Nat. Volatiles & Essent. Oils, 2021; 8(4): 7100-7122

NVEO
Natural Volatiles & Essential Oils

Clinical Case Of A Woman's Pregnancy With Acute Intermittent Porphyria And Thrombocytopenia

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Abstract.

Acute intermittent porphyria is a rare disease of autosomal dominant type of inheritance due to mutations ofthe gene that encodes enzyme porphobilinogen deaminase in heme metabolism. Pregnancy is recognized as one of the factors that can lead to recrudescencesduring this disease. Literature data are limited in description of combination of acute intermittent porphyria and pregnancy to individual cases or a series of cases. We present a case of pregnancy and delivery of a patient with acute intermittent porphyria and thrombocytopenia.

The patient of 29 years old with III pregnancy and an expectedact of delivery was hospitalized in the State Institution "IPOG named after acad. O. M. Lukyanova of the NAMS of Ukraine" at 35 weeks. During her pregnancy she has suffered two moderate attacks. She performed delivery by caesarean section at 38 weeks due to deterioration of the antenatalfetuscondition. During pregnancy, delivery, the postpartum period,permitted medicines were carefully selected. The woman with a child in satisfactory condition were discharged on the 5th day.

Problem Description.

Porphyria is a group of rare diseases associated with interference of heme biosynthesis process. There are seven nosological forms of the disease according to the genetically determined defect of each enzyme of the biochemical chain, except synthase of delta-aminolevulinic acid (-ALA).

Acute forms occur with a frequency of 7-12 cases per 100,000 healthy, asymptomatic carrier state of the genetic defect ~ 50-100 cases per 100,000 of population.

Classification. Depending on the tissues where there is a predominant interference of porphyrin metabolism, there are two main groups: hepatic and erythropoietic.

I Hepatic:

- Porphyria due to dehydratase deficiency
- Acuteintermittent porphyria (AIP)
- Hereditary coproporphyria
- Variegate porphyria (VP)

- Late cutaneous porphyria (LCP)

II Erythropoietic porphyria:

- Congenital erythropoietic porphyria (Günther's disease)
- Erythropoietic protoporphyria.

There is also a classification that reflects the division into forms with skin lesions (late cutaneous porphyria, hereditary coproporphyria, variegate porphyria, congenital erythropoietic porphyria, erythropoietic protoporphyria) and acute, provoking (porphyria due to dehydratase deficiency (□-ALA, acute intermittent porphyria, hereditary coproporphyria, variegate porphyria).[16,17]

Each form of porphyria is caused by a genetically determined decrease or absence of activity of a certain enzyme in the heme biosynthesis chain. Enzyme genes are located on different chromosomes and have no group linkage. Decreased enzyme activity to 50% of normal may have no clinical manifestations. According to acute forms, certain factors can provoke the manifestation of the disease and acute attacks. [16] All forms of porphyria with autosomal dominant type of inheritance and low gene penetrance are congenital. Only late cutaneous porphyria can be sporadic. [3]

Provoking Factors:

- Alcohol
- Some medicines (barbiturates, NSAIDs, cephalosporins, sulfonamides, and etc.)
- Hormonal changes (menstrual cycle, pregnancy)
- Insolation
- Bacterial and viral infections
- Starvation. [16, 1, 3, 6,11, 13]

The activity of these factors leads to increased consumption of heme or directly to the activation of the first enzyme in the chain - □-ALA synthetase (activity of progesterone) and accelerated synthesis of intermediary

products. At the stage of the defective enzyme, the accumulation of metabolites in toxic concentrations begins. In acute forms, the accumulation of □-ALA and porphobilinogen (PBG) leads to segmental demyelination of nerve fibers with interference of nerve conduction. [16] These enzymes are accumulated in the urine, which causes it to acquire a red colour. Acute attacks are characterized by such features:

- Acute abdominal pain
- Feeling sick, vomiting
- Tachycardia, hypertension

- Disturbance of the peripheral nervous system, mainly motor functions of the extremities
- Red colour of urine of different shades
- Hyponatremia
- Psychiatric manifestations (from disorientation to psychosis)
- Generalized convulsion
- Bulbar manifestations (dysphonia, dysphagia, dysarthria)
- Respiratory disorders
- Erythema, blisters on open areas. [16, 5, 6, 11]

Diagnosis of acute porphyria consists of a characteristic clinical picture and the detection of elevated concentrations of □-ALA and PBG in the urine. However, the final step should always be genetic confirmation of the defect by DNA analysis. [16, 11] When porphyria is detected, genetic testing is recommended for relatives to detect asymptomatic carriers, especially for women with reproductive plans. In 5 of 15 women in the study of Marsden J.T., et al. porphyria was diagnosed as a result of family screening.

Differential diagnosis is usually difficult, due to low vigilance for this disease, an atypical clinical picture. Lenehan P.M. et al. calls this disease "one of the greatest imitators of modern medicine." Patients often report about repeated visits to the surgical hospital, family doctors, neurologists, psychiatrists. Up to 46% of patients with a subsequent diagnosis of porphyria were operated with laparotomy, appendectomy, cholecystectomy, oophorectomy. [5, 10, 17]

Acute intermittent porphyria (ACP) is the most common hepatic form associated with partial porphobilinogen deaminase deficiency. The prevalence is quite different according to various authors: from 1 per 2000 to 1-2 per 200,000 of population. [1, 10, 17] Only 10-20% of gene carriers have acute attacks, which reflects the significant role of exogenous and endogenous provocations. [8, 17] Women are more prone than men in the ratio from 4:1 to 3:2 in various sources [5, 10, 11] and it is in the reproductive age, which has a pathogenetic explanation in hormonal changes during the menstrual cycle.

The association of acute intermittent porphyria with pregnancy is quite rare. According to earlier publications, this disease was associated with a high risk of exacerbations during pregnancy (54-95%), maternal mortality (27-42.5%), perinatal mortality (8%), worse prognosis with cranial nerve involvement, mortality 60- 90%. [6, 9, 19]

Modern data show less dramatic results. A population cohort study conducted in Norway has showed an increased risk of perinatal loss only for primiparous women with acute active porphyria (GPP, congenital coproporphyria, variegate porphyria) and congenital late cutaneous porphyria.

[3]Mothers with sporadic IBD had an increased risk of SFGA (small fetus for gestational age). No data on maternal mortality were provided. [3]

According to the results of Wolff C. et al., women with porphyria did not have an increased risk of gestational hypertension, premature birth, spontaneous abortion, and low birth weight at birth. An increased risk of early toxicosis was mentioned [7]. Marsden J.T., et al. showed no difference in weight in newborns from mothers with porphyria, the frequency of pregnancy loss compared with the population, in this study there were no cases of maternal death.

The authors express the opinion that in acute porphyria in most cases an uncomplicated course of pregnancy is possible under the condition of careful monitoring, at the same time possible problems during gestation are considered to be, if the disease was not detected preconception [11].

[20]Wolff C. et al. did not detect differences in the weight of newborns, in the frequency of hypertension during pregnancy, in gestational age at birth, this study also did not show cases of maternal mortality. Among the problems of perinatal management is the increased risk of early gestosis (29%), as well as the prescription of off-label medicines in acute attacks (41.6%). [20]

Improvement of statistical data is possible due to a larger number of periconceptionaldiagnosed cases of porphyria, which allows to prevent the use of provocative medicines during acute attacks during pregnancy, to prescribe adequate treatment and appropriate perinatal management. Pregnant women are recommended to wear a bracelet, which indicates the presence of orphan disease with a limited list of medicines allowed for use.

All authors agree that pregnancy is a risk factor for acute attacks. The most dangerous is I trimester of pregnancy and peripartum periods. [7, 8, 10, 11, 12, 15]

One of the formidable complications can be generalized convulsion observed in <10% of GPP and posterior reversible encephalopathy syndrome (PRES).PRES is a rare acute neurological disorder characterized by acute neurological symptoms: convulsion, visual disturbances, headache, feeling sick, vomiting, impaired consciousness, focal neurological deficit, and the corresponding picture of CT, MRI. [8, 12]

Treatment of acute porphyria includes the elimination of the provoking factor, the prescription of pathogenetic and symptomatic treatment. Pathogenetic treatment is to suppress the excessive biosynthesis of porphyrins. The recommended prescription of the heminate alginate medicine (Normosang; Orphan Europe, Paris, France) is 3 mg /kg/day iv slow bolus, but, unfortunately, the medicine is not registered in Ukraine. Also, ensuring an excess intake of carbohydrates (200-600 g of dry glucose), 40% glucose solution 1000 ml ivby drop infusion per day. [16]

Modern publications indicate the safe use of heme preparation during pregnancy [1, 2, 8, 10, 11, 12, 15, 18]

In the presence of acute attacks connected to menstrual cycle (≥ 3 times per year), ovarian function should be suppressed until a delaying time to relapse of several months is reached. [16] Contraception is recommended by copper-containing IUDs and the barrier method. [1] It is recommended to prevent pregnancy during 18 months from the last acute attack. [15].

The choice of analgesia is also problematic. If it is possible to use regional anesthesia - spinal and/or epidural with the use of bupivacaine. If general anesthesia is required, barbiturates and volatile anesthetics (isoflurane, sevoflurane) should be avoided, and the use of propofol is recommended. [12, 13]

Thrombocytopenia is a decrease in platelet level $<150\times10^9$/l. The condition that often accompanies pregnancy is second only to anemia 7-12% of pregnancies are complicated by thrombocytopenia. In 70-80% of cases there is gestational thrombocytopenia. Other causes of thrombocytopenia include hypertensive disorders (12-22%), immune thrombocytopenia (3%), and rare causes (<1%). [21,22,23,24]

Gestational thrombocytopenia is explained by hemodilution, increased clearance of platelets, their accumulation in the placental and splenic circulation. [21] The level of platelets in the great majority of cases does not decrease less than 70×10^9/l. This condition does not require treatment, it is necessary to monitor platelet level during pregnancy. At decrease in their level less than 70×10^9/l the search of other reasons explaining a thrombocytopenia is necessary. Gestational thrombocytopenia is not associated with maternal, fetal or neonatal complications. [21,22,23]

Case Presentation.

We present our own case of the pregnancy follow-up, delivery of a patient with acute intermittent porphyria. Patient P., 29 years old, pregnancy III (the first two pregnancies ended with spontaneous abortions), applied to the women's clinic of the II level of care for antenatal care at the 9^{th} week. The diagnosis of acute intermittent porphyria was established in 2016, after emotional stress in the first time in her life there was an attack of acute abdominal pain with polyneuropathy, changes in hemogram (anemia, increased levels of ALT, AST, alkaline phosphatase, total bilirubin due to direct fraction, hyponatremia, hypochloremia), hematuria.

Before the beginning of the last pregnancy, she was repeatedly hospitalized due to suspicion of acute appendicitis, and was treated for irritable bowel syndrome. As a result of a comprehensive examination the increase in the level of delta-aminolevulinic acid (up to 52.9 mg/24 h at a rate of 1.5-7.5 mg/24 h) and porphobilinogen (up to 93.5 mg/24 h at a rate of 0-3, 4 mg/24 years) was defined. After determining the level of porphyrins, their premetabolites and molecular genetic research, the diagnosis was made: hereditary metabolic disorders from the group of hepatic porphyrias: acute intermittent porphyria, autosomal dominant type of inheritance.

The patient was registered at the Centre for Orphan Diseases NCSH "Okhmatdyt". The patient's process has a chronic recurrent course (~ 3-4 attacks per year), the triggers of the attack are emotional factors, premenstrual state.

This pregnancy is desirable, given the woman's persistent desire to have a child, the state of clinical and laboratory remission of the main disease at the time of pregnancy, a teleconsultation with specialists of the State Institution "Institute of Pediatrics, Obstetrics and Gynaecology named after acad. O.M. Lukyanova of the NAMS of Ukraine" (perinatal centre of 3b level) and it was decided to prolong the pregnancy under close supervision: control of laboratory findings: hemogram, liver tests, electrolyte tests, determination of urinary urobilinogen, markers of placental dysfunction and control of delta-aminolevulinic acid level and porphobilinogen; US - control of the antenatal state of fetus).

The course of pregnancy was complicated by anemia (corrected by intravenous administration of iron saccharate), thrombocytopenia. Prescribing medicines (multivitamin complexes, calcium supplements, etc.) with an assessment of their porphyrinogenic activity.

At the 35th week, there were clinical signs of an attack of the main disease - a pregnant woman was hospitalized in the State Institution "IPOG y named after acad. O.M. Lukyanova of the NAMS of Ukraine" for careful observation and preparation for delivery. The state was corrected by oral rehydration with a solution of 40% glucose. During hospitalization, careful monitoring of laboratory findings and fetal status was conducted. In the general analysis of blood there were platelets 130×10^9/l. This condition is regarded as gestational thrombocytopenia.At this level of platelets there is no need for in-depth diagnosis. In the dynamics, the platelet level was not lower than 110×10^9**/**l. At the 37th week, delivery is planned through the natural birth canal with rational anesthesia by the EDA method and possible changes in the birth plan in case of deterioration.

At the 38th week there was the repeated bout of porphyria (progressive weakness, porphyrin plaques on the face, intermittent abdominal pain; laboratory: positive test for urobilinogen in urine, microhematuria; moderate increase in liver enzymes, porphobilinogen levels, mild hypoglycemia, despite oral rehydration with glucose solution). Ultrasound of the fetus showed a decrease in resistance in the pool of SCA (RI 0.53), increased resistance in the fetal aorta (C/D -11), fetal heart rate with episodes of bradycardia (100-108 beats/min.) and tachycardia (165-184 beats/min.).

Multidisciplinary council of doctors consisting of the administration of the institution, obstetricians-gynaecologists, ultrasound doctors, neonatologists, taking into account clinical and laboratory data indicating exacerbation of porphyria, deterioration of fetal condition during dynamic monitoring, while "not fully developed" maternal passages of the pregnant and impossibility the

immediatenatural birth, the decision was made to give birth immediately by emergency cesarean section.

Anesthesiological provision of the operation and postoperative period: EDA using 0.25% -0.5% marcaine solution. Method of cesarean section: according to Stark. Aa alive full-term boy with an Apgar score of 8/8 points, weighing 2740 g and a length of 51 cm was removed. The duration of the operation is 31 minutes.

Prevention of uterine hypotension and bleeding: intravenous administration of carbetocin. Prevention of inflammatory complications with ampicillin. Infusion support intraoperatively: balanced crystalloids: sterofundin and 20%-40% glucose solution up to 2.5-3 liters. In the postoperative period, a decision was made to demedalize and limit the use of porphyrinogenicmedicines.The course of the postoperative period without complications, wound healing by first intention. Platelets in the postpartum period: 131×10^9/l (1^{st}day), 126×10^9/l (2^{nd} day). Platelets of the newborn - 196×10^9/l. Discharged with a child in satisfactory condition on the 5^{th} day. Recommendations for the control of the main disease are provided.

Pathohistological examination of the placenta revealed signs of desynchronosis of villi development (against the background of villi corresponding to gestational term there are large foci of villi with immaturity) along with signs of placental aging in the form of significant deposits of calcifications, fields of maternal infarcts, stromal sclerosis and vessels decrease in stem and acroteric villus, necrotic patches and

degeneration in the basal layer of the decidual membrane. These findings indicate placental dysfunction, which in its turn explains the changes in fetalhemodynamics that caused the urgent timely delivery.

Discussion.

The problem of orphan diseases in pregnant women in the vast majority of obstetricians and gynaecologists are extremely rare, but when it touches a certain woman and her unborn child, the specialist faces a number of very specific issues that need to be solved in the right way. The first is to search for information and qualified specialists in this field. We want to share useful links and information about specialized centres that may be useful for patients with porphyria. There is an information portal EUROPEAN PORPHYRIA NETWORK. In the practice of some European countries, specialized centres and national registers of patients with porphyria are created, for example, in Norway- Norwegian Porphyria Centre (NAPOS)and Norwegian Porphyria Register, inGreat Britain – Porphyria Clinicwith its register. This essentiallysimplifies the systematization of data and allows observation of the patient throughout life. NAPOS is responsible for creating a portal of safe medicines for acute porphyria, adapted for three countries - Sweden, Great Britain,

Norwayhttp://www.drugs-porphyria.org. In the USA - American Porphyria Foundation - www.porphyriafoundation.com .

In Ukraine, from the available information, it was possible to identify such centres dealing with orphan diseases, including porphyria - at NCSH "Okhmatdyt" there is a centre of orphan diseases, that deals with children, Kharkiv interregional specialized medical and genetic centre of rare (orphan) diseases, in the clinic of Alexander Clinical Hospital of Kyiv city, there is office of orphan diseases. Consultation, management and delivery of pregnant women - SI "IPOG named after acad. O. M. Lukyanova of the NAMS of Ukraine ".

Unfortunately, there is not a unified register of patients with porphyria in Ukraine. As a high-risk group of manifestation are women of reproductive age, and pregnancy is a risk factor for acute attacks, systematization of patients' data would be a significant help in achieving the goal of timely diagnosis, qualified obstetric and gynaecological, perinatal care and competent preconception counselling for successful implementation of reproductive plans.

Most literature sources present individual cases or series of cases of the disease. In the available literature, we have found 20 described cases of termination of women's pregnancy with porphyria (table). Most of the authors believe that pregnancy and childbirth of women with porphyria are accompanied by certain complications.

Table Cases of women's pregnancy with porphyria

№ s/n	Authors	Case description	Result	The course of the postpartum period
1.	Markovitz M., 1953	Year 1944. 23 years old. Was admitted with complaints for pain in the legs. Periodically disturbed abdominal pain, constipation. Appendectomy was made 3 years ago, the appendix is unchanged. Abdominal pain, feeling sick, vomiting, constipation continued to bother. Weight loss.Weakness in the hands, tremor, spasticity in the legs. Lack of ability to stretch the	Hysterotomy. Termination of pregnancy. Fetus weighing 100g.	Discharged 6 weeks after surgery with an improved neurological picture. She died 4.5 months later.

		fingers. Hyperactivity of tendon reflexes. Sensitivity is not violated. After 6 weeks, the increase in porphobilinogen in the urine was detected. Progressive neurological symptoms. Hypertension up to 200/140 mm Hg. Disorders of swallowing, nystagmus. Detected pregnancy. Terminated. Barbiturates for sedation. One and a half months after with the beginning of menstruation pain in arms, chest, abdomen, vomiting, hypertension (164/114), tachycardia, muscle atrophy, drooping hands, feet. Enteral feeding. In 3 months, death from respiratory failure.		
2.	Vine Sh. Et al, 1957	Primigravida, 22 years old. Pregnancy is spontaneous, 8 weeks. Hospitalized with complaints of inability to spread the fingers. There were no other neurological symptoms. From the anamnesis frequent "nervous breakdowns".Objectively - without pathological findings. Uroporphyrin 46.17 mg, coproporphyrin 3172 mg. Family history: two uncles died of progressive paralysis, the mother was diagnosed with porphyria after a laboratory examination,	Spontaneous miscarriage	Death

		examination of sisters and nieces gave negative results. From the 11th day prednisolone, from the 13th on the background of progression of muscle weakness with gradual disorders of swallowing, respiration, iv ACTH, potassium chloride, respiratory support, vitamin B12, paraldehyde, codeine, enteral feeding. On the 50th day - a spontaneous miscarriage. On the 63rd day - respiratory arrest, death. Pathological examination showed peripheral neuropathy due to porphyria.		
3.	Hunter D. J.S., 1971	Year 1967. 23 years old. The first pregnancy. From the 31stweekpressure rise, took amital-nitrium (amobarbital). At the 36th week, she was hospitalized with epigastric pain, vomiting, blood-tinged discharge, hypertension, and tachycardia. Morphine is prescribed.	PPROM. Forceps, pudendal anesthesia. Meconium waters.A girl 2330.	Postpartum period: abdominal pain, tachycardia, hypertension, increased blood urea. On the 8th day vomiting. Morphine due to epigastric pain. Cancellation of barbiturates. The 16th day - changes in speech, paraesthesia in the extremities. Discharged with phenobarbital. At the 6th week in a psychiatric hospital the diagnosis of AIP, effective treatment with chlorpromazine was established.
		Year 1969, the same patient, II pregnancy. From 16 weeks porphyrins in urine. Up to 30	Spontaneous delivery. A girl 2780.	W/c

		weeks without complaints. At 30 weeks weakness, heartburn, weight loss. Hospitalization. Year 1971. III pregnancy.		
4.	Lenehan P.M. et al., 1982	21 years old. Pregnancy 12 weeks. Family history is unknown. Within 8 weeks abdominal pain. Urinary tract infection. Sulfamethoxazole. After 11 weeks, re-hospitalization with abdominal pain. At 29 weeks acute nonspecific abdominal pain, vomiting. GIP was found (increased urinary porphobilinogen, delta-aminolaevulinic acid, coproporphyrin, uroporphyrin).Recrudescence: hypertension, tachycardia, hyperventilation with respiratory alkalosis, paralytic ileum, electrolyte disturbances - hyponatremia, hypokalemia. Anemia. Blood transfusion. Progressive motor neuropathy with damage to the respiratory and limb muscles. Moderate psychosis.	Spontaneous delivery at 40 weeks. A girl, 3080. Forceps to shorten II labour stage.	Progressive improvement in the postpartum period. Discharged on the 8th day with residual muscle weakness. In 6 weeks, urine is positive for porphyrins.
5.	Soriano D., 1996	23 years old II pregnancy.In the anamnesis of 1 childbirth. At 36 weeks she was hospitalized with ophthalmoplegia, ataxia, disorientation. From the age of	PPROM. Cesarean section under general anesthesia due	Iv glucose. State improvement in a week, regression of neurological symptoms. Discharged with improvement, residual effects: apathy, ataxic

		12 years recurrent abdominal pain, arthritis. Diagnosed with Family Mediterranean Fever, colchicine treatment. Normal liver biopsy. 18years old bipolar disorder.Hospitalization in a psychiatric hospital with a manic episode, treatment with lithium and haloperidol. She stopped taking lithium medicines a few months before hospitalization. And pregnancy is uncomplicated, cesarean delivery due to lack of labour progression. Up to 34 weeks this pregnancy is without complications. Two weeks before hospitalization, mental disorders include anxiety, irritability, memory and concentration disorders, which progressed to delirium. Neurologically revealed disorders of the cranial nerves III and IV, weakness of the legs, areflexia of the patellar reflexes, hypoesthesia of all extremities, horizontal nystagmus. EEG, electromyography and tanzylon test are normal (excluding myasthenia). CT, old heart attacks in the frontal lobe, in caudate nucleus. MRT, moderate cortical atrophy, lacunar infarction.Spinal fluid is normal. In urine the general porphyrins, delta-	to neurological status. A healthy boy.	gait, dysarthria, weakness and ataxia of the right hand.

		aminolevulenic acid are raised, normal porphobilinogen. The activity of the enzyme porphobilinogen desaminase is reduced by 50%. AIPis diagnosed. High-carbohydrate diet without effect.		
6.	Aggarwal N.et al., 2002	Primigravida 25-year-old was registered at a specialized centre at 12 weeks. The diagnosis of AIP was made 7 years ago, a manifestation with acute abdominal pain, legs pain, discoloration of urine in the light, increased levels of uroporphyrinogen. Her brother was diagnosed AIP at that time.The last attack was 3 years ago, provoked by famine. Acute anemia at 25 weeks (Hb 60 g/l), transfusion of 2 volumes of blood. Uroporphyrinogen is negative during pregnancy. There were no recrudescences during pregnancy. From 30 weeks of FGR, she denied interventions for social reasons.	Spontaneous delivery at 38 weeks. Hyperhydration during childbirth (Ringer's lactate). Episiotomy under bupivacaine locally. Iv oxytocin to prevent bleeding. Girl, 1900, 8-9 points.	Adequate nutrition, rehydration. Postpartum period without complications, discharged on the 5th day with a child.
7.	Sahu M.t et al., 2006	Re-pregnant, with a history of 1 childbirth, 1 abortion. 32 years old. Diagnosis of AIP 5 years before pregnancy. Pregnancy 8 weeks. Previous pregnancy 28 weeks. The first attack of abdominal pain, regarded as	The couple, fearing recrudescences of AIP, has chosen to terminate the pregnancy. 200	P/o p-d w/c. For p/o anesthesia 3 additional injections. Prophylactic antibiotics are amoxicillin, carbohydrate-enriched diet. Discharged the next day.

		pancreatitis, later during pregnancy twice in the third trimester abdominal pain conservatively treated. Delivered by urgent emergency CS due to fetal distress under SMA. Early p/o p-d w/c. Acute abdominal pain, vomiting on the 8th day of p/o period. Laparotomy, right salpingoophorectomy, formation of 5 cm was detected on the 1st day. Generalized tonic-clonic convulsions, recurrence of abdominal pain, unstable blood pressure, without focal neurological deficit.Increased content of uroporphyrinogen, d-ALA. CT, MRT - the norm. Clonazepam, chlorpromazine, 10% dextrose. In the next 1-2 cases of abdominal pain per year with hospitalization. Urinary porphyrinogen is positive during this pregnancy.	mg of misoprostol in the posterior arch. 5% dextrose in 2 hours.In 2 hours, vacuum aspiration under combined spin-epidural anesthesia using hyperbaric bupivacaine.	
8.	Marsden J.T. et al., 2010	AIP is established at the age of 19 after an acute attack associated with the premenstrual period. Prophylactic treatment with hemin arginate in the premenstrual period is effective. I pregnancy at the age of 25 was a spontaneous abortion. This pregnancy II, at 26 years old. More frequent attacks of acute	38 weeks of emergency caesarean section due to an acute attack. Without perinatal complications.	W/c. The child develops without disorders.

		pain, increasing the frequency of infusions of hemearginate up to 1 time per week. Elevated urinary PBG levels were observed before and during pregnancy. There is another uncomplicated pregnancy in the catamnesis, management with heminatearginate, the birth of a healthy baby.	.	
9.	Marsden J.T. et al., 2010	25 years without a previous diagnosis. One year ago, the pregnancy ended with abortion at 21 weeks due to fetal CHD. This pregnancy was complicated at 8 weeks by acute abdominal pain, feeling sick, vomiting, generalized tonic-clonic seizures. AIP was established, elevated levels of urine PBG were detected. Heminatearginate treatment with antiemetics.	38 weeks cesarean section, the baby is healthy.	W/c
10.	Marsden J.T. et al., 2010	19 years after the acute attack, AIP was diagnosed. 28 years I pregnancy. Legs pain throughout pregnancy, analgesics. Moderately increased PBG in urine	40 weeks natural childbirth.	W/c
11.	Marsden J.T. et al., 2010	At the age of 23 AIP was diagnosed after the attack. 29 years I pregnancy. At 37 weeks,	Cesarean section, a healthy girl	W/c

		abdominal pain, preeclampsia	without congenital porphyria.	
12.	Marsden J.T. et al., 2010	At the age of 12,VP was diagnosed with by family examination. Pregnancy without manifestations.	Cesarean section for fetal distress at 40 weeks.	W/c
13.	Marsden J.T. et al., 2010	25 years, 4 weeks of pregnancy. Acute symptoms and skin manifestations. VP. Without treatment. Next (after 2 and 5) pregnancies w/c	12 weeks - spontaneous abortion. II, III pregnancies - urgent natural childbirth.	-
14.	Marsden J.T. et al., 2010	AIP at age 21 at 20 weeks of pregnancy. Diagnosed due to family history, asymptomatic. II pregnancy is asymptomatic. The first attack 8 years after I childbirth.	-	-
15.	Marsden J.T. et al., 2010	VP at age 29 during the 4th pregnancy due to family history. 1, 2 pregnancies - spontaneous abortions up to 12 weeks. 3rd – aa alive child	Normal childbirth.	-
16.	Martinez N., 2011	34 years old woman of Caucasian nationality. Family history is unknown. Smoking in the past. The victim suffered a terrorist attack - myringoplasty, an artificial eyeball, had a course of psychiatric treatment for post-traumatic stress disorder. Complaints of abdominal pain, pain in the episiotomy wound,	There is no information about the child.	Discharged with improvement.

		during the early postpartum period, that not stopped with painkillers. Disorder with anxiety and depression was diagnosed. After 4 days, generalized seizures. Fentoin, midazolam, mannitol. Progressive changes of consciousness to lethargic with disorientation. Increased d-ALA, PBG, total porphyrins, coproporphyrins, uroporphyrins. AIP. Iv heme alginate.		
17.	Meena P. et al.[1], 2011	G5P2L2A2 Pregnancy V of a 36-year-old patient who was diagnosed with acute intermittent porphyria 8 years ago, a history of 2 childbirths, 2 abortions. The last attack 6 months before pregnancy, since then she took gabapentin 300 mg tablets. Pregnancy was detected at a preventive examination within 10 weeks 4 days	At the patient's insistence, the pregnancy was terminated by vacuum extraction under spinal anesthesia. Used medicines: preoperatively - 5% dextrose, injections of morphine and propafol intraoperatively. Augmentin, pantoprazole, paracetamol postoperatively.	Discharged on the 3rd day. Barrier contraception is recommended.
18.	Zhang J. et al, 2017	A 25-year-old woman was taken with complaints of paroxysmal abdominal pain, bloating,	At 36-37 weeks, the boy is alive, by caesarean	On the 2nd day of the postpartum period, headache, dizziness, blurred vision. BP

		constipation. In cousins AIP, inherited from the father. B-hCG is elevated, early pregnancy is diagnosed. Redness of urine during insolation. Porphyrin in urine, intracellular zinc-porphyrin 10.3µg/gHb (N 0-4.7). AIP was diagnosed. Glucose 14% iv for 12 days, esomeprazole iv for 8 days, injections of amino acid compounds for 12 days.Discharged with improvement. At 20 weeks she was hospitalized with abdominal pain, dizziness - recrudescence of AIP. Iv glucose, amino acid solutions, medium-chain, long-chain triglyceride emulsions. The symptoms did not regress. Hemearginate (Normosang) 3 mg/kg/day for 4 days, + albumin, leukocyte-depleted erythrocyte mass of 6 units were added. Discharged with improvement. At 27 weeks she was hospitalized with abdominal pain, feeling sick and vomiting. Positive urine protein, urine bilirubin. Heminearginate, albumin, leukocyte-depleted erythrocyte mass. Discharged. At 32 weeks she was hospitalized with abdominal pain, feeling sick and vomiting. Heminearginate, 4	section.	170/110. Nitrendipine 10 mg. MRT, MRA, MRV, diffusion weighted image. Posterior reverse encephalopathy syndrome (PRES). Iv mannitol for 7 days, 3 times convulsions - diazepam, hemearginate 5 mg/kg/day, additionally calcium gluconate, sodium chloride, magnesium sulfate. A series of repeated imaging techniques showed bilateral regression of changes in the occipital lobes. Discharged on the 12th day.

		mg/kg/day.		
19.	Mital T.K. et al.[2], 2020	The mother was taken to the clinic in the early postpartum period after delivery a few hours ago with a dead fetus in another hospital, in a state of severe anemia. This pregnancy I took place against the background of previously established hypothyroidism, which is medically compensated, edema of the extremities.LCP was diagnosed at the age of 11. She was treated with immunomodulators and steroids. Antenatally received 3 doses of injectable iron sugar due to anemia. During pregnancy, the number of blisters on the extensor surfaces of the extremities increased, after childbirth their number decreased. The patient's elder sister also has porphyria, but has two healthy children due to two uncomplicated pregnancies. Normal hemodynamics during hospitalization. Hypertrichosis on the face. Areas of hyperpigmentation all over the body with scars, spots, especially in places unprotected from the sun. CHD was defined: ASD. Splenomegaly. Hemoglobin in the	Stillbirth.	-

		dynamics of 52 g/l, 78 g/l after 2 doses of packed red blood cells transfusion. Total bilirubin is increased to 1.3 mg/dl. Retrospectively: increase in the level of serum porphyrin to 220 nmol/l (N <15 nmol/l), increase in porphyrin in urine to 360 nmol / l (N <140 nmol/l). Injections of multivitamins, vitamin C tablets, iron sulfate, calcium, sun protection was recommended.		
20.	Cerovac A. et al., 2020	26 years old. Examined for spontaneous abortion, which began at 8 weeks of pregnancy, suffered from abdominal pain, constipation, muscle weakness, vomiting, dark urine. At home she had bout of cramps. Took dydrogesterone 10 mg 3g/day for 2 weeks.Higher levels of d-ALA, PBG in the urine. Iv glucose solution. AIP is in the anamnesis. The last attack 7 years ago in the form of vomiting, acute abdominal pain, frequent urination, blood in the urine, hyperthermia. Before during 4 months took COCs due to irregular menstrual cycles.On the 1st day of the cycle she had tonic-clonic convulsions to a state of epilepticus status, which was not removed by the maximum doses	V/ anesthesia (propofol, alfentanil, diazepam). Vacuum aspiration, curettage.	Rapid recovery of consciousness, in-touch capabilities. P/oper. p-d w/c. Markers have decreased within 4 weeks.

		of diazepam, only short iv anesthesia (midazolam maleate).On MRI, posterior reverse encephalopathy syndrome (PRES). Hyponatremia, hypokalemia, hypomagnesemia, hypocalcemia. Increased contents of pagal porphyrins, uroporphyrin, coproporphyrin, d-ALA, PBG. Hemineararginate, glucose, symptomatic treatment. Complete recovery. She hasn't seen a doctor for 7 years.		

Conclusions.

1. Pregnancy and childbirth of women with porphyria belong to the group of extremely high risk (probability of acute attacks with neurological complications, increased frequency of abortions, premature births, low weight childbirth, early gestosis).
2. Antenatal supervision of such pregnant women should be carried out with the participation of subject matter specialists in the main disease with control of □-ALA and PBG in urine, monitoring of the fetus state, delivery should be carried out in the perinatal centreIIIb level with the participation of a multidisciplinary team.
3. The result of pregnancy is significantly improved under the conditions of the diagnosis of acute porphyria before pregnancy, careful monitoring of the woman's health, preconception counselling, pregnancy not earlier than 18 months after the previous acute attack. Great importance is the family preventive examination in the case of the diagnosis of a relative.
4. Timely administration with pathogenetic treatment avoids serious complications for both mother and fetus. The safety of hemearginate during pregnancy has been proven.
5. The examination of the newborn is necessary, taking into account the autosomal dominant type of inheritance.

References.

1. Meena P, Jain S, Rajaram S, Gupta B, Goel N. Acuteintermittentporphyriaandpregnancy: anobstetricchallenge. Int J ReprodContraceptObstetGynecol 2016;5:542-4.

2. Mital T.K., Fuke R.P. Pregnancyinporphyriaanditscomplications: a casereport. Int J ReprodContraceptObstetGynecol 2020;9:4722-5.
3. Tollånes M.Ch., Aarsan A.K., Sandberg S. Excessriskofadversepregnancyoutcomesinwomenwithporphyria: a population-basedcohortstudy. J InheritMetabDis 2011;34:217–223 DOI 10.1007/s10545-010-9231-2
4. VineSh. A reviewoftherelationshipbetweenpregnancyandporphyriaandpresentationof a case. AnnalsofInternalMedicine 1957;47:834-840.
5. Markovitz M. Acuteintermittentporphyria: a reportoffivecasesand a reviewoftheliterature. AnnalsofInternalMedicine 1954; 41:1170-1182.
6. Aggarwal N., Bagga R., Sawhney H., Suri V., Vasishta K. Pregnancywithacuteintermittentporphyria: A casereportandreviewofliterature. J. Obstet. Gynaecol. Res. 2002;28;3: 160–162
7. Wolff C., Merino R.A. Porfiria y embarazo. RevMédChile 2008; 136:151-156
8. Zhang J., Hu Y., Zheng J., Gao J., Hou H., LIu N., Wang Y. Treatmentofacuteintermittentporphyriaduringpregnancyandposteriorreversibleencephalopathysyndromeafterdelivery: A casereport. ExperimentalAndTherapeuticMedicine 2017;14: 5554-5556
9. Hunter D.J.S. Acuteintermittentporphyriaandpregnancy. J.Obst&Gynaec. Brit. Cwlth. 1971; 78:746-750
10. Lenehan P.M., Turner M.J., Boylan P., MacDonald D. Acuteintermattentporphyriainpregnancy – A CaseReport. IrishJournalofMedicalScience 1982;151;155-157
11. Marsden J.T., Rees D.C. A Retrospectiveanalysisofoutcomeofpregnancyinpatientswithacuteporphyria. J InheritMetab Dis.2010;33:591-596
12. Cerovac A., Brigic A., Softic D., Barakovic A., Adzajlic S. UncontrolledAcuteIntermittentPorphyriaas a CauseofSpontaneousAbortion. MedArch. 2020; 74(2): 153-155.
13. Sahu M.T., Rajaram S., Saxena A.K., Goel N., Ghumman S. MedicalTerminationofPregnancyinAcuteIntermittentPorphyria. GynecolObstetInvest 2006;62:38–40
14. Soriano D., Seidman D.S., MashiachSh., Sela B., Blonder J. Acuteintermittentporphyriafirstdiagnosedinthethirdtrimesterofpregnancy. Casereport. J.Perinat.Med. 1996;24:185-189

15. Martínez N., Nieto A., Guzmán M., Heron S., Zapico A. Porphyriaandpregnancy. Casereport. ColombiaMédica 2011;42;1:107-110
16. PustovoitY.S., KravchenkoS.K., ShmakovR.H., SavchenkoV.H. DiagnosisandtreatmentofacuteporphyrIas. NationalstudyguideMoscow, 2018.
17. Antonenko K.V., SyrotaN.V., VakulenkoL.O., Kutsenko O.V., Shchyrskyi T.O. Themysteriousdiseaseofporphyria: thedifficultyofdiagnosis. Analysisof a clinicalcaseofporphyriapolyneuropathy. UkrainianJournalofNeurology.2019;1:55-59.
18. Badminton M.N., Deybach J.C. Treatmentofanacuteattackofporphyriaduringpregnancy 2006 Eur J Neurol 13(6):668–669
19. Brodie M.J., Moore M.R., Thompson G.G. etal. Pregnancyandtheacuteporphyria. Br J ObstetGynecol 1977;84:726–731
20. Wolff C., ArmasMerino R. Porphyriaandpregnancy. RevMedChil 2008;136:151–156
21. Pavord S., Hunt B. TheObstetricHematologyManual. CambridgeUniversityPress 2010.
22. ProvanArnoldBusselUpdatedinternationalconsensusreportontheinvestigationandmanagement ofprimaryimmunethrombocytopenia. Blood. 2019;3;22:3780-3817.
23. ClinicalPracticeGuidelinesonThrombocytopeniainPregnancy. AmericanSocietyofHematology. Thrombocytopenia- pocket-Guide; 2013.
24. Gernsheimer T., James A.H., Stasi R. How I treatthrombocytopeniainpregnancy. Blood. 2013;121;1:38-47.