



Use of Essential Phospholipids (EPL) from Soybean in GESTOSIS

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Abstract

Gestosis, toxicosis, and preeclampsia are synonyms for a multifactorial manifestation during pregnancy, which may present different degrees of severity and occur in early pregnancy (e.g. hyperemesis gravidarum) or during the last months of pregnancy, or even short time before delivery (late gestosis). A life-threatening pregnancy complication is the HELLP syndrome. It is considered usually to be a variant or complication of pre-eclampsia. Both conditions occur normally during the later stages of pregnancy, or sometimes after childbirth. "HELLP" is an abbreviation of the three main features of the syndrome: Hemolysis, Elevated Liver enzymes, and Low Platelet count.

Summary

Risk factors appear to be first pregnancy of the mother and, especially, when she is of an advanced age already, suffers from preexisting vascular alterations, chronic nephropathies, disorders of liver function and diabetes mellitus. A large number of hypotheses on the origin of the often dangerous syndrome have been established; none of them, however, proved to be convincing.

On the pathophysiologic level can be seen, among others, uteroplacental disorders of circulation with morphological changes of the placenta, partly abruption of the placenta, modified vessel function (angiosperms) and coagulation disorders, as well as hepatic and renal insufficiency with associated metabolic disturbances.

The fetus runs the risk of retarded growth, hypoxia (even respiratory distress syndrome) and premature birth. At the same time, the syndrome threatens the mother's life.

Considering the severity of the condition, particularly predisposed pregnant women need to be carefully controlled to impair the disease, or at least to early diagnose and treat it adequately.

Due to the multifactorial character of the condition, a large number of measures are required to retard the birth of a vital child to the calculated term, to reduce the rate of perinatal mortality, and to prevent the death risk for the mother.

First of all have to be taken measures to reduce hypertension, to dissolve vascular spasms, to improve renal circulation and liver function, to correct lipid disorders and to support mother and child with high-protein nutrition.

As the Essential Phospholipids (EPL) are known to improve hepatic and renal dysfunction, and dyslipidemia [1], among others, their additional usefulness in gestosis is postulated and will be summarized in this short expert report.

Four experimental and 20 clinical studies have been carried out since 1963 with a total of 1,057 pregnant women presenting the syndrome with various degrees of severity. In addition to basis therapy, the patients were treated with 250 mg-1,000 mg of EPL i.v. and/or 900mg-1,800 mg of EPL per os.

Experimental Results

In rabbits, EPL infusion (>0.3 g/kg between, emulsified with ethanol in 250 ml 5% glucose), administered between day 21 and 30 of gestation, affected the uterus, presumably the myometrium, and more than 50% of the animals delivered. If one unit of oxytocin was administered i.m. 24 hours after the onset of the infusion, more than 87% of the rabbits delivered within a few minutes. Up to the 29th day of gestation, the delivery was not affected even with much higher doses of oxytocin alone. Myometrium preparations of rabbits at the 24th or 25th day of gestation did not have a significant sensitivity to oxytocin, but there was a rather considerable spontaneous activity. The myometrium

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of rabbits, which had been given infusions of EPL on the 24th day of gestation, showed the same behavior as the myometrium of rabbits at the end of gestation, i.e. a high sensitivity to oxytocin and no spontaneous activity.

Infusions in pregnant ewes completed the experimental investigations of the author with EPL + B-vitamins, dissolved in deoxycholic acid as phospholipid solubilizer, in doses equivalent to the very high amount of 10 g-40 g of EPL.

The author came to the conclusion that it was possible to induce premature labor uniformly in rabbits and ewes with EPL infusions. The infusion resulted in sensitizing the uterus such that labor occurred with only 1-3 IU of oxytocin.

It is noteworthy to mention that the EPL emulsion with ethanol had a better compatibility than EPL with deoxycholic acid as solubilizer but it has also to be considered that the dosages employed by far exceeded the manufacturing recommendation [2,3].

In 1988, Ailamazyan EK et al. [4] investigated the influence of EPL on induced peroxidation during pregnancy. Rats with Placental Insufficiency (PI), induced by means of dosed ligation of the preplacental vessels in all the fetus receptacles, were compared to control groups and a group of rats with PI receiving EPL i.p. in doses rated at 0.1 ml/kg between every day from the time of operation to the time of slaughtering. The major copper transport ferroxidase ceruloplasmin (CP) and plasma copper (CU) and CU/CP ratio in plasma, and the copper-containing antioxidative enzyme superoxide dismutase (SOD) in erythrocytes (hemolysis) decreased, while the SOD-activity in plasma and placenta increased in PI. The essential phospholipids corrected these hypoxia-induced changes (less peroxidation to be corrected) and reduced the SOD-activity of plasma and normalized the other biochemical shifts. Protein synthesis improved, too.

Six years later Zaichenko AV [5] published a comparative study of the antioxidative activity of EPL versus salbutamol hemisuccinate in rats with CCl₄-induced fetoplacental insufficiency. Beginning on day 10-11 of pregnancy 200 mg of EPL/kg between were administered within 7 days i.g. 2 hours before and 2 hours following the once daily CCl₄-injections and compared to control groups and to a group, in which 30 mg/kg between of salbutamol was given i.g. 2 hours before and after the daily CCl₄-injections.

Both products were antioxidatively effective, salbutamol being slightly more effective. In serum, equal efficacy of both drugs was seen for lipid hydroperoxides while the antioxidative activity in percent seemed to be higher under salbutamol. In liver homogenate, both products were equally effective on malondialdehyde (MDA) and SOD, too. Regarding placenta and uterus, the same was the case for lipid hydroperoxides, MDA and SOD (in uterus, while less for EPL in placenta), glutathione peroxidase, glutathione reductase, and for glutathione-S-transferase and catalase (both measured in placenta only).

Early Gestosis in Humans

Mücke HG [6] reported already in 1963 the successful EPL treatment of 47 patients suffering from severe hyperemesis gravidarum. In 28 women, the symptoms disappeared after 1 injection, in 11 cases after 2 injections, and in the remaining 8 women after 3-4 injections. The ampoules with EPL were administered every other day. No adverse drug reactions (ADRs) were observed.

At a later date, Hartel J [7] confirmed these positive results. Nausea and vomiting subsided in a patient with intact intrauterine pregnancy after the 1st EPL injection (250 mg EPL/d) in gestation week 18, after the medication administered before (antiemetics and high dose of vitamin B₁₂) did not show any effect. Further 6 patients with less pronounced symptoms showed the same positive results with EPL.

Jaisle F [3], in contrast, did not achieve relief from symptoms in his patients suffering from hyperemesis gravidarum, even when increasing the dose to 1,000 mg of EPL per infusion per day over 4 days. On the other hand, the EPL infusion led to a decrease of the total lipids (in humans and in animals) within the first few hours after the infusion and a considerable decrease of the urea nitrogen without a significant influence on the total serum protein.

Late Gestosis in Humans

In a much larger number of patients (n=941) EPL (in combination with basic treatment) was given in the last trimester of pregnancy.

Fifty- two women with gestosis during the last 3 months of pregnancy (n=22) or shortly before delivery (n=30) received a basic therapy of 500 mg EPL i.v. per day. On average, 7 days of treatment were necessary. In the mean, patients' edema mobilized 4 days after starting therapy or 3 days after delivery. At the same time, blood pressure as well as urine and diuretic findings became normalized. Symptoms of eclampsia disappeared after 5 days of treatment or 3 days after delivery. Normalization of total lipids, cholesterol, ketone bodies as well as of the liver and kidney function tests was observed within a short period of time. According to the authors such rapid and complete improvements were rarely seen with conventional treatment alone [8].

The aim of the study of Kovačević M and Gavrić S [10] in 37 patients with primary (n=32) or secondary (n=5) preeclampsia was to eliminate gestosis-induced liver damage by administration of 3-6 capsules (900 mg-1,800 mg) of EPL p.o. for 7 days. In some cases also EPL was i.v. applied. Besides indispensable medication, such as anti hypertensives, diuretics, antibiotics and a salt-free diet, no other preparations were given. After the 7-day treatment total protein increased in more than 90% of the women. A rise in the albumin and γ-globulin levels and a fall in the α₂- and β-globulin levels were recorded. Except for an elevation of β-lipoproteins by 15% on average, no changes were observed in lipids. Serum copper values that were already increased at the start of therapy further rose in 60% of the patients. Serum transaminases continued to fall in 50% of the cases within the normal range. The subjective well-being of the women improved quickly, and the drug was very well tolerated.

At the same symposium Arandelović D and co-workers [11] treated 42 pregnant women with toxicosis, preeclampsia and eclampsia, and prolonged the daily administration of 500 mg EPL i.v. or 1,800 mg EPL p.o. per day to 10-15 days. Additionally, a special diet, symptomatic therapy and 1 tablet of Gestanon (progesterone substitution; 3 × 1/d) were given. As a result of drug treatment, in preeclampsia the symptoms pain, nausea, malaise and insomnia rapidly receded, the occurrence of eclamptic attacks being diminished. Increased blood pressure decreased in most cases, edema and proteinuria disappeared, and kernicterus was not observed. With only 6 stillbirths (5 of them premature births), the infantile mortality rate was lowered to a minimum in cases of toxicosis where treatment was instituted early. No ADRs were reported.

As dyslipidemia is frequently seen during pregnancy, and as its treatment with lipid lowering agents is not riskless De Aloysio D [12] and Ailamazyan EK [13] focused on the clinical picture and disordered lipid metabolism, and the possibility to treat it with EPL. De Aloysio D [12] treated 6 patients with 500 mg EPL i.v. in addition to a sedative-hypotensive therapy up to 12 days. Ailamazyan EK [13] treated 38 patients for 10 days with a standard therapy of magnesium, vasodilators, proteins, rheological preparations and Sygethin, and added 500 mg EPL i.v. and 1,800 mg EPL p.o. daily, followed by 1,800 mg EPL p.o. per day until delivery. This EPL-group was compared to 25 patients who received standard treatment only, and to 20 healthy pregnant women.

Both authors observed with EPL clear improvements and even normalization of the pathological lipid values.

Additionally, Ailamazyan EK [13] noted a significantly higher mean growth of the biparietal diameter of the head of the fetuses due to the additional EPL treatment compared to control, and the newborns presented a significantly higher birth weight, too.

According to the author, the penetration of total lipids and triglycerides through the placenta and their utilization by the fetus were increased, thus promoting prevention and treatment of intrauterine fetal hypotrophy.

Rendina GM et al. [14] assessed the duration until disappearance of symptoms. They administered 1,000 mg EPL per infusion per day for 10 days to 50 patients with gestosis of different degrees of severity and compared the results to 50 similar cases with toxicosis in pregnancy, which were treated in addition to basis therapy with infusions of glutathione, vitamin B₁₂ and uridine-5-diphosphoglucose. Forty-six patients presented no more symptoms after 10 days of EPL treatment, and the remaining 4 patients after 15 days. In the control group, 40 patients were asymptomatic after 10 days, and the remaining 10 cases after 22 days. No intolerance reactions to the study medication were noted.

In addition to the studies of De Aloysio D [12] and Ailamazyan EK [13], Mariani S and coworkers [15] investigated if a diet with EPL can be a better alternative to correct dyslipidemia of pregnant women in comparison with a diet alone. The authors selected 11 women with primary hyperlipidemia in the last trimester of pregnancy and compared them in a randomized controlled study to a corresponding control group. The women of the control group got a low-fat (with especially unsaturated fatty acids), protein-rich and normal glucose-input diet, the women of the EPL-group additionally 1,800 mg of EPL per day. Treatment duration was 4.1 weeks. While the triglycerides and cholesterol reduced in the mean by 8.6% and 7.6% in blood, the percentages were 14.9% and 15.4% under diet plus EPL. The difference for cholesterol was significant between the groups ($P<0.02$). No ADRs were reported.

Since the end of the eighties, authors of clinical studies not only looked for clinical improvements but started to investigate more intensively the mode of action of EPL in clinical gestosis.

Following his experimental investigations of 1988 [4], Ailamazyan EK [16] performed a clinical study with 163 pregnant women with late gestosis of different grades who received EPL (500 mg i.v. and 2,100 mg p.o. per day for 10 days and, until the beginning of labour, 2,100 mg p.o. per day) in addition to basis therapy. After delivery, the newborns were administered 50 mg/d -

100 mg/d of EPL i.v. in a 5% glucose solution during the first 7 days. No perinatal death occurred in the EPL-treated group, and the weight at birth was higher. With basis therapy alone the death rate was 5.1%, and hypotrophy of newborns was observed in 8.5%. Blood levels of phospholipids and triglycerides, as well as the values of Diene Conjugates (DC), MDA and SOD in blood and erythrocytes were normalized. With a higher grade of nephropathy the effects obtained with EPL were less pronounced.

Out of 145 pregnant women with late gestosis, allocated according to the severity of nephropathy (mild, moderate, severe), the duration of the disease and the condition of the fetus, 33 patients were treated with EPL [17]. All patients received for 14 days either routine treatment, or they were administered vitamin E and C and/or EPL or Solcoseryl. The dose and way of administration of EPL were not specified. The inclusion of EPL in the comprehensive treatment proved effective in 7 of 8 patients with mild, 13 of 18 with moderately severe and 6 of 7 with severe nephropathy. Discontinuation of the medication led to a relapse within 2-6 days. Alteration of serum lipid peroxidation activity (POL) and considerable reduction of erythrocyte POL activity were associated with restoration of the barrier and membrane function. Compared to the other treatments, the most evident effect on the serum antioxidant activity was exhibited by EPL, manifested by the rise of the level of ceruloplasmin and increased CP/transferring coefficient. No ADRs were reported.

The risk to develop HELLP is increased if women suffer already from liver disease before getting pregnant.

Kurbanova FR et al. [18,19] treated pregnant women who suffered from acute or chronic hepatitis. Sixty in-patients with acute hepatitis (HBsAg⁺ n=45) and 62 with chronic hepatitis (HBsAg⁺ n=43; chronic active hepatitis (CAH) n=22, chronic persistent hepatitis (CPH) n=40) were compared to 45 healthy pregnant women. Twenty acute cases, 20 with CAH and 12 with CPH received not only basic treatment of, among others, glucose i.v., vitamins and chologogues but also 1,800 mg EPL p.o. per day over 20 days. On the whole, the EPL-treated patients showed a more marked inhibition of POL (DC) and MDA). The AST-activities were approximately comparable in all groups. A more pronounced effect of EPL on ALT was only seen in the patients with CPH, and total and direct bilirubin decreased mostly more pronounced in the EPL-group than with basis therapy alone. Blood phospholipid composition was restored to normal. ADRs potentially in causal relation with EPL were not reported.

Iron deficiency anemia is a risk factor for pregnant women, especially when combined with some others disease.

Therefore, Makarchuk OM and Ostrovs'ka OM [20] enrolled 120 cases with anemia of various severities: 60 women suffered from anemia and cytomegalovirus plus herpes infection, 40 cases from anemia and cytomegalovirus alone and 20 patients from anemia plus genital herpes type I. All patients received antiviral and immunomodulatory drugs within a complex course of treatment, 70 patients additionally EPL p.o. (dose and duration of treatment not specified). During treatment, dysproteinemia (esp. on transferrin and haptoglobin concentrations), MDA and DC, and the ceruloplasmin activity were influenced by the basic treatment in pregnancy with mild anemia, while the additional administration of EPL made the complex treatment effective enough to improve antioxidation and to reduce POL intensity in all pregnant women. The multiple therapy

promoted the improvement of impaired protein synthesizing function of the liver with albumin levels increased by 26% ($P<0.05$), decreased ceruloplasmin and β -lipoproteins (ceruloplasmin by 32% ($P<0.05$)), and stabilized α_2 -macroglobulins with an increase of this fraction by 72% ($P<0.05$). The activity of the investigated enzymes ALT, AST, AP, arginase, and ornithine carbamoyl transferase reduced, too. The results show the improved hepatic functioning by the use of EPL orally administered.

Interesting are also the results published by Romanenko TG et al. [21] in 2009, who investigated, to what extent EPL can prevent preeclampsia during pregnancy complicated by liver pathology. In the 1st part of their study, 30 pregnant women were treated as usual, and 30 additionally with 1,800 mg of EPL p.o. per day during the 10-12, 20-122, 30-32 and 36-38 weeks of pregnancy. All patients suffered from hepatic and biliary disorders, 7 and 9 had angioneurosis, 8 and 11 neuroendocrinological disorders, 9 and 11 cardiac diseases without abnormality in blood flow, and 4 and 5 women kidney disorders. In the 2nd part of the study, 43 women with pre-gestosis received together with the usual complex therapy 1,800 mg of EPL p.o. per day for 21-28 days. They were compared to 53 patients of control. A refresher course was given in 14 days.

During the 1st course of treatment, increased anemia level and somatic pathology were seen in 30% and 13.3% of the control cases versus 16.6% and 10% under EPL. After the 20th week of pregnancy, the differences became more evident. During treatment with EPL, obstetric complication, such as gestational anemia, decreased from 60% to 30%, placental insufficiency from 36.6% to 16.6%, preeclampsia from 33.3% to 16.6% and primary somatic pathology from 13.3% to 6.6%. As a result, EPL reduced the prevalence of preeclampsia by a factor 2.

Out of the patients with pregestosis further development of preeclampsia was registered in 6 of 43 cases (13.9%) but in 13 of 53 cases (24.1%) of the comparison group ($P<0.05$). The effectiveness of the additional EPL administration was also indicated by a decrease in frequency of delivery complications among the women with liver pathologies: comparing EPL to control, premature breaking of waters was 30% vs. 16.6%, fetal distress 16.6% vs. 6.6%, labour action anomalies 13.3% vs. 6.6%, prevalence of abdominal delivery 16.6% vs. 10%, and frequency of asphyxia in the medium rate from 13.3% to 6.6% and in the severe rate from 6.6% to 3.3%.

At the last stage, due to the proposed method of medical and preventive treatment, the level of exacerbation of hepatic pathology decreased significantly from 13.3% to 3.3%, the frequency of subinvolution from 6.6% to 3.3%, and wound infection from 6.6% to 3.3%. A decrease of CD4+ with a simultaneous increase of CD8+ was registered in the control group (it is a pity that the authors communicated only relative values and no absolute values).

In addition to [18,19,21], Boris EN et al. [22] investigated in a randomised controlled study the function of EPL against artichoke in the complex treatment of fetoplacental insufficiency of pregnant women with preeclampsia lesions of the hepatobiliary system. Fifty patients got a standard complex treatment (not defined) plus artichoke (dose not defined) and 55 patients 900 mg of orally administered EPL for one month.

Both preparations showed clinical efficacy but EPL was more efficient. The clinical recovery indices (especially edema, pain in the right hypochondrium, lack of appetite, stool disorders,

skin itching and nausea) were 91.3% for EPL and 83.7% for the medicine that contained artichokes. The same was the case especially for conjugated bilirubin, AST, AP and cholesterol. In total, the efficiency of EPL was 89.5% and for the comparison group 76.8%. Fetal heart rate, condition of the fetoplacental system and biophysical parameters of the fetuses were more improved or normalized under EPL.

The latest three studies combine [23,24] EPL with Ursodeoxycholic Acid (UDCA) or compare it to UDCA [25] in pregnant cases with intrahepatic cholestasis.

Brzozowska M and coworkers [23] treated 38 women with intrahepatic cholestasis of pregnancy (ICP) with daily 750 mg UDCA and 900 mg EPL p.o. Acute and chronic hepatitis were ruled out. Treatment duration was 14 days. Analyses were done on day 7 and 15, besides bile acids, which were determined after 15 days only. There was a complete regression of pruritus in all patients until day 15, and mean levels of ALT, AST and bile acids significantly improved after 7, respectively 15 days. Gamma-GT was said to be significantly improved in those cases where elevated (but no data were shown). AP was not significantly changed and bilirubin remained normal.

Marciniak B et al. [24] subdivided their patients into 3 groups, depending on the total serum concentration of bile acids (BA): group 1 with n=13 and BA<15 $\mu\text{mol/L}$, group 2 with n=13 and BA from 15-20 $\mu\text{mol/L}$ and group 3 with n=15 and BA >20 $\mu\text{mol/L}$. Patients in group 1 were treated with 1,800 mg/d of EPL, group 2 with 750 mg/d of UDCA and group 3 with 1,500 mg of UDCA plus 1,800 mg of EPL per day. There was a significantly better improvement (i.e. significantly higher difference in transaminases activity and BA levels before starting the pharmacotherapy and during childbirth) in group 3 than in group 1. The effectiveness of the combined treatment is also supported by the difference of BA concentrations in the serum of pregnant women before the start of treatment and in the umbilical cord blood of newborns. While the mean difference in the BA levels before treatment and in the umbilical cord blood was nearly 35 $\mu\text{mol/L}$ in patients treated with UDCA and EPL, this difference amounted to about 10 $\mu\text{mol/L}$ in group 2, and equal zero in group 1. However, a statistically significant difference in this parameter was only seen between groups 1 and 3. The authors conclude that combination therapy with UDCA and EPL appeared to be an effective method of treatment of obstetric cholestasis, especially in the case of early onset and/or severe course of the disease.

Corticotropin-Releasing Hormone (CRH) is one of the most potent vasodilatory factors in the human feto-placental circulation. The pilot study of Zhou F et al. [25] investigated in a prospective nested case-control study 16 cases with ICP with 750 mg/d of UDCA and 14 cases with SAMe 1,000 mg/d or EPL 1,800 mg per os per day. Maternal serum samples were obtained in diagnosis and at 37-37 (+6) weeks of gestation. Placental tissues were obtained from participants after delivery. The UDCA group had greater reduction in maternal serum ALT, AST and TBA levels in ICP patients (all $p<0.01$). Maternal serum CRH concentration in the UDCA group after treatment was significantly higher than before treatment and significantly higher than in the comparison groups. Additionally, the placental CRH expression was significantly higher under UDCA. However, the study has to be confirmed by a larger one with separate analyses of the control treatments.

In 2006, a dissertation was published, which focused on

pregnancy-related Acute Fatty Liver (AFLP) [26]. The women were divided into 2 groups: the 1st one included 60 women with AFLP in the pre-icteric phase, the 2nd one 49 cases with the icteric phase of the disease. Both groups were sub-divided into 3 further groups: group 1a (n=16) and 2a (n=12) received standard treatment, group 1b (n=31) and 2b (n=23) additionally Chophytol, immunomodulin, lactulose and EPL i.v. (2 × 5.0 mL (?)/d for 7 days in pre-icteric cases and EPL i.v. 3 × 5.0 mL (?)/d for 5 days and 2 × 5.0 mL (?) for further 5 days in icteric cases, followed by EPL i.v. 1 drop × 4 times/d for 3 to 4 weeks or more in all cases). The groups 1c (n=13) and 2c (n=14) received additionally plasmapheresis. The groups were compared to a control group of healthy 30 pregnant women. The treatment efficiency was evaluated according to complex examination in dynamics, including clinical, biochemical, immunological and morphological analyses, as well as on the course, the results of pregnancy, delivery and post-natal period.

Under pre-icteric condition, clinical improvement was registered in group 1a in 86%, in group 1b in 95.8%, and under additional plasmapheresis in 97.6% of the cases by the 10th day, and under icteric condition in 50%, 82.6% and 85.7% of the patients.

Perinatal fetal loss was 81.2% in group 1a. This parameter was successfully reduced in group 1b by 29.6%, and under additional plasmapheresis by 42.8%. Perinatal fetal loss of 83.3% under standard treatment was reduced 1.2 and 1.4 times in the icteric group, respectively.

Caesarian operation prior to amputation and total hysterectomy under pre-icteric condition were 3.9 and 5.8 times less frequently performed in group 1b compared to group 1a, and total hysterectomy in group 1c 2.3 times less frequently than in group 1a.

In the icteric phase against the background of conventional therapy without correction of the preliminary disseminated intravascular coagulation syndrome and due to late termination of pregnancy, operation expansion to amputation, total hysterectomy and relaparotomy were 1.9, 3.5 and 2.3 times more often done in group 2a than in group 2b and 2c.

Maternal mortality was 12.5% in group 1a and 33.3% in group 2a, while no mortality was seen under complex therapy and in combination with plasmapheresis. Short preoperative preparation with the application of the complex therapy and urgent delivery reduced the maternal mortality by 3.6 and 4.9 times in groups 2a and c, resp., and perinatal mortality by 1.3 times under icteric condition of the disease.

Clinical and biochemical parameters normalized quicker groups 1b, c and 2b, c, and the patients were discharged after complex therapy and plasmapheresis after 12.7 ± 0.5 days (pre-icteric group) and 11.4 ± 0.5 days (icteric group) compared to 14.0 ± 0.6 days and 16.4 ± 0.7 days under standard treatment.

Guidelines

Due to the complexity of gestosis, different treatment approaches and drug combinations are proposed. Among others, late pregnancy toxicosis is frequently associated with changes in the clotting system, which may lead to the development of a disseminated intravascular coagulation syndrome with microcirculatory organ and tissue disorders.

Correspondingly, Selepei YD [27] suggested 1992 in case of mild

toxicosis a drug combination of estradiol, heparin, rheopolyglucin, curantyl, prednisolone and 3 × 1 capsule of EPL per day, in severe forms of gestosis plus prelabor prophylaxis, nephropathy-associated therapy comprised antihypertensive agents, antispasmodic drugs, diuretics, glucose, vitamins, albumin and hemodez.

One of the consequences of the successful treatment of patients with gestosis was that the Society of Obstetricians and Gynecologists of St. Petersburg and North-Western Region in combination with the Institute for Obstetrics and Gynecology named after D.O. Otta and the Russian Academy of Medical Sciences published in 2005 methodical recommendations for obstetricians and gynecologists [28].

Firstly, they evaluated the usefulness of EPL in correcting the phospholipid metabolism as well as clinical and physiological condition of fetuses and newborns given birth by mothers with severe forms of gestosis. Their recommendation based on more than 10,000 pregnant women with severe forms of long lasting gestosis who were diagnosed to have chronic hypoxia and/or hypotrophy of the fetus. EPL was administered after the 28th-30th week of pregnancy. Daily 500 mg of the preparation along with 200 ml-300 ml of 5% glucose solution were intravenously administered within 10 days. The same women were simultaneously administered EPL capsules (3 × 2 capsules = 1,800 mg/d) until delivery. Newborns of EPL-administered mothers were also recommended to be slowly injected with 50 mg-100 mg of EPL dissolved in 10 ml of 5% glucose solution. Compared to the newborns and their mothers who had not been administered EPL in the early neonatal period, EPL as a part of complex therapy of gestosis demonstrated by the 3rd day of their lives normalization of pH, pCO₂ and buffer capacity findings while by the 7th day of life the newborns displayed complete compensation of metabolic acidosis. More data about the successful use of EPL to improve/correct pathological clinical and physiological conditions of fetuses and newborns (on growth of the biparietal size of the head and the inter perpendicular diameters of the fetus, changes in phospholipids and other lipids in newborns and mothers, arterial-and-venous difference in umbilical vessels of newborns, cardiovascular activity of the fetuses [structure of cardiac rhythm]) are described in the guideline. According to the authors, both newborns and their mothers did not display even a single case with side-effects or complications. Secondly, they recommended the administration EPL (e.g. 1,800 mg EPL/d within 1 month) in the frame of the complex prevention of placental insufficiency. Last but not least the authors confirm the usefulness of EPL for pregnant women with liver disease, and they emphasize that a time-consuming tactics of non-administration of EPL in cases of pregnancy with gestosis is unacceptable.

The paper of Boris EN et al. [22] mentions that the Ministry of Health of Ukraine included EPL in the list of drugs for the prevention and treatment of preeclampsia and placental insufficiency.

Discussion

Due to its complexity and frequently severity, gestosis remains a potential life-threatening disease, especially when combined with acute fatty liver, with a maternal mortality up to 25% and perinatal mortality up to 56% [26]. A validated standard treatment is not known. One of the approaches is the inclusion of EPL into therapy, especially as liver damage/disease is frequently correlated with gestosis. Though the majority of the available EPL studies is already of older origin and published in secondary journals, EPL showed impressive

results, especially the intravenous preparation. However, despite no significant side-effects were observed, the intravenous form should be put into question as DNA damage by the EPL-solubilizer deoxycholic acid cannot be completely excluded [29]. Apart from that, the oral form of EPL is efficient and completely safe, and it can be taken by the mother at any time of her pregnancy.

Besides the described results of this report, other reasons are to be considered why the administration of EPL is useful for the treatment of gestosis. One example is that choline as part of phosphatidylcholine in EPL is important for the brain tissue during fetus development, since it serves as well as component of the cellular membranes as acetylcholine precursor. Additionally, it is known nowadays that 1,2-Dilinoleoylphosphatidylcholine (DLPC), the quantitative and qualitative key ingredient in EPL, facilitates hippocampal synaptic transmission in the brain [30]. Further examples for the usefulness of EPL treatment in gestosis are that it reduces the risk of infantile respiratory distress syndrome in case of premature delivery [31], and that it reduces the risk of HELLP due to its special effects on liver diseases, especially when the women suffer from preexisting liver disease.

Bearing in mind the frequent and manifest disruption of liver function in pregnant women suffering from early toxicosis, treatment should include the preparation for prophylactic purposes in person at-risk group and also as part of the full range of therapeutic measures to treat toxicosis of any degree of severity [32]. Precondition is a sufficiently high dose of EPL (1,800 mg/d) and long duration of treatment (at least until disappearance of all symptoms, pathologic clinical finding and biochemical disturbances).

Summary

Summarizing the results of the 4 experimental and 22 clinical studies, distinct favourable changes were detected with EPL in gestosis, which confirm its efficacy as adjuvant treatment in this disease.

In the patients suffering from early to late gestosis, the subjective symptoms and clinical findings, such as on hyperemesis gravidarum and oedema, clearly improved or disappeared. The positive effects were also seen with respect to accompanying disturbances, such as lipid peroxidation, renal disorders, pathological liver function and hyperlipidemia, hypoxia of the foetus and with respect to the newborns physical appearance and constitution. In case of ICP, EPL should be combined with UDCA. Not a single case of ADR was reported.

References

- Gundermann KJ. Biological Activity of Polyunsaturated Phosphatidylcholine (PPC) in Different Diseases. In: Cevc G, Paltauf F, editors. *Phospholipids: Characterization, Metabolism, and Novel Biological Applications*. Illinois: AOCS Press Champaign; 1995. p. 208-27.
- Jaisle F. Phosphatides and their effect on pregnancy and labor. Z Geburtshilfe Gynakol. 1965;163:158-95.
- Jaisle F. Infusion of phosphatides in animals in the last third of gestation. Bibl Gynaecol. 1966;42:191-7.
- Ailamazyan EK, Taranova NP, Shabunovich LV, Zhouravlov AV. The effect of Essentiale preparation on the activity of ceruloplasmin and superoxide dismutase of the blood in placental insufficiency in rats. Zh Eksp Klin Med. 1988;28:599-604.
- Zaichenko AV. A comparative study of the antioxidant activity of salbutamol hemisuccinate and Essentiale in rats with experimental photoplacental insufficiency. Eksp Klin Farmakol. 2004;67(3):38-41.
- Mücke HG. The treatment of vomiting in pregnancy with Essentiale. Der Landarzt. 1963;39:34-5.
- Hartel J. Casuistic contribution to the subject of hyperemesis gravidarum. Ärzt Praxis. 1965;17:1049-50.
- Bottiglioni F, Tirelli R. "Essential" phospholipids in the treatment of gestosis. Ärzt Praxis. 1968;20:2656-7.
- Graf H. Therapy of pregnancy toxemias (EPH-gestosis, preeclampsia). Dtsch Med Wochenschr. 1972;97(17):698-9.
- Kovacevic M, Gavric S. EPL substance (Essentiale) in the treatment of gestosis. In: Bosnajek Nattermann, Sarajevo, editors. *Essentiale® radovi jugoslavenskih autora*. 1975. p. 63-9.
- Arandelovic D, Stojiljkovic D, Cvetkovic A, Jordacevic J. Therapeutic effect of EPL and Gestanon on liver enzyme induction and prevention from the risk of gestosis. In: Bosnajek Nattermann, Sarajevo, editors. *Essentiale® radovi jugoslavenskih autora*. 1975. p. 55-61.
- De Aloysio D. Determination of individual lipemic fractions and of the fatty acids contained before and after treatment with "essential" phospholipids of toxicosis in the last trimester of pregnancy. Revista italiana di ginecologia. 1975;56:31-48.
- Ailamazyan EK. Effect of exogenous phosphatides on the lipid metabolism parameters in pregnant women with late toxemia and in their neonates. Akush Ginekol. 1983;8:56-8.
- Rendina GM, Maselli G, Patrono D. Polyunsaturated phosphatidylcholine in the treatment of gestosis. Il Policlinico - Sez Medica. 1977;84:1-6.
- Mariani S, Frantellizzi R, Rauseo R, Volpini G, Zanetti H, Cesa F. Treatment with polyunsaturated phosphatidylcholine of dyslipidemia in pregnancy. Clin Ter. 1988;125(4):277-85.
- Ailamazian EK. Antioxidants in the combined therapy of late pregnancy toxicoses and chronic fetus hypoxia. Akush Ginekol (Mosk). 1991;(3):30-4.
- Shalina RS, Kush IB, Oreshkina VP, Azizova OA, Kozlov AV, Panasenko OM. Antioxidative drugs as a part of combined therapy in patients with late gestosis. Akush Ginekol. 1989;65:37-41.
- Kurbanova FR. Peroxidation of lipids in pregnant women with hepatitis and its correction with Essentiale. Med Zh UZB. 1990;61:59-61.
- Kurbanova FR, Bashirova NB, Babakhodzhaev NK, Musabaev IK, Tadzhieva SA. Effect of the preparation "Essentiale forte" on lipid peroxidation parameters in pregnant women with liver diseases. Proceedings of 3rd Cong Obstet Gynecol; Uzbekistan, Tashkent; 1990: p. 93.
- Makarchuk OM, Ostrov'ska OM. Evaluation of liver function in pregnant women with iron deficiency anemia combined with cytomegalovirus and herpes infection and complex treatment of them. Zdr Zhen. 2007;30:7.
- Romanenko TG, Jaloba GN, Morozova OV. Prevention of preeclampsia during pregnancy complicated by liver pathology. Women's Health. 2009; 39:60-2.
- Boris EN, Tupis OY, Gak IA, Onishchik LN. Function (role) of hepatoprotectors in complex treatment of fetoplacental insufficiency of pregnant women with preeclampsia and lesions of hepatobiliary system. Women's Health. 2009;42:40-3.
- Brzozowska M, Kowalska-Koprek U, Karowicz-Bilinska A. Influence of pharmacological treatment on selected parameters of intrahepatic cholestasis of pregnancy. Ginekol Pol. 2010;81(2):94-8.
- Marciniak B, Kimber-Trojnar Z, Leszczynska-Gorzelak B, Patro-Malyza J, Trojnar M, Oleścuk J. Treatment of obstetric cholestasis with polyunsaturated phosphatidylcholine and ursodeoxycholic acid. Ginekol

- Pol. 2011;82(1):26-31.
25. Zhou F, Zhang L, He MM, Liu ZF, Gao BX, Wang XD. Corticotropin-releasing hormone expression in patients with intrahepatic cholestasis of pregnancy after ursodeoxycholic acid treatment: an initial experience. *Curr Med Res Opin.* 2014;30(8):1529-35.
26. Niyazmetov RE. Clinico-immunological and morphological properties of acute pregnancy-induced fatty liver. Modern methods of early diagnosis and treatment. Uzbekistan: Dissertation Tashkent; 2016.
27. Selepeč IaD. Prevention of functional disorders of blood coagulation and fetoplacental complex in pregnant women with late gestosis. *Akush Ginekol (Mosk).* 1992;68:17-9.
28. Society of Obstetricians and Gynecologists of St.Petersburg and North-Western Region. Institute for Obstetrics and Gynecology named after D.O.Otta: Correction of disturbances of phospholipid metabolism in obstetrics and perinatology. St.Petersburg; 2005: p. 21-6.
29. Bernstein H, Bernstein C, Payne CM, Dvorakova K, Garewal H. Bile acids as carcinogens in human gastrointestinal cancers. *Mutat Res.* 2005;589(1):47-65.
30. Küllenberg D, Taylor LA, Schneider M, Massing U. Health effects of dietary phospholipids. *Lipids Health Dis.* 2012;11:3.
31. Stephanskaya GK, Tovstanovskaya VA. Antenatal prevention of the respiratory disorders syndrome in premature babies by the use of Essential. Proceed. Dnepropetrovskaya Province Sci Clin Conf Obstet Gyn Urol, Dnepropetrovsk. 1988: p. 41-4.
32. Ignatko IV, Davydov AI. Pathogenesis, diagnosis and treatment of early gestational toxicosis. *Med Express.* 2008;3:35-8.