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ORIGINAL ARTICLE

OBSTETRIC AND PERINATAL ASPECTS OF METABOLIC DISORDERS IN PREGNANT WOMEN

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Valerii V. Korsak, Yurii Y. Bobyk, Iryna I. Patskan
STATE HIGHER EDUCATIONAL INSTITUTION "UZHHOROD NATIONAL UNIVERSITY", UZHHOROD, UKRAINE

ABSTRACT

The aim: To determine the feasibility of using Tivortin in metabolic disorders during pregnancy and its effect on the course of pregnancy, childbirth, fetal and neonatal status.

Materials and methods: We examined 210 pregnant women with metabolic disorders using clinical and laboratory data, uterine artery Doppler, determination of lipid peroxidation and antioxidant system, leptin and placental growth factor content. The fetal condition was assessed by ultrasound examination with Doppler, determination of biophysical profile, and cardiotocography.

Results: Metabolic disorders in pregnant women increase the risk of obstetric and perinatal complications by activating lipid peroxidation and inhibiting the antioxidant system, reducing the content of placental growth factor and increasing the level of leptin in the blood plasma. After treatment, there was a significant decrease in leptin levels and an increase in placental growth factor levels, normalization of lipid peroxidation and antioxidant system, uterine artery pulsatility index and umbilical cord peak systolic velocity index, systolic-diastolic ratio, fetal biophysical profile and cardiotocography. The incidence of complications in childbirth decreased by 3 times, surgical interventions – by 2 times, postpartum infectious complications – by 1.7 times, and the birth of infants in a state of asphyxia – by 1.8 times.

Conclusions: Metabolic disorders in pregnant women are a significant factor in the development of obstetric and perinatal complications due to the intensity of lipid peroxidation and depression of the antioxidant system, and a decrease in the content of placental growth factor. The use of Tivortin in the treatment of pregnant women with metabolic disorders has proven its safety and efficacy.

KEY WORDS: pregnancy, metabolic disorders, Tivortin

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INTRODUCTION

The problem of metabolic disorders in obstetric practice is relevant both scientifically and practically, since these disorders are caused by genetic, hemodynamic, neurohumoral features and are manifested by a complex of pathogenetically interrelated disorders of tissue sensitivity to insulin, carbohydrate, lipid, purine metabolism, etc. According to WHO recommendations, the criteria for metabolic syndrome are obesity (body mass index >30 kg/m^2), blood pressure >160/90 mm Hg, and impaired glucose tolerance. According to the results of epidemiological studies over the past ten years, obesity in pregnant women occurs in 15-38% of cases and is associated with a high risk of complications during pregnancy, childbirth and the postpartum period due to an increased risk of gestosis, abnormal labor, bleeding, gestational diabetes, hypertension, as well as premature and delayed delivery [1-3]. Studies have shown that late gestosis occurs most often, and in 75% of cases it is complicated by the development of feto-placental insufficiency. Gestational diabetes develops in at least 3% of pregnant women and is caused by significant changes in carbohydrate metabolism, which are aimed at meeting the needs of the fetus and placenta, but also have a diabetogenic effect [4]. The incidence of metabolic disorders during pregnancy is 5-20%, which leads to numerous obstetric complications, high perinatal morbidity and mortality, and existing therapeutic and preventive measures are not always effective [5]. Pathological manifestations in these pathologies are multisystemic in nature, which is due to endothelial dysfunction, for the correction of which it is advisable to prescribe nitric oxide donors, namely L-arginine [6].

THE AIM

The aim was to determine the feasibility of using Tivortin in metabolic disorders during pregnancy and its effect on the course of pregnancy, childbirth, fetal and neonatal status.

MATERIALS AND METHODS

We examined 210 women aged 18 to 34 years with metabolic disorders at 16 to 36 weeks of pregnancy. The groups of pregnant women were homogeneous in terms of age, anamnesis, clinical and laboratory findings. 60 pregnant women with moderate preeclampsia were divided into 2 groups. Group I included 30 patients who were treated according to the clinical protocol with additional prescription of Tivortin, and Group II included 30 women who received treatment according to the clinical protocol. Similarly, 60 women with gestational diabetes were divided into groups III and IV. Among the 60 obese women, 30 pregnant women received tivortin along with diet and physiotherapy (group V), and 30 pregnant women received conventional treatment (group VI). The control group included 30 women with physiologically normal pregnancies.

The active ingredient of Tivortin (manufactured by Yuria-Pharm LLC, Ukraine) is L-arginine, which has antihypoxic, membrane-stabilizing, cytoprotective, antioxidant effects, acts as an active regulator of intermediate metabolism and energy supply processes, and plays a role in maintaining hormonal balance in the body. The drug is certified for use during pregnancy.

Tivortin was administered for 7 days once a day, 100 ml intravenously drop (slowly), then tivortin aspartate 1 g (5 ml) for 14 days orally 4 times a day in courses at 16 and 26 weeks of gestation. The effectiveness of the treatment was evaluated in dynamics in pregnant women of all groups based on clinical picture; laboratory data; uterine artery Doppler; determination of lipid peroxidation (LPO), in particular, malondialdehyde (MDA) and diene conjugates (DC) and antioxidant system (AOS), namely ceruloplasmin (CP) and catalase (C); leptin and placental growth factor (PGF) levels were determined at 26 weeks of gestation. The fetal condition was monitored in the dynamics by ultrasound with Doppler, determination of biophysical profile, cardiotocography using Dawes/Redman criteria and STV index, which reflects the degree of metabolic acidemia. For comparison, the parameters of the control group were used. The results were analyzed using the methods of variation statistics and considered significant at $p < 0.05$.

RESULTS

It was found that moderate preeclampsia was accompanied by a significant increase in the incidence of preterm labor, growth retardation syndrome, and fetal distress compared with the control group. In labor, the main complications were premature rupture of membranes, abnormal labor activity and fetal distress, $p < 0.05$. These complications were the main indications for cesarean section, the frequency of which was significantly higher compared to the control group. At the same time, there was an increase in the level of malondialdehyde in group I to 3.25±0.45 μmol/mL and in group II to 3.29±0.34 μmol/mL against 2.21±0.11 μmol/mL in the control group, $p<0.05$. The level of diene conjugates increased in group I to 24.3±0.3 μmol/l, and in group II to 26.8±0.2 μmol/l against 9.5±0.3 μmol/l in the control group, $p<0.05$. Against the background of intensification of peroxidation processes, significant changes in the antioxidant defense system were revealed. In particular, the activity of ceruloplasmin significantly changed (39.28±0.67 mg/dl in group I and 37.16±0.53 mg/dl in group II vs. 22.41±0,97 mg/dl in the control group), catalase (11.63±0.64 mg H_2O_2 /ml in group I and 12.36±0.35 mg H_2O_2 /ml in group II and against 14.56±0.52 mg H_2O_2 /ml in the control group). The results of the study indicate the presence of a significantly higher level of leptin (26.6±1.34 ng/ml in group I and 27.2±2.47 ng/ml in group II versus 10.7±0.57 ng/ml in the control group). In addition, a significantly lower level of placental growth factor was observed (638±11.8 pg/ml in group I and 754.3±7.4 pg/ml in group II versus 1102±15.8 pg/ml in the control group).

The course of pregnancy in patients with gestational diabetes was complicated by vomiting, spontaneous premature termination of pregnancy, late gestosis, polyhydramnios, inflammatory diseases of the urinary tract, progressive anemia, and macrosomia. The incidence of spontaneous abortion was 29.6%, in the control group – 7%, $p<0.05$. Late gestosis occurred more often before 34 weeks of pregnancy and was observed in 24% of cases, while in the control group – 2%, $p<0.05$. Polyhydramnios was observed in 15% of cases, in the control group – 1%, $p<0.01$. Urinary tract infection complicated the course of pregnancy in 19.4%, and in the control group in 7% of patients, $p<0.05$. In labor, premature rupture of the fetal bladder, clinically narrow pelvis, abnormal labor activity, fetal distress, surgical delivery, and newborn asphyxia were significantly more common compared to the control group, $p<0.05$. The content of malondialdehyde in group III was 3.11±0.25 μmol/mL, and in group IV – 3.19±0.19 μmol/mL against 2.21±0.11 μmol/mL in the control group, $p<0.05$. The level of diene conjugates increased in group III to 22.4±0.5 μmol/l, and in group IV to 25.5±0.2 μmol/l against 9.5±0.3 μmol/l in the control group, $p<0.05$. Ceruloplasmin activity changed significantly (43.32±0.24 mg/dl in group III and 39.35±0.35 mg/dl in group IV vs. 22.41±0,97 mg/dl in the control group), catalase (10.35±0.43 mg H_2O_2 /ml in group III and 11.93±0.32 mg H_2O_2 /ml in group IV against 14.56±0.52 mg H_2O_2 /ml in the control group). The level of placental growth factor

was 568±10.7 pg/ml in group III and 606.8±12.7 pg/ml in group IV against 1102±15.8 pg/ml in the control group, p<0.05. Leptin levels in groups III and IV did not differ significantly from those in the control group.

Obesity during pregnancy significantly increases the risk of gestational hypertension, preeclampsia, preterm or delayed delivery, abnormal labor, postpartum hemorrhage, fetal growth retardation syndrome, newborn asphyxia, macrosomia, gestational diabetes, fetal distress compared to the control group, p < 0.05. In addition, the results of the study indicate that obese women had significantly higher levels of leptin (39.6±1.23 ng/ml in group V and 37.2±2.27 ng/ml in group VI versus 10.7±0.57 ng/ml in the control group). The level of placental growth factor was 538±8.7 pg/ml in group V and 706.8±9.7 pg/ml in group VI versus 1102±15.8 pg/ml in the control group, p<0.05. The content of malondialdehyde in group V was 3.09±0.13 μmol/mL, and in group VI – 3.12±0.9 μmol/mL against 2.21±0.11 μmol/mL in the control group, p<0.05. The level of diene conjugates increased in group V to 19.4±0.7 μmol/l, and in group VI to 21.5±0.6 μmol/l against 9.5±0.3 μmol/l in the control group, p<0.05. Ceruloplasmin activity changed significantly (33.12±0.34 mg/dL in group V and 36.31±0.4 mg/dL in group VI vs. 22.41±0,97 mg/dl in the control group), catalase (9.87±0.59 mg H_2O_2/ml in group V and 10.25±0.42 mg H_2O_2 /ml in group VI against 14.56±0.52 mg H_2O_2 /ml in the control group).

In order to correct the identified disorders, along with treatment in accordance with the current clinical protocols of each nosology, we used the drug Tivortin. In patients of group I, proteinuria and edema decreased, blood pressure normalized, the percentage of preterm delivery and progressive anemia of pregnant women decreased, the pulsatile index of the uterine artery and the index of peak systolic velocity of the umbilical cord vessels in the second trimester of pregnancy normalized, a lower incidence of early preeclampsia and its transition to severe preeclampsia in the dynamics of observation and treatment was noted compared with pregnant women of group II, p<0,05 (Table I).

Along with this, the level of malondialdehyde in group I decreased to 2.25±0.54 μmol/mL versus 3.25±0.45 μmol/mL before treatment, p<0.05. In group II, the level of malondialdehyde decreased to 2.29±0.53 μmol/mL versus 3.29±0.34 μmol/mL before treatment, p<0.05. At the same time, the level of diene conjugates in group I decreased to 10.2±0.4 μmol/mL versus 24.3±0.3 μmol/mL before treatment, p<0.05. In group II, a decrease in the level of diene conjugates reached 11.6±0.6 μmol/mL versus 26.8±0.2 μmol/l before treatment, p<0.05. The increase in the activity of antioxidant defense was manifested by a significant change in ceruloplasmin activity to 26.34±0.45 mg/dL in group I against 39.28±0.67 mg/dL before treatment, p<0.05. In group II, ceruloplasmin activity was 28.12±0.35 mg/dL versus 37.16±0.53 mg/dL before treatment, p<0.05. The level of catalase in group I was 12.13±0.32 mg H_2O_2 /ml versus 11.63±0.64 mg H_2O_2 /ml before treatment, p<0.05. At the same time, in group II, it was 12.16±0.44 mg H_2O_2 /ml versus 12.36±0.35 mg H_2O_2 /ml before treatment, p>0.05. There was a significantly lower level of leptin 13.37±0.4 ng/ml in group I against 26.6±1.34 ng/ml before treatment, p<0.05 and 15.4±0.5±0.4 ng/ml in group II against 27.2±2.47 ng/ml before treatment, p<0.05. At 26 weeks of gestation, placental growth factor levels were: in group I 655±8.8 pg/ml versus 638±11.8 pg/ml before treatment (p>0.05), and in group II 783.4±5.4 pg/ml versus 754.3±7.4 pg/ml before treatment, p>0.05. The level of glycemia decreased in pregnant women of both groups III and IV, but in group III it was significantly lower than in group IV, p<0.01. Due to changes in carbohydrate metabolism during treatment, insulin therapy was adjusted in pregnant women. In group III, up to 22 weeks, the insulin dose decreased by 16%, in group IV – by 4%, p < 0.05. At 23-38 weeks of pregnancy, the insulin dose in group III decreased by 3.2%, and in group IV it increased by 11%, p<0.05 (Table II).

Along with this, the level of malondialdehyde in group III decreased to 2.05±0.51 μmol/mL versus 3.11±0.25 μmol/mL before treatment, p<0.05. In group IV, the level of malondialdehyde decreased to 2.09±0.23 μmol/mL versus 3.19±0.19 μmol/mL before treatment, p<0.05. At the same time, the level of diene conjugates in group III decreased to 12.3±0.4 μmol/mL versus 22.4±0.5 μmol/mL before treatment, p<0.05. In group IV, the decrease in the level of diene conjugates reached 13.4±0.3 μmol/mL versus 25.5±0.2 μmol/l before treatment, p<0.05. Ceruloplasmin activity significantly changed to 29.67±0.34 mg/dL in group III against 43.32±0.24 mg/dL before treatment, p<0.05, and in group IV it was 27.21±0.37 mg/dL against 39.35±0.35 mg/dL before treatment, p<0.05. The level of catalase in group III was 13.06±0.41 mg H_2O_2 /ml versus 10.35±0.43 mg H_2O_2 /ml before treatment, p<0.05. At the same time, in group IV, it was 12.08±0.23 mg H_2O_2 /ml versus 11.93±0.32 mg H_2O_2 /ml before treatment, p>0.05. The content of placental growth factor in group III was 752±5.8 pg/ml versus 568±10.7 pg/ml before treatment (p>0.05), and in group IV 791.4±6.3 pg/ml versus 606.8±12.7 pg/ml before treatment, p>0.05. The level of leptin in groups III and IV after treatment did not differ significantly from the control group. After the treatment, the percentage of gestational hypertension, preeclampsia, preterm labor, abnormal labor activity, postpartum hemorrhage, fetal growth retardation syndrome, macrosomia, ges-

Table I. Changes in the indexes of malondialdehyde (MDA), diene conjugates (DC), ceruloplasmin (CP), catalase (C), placental growth factor (PGF), leptin (L) in preeclampsia

Index	Control group	I group		II group	
		Before treatment	After treatment	Before treatment	After treatment
MDA μmol/mL	2,21±0,11	3,25±0,45*	2,25±0,54°	3,29±0,34*	2,29±0,53°
DC μmol/l	9,5±0,3	24,3±0,3*	10,2±0,4°	26,8±0,2*	11,6±0,6°
CP mg/dl	22,41±0,97	39,28±0,67*	26,34±0,45°	37,16±0,53*	28,12±0,35°
C mg H2 O2 /ml	14,56±0,52	11,63±0,64*	12,13±0,32*°	12,36±0,35*	12,16±0,44*
PGF pg/ml	1102±15,8	638±11,8*	655±8,8*	754,3±7,4*	783,4±5,4*
L ng/ml	10,7±0,57	26,6±1,34*	13,37±0,4°	27,2±2,47*	15,4±0,5°

Note: * - significant difference of indexes compared to control group, p<0,05;
° - significant difference of indexes before and after treatment, p<0,05

Table II. Changes in the indexes of malondialdehyde (MDA), diene conjugates (DC), ceruloplasmin (CP), catalase (C), placental growth factor (PGF), leptin (L) in gestational diabetes

Index	Control group	III group		IV group	
		Before treatment	After treatment	Before treatment	After treatment
MDA μmol/mL	2,21±0,11	3,11±0,25*	2,05±0,51°	3,19±0,19*	2,09±0,23°
DC μmol/l	9,5±0,3	22,4±0,5*	12,3±0,4°	25,5±0,2*	13,4±0,3°
CP mg/dl	22,41±0,97	43,32±0,24*	29,67±0,34°	39,35±0,35*	27,21±0,37°
C mg H2 O2 /ml	14,56±0,52	10,35±0,43*	13,06±0,41*°	11,93±0,32*	12,08±0,23*
PGF pg/ml	1102±15,8	568±10,7*	752±5,8*	606,8±12,7*	791,4±6,3*
L ng/ml	10,7±0,57	12,6±0,43	11,4±0,15	9,7±1,71	10,3±0,8

Note: * - significant difference of indexes compared to control group, p<0,05;
° - significant difference of indexes before and after treatment, p<0,05

Table III. Changes in the indexes of malondialdehyde (MDA), diene conjugates (DC), ceruloplasmin (CP), catalase (C), placental growth factor (PGF), leptin (L) in obesity

Index	Control group	V group		VI group	
		Before treatment	After treatment	Before treatment	After treatment
MDA μmol/mL	2,21±0,11	3,09±0,13*	2,09±0,12°	3,12±0,9*	2,17±0,31°
DC μmol/l	9,5±0,3	19,4±0,7*	11,4±0,6°	21,5±0,6*	12,7±0,4°
CP mg/dl	22,41±0,97	33,12±0,34*	26,37±0,34°	36,31±0,4*	25,14±0,35°
C mg H2 O2 /ml	14,56±0,52	9,87±0,59*	12,26±0,21*°	10,25±0,42*	11,13±0,24*
PGF pg/ml	1102±15,8	538±8,7*	552±2,8*	706,8±9,7*	725,4±4,3*
L ng/ml	10,7±0,57	39,6±1,23*	14,13±0,2°	37,2±2,27*	15,3±0,6°

Note: * - significant difference of indexes compared to control group, p<0,05;
° - significant difference of indexes before and after treatment, p<0,05

tational diabetes decreased in obese pregnant women (group V) compared to pregnant women of group VI, p < 0.05 (Table III).

In addition, the results showed that obese women had significantly lower levels of leptin – 14.13±0.2 ng/ml in group V versus 39.6±1.23 ng/ml before treatment, p<0.05 and 15.3±0.6 ng/ml in group VI versus 37.2±2.27 ng/ml before treatment, p<0.05. The concentration of placental growth factor was: in group V – 552±2.8 pg/ml vs. 538±8.7 pg/ml before treatment, p>0.05, and in group VI – 725.4±4.3 pg/ml vs. 706.8±9.7 pg/ml before treatment, p>0.05. At the same time, the level of malondialdehyde in group V decreased to 2.09±0.12 μmol/mL versus 3.09±0.13 μmol/mL before treatment, p<0.05. In group VI, the level of malondialdehyde decreased to 2.17±0.31 μmol/mL versus 3.12±0.9 μmol/mL before treatment, p<0.05. At the same time, the level of diene conjugates in group V decreased to 11.4±0.6 μmol/mL versus 19.4±0.7 μmol/mL before treatment, p<0.05. In group VI, the decrease in the level of diene conjugates reached 12.7±0.4 μmol/mL versus 21.5±0.6 μmol/l before treatment, p<0.05. In addition, ceruloplasmin activity significantly changed to 26.37±0.34 mg/dL in group V versus 33.12±0.34 mg/dL before

treatment, p<0.05. In group VI, ceruloplasmin activity was 25.14±0.35 mg/dL versus 36.31±0.4 mg/dL before treatment, p<0.05. The level of catalase in group V was 12.26±0.21 mg H_2O_2/ml versus 9.87±0.59 mg H_2O_2/ml before treatment, p<0.05. At the same time, in group VI it was 11.13±0.24 mg H_2O_2/ml versus 10.25±0.42 mg H_2O_2/ml before treatment, p>0.05.

Thus, standard therapy contributed to a significant suppression of excessive lipid peroxidation activity with a simultaneous increase in the activity of the antioxidant system, except for catalase, which indicates both profound changes in free radical oxidation in moderate preeclampsia, obesity and gestational diabetes, and the difficulty of their correction, which actually led to the expediency of using the drug Tivortin. Compared with groups II, IV, VI, pregnant women in groups I, III, V had a 3-fold decrease in the incidence of complications in childbirth, a 2-fold decrease in surgical interventions, a 1.7-fold decrease in postpartum infectious complications, a 1.8-fold decrease in the incidence of infants born in asphyxiation, and a corresponding decrease in hospital stay, p<0.05. Doppler ultrasound of the umbilical cord vessels showed normalization of the systolic-diastolic ratio after the course of Tivortin therapy (from 3.84±0.04 to 3.1±0.06, p<0.01). In groups II, I V and VI, this indicator did not change significantly (from 3.72±0.04 to 3.51±0.04, p>0.05). Determination of the fetal biophysical profile and cardiotocography using the Dawes/Redman criteria and STV index indicate a significant improvement in the fetal condition in pregnant women after treatment with Tivortin compared to groups II, IV and VI, which is confirmed by a satisfactory assessment of newborns on the Apgar scale. The use of Tivortin therapy in the complex treatment of pregnant women with metabolic disorders significantly reduced the percentage of surgical deliveries compared to groups II, IV and VI due to a decrease in the number of indications for cesarean section on the part of both the fetus and the mother.

DISCUSSION

The problem of reproductive health of the population of Ukraine is urgent [7]. The complexity of solving the issues that define this problem is due not only to the direct state of health of the population of our country, but also to a significant number of risk factors that influence the development of their disorders. Metabolic disorders during pregnancy are associated with a higher risk of complications during childbirth, surgical delivery, with a higher risk of developing a number of postpartum complications, such as bleeding, deep vein thrombosis, and the development of infectious complications. In addition, the metabolic syndrome during pregnancy is a risk factor for the birth of children both underweight and pathologically overweight, which, in turn increases the risk of developing metabolic disorders in this group of children further in life, i.e. contributes to the implementation of a growth program that leads to diabetes mellitus, obesity, arterial hypertension, etc.

At the same time, it should be borne in mind that the results of each analysis should be optimally interpreted taking into account all relevant anamnestic, clinical, other laboratory and instrumental data, which allows to identify to detect pathology with greater reliability than each method alone. Moreover it is possible to use the data obtained for risk assessment, early diagnosis, severity of the pathological process diagnosis, severity of the pathological process and effectiveness of its treatment. Therefore, the main task of treating metabolic syndrome is to identify and correct entire spectrum of existing metabolic disorders and prevention of the development of obstetric and perinatal complications. Accordingly, the research topic is relevant and has a certain scientific novelty. The goal was fully achieved and the relevant conclusions were drawn. The results are reliable and original. The incidence of metabolic disorders in pregnant women is increasing every year, so it is important to study the pathogenetic mechanisms of this pathology in all possible manifestations, which will allow the development and implementation of a set of effective therapeutic and preventive measures to reduce obstetric and perinatal complications in a certain category of patients.

CONCLUSIONS

The presence of metabolic syndrome in women is a significant risk factor for the development of obstetric and perinatal complications due to the significant intensity of lipid peroxidation, severe depression of the antioxidant system, decreased placental growth factor content and increased plasma leptin levels. Determination of these indicators in the dynamics of observation and treatment can serve as an additional diagnostic and prognostic criterion for a satisfactory clinical course of pregnancy and the effectiveness of therapeutic measures aimed at correcting disorders. The results of the studies proved the safety and efficacy of Tivortin in the complex treatment of pregnant women with metabolic disorders, which improves the course of pregnancy, childbirth, fetal and neonatal condition.

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ORCID and contributionship:
Valeriy V. Korsak: 0000-0002-7907-7830 [A,B]
Yuriy Y. Bobik: 0000-0002-6494-0638 [B,C,F]
Irina I. Packan: 0000-0002-0227-5548 [A,D,E]

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CORRESPONDING AUTHOR

Valeriy V. Korsak
Uzhhorod National University
14 University St., 88000 Uzhgorod, Ukraine
tel: +3800506729654
e-mail: valera.korsak@uzhnu.edu.ua

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A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article