Review Article

Application of dietary fish oil in dairy cow reproduction

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Abstract: Feed fats are commonly used as a component of high-yielding cow diet rations. Many studies have been conducted on the effects of fat supplementation on metabolism, milk composition, and improvements in dairy cow reproduction. The positive effects on fat (vegetable oil) and energy supplementation on improvements in reproduction are well documented. Consumption of polyunsaturated fatty acids (PUFAs), including n-3 acids, in appropriate feed doses improves fertility of dairy cows. A fat source with high levels of acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is marine oil, especially fish and algae. By modification of cow rations, EPA and DHA can be utilized to reduce synthesis of $PGF_{2\alpha}$ in the endometrium, which can prevent luteolysis of the corpus luteum during early pregnancy. The PUFAs also may have a direct impact on key genes and their proteins that regulate biochemical processes and pathways between the corpus luteum, the uterus, and the embryo. The effect of n-3 fatty acids on the survival of embryos is not yet clearly defined.

Key words: Dairy cows, reproductive, fatty acid, fish oil, prostaglandins

1. Introduction

Fats are used commonly as a component of feed for high-performance dairy cows due to the difficulties involved in satisfying their energy needs, especially in the first period of lactation (about 100 days after parturition). Dairy cow diets are supplemented with fat primarily to increase the energy density of the diet and thus to enhance milk production, growth, and reproduction (1). The increase in dry matter intake in early lactation is gradual, while a rapid increase in milk production occurs after calving. This affects high-yield cow energy status by causing a period of negative energy balance (NEB). Energy deficiency leads to increased lipolysis and release of free fatty acids (FFAs) into the blood. Excess FFA concentrations in the blood cause accumulation of triglycerides in the liver and significant increase in production of ketone bodies (2,3). In early lactation, NEB of dairy cows delays the start of normal ovarian activity. Energy deficit also disrupts hormone status, mainly by reducing secretion of luteinizing hormone, thus contributing to abnormal development of ovarian follicles (3). Additionally, the number of estrous cycles are reduced, estrus symptoms are poorly manifested, the quality of oocytes falls, and embryo mortality increases. These factors lower the efficiency of artificial insemination and successful reproduction rates (4).

Furthermore, fat influences metabolic changes and reproductive functions depending on the amount, type, physical form, and profile of the fatty acids in the ration. When fat is fed at the beginning of lactation, it can satisfy to some extent the energy needs associated with the synthesis of milk rather than fat reserves. The influence of unprotected fat can be unfavorable because of decreasing number of cellulolytic bacteria and protozoa. Moreover, the adhesion between microorganism and feed in the rumen is disrupted. The negative effect of fat on ruminal fermentation can be reduced by its 'protection'. On the one hand, this concerns the protection of the environment of the rumen, and on the other it refers to fat security before hydrogenation. The protected fat can be obtained by various methods such as encapsulation and calcium salt formation of fatty acids (5,6), although Ca salts will be affected by a number of factors including ruminal pH and degree of unsaturation and chain length of the fatty acid.

Vegetable oils contain a number of monounsaturated fatty acids and polyunsaturated fatty acids (PUFAs) (e.g., oleic, linoleic, linolenic). Palm oil contains about 35% palmitic acid C16:0 (saturated acid). Extruded oil seeds are subjected to only partial protection. Fish oil contains many long-chain PUFAs, including eicosapentaenoic acid (EPA) C20:5 n-3 and docosahexaenoic acid (DHA) C22:6 n-3 (7–10). Likewise, marine algae seaweeds contain high levels of PUFAs, especially DHA (11). Research shows that better quality oocytes are found in cows treated with higher (800 g/day) levels of protected fat (calcium salts) in the ration as

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compared to lower amounts (200 g/day) (12). By using fats rich in unsaturated fatty acids (43.2% C18:1 trans), a higher percentage of fertilization and embryo development (more blastomeres) can be achieved in contrast to cows receiving palm oil (8). Introduction of PUFAs (EPA and DHA) into cow diets may significantly reduce synthesis of $PGF_{2\alpha}$ in the endometrium during early pregnancy (13,14). These PUFAs may have a direct impact on key genes and proteins that regulate biochemical processes and affect survival of embryos (15). Free arachidonic acid (AA), or other PUFAs, generated is then metabolized by prostaglandin endoperoxide synthase (PTGS) enzymes, of which PTGS1 and PTGS2 are the most relevant to reproductive biology (14). Although EPA is a substrate for both PTGS1 and PTGS2, its metabolism via PTGS1 is poor (about 10% that of AA), which means that its ability to generate 3-series PGs is also poor (16). Not only is EPA an inhibitor of PTGS1 activity and 2-series PG generation, but it also does not induce a concomitant increase in 3-series PG generation via PTGS1.

2. Reproduction problems and importance of PUFAs in feeding

Reproductive disorders are a serious problem in all countries with high-performance dairy cows. Heat stress is major factor that lowers effectiveness of artificial insemination, causing irregularities in estrus. One reproductive failure is mortality of embryos during the preimplantation period, which may be as high as about 30% in the first month after insemination (17).

Many metabolic and endocrine signals involved in reproductive processes are regulated by nutritional status. Maintaining a high level of progesterone in the blood (the active corpus luteum) is a condition of pregnancy in the preimplantation period. Many studies have highlighted the importance of 2-series prostaglandins, in particular $PGF_{2\alpha}$. Embryonic trophoblast secretes interferon-tau (IFN-t) between 14 and 18 days after fertilization in order to reduce the release of $PGF_{2\alpha}$ from the endometrium (18,19). If the embryo cannot inhibit the synthesis of $PGF_{2\alpha}$, luteolysis and termination of pregnancy occur. The antiluteolytic properties of IFN-t rely on inhibition of expression of oxytocin receptors and the reduced expression of cyclooxygenase (COX-2), which is responsible for the secretion of prostaglandins (20). The result of this interaction is a change in the secretion profile by endometrial prostaglandin $PGF_{2\alpha}$ in favor of PGE2, which is an inhibitor of luteolysis. If the fertilized egg cannot control synthesis of $PGF_{2\alpha}$, luteolysis of the corpus luteum and abortion occur. Under the influence of IFN-t in early pregnancy, the concentration of AA in the endometrium decreases.

One mechanism to affect development and maintenance of pregnancy could be increased concentrations of PUFAs. By modification of the feed of cows, EPA and DHA can be used to reduce synthesis of $PGF_{2\alpha}$ in the endometrium during early pregnancy (21). These acids can inhibit synthesis of $PGF_{2\alpha}$ by reducing the availability of AA, a precursor of prostaglandins, and by increased competition with AA binding to specific prostaglandin synthase (15,22–24). During biosynthesis, linoleic acid (C18: 2n-6) is converted to AA (C20: 4n-6), a precursor of type-2 prostaglandins. Similarly, in the enzymatic processes of elongation and desaturation of n-3, fatty acids (α-linolenic acid, C18: 3n-3) are converted to EPA (C20: 5n-3), a precursor of prostaglandin series-3 (Figure 1). Competition between acids of n-3 and n-6, which are precursors of prostaglandin synthesis of different pathways, is possible. Thus, a change in lipid metabolism may affect synthesis of prostaglandins.

3. Effect of fish oil on cow reproduction

Feed fat can influence successful reproductive outcomes in 2 processes: 1) fatty acids are the precursors of the synthesis of steroid hormones (via cholesterol carried by LDL); and 2) fatty acids are the precursors of the synthesis of prostaglandins (AA) (10). A positive effect of fat addition to the feed ration (from Ca salts of fish oil fatty acids) may also arise from an increase in glucose and insulin in plasma (13), which can stimulate growth of ovarian follicles. Zachut et al. (10) observed that large amounts of dietary n-3 fatty acid (providing 242.2 g of C18:3 n-3) effectively pass to the blood, affecting the activity of the ovaries and increasing the cleavage rate of fertilized oocytes. Selective uptake of fatty acids by the oocytes shows sensitivity to changes in the membrane composition. This may lead to changes in membrane properties, such as, for example, changes in the viscosity and membrane performance characteristics (12,26,27).

It is claimed that the use of fats rich in unsaturated fatty acids would result in more effective insemination and embryo development (more blastomeres) in comparison to cows receiving palm oil (8). Similarly, a beneficial effect on folliculogenesis can be implemented by feeding cows encapsulated linseed oil, 3.8% dry matter, and 40.8% flaxseed oil (10). These studies claimed to demonstrate a larger number of follicles and more and larger oocytes. Evans et al. (28) and Mossa et al. (29) confirmed that application of n-3 fatty acids causes an increase in folliculogenesis by increasing the number and size of oocytes during the estrous cycle, which positively affects the performance of dairy cattle fertility. The presence of n-3 fatty acids in the diet causes a change in the fatty acid profile in the cumulus–oocyte complexes (COCs), in a similar manner as in the follicular fluid and granulosa cells (27). The diet used in these studies contained flaxseed oil and fish oil. These studies indicate the existence of selective
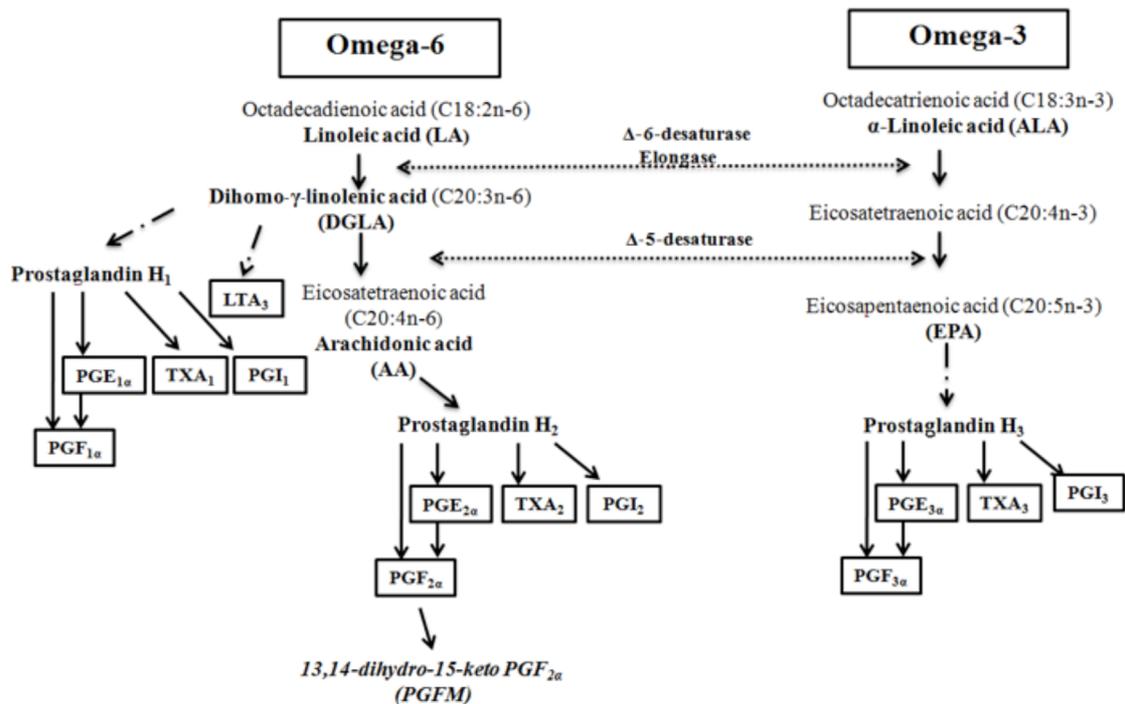
Figure 1. Effect of polyunsaturated fatty acids in the feed on prostaglandin synthesis pathways [authors' modification of work by Wathes et al. and Mattos et al. (14,25)].

uptake of various fatty acids of n-3 by COCs, which favors the penetration of the longer n-3 fatty acid into the oocyte rather than a shorter chain, such as ALA.

In vitro, EPA and DHA inhibited $PGF_{2\alpha}$ secretion in cultured endometrial cells (BEND) (30). The effect of linoleic acid (n-6) was considerably lower than that of EPA and DHA in inhibiting secretion of $PGF_{2\alpha}$ (Figure 2). These findings suggest that the effects of EPA on secretion of $PGF_{2\alpha}$ are mediated by mechanisms that involve competition of precursors for processing by PG endoperoxide H synthase enzymes and regulation of enzyme activity. Reduction of $PGF_{2\alpha}$ secretion in response to stimulation with phorbol 12,13-dibutyrate was caused by dose-dependent concentrations of the n-3 PUFAs. However, feeding of n-3 fatty acids to heifers did not affect expression of genes in the endometrium encoding the oxytocin receptor, phospholipase C, cyclooxygenase-1 (COX-1), COX-2, or PGE-9-reductase (31). The expression of genes that are responsible for synthesis of prostaglandins in the endometrium may depend on supplementation with an oral dose of PUFA n-3. In in vitro cultures, n-3 inhibition of biosynthesis of $PGF_{2\alpha}$ also depends on the n-6:n-3 fatty acid ratio, and the introduction of EPA and DHA into the cell culture reduced the production of $PGF_{2\alpha}$ (32). Conjugated linoleic acids (mixture isomers; CLAs) also inhibited synthesis of $PGF_{2\alpha}$ in the uterus independent of the concentration of linoleic acid or the n-6:n-3 ratio (33).

PUFAs affect many factors related to the synthesis and metabolism of essential reproductive hormones such as progesterone (P4) and estradiol (E2). According to Walsh et al. (34), an important role is played by P4. The test cows exhibited both delayed increase in plasma concentrations of P4 after ovulation and lower plasma concentrations of P4 in the luteal phase. In addition, low levels of interferon t on the 16th day after insemination provided the latest development of the embryo. The use of food supplements containing fish oil during the estrous cycle increased the synthesis of P4. The increase in plasma P4 during the estrous cycle can vary endometrial secretion to stimulate the development of the embryo, which leads to an enhanced ability of the embryo in signaling its presence in the uterus (4).

Inhibition of prostaglandin production by n-3 fatty acids prevents regression of the corpus luteum after prolonged release of P4 (24). After application of fish meal or fish oil in the nutrition of cows, DHA and EPA concentrations in the lipids of the uterus increased together with a reduction of $PGF_{2\alpha}$ in the endometrium (22,23). Mattos et al. (35) found that administration of fish meal to lactating cows reduced secretion of $PGF_{2\alpha}$, while Wamsley et al. (36) observed that supplementation did not affect secretion of $PGF_{2\alpha}$ in heifers that had normal concentrations of P4. With reduced concentrations of P4, heifers responded with a downward trend in concentration of $PGF_{2\alpha}$. Heravi
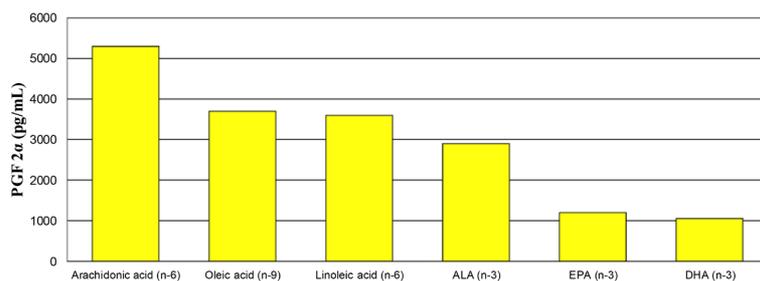
Figure 2. $PGF_{2\alpha}$-induced secretion in cultured endometrial cells (BEND) (29).

Moussavi et al. (37) also concluded that supplementation with fish meal (from 1% to 5% DM) and protected fish oil resulted in a significant increase in the concentration of n-3 acids (EPA, DHA) in the endometrium, but there was no effect on synthesis of COX-2 or $PGF_{2\alpha}$ in the endometrium. Childs et al. (15) confirmed that the use of protected fish oil caused a significant increase in the content of EPA and DHA in the endometrium (Table 1). There was a positive correlation between the content of EPA ($R^2 = 0.86$, P < 0.0001) and the total amount of n-3 PUFA ($R^2 = 0.77$, P < 0.0001) in the blood and the endometrium. However, fish oil did not affect secretion of $PGF_{2\alpha}$. In turn, Silvestre et al. (38) showed that pregnancy by artificial insemination increased at 30 and 60 days after the second insemination in cows fed fish oil and palm oil. Fertilization in cows fed fish oil was associated with reduced production of TNFα when neutrophil lipopolysaccharide was stimulated during the whole period of insemination (38).

In our study (39), carried out according to the methodology proposed by Mattos et al. (22) and Heravi Moussavi et al. (13), we evaluated the effect of long-term use of protected fish oil and algae on secretion of 13,14-dihydro-15-keto $PGF_{2\alpha}$ (PGFM). The procedure was used to assess the impact of supplementation of EPA and DHA in reducing the secretion of $PGF_{2\alpha}$ in the endometrium. Findings indicated no statistical difference between the groups after i.v. administration of oxytocin, and the dynamics of PGFM concentration were similar in

each group (Table 2). It was reported that a small increase in the concentration of PGFM was observed 30 min after administration of oxytocin in all groups receiving increased PUFA.

There have also been investigations as to whether the ability to synthesize IFN-t depends on the size of the CL (40), whereby insufficient CL size cannot corroborate the theory for the synthesis of the $PGF_{2\alpha}$, consequently leading to luteolysis. Increases in the amount of protected fish oil led to a CL increase at day 7 of the synchronized estrus cycle (control: 17.5 mm; high content of fish oil: 24.1 mm), with no effect on the diameter of CL on days 17 and 18 (15). Our study showed significant differences in the size of dominant follicles in the ovaries at 60 days postpartum after application of protected salmon fish oil (control: 12.10 ± 3.83 mm; salmon fish oil: 15.57 ± 3.69 mm (39).

Cholesterol is responsible for synthesis of steroid hormones, in particular P4 and E2. The high content of n-3 in the diet is associated with low levels of serum cholesterol, which may reduce synthesis of P4 (41). In previous studies, cholesterol concentration after application of protected fish oil increased in the blood serum of cows at peak lactation (9).

Unsaturated fatty acids have an influence on the expression of genes involved in various metabolic processes (42). Peroxisome proliferator-activated receptors (PPARα, PPARγ, and PPARδ) are a family of nuclear receptors that

Table 1. Fatty acid content in the endometrium (mg/g) using different amounts of protected fish oil [modified from Childs et al. (15)].

Fatty acid	Control	Low content (1.04% DM)	High content (4.15% DM)
AA (C20:4 n-6)	0.29[a]	0.22[ab]	0.17[b]
EPA (C20:5 n-3)	0.03[a]	0.10[b]	0.18[c]
DHA (C22:6 n-3)	0.11[a]	0.27[b]	0.33[b]
n-6/n-3	3.63[a]	1.80[b]	1.06[c]

a, b, c: Within rows, concentrations with different letters are significantly different (P < 0.05).

Table 2. Dynamics of 13,14-dihydro-15-keto $PGF_{2\alpha}$ (pg/mL) content changes after oxytocin injection [authors' modification of the work of Kupczyński (39)].

Item		Time after administration of oxytocin (min)				
		0	30	60	120	150
Fish oil	x	362.33[A]	882.89[B]	802.11[B]	613.34[C]	549.77[D]
	SD	217.41	266.04	305.83	302.19	201.28
Marine algae	x	356.38[A]	744.80[B]	761.03[B]	618.73[C]	396.43[D]
	SD	230.87	271.19	395.92	274.64	280.49
Control	x	361.35[A]	948.99[B]	725.01[B]	562.64[C]	538.33[D]
	SD	203.88	216.35	380.66	247.09	290.52

A, B, C, D: Significance of differences between blood donation appointments in different groups at $P < 0.01$.

are activated by binding to natural ligands, such as PUFAs (43). Adjustment of the liver fatty acid transcription gene is controlled by transcription factors PPARγ and SREBF1. Transcription factors regulate the activity of many genes involved in fatty acid transport (SLC27A1 and FABP1), synthesis of triacylglycerols (DGAT1), and fatty acid oxidation (CPT1, ACOX1, and ASCL1) (44). In Hutchinson et al.'s studies (1), expressions of the genes ASCL1, FABP1, and SREBF1 were reduced in the case of cows supplemented with fish oil as compared to other dietary strategies involving the use of flax seed and using synthetic isomers of CLA. Differences in the fatty acid composition of the original fish oil supplementation may be the cause for the differences in hepatic gene expression. Unlike the other additives used, which contained fatty acids of C18 or fewer carbon chains, fish oil contains a considerable number of very-long-chain PUFAs, EPA, and DHA. Deckelbaum et al. (45) found that EPA, DHA, and AA have more inhibitory effects on the expression of SREBF1 than shorter-chain PUFAs. This hepatic inhibitory effect results in a reduced expression of FABP1 and ACSL1 genes, as well as SREBF1, which is the principal modulator of these genes. Recent research has focused on

determination of the effect of fish oil and marine algae on mRNA abundance of genes encoding proteins required for FA uptake, de novo FA synthesis, desaturation, and transcriptional regulation of lipid synthesis in mammary and liver tissues in lactating dairy cows (46).

4. Conclusion

Supplementing dairy cow diets with fats containing PUFAs may improve reproductive functions through positive effects on the endocrine system, ovum, embryo, and synthesis of prostaglandins. Use of PUFAs in animal feed in the form of fish oil supplementation caused a visible increase in the concentration of acids of the n-3 acid in the milk and endometrium. The influence of EPA and DHA fatty acids on the synthesis of PGF_2 is not straightforward. The n-3 fatty acids are likely to improve the survival rate of embryos in cattle. Some studies indicate an antiluteolytic impact of EPA and DHA, by inhibiting secretion of $PGF_{2\alpha}$ in the uterus through the mechanisms of reducing the availability of AA precursors. Moreover, the increased supply of PUFAs during the first period of lactation can prevent NEB and increase productivity of cows. In the near future, the role of fatty acids, including n-3, will play increasingly greater importance in animal nutrition.

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