro.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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