

Influence of Liver Enzymes on the Development of the Syndrome of Nausea and Vomiting of Pregnant Women

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Abstract Nausea and vomiting of pregnant women is one of the most common pathological conditions in early pregnancy. According to various authors, from 70 to 85% of pregnant women experience this condition to one degree or another. Despite the prevalence of these manifestations and the negative consequences associated with them, today there is no consensus on both the causes and mechanisms of the development of nausea and vomiting, and on common approaches to the treatment of this pathology. To date, of all the causes of this condition considered, the most acceptable is liver damage. So, according to a number of authors, liver function is affected in about 50% of women hospitalized for excessive vomiting of pregnant women.

Keywords Nausea and vomiting, Pregnancy, Liver enzymes

1. Introduction

Most women experience nausea and vomiting in early pregnancy. Symptoms usually begin around 8–12 weeks of gestation and subside or disappear completely by 16–18 weeks. Approximately 5% of women experience nausea and vomiting for up to 22 weeks. The most severe manifestation of nausea and vomiting during gestation is hyperemesis gravidarum (uncontrollable vomiting of pregnant women). Persistent vomiting is potentially life-threatening, occurring between 0.8% and 3.2%. Whether the symptoms of intractable vomiting have a negative impact on the course and outcome of gestation is still the subject of debate in scientific circles. But scientists agreed that they can significantly worsen the quality of life of pregnant women.

For example, the Norwegian Maternal and Child Cohort Study (MoBa), which included 108,000 births, aimed to investigate the relationship between intractable vomiting and adverse pregnancy outcomes. The MoBa's target group consisted of all women receiving antenatal care in Norway and the participation rate was around 40%. Overall, 814 of 71,468 women (1.1%) had uncontrollable vomiting. According to the results of this study, intractable vomiting is associated with preterm labor, shortened gestational age, low birth weight, low Apgar score at 5 minutes, transfer of the infant to intensive care, perinatal death.

To date, of all the causes of this condition considered, the most acceptable is liver damage. So, according to a number of authors, liver function is affected in about 50% of women hospitalized for excessive vomiting of pregnant women. This

condition is the cause of altered liver function test results in 32% of pregnant women at all gestational ages and in 94% of patients in the first trimester of pregnancy. Despite the optimistic forecast, nausea and vomiting of pregnant women is not such a harmless problem.

Thus, according to estimates of various experts in 2002 in the United States, the financial costs of treating patients with this pathology amounted to more than 130 million dollars. In this case, only the funds spent on hospitalization were taken into account, and losses associated with disability were not taken into account.

The main task of the treatment of nausea and vomiting of pregnant women is the early diagnosis and treatment of the initial (mild) manifestations of symptoms, and, consequently, the prevention of the development of severe forms of the disease.

Toxicosis of pregnant women include vomiting of pregnant women, salivation (ptyalism), as well as rare forms - dermatoses, cholestatic jaundice, neuropathy and psychopathy of pregnant women, tetany, osteomalacia. Vomiting of pregnant women accounts for 90% of cases of all toxicosis [1].

Excessive nausea and repeated vomiting are the leading clinical symptoms requiring hospitalization.

Risk factors for pregnancy vomiting include hyperthyroidism, psychiatric illness, prediabetes, an above-normal body mass index, hydatidiform mole, and a history of previous pregnancies and deliveries [9]. A number of studies additionally highlight such a risk factor as the female sex of the unborn child [14]. A relationship between *Helicobacter pylori* and pregnancy vomiting cannot be ruled out [4].

There are several theories of early toxicosis: reflex, neurogenic, hormonal, allergic, immune, cortico-visceral. In the pathogenesis of early toxicosis, the leading role is occupied by a violation of the functional state of the central nervous system [6]. In the early stages of pregnancy, the symptoms of early toxicosis (neurosis) are manifested by a disorder in the function of the gastrointestinal tract. Food reflexes are associated with the autonomic centers of the diencephalic region. The afferent signals coming here from the periphery can be perverted, changes are possible in the centers of the diencephalic region themselves, which can change the nature of the response efferent impulses.

When the sensitivity of the system is disturbed, a change in reflex reactions quickly occurs, a violation of nutritional functions: loss of appetite, nausea, hypersalivation, vomiting [1,2,8].

A huge role in the pathogenesis of early toxicosis is played by neuroendocrine and metabolic disorders, in this regard, with the progression of vomiting, water-salt (hypokalemia), carbohydrate, fat and protein metabolism are gradually disturbed against the background of increasing dehydration, exhaustion and weight loss (35). During starvation, glycogen stores in the liver and other tissues are initially consumed. Then catabolic reactions are activated (fat and protein metabolism increases). Against the background of inhibition of the activity of enzymatic systems of tissue respiration, the energy needs of the mother's body are satisfied due to the anaerobic breakdown of glucose and amino acids. Under these conditions, β -oxidation of fatty acids is impossible, as a result of which underoxidized metabolites of fat metabolism accumulate in the body - ketone bodies (acetone, acetoacetic and β -hydroxybutyric acids), which are excreted in the urine [1,8]. In addition, ketosis is maintained by increased anaerobic breakdown of ketogenic amino acids. Against this background, ketonuria develops, oxygenation of arterial blood decreases, and the acid-base balance shifts towards acidosis [1]. The rheological properties of blood change, manifested in a decrease in circulating blood volume (BCV), an increase in hematocrit, an increase in the aggregation ability of red blood cells, and an increase in blood viscosity.

Changes in the organs of a pregnant woman are initially functional in nature, and then, as dehydration increases, catabolic reactions intensify, intoxication with incompletely oxidized products, they pass into dystrophic processes in the liver, kidneys and other organs. Initially, protein-synthetic, antitoxic, pigment and other functions of the liver, excretory function of the kidneys are disturbed; subsequently, dystrophic changes are noted in the central nervous system, lungs, and heart [1,2,8].

Hepatic dysfunction in the form of increased levels of ACT and AJIT was found in 67% of patients with vomiting of pregnancy (RP) [12]. Abnormal levels of liver enzymes have been noted with late onset RB, more severe ketonuria, and hyperthyroidism [11,12]. The cause of elevated liver enzymes during pregnancy vomiting remains unclear. The content of ACT and AJIT returns to normal levels, after the

cessation of vomiting and under the condition of adequate nutrition of the pregnant woman [6,13].

Serotonin is a key factor in the regulation of several autonomic functions of the gastrointestinal tract, including motility, secretion, and visceral sensitivity [10]. This neurotransmitter has also been suggested as an etiological factor in the occurrence of RB [5]. But, if serotonin contributes to the pathogenesis of RD, one would expect that serotonin receptor antagonists will be superior to other drugs in reducing RP, however, the results presented in randomized control trials on the superiority of serotonin receptor antagonists over dopamine antagonists and antihistamines are still inconsistent.

2. Materials and Methods

To achieve this goal and solve problems, a prospective observation of 44 pregnant women with moderate and severe forms of nausea and vomiting syndrome, whose average age was 24.8 ± 0.8 years, was carried out. The study was conducted in the gynecology department of the 4th I. Irgashev City Clinical Hospital for the period from 2019 to 2022.

The retrospective study included 42 pregnant women who received traditional therapy (detoxification, desensitizing therapy, saline solutions, antiemetics). The prospective study included 44 pregnant women who were diagnosed with the severity of the disease on the basis of the Koren scale.

Test and consultation with an endocrinologist;

The study of the level of bilirubin, liver enzymes ALT, AST, total protein made it possible to judge the functional state of the liver.

Transaminases (ALT, AST) are enzymes found in almost all tissues of the body. An increase in their level can be observed with toxicosis of pregnancy, accompanied by impaired liver function, as well as with hepatitis;

Alkaline phosphatase is one of the main liver enzymes. An increase in alkaline phosphatase simultaneously with the level of transaminases in the first trimester may indicate the severity of toxicosis. Alkaline phosphatase (ALP) is an enzyme that is found in almost all cells of our body, but its greatest amount is found in bone tissue, liver cells, intestinal mucosa and placenta (during pregnancy). Its function is to split off phosphoric acid from organic molecules, thereby participating in the exchange of phosphorus.

The level of alkaline phosphatase depends on many factors - gender, age, prevailing types of nutrition. However, its increase indicates pathological changes in certain organs.

In bone tissue, ALP is located on the surface of cells that are actively involved in bone growth. Therefore, there is a direct relationship between an increase in alkaline phosphatase in the blood and diseases of bone tissue. Enzyme activity rapidly increases in bone cancers.

The increase in alkaline phosphatase due to liver disease has two reasons: firstly, with the death of liver cells (hepatitis, cirrhosis, taking drugs that affect the liver, alcohol) - the

enzyme leaves the destroyed cells; secondly, due to blockage of the bile ducts, when the outflow of bile is disturbed, which occurs due to stones, inflammation, parasites, tumor cells. Normally, alkaline phosphatase is excreted with bile through the intestines, and since the outflow is difficult, the substance is absorbed into the blood.

ALP reaches very high values in women with eclampsia (a disease of pregnant women that clinically resembles an epileptic seizure), which is associated with damage to the placenta. A decrease in activity in pregnant women indicates an underdevelopment of the placenta.

In addition to the above reasons, the activity of alkaline phosphatase increases in diseases of the parathyroid gland (secondary hyperparathyroidism), renal rickets, cytomegalovirus infection, inflammation of the intestine.

Protein and protein fractions in the blood can be lowered in severe toxicosis of the first trimester, accompanied by a lack of nutrition;

Bilirubin total and fractions. Bilirubin is a pigment that is formed in the liver and increases when its function is impaired. Rarely changes in the first trimester.

3. Results

The environment of pregnant women with nausea and vomiting syndrome was primiparous: primiparous - 47%, multiparous - 36%. It should be noted that the interval between births in multiparous women, regardless of the group, was approximately the same and fluctuated on average from 2-3 years.

When studying the obstetric history, it was found that the first pregnancy in 3 (8.57%) women was terminated spontaneously, in 5 (14.2%) women it was complicated by a non-developing pregnancy, in 1 (2.85%) women the pregnancy was interrupted artificially (medical abortion). All these data indicate a burdened obstetric history.

We ranked the history of risk factors, and we can say that the highest frequency was observed in those who had a history of nausea and vomiting in previous pregnancies 29 (69%), 24 (57.1%) primigravidas had severe nausea and vomiting, 21 (50 %), pregnant women suffered from chronic diseases of the gastrointestinal tract, in 15 pregnant women the syndrome of nausea and vomiting was associated with pathology of the endocrine system, in 13 pregnant women they suffered from obesity, in 11 (26.2%) they had a male fetus. In 9 pregnant women, nausea and vomiting were associated with psychological factors.

A particular problem is severe or excessive vomiting with a characteristic relapsing course, resistance to treatment, and a violation of the quality of life of a pregnant woman. Excessive vomiting is a severe and complex variant of the course of the syndrome, the most common manifestations of which include persistent vomiting not associated with other conditions, severe ketonuria as a manifestation of acute starvation, and loss of at least 5% of body weight. May also be accompanied by electrolyte imbalance, liver function.

4. Statistical Analysis

4.1. Demographic Information

When questioning all 44 patients, it was found that the referral diagnosis - severe vomiting in 28 women (63.6%) was made on the basis of only the number of episodes of vomiting, general weakness, not holding food. In the remaining 16 (36.3%) pregnant women, in addition to the above complaints, the diagnosis was also formulated on the basis of laboratory tests. All patients examined in the Department of Pathology of Pregnancy were aged 19-29 years, mostly primiparous: primiparous - 19, multiparous primiparous - 13, multiparous - 12.

From the obstetric anamnesis, it was found that in the previous pregnancy 11 (25%) had nausea and vomiting of moderate and severe severity, 3 (6.3%) of them had a spontaneous abortion, 1 (2.2%) had a non-developing pregnancy and in 1 patient (2.2%), the previous pregnancy was terminated due to treatment failure and progressive worsening of the condition.

The timing of the development of nausea and vomiting during this pregnancy ranged from 6 to 12 weeks. Eleven (25%) pregnant women complained exclusively of excruciating nausea, but without vomiting; only vomiting bothered 10 (22%) pregnant women, both symptoms - nausea and vomiting were noted by 23 (52%) patients. Regarding the frequency of daily episodes of vomiting, it was found that out of 33 pregnant women, 13 (39.3%) patients indicated that vomiting was associated with fluid or food intake, that is, 5-6 episodes. Only in 20 (60.6%) patients, the frequency of vomiting reached 7 or more times. Thus, based on a more detailed questioning of those admitted regarding the number of vomiting episodes, we made a preliminary conclusion that the diagnosis of severe vomiting, based only on this criterion, does not reflect the true picture of the disease.

4.2. Results of Statistical Analysis

In a survey of 44 pregnant women, of which 6 patients had no appetite disorders, 15 had decreased appetite, and 23 had no appetite. The duration of nausea and discomfort in the epigastric region over the past 24 hours was up to 1 hour in 10 patients, 2-3 hours in 18, 4-8 hours in 9, persistent nausea in 7 pregnant women. Of the 44 pregnant women, 24 patients noted salivation (ptyalism): 11 - moderate, 13 had severe salivation. Fainting was not observed in any pregnant woman, 8 patients complained of dizziness. 14 pregnant women had tachycardia. 17 patients were diagnosed with hypotension.

Yellowness of the skin, icterus of the sclera were noted in 7 patients. Changes in liver tests were observed in 6 pregnant women. A high level of acetoneuria (+++) was diagnosed in 19 pregnant women. The pathological level of proteinuria was detected in 9 women. No edema of the lower extremities was noted. The spectrum of background chronic pathology was dominated by mild iron deficiency anemia in 19 patients

and diseases of the gastrointestinal tract (chronic hepatitis, chronic cholecystitis) in 16 patients.

In a comparative analysis of diagnostic approaches, it turned out that the use of a modified scale for assessing the severity of nausea and vomiting made it possible to establish that the severity of the pathology in 9 (2.1%) pregnant women corresponded to a mild degree, in 6 (1.4%) pregnant women there were signs of moderately severe vomiting, and in 29 (67.6%) pregnant women - signs of a pronounced, severe form of the syndrome. Thus, out of 44 pregnant women hospitalized according to the direction of the doctors of the antenatal clinic, the diagnosis of "Severe vomiting of pregnant women" turned out to be competent in relation to 29 pregnant women. In 15 pregnant women, this diagnosis was not confirmed: 9 of them had a moderate course, 6 had a mild course of the syndrome. This means that 6 patients were unreasonably hospitalized.

5. Discussion

In conclusion, it can be noted that the results of a comprehensive assessment of the severity of nausea and vomiting in pregnant women using a modified scale and laboratory and instrumental diagnostic methods demonstrate its advantages in comparison with an approach based only on the number of episodes of vomiting and laboratory diagnostics.

The prospective group included 44 pregnant women with severe and severe nausea and vomiting. Of these, 29 women had a severe form of the syndrome according to the Koren score scale. In the prospective group, complex therapy was used: assessment according to a modified scale, laboratory and instrumental examination, rational nutrition, and, along with conventional methods of treatment, ondansetron was used.

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The mean gestational age in these patients was 6.2 weeks.

In the retrospective group, in the 1st trimester, 7 (15.9%) had a spontaneous miscarriage, 29 (65.9%) had a severe form of nausea and vomiting syndrome.

In the second trimester, spontaneous late-term miscarriages that began were observed in 2 (4.54%) pregnant women.

In the III trimester in 2 (4.54%), according to Doppler, there was a violation of the uteroplacental blood flow; 1 (2.27%) had low placentation, 2 (2.27%) had

polyhydramnios, and 3 (6.81%) had oligohydramnios.

In 42 (95.4%) of the examined women, the pregnancy ended in timely delivery, in 2 (4.54%) patients the delivery occurred prematurely.

Complications in childbirth: 3 (6.81%) had cervical rupture, 1 (2.27%) had episiotomy, 2 (4.54%) had operative delivery due to low placentation. Prenatal rupture of amniotic fluid (PROM) in 1 (2.38%).

Further analysis of the course of pregnancy in the II and III trimesters showed that the most common complications in 6 (15%) retrospective and 3 (13%) prospective groups of women examined were preeclampsia, in 6 (26%) patients in the prospective group of the group who used sturgeon and modified nutrition, and 14 (33.3%) women of the retrospective comparison group had threatened abortion, 2 (8.7%) of the prospective and 9 (21.4%) of the comparison group had ORPS, in 2 (8.7%) of prospective observations and in 5 (12%) comparison groups, polyhydramnios was detected, in 3 (13%) and 11 (26.1%) cases, respectively, oligohydramnios.

The condition of 23 newborns in the prospective group, the Apgar score at 5 minutes of birth was 7-8 points. Of these, 5 had mild asphyxia, 2 (4.54%) had low birth weight due to premature birth. Treatment is based on carrying out dietary and regimen measures recommended for nausea and vomiting of pregnant women of mild to moderate severity. Drug treatment consists in the complex treatment of general strengthening and then, in the absence of effect, antiemetic drugs Ondansetron (domegan, zofetron, zofran, isotron, sturgeon, setron, emeset, emetron) - solution 0.2% -2.0 (4 mg) or 0.2% -4.0 (8 mg) in / in slowly, drip per 100 ml of physical. solution \times 1-2 rubles / day.

6. Conclusions

If natural nutrition (peros) is not possible, food and isotonic solutions are given through a naso-enteral tube. As the condition improves, oral feeding is resumed, and tube feeding should be stopped 1 hour before the trial breakfast. Protein intake should be 1.3 g/kg/day. Parenteral administration of nutrient mixtures must be carried out according to strict indications and has many side effects.

Parenteral nutrition is provided through a central venous catheter. Pregnant women on parenteral nutrition should be examined 2 times a week to determine electrolytes and acid-base balance and 1 time per week to study coagulation status, liver function tests, creatinine, glycemia and transaminases.

With parenteral nutrition, it is necessary to remember about essential fatty acids, minerals and vitamins. In particular, it is important for pregnant women to receive at least 400 mg of folic acid per day. Be sure to add K⁺ 40 mgEq/l (but not more than 80 mgEq/l). Recommended 10 mEq/l per hour with adequate urine output.

The expansion of traditional treatment with modified eating behavior and taking ondansetron leads to a

significantly faster minimization of nausea and vomiting, elimination of forced starvation, normalization and stabilization of the patient's condition, preservation of reproductive status, which makes it possible to recommend the use of this drug in the treatment of severe nausea and vomiting.

The clinical efficacy of the recommended treatment was expressed in a decrease in reproductive losses, reducing the frequency of spontaneous abortions by 2 times, preterm birth by 1.5 times, the birth of low birth weight babies by 25%, and optimization of the APGAR score at 5 minutes.

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