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THE SIGNIFICANCE OF HOMOCYSTEINE IN PATHOGENETIC MECHANISMS OF GESTATIONAL COMPLICATIONS

Siusiuka V.
Doctor of Medical Sciences, associate professor
Department of Obstetrics and Gynecology
Zaporizhzhia State Medical University
Boguslavska N.
Candidate of Medical Sciences
Deputy director of a municipal non-profit enterprise
«Regional perinatal center» of the Zaporizhzhia regional council
Department of Obstetrics and Gynecology
Zaporizhzhia State Medical University
Kyryliuk A.
Candidate of Medical Sciences
Director of a municipal non-profit enterprise
«Regional perinatal center» of the Zaporizhzhia regional council,
Department of Obstetrics and Gynecology
Zaporizhzhia State Medical University,
Babinchuk O.
Candidate of Medical Sciences
Head of the maternity ward of a municipal non-profit enterprise
«Regional perinatal center» of the Zaporizhzhia regional council,
Department of Obstetrics and Gynecology
Zaporizhzhia State Medical University,
Bachurina O.
Head of the consultative and diagnostic department
Of a municipal non-profit enterprise
«Regional perinatal center» of the Zaporizhzhia regional council
Yershova O.
Department of Obstetrics and Gynecology
Zaporizhzhia State Medical University
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Abstract

The article presents data of national and world literature on the research of premature birth. The analysis shows an interconnection between the level of homocysteine in the blood plasma and obstetric complications. For today, it is important to research the level of homocysteine in the blood plasma of women whose pregnancies are complicated by preeclampsia, premature birth, fetal growth retardation, as well as during postterm pregnancy.

Keywords: pregnancy, homocysteine, hyperhomocysteinemia, postterm pregnancy, obstetric and perinatal complications.

The current object of modern scientific research is homocysteine (HC) as an important physiological factor and predictor of many pathological conditions in hyperhomocysteinemia (HHC). Currently, in the laboratory diagnosis of a number of diseases, the indicator is HC, which is a sulfonated analogue of aspartate. Its role as a potential neurotransmitter that activates glutamate receptors is considered. There is a positive relation between stroke and HC concentration in people with no previously identified cardiovascular disease. It was also found that HC in high concentrations has a toxic effect on the endothelium and accelerates the development of atherosclerosis [1, 2].

HC is a sulfur-containing amino acid. As a chemical was described in 1932. HC enters the human body mainly with animal proteins in the form of methionine – the metabolic precursor of HC. HC is found in three forms in the blood: free HC, bound to albumin and in the form of disulfides, mainly with cysteine or as homocystin. The term «total plasma homocysteine» combines all these three forms [3, 4, 5, 6, 7].

In 1962 HC was found in the urine of mentally retarded children. Gerritsen T. et. al. (1964) described a genetic defect in the enzyme cystathionine-β-synthase, which is clinically manifested by a significant increase the concentration of HC in the blood plasma and homocysteinuria. This hereditary pathology is accompanied by atherosclerotic vascular lesions, thromboembolic complications are common. More than 50% of patients have acute cardiovascular complications, 25% of patients with this hereditary defect die from cardiovascular diseases before reaching the age of 30. Adult patients which suffer from coronary artery diseases have often impaired metabolism of HC. In the following decades, the technical difficulties of identifying HC in the blood plasma limited the detailed study of the problem of HHC for other cardiovascular diseases [8, 9, 10, 11, 12, 13, 14, 15, 16].

In the body HC is metabolized in two main ways: transulfation and methylation. About half of the HC

remethylates with the formation of methionine, which is the most important component of the metabolism of single-carbon compounds [17, 18, 19].

HC is formed from methionine by demethylation, thus forming a methyl group, which is converted to S-adenosylmethionine. This reaction is important for such biochemical processes as the synthesis of purine and pyrimidine bases, nucleic acids, protein, phospholipids, myelin, polysaccharides, catecholamines, choline [20]. S-adenosylmethionine is a universal biological source of methyl groups in the body. The product of methylation reactions, where S-adenosylmethionine gives a methyl group, is S-adenosylhomocysteine, which in turn under the action of specific hydrolases is cleaved into adenosine and HC. This reaction is reversible, and increasing the level of total HC leads to increased levels of S-adenosylhomocysteine [21, 22, 23].

Remethylation of HC to methionine in most tissues is carried out with the participation of methionine synthase (MS) and coenzyme vitamin B12. In some tissues, mainly in the liver, remethylation occurs with the help of enzyme betaine-homocysteine-methyltransferase. In this reaction, the source of the methyl group is betaine. Normally, about 50% of HC is transulfationed. As a result of this reaction, HC combines with serine by cystathionine-β-synthase (CBS) (B6-dependent enzyme) and modifies as cysteine and α-ketobutyrate [4, 24, 25].

The concentration of HC in the blood can vary depending on taking a number of medications. The mechanism of their action is related to the effect on renal function, as well as on the level of vitamins and hormones, as it was established by Welch and Loscalo (1998). According to Morgan and Baggott (2010), methotrexate (a folic acid antagonist which is used to treat rheumatoid arthritis), anticonvulsants, in particular phenytoin, deplete the supply of folic acid in the liver, according to Mintzer et al. (2009) and metformin (a drug which is used to treat type 2 diabetes) negatively affect the level of HC. On the contrary, Hak et al. noted that taking certain hormones, such as 17-estradiol, reduces the level of HC in the blood of women in menopause. It is believed that the level of HC is in feedback with estrogen and increases in postmenopausal women. Shah S. in research showed the connection of HC not only with estrogen but also with cognitive functions in women in menopause [26, 27].

During life the level of HC in the blood gradually increases. The content of total HC in the blood plasma of a healthy person is 5-15 μmol /l. Before puberty, the levels of HC in boys and girls are approximately the same (about 5 μmol /ml). During puberty, the level of HC increases to 6-7 μmol /ml and in boys this increase is more clear than in girls. In adults, the level of HC is 10-11 μmol /ml, but in men this indicator is usually higher than in women. Over the years, the level of HC gradually increases, and in women the rate of this increase is higher than in men. The gradual increase of the level of HC over the years is explained by a decrease of renal function, and higher levels of HC in men – more muscle mass [28].

The level of total HC is considered to be abnormal if it is in the 95th percentile of the distribution of this indicator in the «normal population», just as well as the concepts of hypertension and hypercholesterolemia were defined. For example, after methionine loading, HHC is defined as the level of total HC above two standard deviations from the mean. On an empty stomach, the «normal» level of total HC of plasma is from 5 to 15 μmol /l, and its level above is divided into mild (16-30), medium (31-100) and severe (100 μmol /l) HHC [29].

As for the effect of thyroid hormones on HC, according to the modern ideas, hypothyroidism leads to increase of the level of HC, and in hyperthyroidism there is a slight decrease of it. The mechanisms of HHC in this case are unknown. Given the important role of vitamin B12 in HHC metabolism, pernicious anemia, which often accompanies hypothyroidism, can have some significance. It is also possible that hypodynamia also contributes, which is a serious factor in the development of HC. Hyperprolactinemia, which often associated with primary hypothyroidism, can be the reason of elevated HC levels in people with hypothyroidism. Thus, Yavuz D. H et al. detected increased concentrations of HC in premenopausal women with hyperprolactinemia. According to the statements of this author, treatment with bromocriptine was accompanied by a decrease of the concentration of these substances in the blood [30].

During pregnancy the level of HC has a tendency to decrease. This decrease occurs on the edge of the first and second trimesters of pregnancy, and then the level of HC remains relatively stable. Normal levels of HC are restored in 2-4 days after childbirth. It is considered that decreasing the level of HC during pregnancy contributes placental circulation. The level of HC in the blood is inversely proportional to the weight of the fetus and newborn.

A significant role of HHC is given to the development of various vascular pathology, especially controversial is the question – whether HHC is the cause or consequence of the pathological process [31]. The level of HC in the body of a pregnant woman is determined by many factors, including folic acid and vitamin B12, impaired renal function, various changes in the activity of enzymes in the human body as a result of genetic polymorphism of the population. Haque W. M. proved that during normal pregnancy the serum concentration of HC should decrease. And the disorder of HC metabolism in both the mother organism and the fetus leads to neural tube defects, various manifestations of placental vasculopathy, which are realized in the future as preeclampsia or placental abruption. Apart from folic acid, as Haque W. M. has consistently shown, halving the risk of neural tube defects in the fetus, no other strategies have been found for HC metabolism, as this prevention scheme reliably reduces the frequency of these and other common obstetric pathologies.

Aubard Y. et al. investigated the metabolism of HC during pregnancy, noting that it depends primarily on three enzymes and several cofactor vitamins (vitamins B6, B9 and B12) [32]. Genetic abnormalities

in these enzymes or a deficiency of these vitamins leads to HHC. The discovery that HHC can also be responsible for some complications during pregnancy has been made relatively recently. Research projects in this area are still infrequent and reports on a limited number of patients. One of the most serious complications of pregnancy associated with HHC is preeclampsia, which leads to an increased frequency of maternal morbidity, mortality, and the frequency of birth of premature infants and babies with FGR [7, 33].

Clinical research have shown an interconnection between HHC and thrombosis, both arterial and venous. HHC is now considered as a risk factor for a number of obstetric complications, such as miscarriage, preeclampsia, premature abruption of the normally located placenta, etc. [34].

Daly S. et al. investigated the significant association of HHC in women during pregnancy with vascular diseases in their later lives [35]. Data from a cohort of women with a preeclampsia in the past during pregnancy indicate that they are at increased risk of developing cardiovascular and cerebrovascular diseases later in life. Elevated HC concentrations may be a common link between the above nosologies.

Genetic defects of the homozygous genotype, as noted by Ruqolo S. et al., cause high levels of HC in the blood plasma; lead to a decrease in the activity of enzymes responsible for its metabolism, for example: lack of cystathionine beta-synthase; deficiency of methylcobalamin production; 5-10 methylenetetrahydrofolate reductase (MTHFR) deficiency [36]. However, even heterozygous genotypes with a variable frequency from 1/70 to 1/200 and directly 5-15% for the C677T mutation 5-10 MTHFR can detect a mild form of HHC. The rapid effects of HHC on maternal and fetal morbidity during pregnancy and childbirth have been widely demonstrated in the international literature.

The study of the role of HHC in the first trimester of pregnancy included a group of 100 women from 8 to 12 weeks of gestation. Serum HC levels were checked after a night fasting [37]. Significantly elevated HC levels were found by researchers in women with a previous history of hypertensive disorders during pregnancy and previous pregnancy losses during the second or third trimester. No significant differences in HC levels were found in women with previous gestational diabetes, preterm childbirth, or fetal malformations. HC levels were significantly elevated in women who had hypertension during pregnancy, oligohydramnios and meconium stained amniotic fluid, spontaneous abortion, or low birth weight.

The interconnection between HC level and pregnancy history was investigated by linear and logistic regression, multiple covariate control, including life history, family history, hypertension, diabetes mellitus, obesity, tobacco consumption, demographic factors [38]. Researchers have linked HHC in women decades after pregnancy with hypertension in previous pregnancies and HHC, which is an important factor in trying to prevent primary cardiovascular disease.

Brustolin S. et al. observed during pregnancy in the examined women an increase in the level of HC for each trimester of pregnancy and a simultaneous decrease in folate levels [39]. In addition, folic acid levels continue to decrease after pregnancy, according to this group of researchers. Maternal smoking also changes the total concentration of HC in children of young age. Serum concentrations of HC were significantly higher in smokers compared to non-smoking pregnant women and in the umbilical cord blood of their newborns.

Cande V. Ananth et al. considered 2 variants of 5-10 methylenetetrahydrofolate reductase deficiency (MTHFR): 677C → T and 1298A → C mutations in genomic DNA isolated from maternal blood in New Jersey in a multicenter case-control study of placental abruption [40]. In this population, neither heterozygosity nor homozygosity for 677C → T and 1298A → C variants in MTHFR were associated with placental abruption.

Wendy J Sturtz et al. studied the interconnection between HHC and the risk of intraventricular hemorrhage in premature newborns [41]. After analyzing 123 children over 32 weeks of gestation and a group of 25 full-term infants – no direct interconnection was found between intraventricular hemorrhage and HC level. To do this, two blood stains were collected on filter paper by high performance liquid chromatography (HPLC) were examined. Male newborns, prenatal steroids and preeclampsia were statistically significantly associated with differences in HC levels.

Investigations which have been conducted in recent decades is constantly expanding the understanding of the metabolic aspects of the pathogenesis of postterm pregnancy. It is established that this triggers a whole cascade of biochemical, genetic, immunological processes, which ultimately lead to the formation of this pathology [42, 43, 44]. There is a fairly clear regularity – with increasing total level of HC in the pregnant woman's body progressively decreases the level of hormones of the mother-placenta-fetus system (progesterone, cortisol, placental lactogen and, in a less degree, estriol). All of the above hormones play an important role in fetal development and in the normal course of pregnancy, as well as in the timely initiation of labor. High levels of HC in the body of a pregnant woman provoke a decrease in the synthetic and regulatory function of the mother-placenta-fetus system and may be the cause of postterm pregnancy [44, 45]. During pregnancy, the level of HC should be reduced, because it helps to improve uteroplacental circulation. This decrease usually occurs on the edge of the first and second trimesters of pregnancy, and then the level of HC remains relatively stable. The level of HC during post-term pregnancy (10,8 mmol /l) is much more higher than this indicator in pregnant women at 37-40 weeks (7,7 mmol /l) [44].

Conclusions

The analysis of the literature data confirmed that there is a clear interconnection between the level of homocysteine in the blood plasma and obstetric

complications. For today it is important to research the level of homocysteine in the blood plasma of women whose pregnancies are complicated by preeclampsia, premature birth, fetal growth retardation, as well as during postterm pregnancy.

References

1. Powers R. W., Minich L. A., Lykins D. L., Ness R. B., Crombleholme W. R., Roberts J. M. Methylenetetrahydrofolate reductase polymorphism, folate, and susceptibility to pre-eclampsia. Soc Gynecol Invest. 1999; 6: 74-9.

2. Roque H., Paidas M. J., Funai E. F., Kuczynski E., Lockwood C. J. Maternal thrombophilias are not associated with early pregnancy loss. Thromb Haemost. 2004; 91 (2): 290-5.

3. Scazziota A., Pons S., Raimondi R., Fernandez C, Altman R. Is C677T mutation in the methylenetetrahydrofolate reductase (MTHFR) a risk factor for arterial thrombosis? 16th Congress oh thrombosis and haemostasis. Porto, 2000.

4. Silva-Pinto A., Fidalgo T., Marques D., Tamagnini G. Hyperhomocysteinemia and methylenetetrahydrofolate reductase (MTHFR) mutations in patients with stroke. 16th Congress oh thrombosis and haemostasis. Porto, 2000.

5. Sztenc S. Hyperhomocysteinemia and pregnancy complications. Ginekol Pol. 2004; 75 (4): 317-25.

6. Vollset S. E., Refsum H., Irgens L. M., Emblem B. M, Tverdal A., Gjessing H. K., Monsen A. L., Ueland P. M. Plasma total homocysteine, pregnancy complications, and adverse pregnancy outcomes: the Hordaland Homocysteine Study. Am J Clin Nutr. 2000; 71: 962-68.

7. Davydova Yu. V. Prevention of impaired homocysteine metabolism and folic acid deficiency: importance for reducing the incidence of perinatal and somatic complications in women. Perinatology and pediatric. Ukraine. 2018; 2 (74): 57-60.

8. Weis D. Hyperhomocysteinemia in hypothyroidism (Letter; response by Faiman C., Jacobscn D.W., Green R.). Ann Intern Med. 2000; 132: 677.

9. Amigo M. S. The antiphospholipid syndrom: what is the prognosis? Lupus. 1998; 7: 1-2.

10. Beer A. E., Kwak J. Reproductive medicine program. Finch University of Health Science, Chicago Medical School. 2000.

11. Delucia D., Vel Giudice V., Lautherano M., Maisto G., Marotta R., Marra M. Antiphospholipid antibodies associated to migraine in patient suffering from TIA.16-th Congress on thromb and haemost, Porto, 2000.

12. Entrican G. Immune regulation during pregnancy and host-patogen interactions in infectious abortion. Journal of Comparative Pathology. 2002; 126, 2-3: 79-94.

13. Eskes T. K. Clotting disorders and placental abruption: homocysteine a new risk factor. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2001; 95: 206-212.

14. Gandra M. J., Fraga M., Saraiva G. P. Anticardiolipin antibodies and high risk pregnancy. 16-th Congress on thromb and haemost, Porto, 2000.

15. Gardner L. Moffett A. Dendritic cells in the human decidua. Biology of Reproduction. 2003. 69, 4: 1438-1446.

16. Gris J. C. et al. Antiphospholipid and antiprotein syndromes in non-trombotic, non-autoimmune women with unexplained recurrent primary early fetal loss. Thromb. Haemost. 2000; 84: 228-236.

17. Heikkinen J., Mottonen M. Phenotypic characterization of human decidual macrophages. Clinical and Experimental Immunology. 2003; 131: 498-505.

18. Huddleston H., Schust D. J Immune interactions at the maternal-fetal interface: a focus on antigen presentation. American Journal of Reproductive Immunology. 2004; 51, 4: 1933-1936.

19. Hunt J. S., Petroff M. G., Burnett T. G. Uterine leucocytes: key players in pregnancy. Seminars in Cell and Developmental Biology. 2000; 11 (2): 127-137.

20. Loke Y. W., King A. Immunological aspects of human implantation. Journal of Reproduction and Fertility. 2000; 55: 83-90.

21. Moffett-King A. Natural killer cells and pregnancy. Nat. Rev. Immunol. 2002; 2, 9: 656-663.

22. Ogunyemi D., Ku W., Arkel Y. The association between inherted thrombophilia, antiphospholipid antibodies and lipoprotein a levels with obstetrical complications in pregnancy. J. Thromb. Thrombolysis. 2002; 14, 2: 157-162.

23. Parham P. NK cells and trofoblasts: parthners in pregnancy. Journal of Experimental Medicine. 2004; 200, 8: 951-955

24. Raijmakers M. T., Zusterzeel P. L., Steegers E. A., Peters W. H. Hyperhomocysteinemia: a risk factor for preeclampsia? European Journal of Obstetrics & Gynecology and Reproductive Biology. 2001; 95: 1605-1611.

25. Robertson S. A., Redman C. W. Immune modulators of implantation and placental development -a workshop report. Placenta. 2003; 24: S16-S20.

26. Steinborn A., Sohn C. Preeclampsia, a pregnancy-specific disease, is associated with fetal monocyte activation. Clinical Immunology. 2001; 100, 3: 305-313.

27. Young A., Thomson A. J., Ledingham M. A., Jordan F., Greer I. A., Norman J. E. Immunolocalization of proinflammatory cytokines in myometrium, cervix and fetal membranes during human parturition at term. Biology of Reproduction. 2002; 66, 2: 445-449.

28. Zaretsky M. V. Alexander J. M., Byrd W., Bawdon R. E. Transfer of inflammatory cytokines across the placenta. Obstetrics and Gynecology. 2004; 103, 3: 546-560.

29. Zorzi W., Thellin O., Coumans B., Melot F., Hennen G., Lakaye B., Igout A., Heinen E. Demonstration of the expression of CD95 ligand transcript and protein in human placenta. Placenta. 1998; 19, 4: 269-277.

30. Abbate R., Sofi F., Gensini F., Fatini C., Sticchi E., Fedi S. Thrombophilias as risk factors for disorders of pregnancy and fetal damage. Pathophysiol Haemost Thromb. 2002; 32 (5-6): 318-21.

31. Hague W.M. Homocysteine and pregnancy. Best Pract Res Clin Obstet Gynaecol. 2003; 17(3): 459-69.

32. Aubard Y., Darodes N., Cantaloube M., Aubard V., Diallo D., Teissier MP. Hyperhomocysteinemia and pregnancy: a dangerous association. Gynecol Obstet Biol Reprod. 2000; 29(4): 363-72.

33. Khmil S. V., Malanchuk L. M., Franchuk, U. Y. Pre-conceptual selection of women at high risk for late gestosis (literature review). Actual Problems of Pediatrics, Obstetrics and Gynecology. 2019; 2: 98-102.

34. Linnikov S. Hyperhomocysteinemia as the pathogenetic factor in obstetrical complications. Science and Education. 2020; 1: 49-52.

35. Daly S., Molloy A. M., Mills J. L. et al. Maternal and fetal plasma homocysteine concentrations at birth: the influence of folate, vitamin B12, and the 5,10-methylenetetrahydrofolate reductase 677C→ T variant. Am J Obstet Gynecol. 2002; 186 (3): 499-503.

36. Rugolo S., Mirabella D., Cantone S. M. et al. Hyperhomocysteinemia: associated obstetric diabetes and fetal malformations. Minerva Ginecol. 2005; 57 (6): 619-25.

37. Mascarenhas M., Habeebullah S., Sridhar M. G. Revisiting the role of first trimester homocysteine as an index of maternal and fetal outcome. journal of pregnancy. 2014; 2014:123024.

38. White W. M. Turner S. T., Bailey K. R. et al. Hypertension in pregnancy is associated with elevated homocysteine levels later in life. Am J Obstet Gynecol. 2013; 209 (5): 10.1016/j.ajog.2013.06.030.

39. Brustolin S., Giugliani R., Félix T. M. Genetics of homocysteine metabolism and associated disorders. Braz J Med Biol Res. 2010; 43 (1): 1-7.

40. Ananth C.V., Elsasser D.,. Kinzler W. L et al. Polymorphisms in methionine synthase reductase and betaine-homocysteine s-methyltransferase genes: risk of placental abruption. Mol Genet Metab. 2007; 91 (1): 104-110.

41. Sturtz W. J., Leef K. H., Mackley A. B. et al. Homocysteine levels in preterm infants: is there an association with intraventricular hemorrhage? BMC Pediatrics. 2007; 7 (38): 10.1186/1471-2431-7-38.

42. Ducloy-Bouthors A. S., Trillot N. Risk factors of thromboembolism associated with pregnancy and the puerperium. Role of inherited andacquired thrombophilia. Ann Med Interne (Paris). 2003; 154 (5-6): 295-300.

43. Nelen W. L., Blom H. J., Steegers E. A., Der Heijer M., Eskes T. K. Hyperhomocysteinemia and recurrent early pregnancy loss:vf meta-analysis. Fertil. Steril. 2000; 74: 196-199.

44. Boguslavskaya N. Yu. Predicting complications of pregnancy and delivery in women with risk of prolonged pregnancy. – Qualifying scientific work as a manuscript. The thesis for obtaining a scientific degree of the Candidate of medical sciences in speciality 14.01.01 – obstetrics and gynecology. – Zaporozhye State Medical University, Ministry of Health of Ukraine, State Institution «Dnipropetrovs'k Medical Academy of the Ministry of Health of Ukraine», Zaporozhye, Dnipro, 2018.

45. Boguslavskaia N. Yu. Prognostic role of hyperhomocysteinemia in prolonged pregnancies according to the roc-analysis findings. Bukovinian Medical Herald. 2017. 21, 1 (81): 26-33.