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Polyunsaturated fatty acids and risk of preterm delivery

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Abstract. – Preterm delivery (PD) is characterized both by increased neonatal morbidity and mortality and by important late pathologic sequelae. From a clinical stand-point, PD may results from a medical condition where the continuation of pregnancy could bring about a marked risk for the foetus and/or for the mother, or from an adverse event where the pregnancy is going to end spontaneously before 37 weeks of gestation.

In the past few years some epidemiological studies have shown that diet may interfere with complex multifactorial processes contributing to the preterm triggering of labour. The attention has been focused on polyunsaturated fatty acids (PUFA) such as alpha-linoleic acid, precursor of Omega-3 series, and linoleic acid, precursor Omega-6 series. Their importance in modulating Prostaglandin concentrations at different levels is already known. Moreover, it has been reported that in clinical situation, such as PD, the endogenous levels of PUFA are unbalanced, with a Omega-6 predominance.

Experimental, observational and clinical studies suggest that dietary intake of Omega-3 fatty acids is capable of significantly prolonging the duration of gestation in the range of 4-7 days; such prolongation would possibly occur through the inhibition of prostaglandins E2 and F2 alpha. In Western population dietary intake of Omega-3 appears to be marginal, and recommended assumption could be reached only by a ten-fold increase in blue fish ingestion. The recommended intake of EPA + DHA should be 1.4 g/daily with a 1:2.5 EPA:DHA.

It is therefore possible to conclude that in light of controlled clinical studies and of the actual categories of risk for preterm delivery, the dietary supplementation of Omega-3, in addition to other pharmacological measures (17α-hydroxyprogesterone caproate), could be implemented for the secondary and/or tertiary prophylaxis of preterm delivery.

Key words:
PUFA, Omega-3, Preterm delivery.

Preterm birth

Epidemiology and risk factors

Preterm birth is defined as the birth occurring before the 37th week of gestation or before 259 days from the first day of the last menstrual period. Preterm delivery (PD) is the most noteworthy pathologic condition occurring during pregnancy and one of the most significant health problems, since it is characterized both by a high neonatal morbidity and mortality and by important late pathologic sequelae. In the past 30 years the incidence of premature births has remained steady; according to world data, it has ranged from 6% to 15% of all deliveries; their specific rate depends upon the various areas of our planet and increases with the progression of the gestational age. In the United States the incidence of premature births is approximately 11%, whereas in Western Europe, where maternal protective measures have been implemented, it is around 6%; also social, racial and institutional factors account for such a remarkable difference. The risk of neonatal mortality is inversely proportional to gestational age; it persists rather high up to the 27th week, gradually decreases from the 28th to the 34th week, and then drops sharply and becomes comparable with that observed with full term births[1].

Among the various risk factors, epidemiologic research has focused the attention on socioeconomic and behavioural factors which are most often associated with preterm delivery and include nulliparity, age <20 or >35 years, black race which is apparently more affected as compared with Caucasian race, short stature, low body weight, low cultural level, repeated and close together pregnancies. In addition, a number of habits should be mentioned, such as cigarette smoking, alcohol and drug (e.g., co-

caine) abuse, poor nutritional status, stressful working conditions and low socioeconomic level; all these factors appear to be facilitating not only the preterm cessation of pregnancy, but also a series of adverse events which often lead to an unfavourable outcome of pregnancy as well as to reproductive failures, such as abortion and foetal death[2].

Etiology and clinical presentation

The etiopathogenesis of PD is currently considered as multifactorial by all the scientists, since several factors of either maternal or foetal origin, in different combinations and to a variable extent, contribute to trigger the onset of such a pathologic situation.

The balance between muscle relaxant and uterotonic factors plays an important role in the regulation of myometrium's contractile activity during the entire course of pregnancy; also the sensitivity of the pregnant myometrium towards contractile substances is physiologically suppressed during pregnancy, whereas it reaches its peak value towards muscle relaxant substances[3]. When the time of delivery is approaching, a gradual increment occurs in myometrial ability of response towards contractile substances: the changes taking place in this complex balance have evident and important clinical implications both in the premature activation of myometrial contractility and in triggering preterm delivery.

At the present time the essential stimulus triggering prematurely myometrial contractility is thought to be the activation of prostaglandin (PG) secretion by the decidua and the foetal membranes, that are the main uterotonic factors. PG action in the mechanisms of labour triggering is exerted through the different expression of PG receptors at myometrial level as well as by means of the balance among the PG synthesizing (COX-1 and COX-2) and PG degrading (PGDH) enzymes in foetal membranes, in the decidua and in the myometrium. In preterm delivery an increased expression of COX-2 takes place together with a greater PG synthesis and a reduced expression of PGDH, leading to a decreased PG metabolization and an increase in PG concentrations[3]. During the inflammatory response occurring in decidual and chorioamniotic inflammation, the numerous involved molecules are capable of stimulating local production of PGs, not only in a direct fashion but also through a macrophage action. Macrophages are present in both decidua and chorion and are thought to stimulate production of cytokines, which in turn would activate local production not only of PGs but also of interleukins and nitrogen oxide (NO)[4].

Several experiments support nitrogen oxide involvement in the induction of cervical maturation, even though the mechanism of action is still unclear. NO metabolites have been assayed *in vivo*; their presence at the level of the uterine cervix was found to increase in parallel with the progression of gestation; they were found in greater amount in pregnant women as compared with non pregnant women. In a pilot study NO cervical levels were found to be much higher in patients with threatening preterm delivery[5]. Following the administration of NO donors the following events were observed: increase in cervical production of PGs, increase in collagen degrading proteolytic enzymes, increase in pro-inflammatory cytokines, and increment in cervical apoptosis. It has been recently shown that, among NO donors, sodium nitroprusside appears to be one of the most effective, as it produces effects similar to those obtained by prostaglandin analogues[6].

From a clinical stand-point, PD may results from: (a) a medical condition in view of which the continuation of pregnancy could bring about a marked risk for the foetus and/or for the mother (such a issue shall not be dealt with in this context); (b) an adverse event in view of which the pregnancy is going to end spontaneously before 37 weeks of gestation. Such an event may take place because of the onset of a hasty labour, frequently preceded by hypercontractility episodes, or because of a premature rupture of membranes (PROM). The spreading of micro-organisms from the cervicovaginal canal to the membranes, decidua and amniotic fluid is very likely the physiopathologic mechanism involved in inducing PD in about one third of the cases. The bacteria directly or indirectly activate, through an amniochorial infection, the inflammatory cascade with conversion of arachidonic acid to prostaglandin E (PGE2) and NO through COX-1, COX-2 and NO-synthetase activation. Then PGE2 causes hypercontractility and lysis of amniochorial structures and together with NO induces a premature cervical maturation. In the remaining cases, instead, etiological factors capable of activating the above mentioned mechanism are unknown.

Polyunsaturated fatty acids and preterm delivery

Polyunsaturated fatty acids (PUFA)

Alpha-linolenic acid (18:3, n-3), precursor of fatty acids of series n-3 (Omega-3), and linoleic acid (18:2, n-6), precursor of polyunsaturated fatty acids (PUFA) of series n-6 (Omega-6), are essential fatty acids and must be introduced with the diet since man in unable of synthesizing them. Although linoleic and linolenic acids are easily found in nature, it has been also evidenced that their transformation from plain polyunsaturated fatty acids into more biologically active derivatives is poorly efficient and it may even result insufficient in several situations. Within the field of the complex sequence of the intervening reactions, this may be due to poor functioning of the enzyme delta-6-desaturase, that may lead to a temporary and determinant cessation in the synthesis of long chain polyunsaturated fatty acids[7].

Structural and functional organization of mammalian cells depends, to a large extent, on the properties of the double lipidic layer; essential fatty acids are absolutely necessary components on account of their architecture. Also physical characteristics and biological properties of cell membranes depend on fatty acids and cholesterol composition; membranes with a greater proportion of saturated fatty acids are located in firmer structures, whereas the presence of polyunsaturated fatty acids warrants a greater elasticity. Membranes containing high proportions of unsaturated fatty acids are the sites of an intense activity of signal transmission. In short, the fatty acid composition of cell membranes may affect (a) membrane's general chemicophysical properties; (b) membrane's permeability; (c) capacity of releasing arachidonic acid; (d) signals transduction; (e) other cellular and intracellular functions. As far as the role of fatty acids in some of the most important physiologic mechanisms is concerned, it is possible to state that omega-3 fatty acids show anti-inflammatory, antithrombotic, antiarrhythmic, hypolipidaemic and vasodilating properties[8]. The effects produced by fatty acids have been documented in the secondary prophylaxis of coronary artery diseases, in arterial hypertension, in type II diabetes mellitus, and in some patients with renal disease, rheumatoid arthritis, ulcerative colitis, Crohn's disease and chronic obstructive pulmonary disease (COPD). Up to the past century, man's diet has roughly shown a 1:1 ratio between omega-6 and omega-3 fatty acids, whereas at the present time such a ratio has changed to 10-25:1, thus indicating the presence of an omega-3 deficiency[9].

Another significant example of the importance of fatty acids in physiologic mechanisms is given by the docosahexaenoic acid (DHA) –DHA (22:6 n-3) belonging to the omega-3 series. DHA becomes biologically available through either alpha-linoleic acid transformation or direct alimentary intake. The relative deficiency or the unbalance in its bioavailability may produce, during certain life situations (i.e., pregnancy, foetal life, rapid growth, senescence, exposure to intense oxidizing activities), a biochemical damage, which, if unduly prolonged, may lead to clinical manifestations characterized by functional and structural impairment of the retina and the visual function[10]. During normal pregnancies, plasma DHA of pregnant women decreases progressively and considerably, with the lowest mean values recorded between the 30th and the 40th week. Low DHA levels persist for a long period after the delivery; in fact, the normalization of its level is still incomplete 6 months postpartum[11].

Population studies

In the past few years some epidemiological studies have shown the interest of the investigators to be focused on the fact that the diet, under particular circumstances, may interfere with complex multifactorial processes which contribute to the triggering of labour before the 37th week. A Danish epidemiologist observed that spontaneous deliveries in Far Oer islands occurred at a gestational age longer, on the average, than that observed in neighbouring northern populations; as a consequence, newborns' weight also was significantly heavier[12].

A subsequent analysis of the alimentary intake showed on a large Danish pregnant female population that a constant ingestion of at least 15 g/daily of fish was associated with a marked reduction in preterm deliveries (1.9%) as compared with the group on a fish-free diet (7.1%). The above mentioned amount of fish corresponds approximately to a daily intake of 0.15 g of fatty acids belonging to series 3, the so called omega-3 fatty acids[13].

On the other hand, even in selected clinical situations, endogenous levels of eicosopen-

taenoic acid (EPA) in red blood cells (RBC) of patients, who had a preterm delivery, were found to be lower as compared with controls at term; in addition, the ratio omega-3:omega-6 was found to be unbalanced, in favour of the latter fatty acids. Such an experimental study substantiates the hypothesis that in the Western population dietetic intake of omega-3 appears to be marginal and this may be important in determining the idiopathic preterm delivery[14]. The authors of such a study have also found that the levels of arachidonic acid (precursor of prostaglandin of series 2) in pregnant women that had a preterm delivery were three times as higher as those found in controls, thus evidencing that the dietetic predominance of omega-6 on omega-3 influences the quality of the composition of membrane phospholipids.

Another study has also demonstrated excessive levels of omega-6 as compared with omega-3 in women who delivered prematurely; this could favour an altered activation of prostaglandins[15].

Measures to prevent preterm delivery

Early diagnosis

Supposing that effective measures capable of preventing the phenomenon exist, they are feasible only when are apt to identify, by means of predictive devices, those categories of patients that are at high risk for preterm labour. The chances for an effective classification of the risk are rather poor, unless there is an obstetrical history of a previous preterm delivery or the presence of certain events pertaining to the ongoing pregnancy (e.g., uterine overdistention, idiopathic hypercontractility, bacterial vaginosis). In the past few years, therefore, several biophysical and biochemical predictors have been proposed, but only a few of them have been tested on large populations, in order to allow for a definitive conclusion on their effectiveness (Table I).

The ultrasound measurement of the cervical canal length has been thoroughly investigated and nowadays it is possible to state that the risk of a preterm delivery is greatly increased in the presence of a cervix measuring <25 mm in length. On the other hand, also the presence of fibronectins at cervicovaginal level in symptomatic populations appears to be an important risk factor. In particular, fibronectin positivity in clinically symptomatic women is indicative of a high risk (20%) of delivery within 7-10 days after the performance of the test; on the contrary, if the test results negative the risk drops down to less than 2%[16]. Home monitoring of uterine activity has been also utilized in some rural populations of the United States. Although some results of such a test appear to be encouraging, its predictive significance is unsatisfactory; in addition, the test is difficult to apply.

Pharmacological prophylaxis

Ritodrine is the most frequently used tocolytic agent in clinical practice; such a drug belongs to the class of selective β_2-agonists to which also salbutamol, terbutaline and fenoterol belong. These drugs show virtually overlapping modalities of administration, efficacy and side effects. However, none of them is specific for uterine receptors; as a consequence, their ability to stimulate also other apparatuses explains the possible onset of systemic side effects, both in the mother and in the foetus. The main side effects involve the cardiovascular system: systemic hypotension induces approximately a 40-60% compensatory increase in maternal cardiac output. In addition, the increment in oxygen demand and the reduction in coronary artery perfusion may contribute to the onset of myocardial ischaemia. At any rate, the most serious complication is pulmonary oedema, which is linked to the antidiuretic effect produced by such drugs. The following events could be demonstrated in relation to the clinical efficacy of β-agonists: their intravenous administration is effective in inhibiting preterm labour for at least 48 hours, thus reducing the number of preterm newborns as well as of low weight babies, without decreasing, however, the incidence of perinatal mortality and severe respiratory complications. An improvement in perinatal outcome is observed only when the drug is administered to women at a gestational age <33 weeks. As far as prophylaxis is concerned, the effectiveness of oral therapy with beta-mimetics (e.g., ritodrine or isoxysuprine) appears uncertain, since up to date none of the studies has demonstrated their real effectiveness in delaying the onset of preterm delivery[17].

Progesterone (P) and its derivatives deserve a separate remark. During pregnancy P exerts noteworthy functions; in fact it produces various effects on implantation, suppression of uterine contractility, inhibition in the development of gap-junctions between

Table I. Biochemical and biophysical tests showing a significant predictive ability as regard to the onset of preterm deliveries.

	Predictors of preterm delivery				
	Maternal circulation	Maternal saliva	Cervico-vaginal secretions	Amniotic fluid	Cord blood
Placental hormones					
CRH	+				
hCG	+		+		
Estriol	+	+			
Foetal and membranous proteins					
AFP	+				
Fibronectin			+		
Cytokines					
IL-6	+			+	+
IL-8	+			+	
IL-2 receptor	+				
Granulocyte-colony stimulating factor	+				
TNF				+	
Local mediators			+		
ONitrogen oxide					
Physical methods					
Cervical canal length ± funneling (echography)					
Home monitoring of uterine activity					

contiguous muscle cells, comprehensive inhibitory control of cervical maturation processes, inhibition of the synthesis of oxytocin receptors, immunosuppressant role both at cervical and at decidual level. During pregnancy, progesterone is produced by the corpus luteum up to the 8th week; then the placenta starts to produce it and subsequently becomes its greater source; its circulating levels at term reach 200-250 ng/ml.

Progesterone is hardly bioavailable in the current pharmacological preparations; therefore, its derivatives, such as 17α-hydroxyprogesterone (17P), have been often utilized. The main features of 17P, with particular reference to its caproate ester in comparison with the other 17P esters, consist in a marked progestational action, a long lasting action and a lack of androgenic and estrogenic effects: These characteristics allow for a single intramuscular administration weekly to produce prolonged progestational effects.

During pregnancy, 17P is utilized in the first trimester in order to reduce the number of spontaneous abortions due to luteal phase deficit and in the second and third trimesters in order to reduce the risk of preterm delivery. In 1975, Johnson et al[18] have shown that the number of premature deliveries in a population at risk could be reduced by weekly administration of 17P. A multicentric study has been recently published in which 17P's activity in reducing the rate of preterm deliveries has been confirmed in those women who had at least a preterm delivery in their medical history. Meis et al[19] have administered either 250 mg of 17P or a placebo once a week in women who had reported a previous preterm delivery. A total of 463 pregnant women were enrolled between the 16th and the 20th week of gestation; the treatment was prolonged up to the 36th week of gestation or until delivery. The incidence of preterm deliveries was found to be statistically lower, as well as the number of neonatal complications.

Omega-3 supplementation

Dietary supplementation of PUFA has been investigated in a few controlled studies that are synthetically shown in Table II. The design of the various controlled clinical studies is quite strict, although rather heterogeneous since the modalities of ingestion of the different components are very diversified. Besides the administered doses, PUFA sup-

Table II. Controlled clinical studies on the effects of supplementation with polyunsaturated fatty acids

Year	Ref.	Treatment	Main effects
1992	20	Dietary supplement with fish oil (621 mg of DHA + 864 mg of EPA/daily), from the 30th week	4 days prolongation of pregnancy
1999	21	DHA-enriched eggs (135 mg/daily), from the 20th week	1) 6% preterm deliveries in treated pts versus 26% in controls 2) 0% weight < 2.500 g in treated pts versus 26% in controls
2000	22	2.7 g/daily of omega-3 (DHA/EPA) versus olive oil, in high risk pregnant women, from the 20th week	Reduction in preterm deliveries from 33% to 21%
2003	23	DHA-enriched eggs (133 mg) versus normal eggs (33 mg), from the 24th week	6 days prolongation of pregnancy

plementation varies from fish oil to eggs enriched with DHA only, or more simply to the evaluation of blue fish intake with a rough estimate of omega-3 and omega-6 contents. In addition, both the patient populations studied and the gestational ages in which the prophylaxis was started are very different (Table II).

Despite such limitations linked to heterogeneity, all the above mentioned studies report that the main result has been a prolongation of the pregnancy in comparison with untreated controls, or else a significant reduction in the incidence of preterm deliveries.

The mechanism of action by which PUFA supplementation induces a prolongation of pregnancy is unknown; this may be due also in view of the fact that we lack both the physiologic notions on the onset of labour in our species and the physiopathologic notions on the preterm delivery. However, as it has been previously reported, there is increasing evidence that prostaglandins, with special reference to those belonging to series 2, namely PGE-2 and PGF-2α, might play a central role in such events. Prostaglandins derive from the conversion of arachidonic acid (AA), an omega-6 fatty acid, whereas eicosopentaenoic acid (EPA), an omega-3 fatty acid, originates prostaglandins belonging to series 3. The latter compounds, in contrast with PGs of series 2, do not possess any uterotonic activity and actually show the property of inhibiting their synthesis through two mechanisms: (a) EPA incorporation into cell membranes at AA's expense and (b) EPA competition with AA towards both the isoenzymes performing the synthesis, that is, cyclo-oxygenase 1 (constitutive) and cyclo-oxygenase 2 (inducible) (Figure 1).

To conclude, although the data above reported cannot be considered as decisive, this brief review of the literature allows us to state that a strong association exists between the phenomenon, hardly understandable as yet, of preterm delivery and the availability of polyunsaturated fatty acids, with special reference to those with a long chain belonging to omega-3 series.

In fact, experimental, observational and clinical studies suggest that dietary intake of omega-3 fatty acids is capable of prolonging significantly the duration of gestation from 4 to 7 days; such a prolongation would occur through the inhibition of series 2 PGs. In this respect very striking appears to be the observation that in sheep, whose labour is triggered by cortisone, an acute treatment with omega-3 (containing 20% of DHA) has blocked pharmacologically induced labour[25].

From a nutritional stand-point, there is undoubtedly a reduced intake of omega-3, with an unbalanced omega-3:omega-6 ratio in favour of the latter. In the United States such a ratio is 1:10 instead of the more appropriate 1:2, although in the past few years it is reduced[26]. On the other hand, the recommended intake of EPA+DHA should be 1.4 g/daily, with a 1:2.5 EPA:DHA ratio; such an intake is hardly obtainable in the diet, since it could be reached only by a ten-fold increase in blue fish ingestion.

In the light of controlled clinical studies and of the present categories of risk for

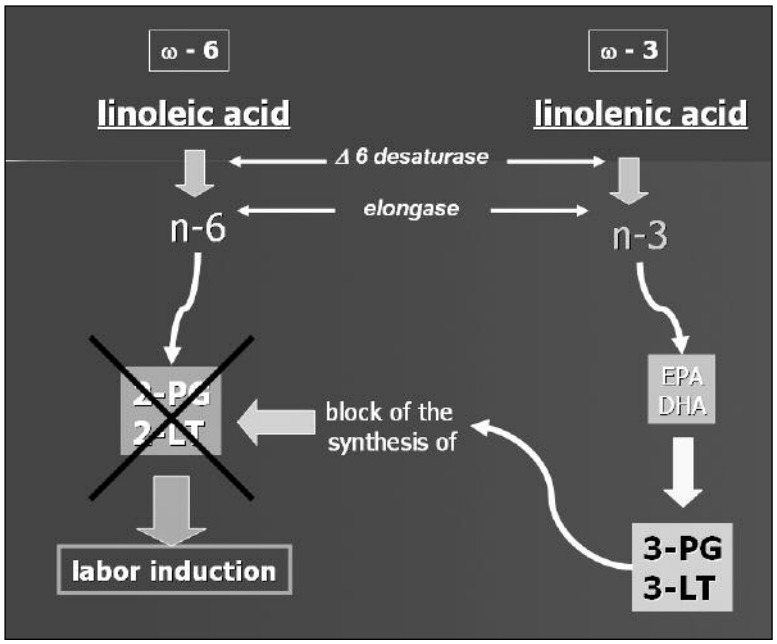

Figure 1. Simplified diagram indicating the pattern by which polyunsaturated fatty acids of omega-3 and omega-6 series influence prostaglandin production, thus conditioning preterm onset of labour.

preterm delivery, it is possible to outline a few clinical scenarios in which the dietetic supplementation with omega-3 could be supposed, in addition to other pharmacological measures, for the secondary and tertiary prophylaxis of preterm delivery (Table III). Such suppositions do not represent therapeutic indications, but plain guidelines aimed at supporting some patient typologies, in view of the fact that for these pregnant women no other clearly effective and safely tolerable measures exist.

Table III. Some clinical situations in which it is possible to obtain a prophylaxis by means of PUFA with or without 17α-hydroxyprogesterone caproate.

Proposal for secondary and tertiary prophylaxis in patients at risk of preterm delivery			
	Start-point of treatment	**17α-hydroxy-progesterone (1 amp./weekly, 341 mg)**	**Omega-3 (1,4 g/die) EPA:DHA 1:2.5**
Previous preterm delivery (spontaneous or PROM)	From the 12th to the 36th week	Yes	Yes
Multiple pregnancy	From the 12th to the 36th week	Yes	Yes
Uterine hypercontractility associated with positive fibronectin and/or cervical lengthening <25 mm	From the onset of symptoms to the 36th week	Yes	Yes
Nulliparous >40 yrs old, multiple fibromyomas, uterine malformations	From the 12th to the 36th week		Yes
Cervical length <25 mm and/or funneling in asymptomatic pt.	From the instrumental diagnosis to the 36th week		Yes
Hypercontractility without any cervical changes	From the onset of symptoms to the 36th week	Yes	Yes

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