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HODGKIN'S LYMPHOMA IN PREGNANT WOMEN: PATIENT MANAGEMENT TACTICS

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Abstract:

Hodgkin lymphoma (HL) is a B-cell malignant lymphoproliferative disorder occurring with a frequency of 2.2 cases per 100,000 population per year, more often in women, with a peak incidence in the range of 16-35 years. The most common type in pregnant women is classic HL, diagnosed with a frequency of 1:1000–1:6000. The authors present a review of the literature on pregnancy in patients with HL, and also describe their own experience of childbirth in 20 patients with HL, of whom 16 (80%) had the disease in the stage of stable remission, and 4 (20%) were diagnosed for the first time during pregnancy. The course of pregnancy was complicated by the development of preeclampsia in 4 (20%) patients, the threat of premature birth in 5 (25%) and anemia in 6 (30%). Delivery occurred on time in 18 (90%) cases, by caesarean section in 4 (20%) cases.

Keywords: Hodgkin's lymphoma, lymphogranulomatosis, pregnancy, lymphadenopathy, polychemotherapy, radiation therapy.

Introduction

Introduction: Hodgkin's lymphoma (HL), or lymphogranulomatosis, is a B-cell malignant lymphoproliferative disease, the incidence of which in Russia is 2.2 cases per 100,000 population per year, and the mortality rate reaches 0.61 cases per 100,000 per year. A characteristic feature of HL is the localization of the pathological process in the early stages with gradual involvement of the lymph nodes of the border areas. Women are more often affected by the disease, and the peak incidence occurs in the age period of 16-35 years [1]. According to the classification of tumors of hematopoietic and lymphoid tissues used by the World Health Organization, HL is divided into classical and nodular with lymphoid predominance. Classic HL includes histological variants with nodular sclerosis (types I and II), mixed-cell variant, classical variant with a large number of lymphocytes and a rare type with lymphoid depletion [2]. Classical HL accounts for 10% of all lymphomas, is the most common type and is diagnosed during pregnancy with a frequency of 1:1000–1:60001. Staging of the disease is based on the degree of involvement of lymph nodes in the pathological process (Ann Arbor classification). At stage I, the lymph nodes of one region or organ are affected, at stage II, two or more regions on one side of the diaphragm, at stage III, the lymph nodes on both sides of the diaphragm and the spleen are involved in the pathological process, and at stage IV, disseminated damage to one or more extralymphatic organs develops. The letter abbreviation (A and B) characterizes the presence or absence of B symptoms (fever above 38 °C for at least three days in a row without signs of inflammation, profuse night sweats, weight loss of 10% of the initial body weight over the past 6 months)1. Clinical manifestations of the disease are varied and include asymptomatic enlargement of peripheral lymph nodes (lymphadenopathy), intoxication (B-symptoms), intermittent fever, pruritus, chest pain, cough, dyspnea and symptoms of compression of the superior vena cava. Some symptoms, such as fatigue, sweating, dyspnea, anemia and thrombocytopenia, can also develop during normal pregnancy, which sometimes complicates the diagnosis of lymphomas1 [3]. The presence of B-symptoms and pruritus in pregnant women is rare [3]. The earliest first sign of HL in pregnant women is the development of localized or generalized lymphadenopathy1. The diagnosis of HL is based on histological examination of material obtained during biopsy or excision of the lymph node [4]. The dominant histological type of tumor in pregnancy is the variant with nodular sclerosis1 [3]. There are no restrictions for performing a biopsy during pregnancy. After histological verification, it is necessary to determine the stage of the disease, which will determine the choice of treatment tactics. The standard scope of examination during pregnancy includes 1 [5]: laboratory tests: general blood and urine analysis, erythrocyte sedimentation rate, biochemical blood test, coagulogram and serological testing for HIV, hepatitis B and C; MRI (without contrast) of the chest, abdominal cavity and pelvis; ultrasound of the abdominal organs and peripheral lymph nodes (if MRI is not possible); CT of the chest organs if MRI is unavailable; X-ray of the chest organs (in two projections, with abdominal shielding, from the second trimester) if CT and MRI are unavailable.

Hodgkin's lymphoma and pregnancy: For any form and stage of HL, there are three possible options for patient management: termination of pregnancy, expectant management, or antitumor therapy. The following provisions are generally accepted [2, 4, 5]:

- > If pregnancy occurs during remission of HL, there is no indication for medical abortion.
- ➤ In case of recurrent HL or unfavorable prognosis in the first trimester, termination of pregnancy is indicated.
- ➤ If HL is detected in the first trimester in women with stages IA and IIA without massive mediastinal lesions and involvement of less than four areas of lymphatic collectors, it is possible to postpone the start of treatment until the second or third trimester.
- From the second trimester, polychemotherapy (PCT) without the use of alkylating drugs is possible. It is mandatory to prescribe low molecular weight heparins throughout the entire gestation period and for 6 weeks after delivery.

- ➤ The timing of delivery is determined individually; in the interests of the fetus, it should be no earlier than 33–34 weeks, and optimally after 37 weeks. Due to possible myelosuppression in the mother and fetus, PCT should be discontinued 3 weeks before delivery.
- Natural childbirth is preferred, cesarean section is performed only for obstetric indications.
- ➤ Pregnant women with symptoms of intoxication, superior vena cava compression syndrome or the threat of HL progression are recommended to start monochemotherapy (vinblastine 6 mg/m2 every 2–4 weeks) or, in case of resistance, polychemotherapy according to the ABVD regimen (doxorubicin, bleomycin, vinblastine and dacarbazine).

Based on retrospective studies, it has been shown that pregnancy does not have a significant impact on the course of HL. An analysis of an international oncology database demonstrated no differences in overall and relapse-free survival rates in 77 pregnant women treated between 1996 and 2025 [6].

The effect of chemotherapy on fetal growth and development

All chemotherapeutic drugs have a teratogenic effect, which is most significant during the periods of implantation (1–2 weeks) and embryogenesis (3–8 weeks). The risk of developing defects or death of the fetus depends on the gestational age, the agent used, and its dose. The risk of developing defects with mono- and combination chemotherapy administered in the first trimester is 15 and 25%, respectively [7]. In the second and third trimesters, chemotherapy is not associated with the formation of defects in the fetus (1.3% compared to 3.1% in the general population) [7].

The placenta plays a key role in drug transfer [8]. Placental cells have a multidrug resistance phenotype that may reduce or prevent the transfer of doxorubicin, vinblastine, and vincristine to the fetus.

The use of PCT in the second and third trimesters can lead to fetal growth retardation, premature birth, stillbirth, neonatal hypotrophy, mental retardation and decreased learning ability [9, 10]. A follow-up study of 43 children aged 3 to 19 years who were subjected to ABVD chemotherapy in utero was conducted, and it was found that no deviations in mental and physical development were detected in any of them during a comprehensive examination [11].

Conducting chemotherapy during pregnancy requires maintaining a careful balance between the effective dose and potential harm to the fetus [12]. Most patients with HL diagnosed during pregnancy can undergo specific treatment, but there is evidence of no worsening of the disease prognosis even when therapy is delayed until the postpartum period [3].

The choice of treatment depends on the trimester, localization of the process and stage of the disease. The beginning of therapy should be postponed until the beginning of the second trimester if the disease is asymptomatic, stable and with supradiaphragmatic localization. However, in case of symptomatic course, massive involvement of lymph nodes, subdiaphragmatic localization or progressive course of HL in the first trimester, it is advisable to consider the possibility of termination of pregnancy1.

Starting from the second trimester, initial treatment is prescribed — combination chemotherapy ABVD or monotherapy with vinblastine [13]. In case of asymptomatic course with supradiaphragmatic localization of involved lymph nodes, treatment can be postponed until the third trimester or postpartum period. In case of symptomatic disease or progressive HL, combination chemotherapy according to the ABVD scheme is prescribed immediately [14]. Pregnant women are prescribed the same doses of polychemotherapy as non-pregnant women, although against the background of the gestational process, blood volume increases, renal and hepatic clearance increases, intestinal peristalsis and albumin levels decrease, a "third space" of the amniotic cavity

appears, and p-glycoprotein is present in fetal tissues and in the endometrium, which causes multiple drug resistance [14, 15].

The most common side effects of chemotherapy are nausea and vomiting. Promethazine, selective serotonin (5-HT) antagonists, neurokinin 1 (NK1) antagonists, and droperidol in combination with diphenhydramine or dexamethasone can be used to relieve it [14].

Radiation therapy during pregnancy has limitations for use and is performed with abdominal shielding only in the II–III trimesters supradiaphragmatically and at a dose of up to 0.1 Gy [3]. The safety of radiation irradiation of the neck and mediastinum with a dose of 35 to 40 Gy (the estimated dose for the fetus is 0.011–0.055 Gy for photons and 0.10–0.14 Gy for cobalt-60) is reported [16]. If all precautions are observed, the prognosis for the fetus after radiation therapy does not worsen [16, 17].

Personal experience of childbirth in patients with HL

The Maternity Hospital at City Clinical Hospital No. 4 of the Samarkand Health Department has been operating since 2023 and specializes in providing medical care to pregnant women with oncopathology. Over 3 years, 20 patients with HL gave birth. The women were aged from 19 to 37 years, with an average of 26.92 years, all of them lived in Moscow and were registered for pregnancy at the antenatal clinic from the first trimester.

Gynecological history was burdened by cervical ectopy in 5 (25%), sexually transmitted infections in 4 (20%), uterine myoma in 1 (5%) and ectopic pregnancy with tubectomy in 1 (5%). Somatic history was burdened by chronic autoimmune hypothyroidism in 4 (20%), varicose veins in 4 (20%), chronic gastritis in 2 (10%) and 1 (5%) patient was diagnosed with chronic pyelonephritis, urolithiasis, and grade 1 obesity.

10 patients (50%) were primigravidas, 9 (45%) had previously given birth. The current pregnancy occurred spontaneously in 19 (95%), in one case - through assisted reproductive technologies.

Of the 20 patients, 5 (25%) had stage IIA HL, 7 (35%) had stage IIB, 2 (10%) had stage IIIA, 3 (15%) had stage IIIB, and 3 (15%) had stage IVB. Remission of HL at the time of pregnancy was in 16 (80%) patients. They had previously undergone courses of polychemotherapy (100%) and radiation therapy (53.3%) with stable remission. In 4 (20%) women, the disease first manifested itself during pregnancy. The table provides information about the patients.

One of the indicators of the quality of life of women who have undergone lymphogranulomatosis is the preservation and implementation of reproductive function. According to a number of authors, after the end of chemotherapy, complete restoration of ovarian function occurs in 70% of patients [17]. The frequency of relapses of lymphogranulomatosis is highest in the first 3 years after the end of treatment and reaches 14% [18]. After childbirth, the number of relapses of lymphogranulomatosis in women who have been in complete remission for more than three years does not exceed 9%, and with uncertain complete or partial remission up to three years, it can reach 44% [19]. According to the Federal State Budgetary Institution "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation, pregnancy and childbirth in women who have undergone lymphogranulomatosis and gave birth in complete remission do not aggravate the prognosis of the disease [20]. The timing of relapses in this group of women corresponds to all indicators in the general population of patients.

In this regard, pregnancy planning is optimal after three years and upon achieving complete remission. Complete remission is understood as the complete disappearance of all manifestations of the disease, including those detected using laboratory and radiation diagnostic methods, as well as clinical symptoms, if they occurred before the start of treatment.

Among the patients who gave birth in the maternity hospital at City Clinical Hospital No. 40, complete remission lasting 2, 3, 4, 5, 7, 8 and 15 years was observed in 14 patients (2 (12.5%) cases for each time period), and in two more women the duration of remission was 9 and 13 years.

In four women, HL was first diagnosed during pregnancy. The main clinical sign was lymphadenopathy, an example of the degree of enlargement of the axial lymph nodes is shown in the figure. In one patient, treatment was postponed until the postpartum period, in three patients, PCT was performed.

The course of pregnancy in patients with a history of HL was complicated by moderate (3/16 (18.75%)) and severe (1/16 (6.25%)) preeclampsia, anemia (3/16 (18.75%)) and the threat of premature birth (25% (4/16)). Timely vaginal delivery was in 12/16 (75%) patients, cesarean section in 4/16 (25%). The weight of newborns ranged from 1690 to 4080 g (on average 3250±75 g). Reproductive losses during the analyzed pregnancy were 1/20 (5%) and were represented by a case of intrauterine death of one fetus in monochorionic diamniotic twins. The patient was delivered at 37 weeks.

Of the four women with manifestation of HL against the background of the current pregnancy, three developed anemia and two had a threat of premature birth. In all cases, the pregnancy ended in vaginal term births, with the weight of the newborns from 2960 to 3500 g (3055 \pm 90 g). The average blood loss during childbirth did not differ in magnitude from that in healthy women and amounted to 420.0 \pm 75.5 ml. There were no complications in the postoperative and postpartum period in any of the mothers.

years Age, years	Parity	Stage / variant histology	Treatment	Pregna	ncy course,	Labor term	Child	
				1	"	///	Mar.	history
35	B-4/R-4 SPV-1W-1 A-1/A-1 V8-1EP-1 P-1/L-1	Stage IHA, nodular sclerosis type Israge IA, grade 2 nodular sclerosis	6 courses of PCT, remission	Threat of SPV Threatened M	Acute bronchitis	Moderate n3 PE	38-39 weeks, Thours 35 minutes Week 38-39, 11 hours 35 minutes	Boy, 3470 g, 50 cm, Apgar score BYF Boy. 3470 g, 50 cm, Apgar score 8/9
25	B-2/R-2 P-1/L-1 SPV-1M-1	Stage II, mixed cells-farity type •	4 courses of PCT, 1 course of adiation theraps; remission	Threat of SPV	Threat of SPV Threatened M	6/o no abnormal- ities	39 weeks 11hours25 ninutes Week 28, 11 hours 25 minutes	Boy, 3560 g, 52 cm, Apgar soon 89 Boy 3560 g, 52 cm, Apgar score 8/9

Continuation of the Table (continued)

Age, years	Parity	Stage/variant histology	Treatment	Pregr	nancy cours	se, trimester	Labor term	Child history
34	B-O/R-O	Stage IIB, grade 1 nodular sclerosis	6 courses of PCT, 1 course of radiation therapy, remission	6/o no abnor- malities	6/o no abnor- malities	Moderate PE	39-40 smoks, 9 hours 20 minutes Week 39-40, 9 hours 20 minutes	Boy, 3000 g, 51 cm, Apgar score 8/9/Wo, 3000 g, 51 cm, Apgar score 8/9
32	B-2/P-2 P-1/L-1 A-1/A-1	Stage IIA, mixed cellularity type	Treatment was postsored until after birth. Treatment was postponed for the gostponed management of	6/0 no arresidas.	ARVI	Cervical lymphaderopathy	37-38 wedo, 5450 min Week 37-38, 5h 50 min	Boy, 2800 g, 51 cm, Apgar score 8/9/Wow 2800 g, 51 cm Apgar score 8/9
33	B-1/P-1 P-9L-1	Stage IIB, grade 2 nodular sclerosis	4 courses of PCT, remission	Simusitis	bto no abnormalities	Mild anemia Mild anemia degrees	33-39 weeks, 6,405 min. Week 38-39, 6h5 min.	Girl, 3380 g, 51 cm, Apgar score 8/9
26	B-O/R-O	Stage IIA, mixed cellularity type	6 courses of ect, remission	Venting ber. Tacko-cit	PE/PE	PE	33 weeks, CS: severe PE	Girl, 1690 g. 42 on, Apgar score \$19
28	B-2/P-2 P-1/L-1 A-1/A-1	Stage II, nodular sclerosis, variant II Stage II, grade 2 nodular sclerosis	4 courses of PCT BEACOPP-14, (ABVD, remission	Venting ber, Tanko-sis	ARNS ARNS	Throat of PR, pyelonephritis, anemia TPTL, pyelonephritis, snemia	38-39 weeks, CS on demand	Girl, 3550 g. 39 cm, Anrap score 8/9/Girl, 3550 g. 39 cm, Apgar score 8/9
24	B-0/R-0	Stage IIB, grade 1 nodular sclerosis	6 courses of PCT BEACOPP-14, radiation therapy, remission	a/0/m	6/0 no abreo multies	Mild anemia Mild anemia	weeks, CS: foral distress 37 Week 37, CS: fetal distress	No data
22	B-O/R-O	Stage IIB, mixed cellularity type	6 courses of ectatacopy-4 6 courses of PCT BEACOPP-14	6/0 no	MCDA, threatened recurrings	Threat of PTLD at 31–32 sents. Aremis. Death of 1 fetus. TPTL at week 32–32. Anemia. Death of 1 fetus	37 weeks 8 hours 10 minutes Week 37,0 hours 10 minutes	Girl, 2960 g, 48 cm, Assir score 879 Get, 2960 g. 48 cm, Apgar score 8/9
25	B-2/P-2 P-9L-1 A-1/A-1	Stage IIIA, grade 2 nodular sclerosis Stage III right femoral head avascular necrosis, III stage III left femoral head avascular necrosis according to the Ficat dassification	6 courses of PCT BACORP-M, remission	6/0 na	Mid anemia	6/o no abnormal- ities	38 weeks planned cs/week 36: planned CS	Girl, 2770 g, 49 cm, Apgar score 8/9 Girl, 2770 g, 49 cm, Apgar score 8/9

contin	ued)							
Age, years		Stage/variant histology	Treatment	Pregnancy course, trimester			Labor term	Child history
						III		nistory
37	B-4/P-4 P-2/L-2 cr A-2/A-2	Stage IIB, mixed ellularity type	remission 1 course of radiation therapy - 4 courses of PCT, 1 course of radiation therapy,	6/O no alorsa crruditiva	6/O na starumstes	Mild anemia	39 weeks, 90 hours 50 minutes Week 39,10 hours 50 minutes	Boy, 3400 g, 55 cm, Apgar score 8/9 Boy, 3400 g, 55 cm, Apgar score 8/9
35	B-O/R-O	Stage IIA, grade I nodular sclerosis	PCT, radiation therapy, retributes	6/0 no abnormalities	árûno slanarmaltins	Mild anemia	40 umiks 10 hours SS ninutes Week 40, 10 hours SS minutes	80, 3830 g 53 cm, Apgar score 8/9
32	B-O/R-O	Stage IIIB, grade 2 nodular scierosis	8 courses of PCT BEACOPP-14, 2 courses of radiation therapy, remission	ber. Toxicosis	6/0 no als normalities	Threat of PR, mild averia TPTL, mild anomia	41 seeks 24 hours 10 minutes Week 61,24 hours 30 minutes	Boy, 4080 g, 56 cm, Apgar score 89 Bey, 4080 g, 56 cm, Apgar score 8/9
23	B-2/P-2 P-151 A-1/A-1	Stage IIIB, grade 2 nodular sclerosis Osteonecrosis of the lettermosal head	8 courses of PCT ABVD, BEACOPP-14	6/O no atmorrodites	Threat of PR	6/e no abnormal- tries	38 mmks, 54 55 min Week 38, 5 h 55 min	Boy, 3500 g, 53 cm, Apparation 89 Bey, 3500 g, 53 cm, Appar score 8/9
28	B-O/R-O	Stage IVB, mixed cellularity type	6 courses of PCT BEACOPP-14, radiation therapy 30 Gy	ARVI Altri	Mild anemia	ARIARVI COVID-19	36-37 weeks ; 10 hours 25 minutes Week 36-37, 10 hours 25 minutes	Girl, 2960 g. 48 en, Annap score 8/8/Girl, 2960 g. 48 cm, Apgar score 8/8
30	B-1/P-1 P-VL-1	Stage IVB, grade 2 nodular sclerosis	6 courses of PCT BEACOPP-14, remission	670 no sto normalities	Anemia	Angmia	38 weeks planned C5 Week 38, planned CS	Girl, 3560 g, 52 cm, Apgar score 8/9 Girl, 3560 g, 52 cm, Apgar score 8/9
31	B-O/R-O	Stage IIIA, grade 1 nodular sclerosis	8 courses of PCT ABVD, resisting Course of PCTABVD, remission	COVID-19	Mone denomalities	Colpitis	38-39 weeks thours 25 meutes Week 38-39, 11 hours 25 minutes	Boy, 3150 g, 50 cm, Apgar score 8/9 Boy, 3150 g, 50 cm, Apgar score 8/9
25	B-O/R-O	Stage IIB, grade 2 nodular sclerosis	6 courses of PCT BEACOPP-14, radiation therapy 40 Gy, remission	Threat CFB Threat-scall M	6/0 no sbrovnatřími	Seeing Edema	29-90 weeks, 8 hours 10 minutes Week 29-40, 8 hours 30 minutes	Boy, 3300 g, 52 cm, Apgar score 8/9 Boy, 3300 g, 52 cm, Apgar score 8/9
19	B-2/R-2 P-2/L-2	Stage IIIB, grade 1 nodular sclerosis	6 courses of PCT, radiation therapy 30 Gy, remission	6/0 no altino mnalitima	6/0 no streamaities	Moderate PE	38-39 weeks 9 hours 30 minutes Week 38-39, 9 hours 30 minutes	Girl, 3300 g, 33 cm, Apgar score 9/9 Girl, 3300 g, 33 cm, Apgar acons 9/9



Figure. Ultrasound data of axial lymph nodes in a pregnant woman with HL. 1-D-2.86 cm 2-D-1.74 cm 3-D-2.48 cm 4-D-2.37 cm :5—D=2.49

Figure. Axillary ultrasound in a pregnant female patient with HL.

1 — D = 2,86 cm; 2 — D = 1,74 cm; 3 — D = 2,48 cm; 4 — D = 2,37 cm; 5 — D = 2,49

Discussion

The clinical picture of classical HL during pregnancy is similar to that in non-pregnant women and may include lymphadenopathy, symptoms of intoxication, signs of compression of the mediastinal organs, and skin itching. Diagnosis is based on histological examination of lymph node biopsy, with excisional biopsy being preferable, since fine-needle aspiration biopsy is insufficient to establish the diagnosis and determine the tumor subtype. Staging is based on the results of MRI of the chest and abdomen according to the Lugano criteria. Treatment of HL should be postponed until the second or third trimester or postponed until the postpartum period. Termination of pregnancy is recommended for most women with HL diagnosed in the first trimester (level 1C). Specific therapy begins in the second trimester and most often includes the use of the ABVD regimen, radiation therapy is prescribed only in exceptional cases (level 2C). In asymptomatic, clinically stable patients with supradiaphragmatic disease, chemotherapy can be deferred until the postpartum period (Level 2C). In our study, out of four patients with HL diagnosed for the first time during pregnancy, chemotherapy was deferred in one case, three patients were treated with the BEACOPP-14 regimen (etoposide, doxorubicin, cyclophosphamide, vincristine, bleomycin, procarbazine or decarbazine, prednisolone). The use of chemotherapy in the second and third trimesters is associated with fetal growth restriction, preterm birth, stillbirth, low birth weight, and cognitive impairment. In our study, all patients delivered at term, and fetal growth restriction and neonatal hypotrophy were not detected. Delivery of patients with HL is performed as close to full-term as possible. Caesarean section is performed only for obstetric indications.

Conclusion

Our own experience of pregnancy management in women with HL and delivery is generally consistent with world experience. When pregnancy occurs against the background of stable remission, there are no significant differences in the frequency of obstetric complications, timing and methods of delivery from the average population indicators. When the disease is first detected, medical tactics depend on the stage of the disease and the gestational age. In our study, in some pregnant women, starting chemotherapy was postponed until the postpartum period due to a favorable prognosis. In some patients, chemotherapy was administered from the second trimester.

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