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LYMPHOMAS DURING PREGNANCY: DIAGNOSTIC AND THERAPEUTIC CHALLENGES

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Abstract. Introduction: *Cancer during pregnancy is relatively rare, but hematologic malignancies such as lymphomas are among the more frequently encountered types. Managing cancer in pregnant patients presents a significant clinical challenge. Diagnosis is often complicated by the overlap between disease symptoms and physiological changes associated with pregnancy, as well as by limitations in imaging modalities and available treatment options. The study aim was to summarize current knowledge regarding the diagnosis and management of lymphoma during pregnancy.* ***Materials and Methods:*** *This study analyzed the medical records of pregnant patients diagnosed with lymphoma and treated at the Department of Hematology, University Hospital in Krakow, between 2011 and 2024.* ***Results:*** *Seven pregnant patients diagnosed with lymphoma were included in the analysis. The median age at the time of diagnosis was 27 years (range: 21-37). Five patients had Hodgkin lymphoma, while the remaining two were diagnosed with plasmablastic lymphoma and primary mediastinal B-cell lymphoma, respectively. The diagnosis was confirmed between the 5th and 30th week of pregnancy. Treatment strategies were tailored individually, taking into account the stage of pregnancy, disease severity, and the overall maternal condition. Only two patients underwent therapy during pregnancy, and no major complications were observed in these cases. Five women gave birth to healthy infants; the remaining two children were later diagnosed with health issues, including Duchenne muscular dystrophy and immune system disorders. One patient experienced a relapse and died six years after the initial diagnosis.****Conclusion:*** *Based on case analyses and a review of the literature, it was concluded that the best outcomes for both mother and newborn are achieved through a multidisciplinary approach, close monitoring, and appropriately tailored treatment strategies.*

Key words: *lymphoma, pregnancy, Hodgkin lymphoma, hematological malignancy, lymphoma during pregnancy*

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INTRODUCTION

Cancer during pregnancy occurs with an incidence of approximately 1 in 1,000 cases. The most commonly diagnosed cancers include gynecological malignancies – cervical cancer (1.2:10,000) and breast cancer (1:3,000-10,000), as well as melanoma (2.6:1,000) and lymphomas (1:1,000-6,000) [1-3]. Hodgkin lymphoma (HL) is diagnosed more frequently than non-Hodgkin lymphoma (NHL) (HL: 1:3,000, NHL: 1:5,000) [4, 5]. Lymphomas identified in pregnant women are typically not advanced at the time of diagnosis, although they more frequently involve reproductive organs, such as the breasts, ovaries, or uterus, compared to the general population. This may be attributed to increased expression of hormonal receptors and augmented blood flow [1, 6].

Cancer during pregnancy presents a significant challenge for medical teams. The diagnosis is complicated due to the overlap between disease symptoms and normal physiological changes during pregnancy, as well as by limitations in diagnostics and treatment options. Additionally, therapeutic interventions may pose risks to the developing fetus [1, 3-5, 7-10]. Given the complexity of the situation, the treatment process should involve not only oncologists, but also a multidisciplinary team including specialists in obstetrics, gynecology, and neonatology [3-5, 9-11].

MATERIALS AND METHODS

A retrospective analysis of medical records was conducted at the Department of Hematology, University Hospital in Krakow, Poland, covering the period from January 2011 to December 2024. The study focused on pregnant women diagnosed with lymphoma within this time frame. The study aimed to summarize the available knowledge regarding the diagnosis and treatment of lymphoma during pregnancy. The inclusion criteria encompassed all patients with a confirmed histopathological diagnosis of lymphoma during pregnancy who received treatment at the aforementioned institution within the specified time frame. Patients were excluded if the diagnosis of lymphoma was established outside of pregnancy or if the entire course of treatment was carried out at another medical center. Information about children's health status was obtained through follow-up telephone interviews with the patients. A total of seven cases meeting the inclusion criteria were identified and analyzed. Medical records were reviewed manually by two independent clinicians and cross-verified by a senior physician. Extracted data included: demographic details (maternal age, parity), pregnancy-related information (gestational age at lymphoma diagnosis, complications, gestational age at delivery, mode of delivery), disease characteristics (lymphoma subtype, presenting symptoms), treatment details (chemotherapy regimens, timing relative to gestational age, multidisciplinary decision-making process), neonatal outcomes (Apgar scores, presence of congenital anomalies). Due to the rarity of lymphoma diagnosed during pregnancy, all eligible cases meeting the inclusion criteria during the 14-year study period were included. As a result, seven patients were identified and analyzed. No a priori sample size calculation was performed due to the retrospective and exploratory nature of the study. Data were analyzed using descriptive statistics. Continuous variables, such as maternal age and gestational age at diagnosis or delivery, were reported as medians and ranges. Categorical variables, such as lymphoma subtype, treatment regimen, and delivery method, were presented as frequencies and percentages. Owing to the small sample size, no inferential statistical tests were applied. The study did not involve any interventions or experimental procedures.

RESULTS

Seven cases were included in the analysis. The patients ranged in age from 21 to 37 years, with a median age at diagnosis of 27 years. In all cases, the diagnosis of lymphoma was made during pregnancy, between the 5th and 30th week. The most frequently diagnosed type of lymphoma was Hodgkin lymphoma (five cases). The remaining two patients were diagnosed with plasmablastic lymphoma and primary mediastinal B-cell lymphoma, respectively. Only one patient (Patient 1), diagnosed with Hodgkin lymphoma, had an extranodal involvement, which was localized in the spleen. No cases involved the reproductive system, and there was no evidence of central nervous system involvement in any patient. Detailed information is presented in Table 1.

Symptoms

Enlarged lymph nodes and fatigue were the most commonly reported symptoms. Although not considered a B symptom, itching – reported by patients 1, 3, and 6 – is a feature often associated with Hodgkin lymphoma. Patients 1 and 7 experienced night sweats. Weight loss was noticed by two patients, 2 and 7. Symptoms like fever, night sweats and weight loss are characteristic of Hodgkin lymphoma and are called B symptoms [12]. Three patients reported a cough.

Table 1. Patient Characteristics

Patient number	Type of lymphoma	Age	The week of pregnancy when lymphoma was diagnosed	Symptoms	Mode of delivery	Gestational age at delivery	Apgar points
1	Hodgkin lymphoma	30	12	Itching, shortness of breath, weakness, night sweats, cough, enlarged lymph nodes in the neck on the left side	Cesarean section	35	7-8-8
2	Hodgkin lymphoma	21	5	Weakness, weight loss (10 kg in a year), cough, enlarged lymph node on the left side of the neck	Vaginal delivery	39	4-7-8
3	Hodgkin lymphoma	22	23	Weakness, itching, palpable enlarged supraclavicular lymph nodes, initially on the right side, then on both sides, feeling of pressure the neck	Cesarean section	36	10-10-10
4	Plasmablastic lymphoma	37	30	Weakness, decreased exercise tolerance, cough with clear sputum, migraine headaches, impaired visual acuity, generalized enlargement of lymph nodes	Cesarean section	33	No information
5	Primary mediastinal large B-cell lymphoma	31	21	Weakness, shortness of breath	cesarean section	35	No information
6	Hodgkin lymphoma	24	17	Itching, enlarged right supraclavicular lymph node	Cesarean section	37	10-10-10
7	Hodgkin lymphoma	27	25	Night sweats, weight loss, enlarged cervical and axillary lymph nodes on the right side	Vaginal delivery	39	10-10-10

More clinically significant symptoms in the context of pregnancy, such as shortness of breath and reduced exercise tolerance, were also reported by patients 1, 4, and 5. They deserve particular attention due to their potential impact on maternal and fetal health. Other reported symptoms included migraine headaches and visual disturbances.

Imaging Diagnostics

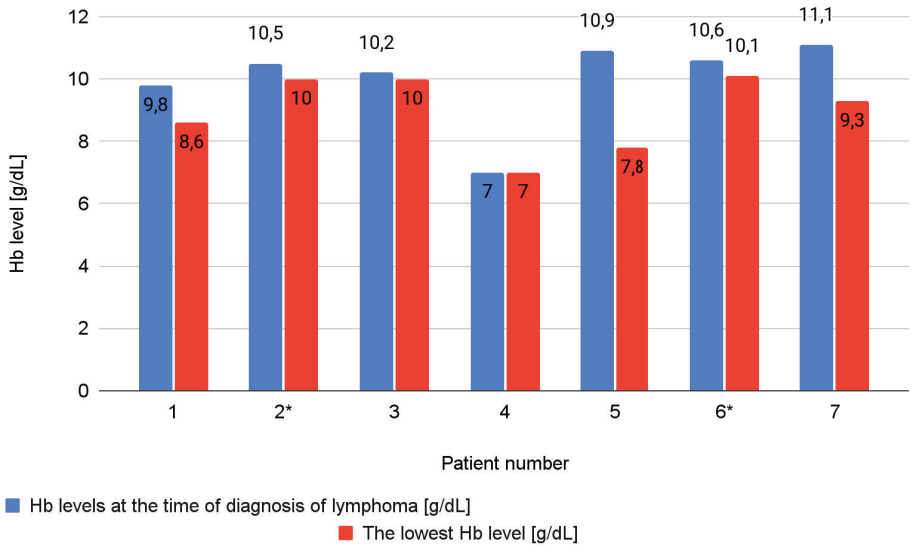
All patients underwent an ultrasound examination to assess the clinical stage of the disease. Additionally, magnetic resonance imaging (MRI) of the chest was performed to four patients – patients 1, 3, 5, 7 – due to shortness of breath and a sensation of pressure on the neck. MRI scans were conducted during the third trimester of pregnancy.

Laboratory Results

The following key parameters were monitored during treatment: hemoglobin (Hb) levels, platelet count, lactate dehydrogenase (LDH), and neutrophil count. A decrease in hemoglobin levels was observed in most cases over the course of the disease. In only one patient the initial and lowest Hb values were the same. The median Hb level at the time of diagnosis of lymphoma was 10.5 g/dL, while the median lowest Hb value was 9.3 g/dL. Detailed values are presented in Figure 1. Two patients required red blood cell concentrate transfusions: Patient 4 received a total of 21 units, and Patient 5 received 8 units. The lowest platelet counts and highest LDH levels are also depicted graphically (Figure 2 and Figure 3). The median platelet count was 203 G/L, and the median LDH level was 431 IU/L.

Treatment

Only two patients received treatment during pregnancy. Both were treated according to the ABVD regimen (doxorubicin, bleomycin, vinblastine, dacarbazine). Patient 2 underwent six cycles of ABVD chemotherapy and consolidation radiotherapy to the area of the residual mediastinal mass. Treatment began at 20



*Patients who received chemotherapy during pregnancy

Fig. 1. Hemoglobin Levels

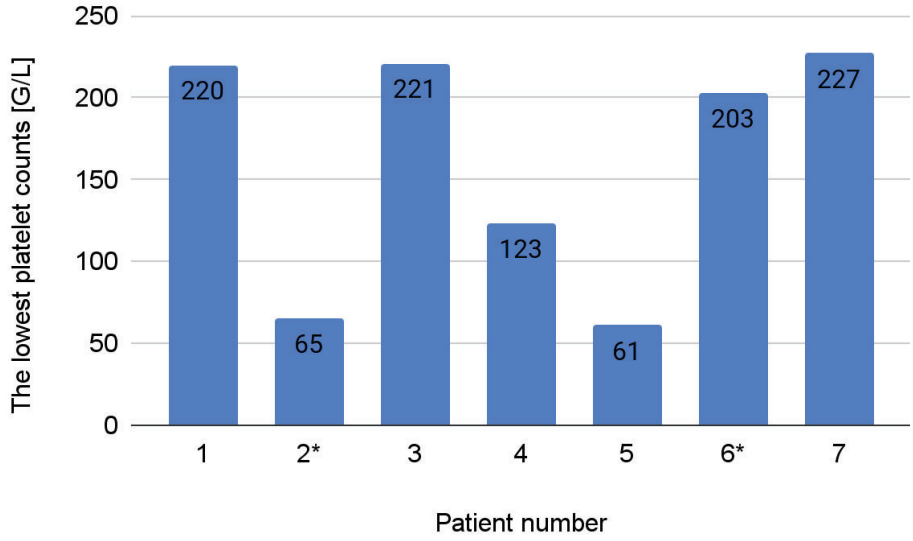


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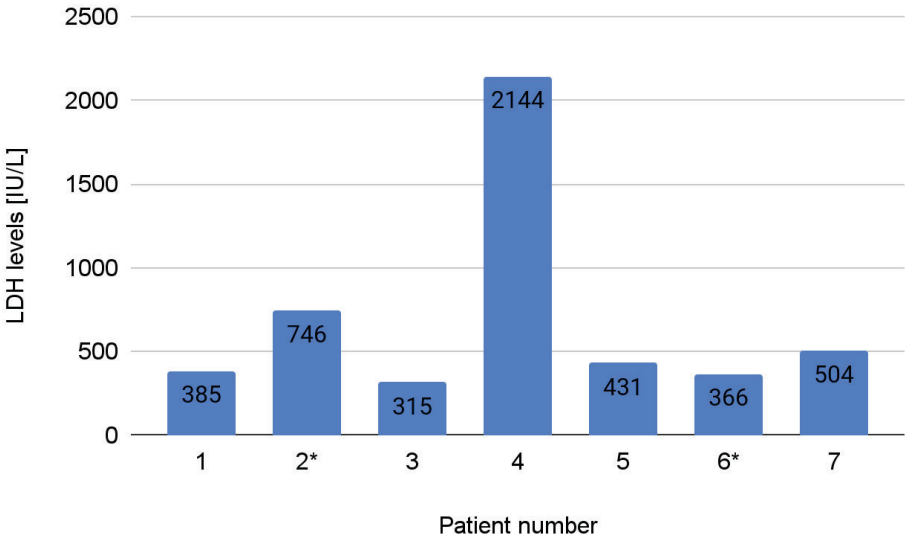
Fig. 2. The Lowest Platelet Counts (G/L)



*Patients who received chemotherapy during pregnancy

Fig. 3. Lactate Dehydrogenase Level

weeks of gestation. Patient 6 received three cycles of ABVD during pregnancy, starting at 32 weeks of gestation, with the remaining cycles administered after delivery. The remaining five patients did not receive chemotherapy during pregnancy. After delivery, Patient 6 underwent second-line ESHAP therapy (etoposide, cytarabine, cisplatin, methylprednisolone), followed by stem cell mobilization and autologous stem cell transplantation (ASCT). A total of six patients received treatment after delivery. ASCT was also performed to Patient 5.

Patients 1 and 7, both diagnosed with Hodgkin lymphoma, underwent similar treatment protocols. They each received two cycles of escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), followed by four cycles of ABVD chemotherapy. Additionally, Patient 7 underwent radiotherapy, receiving 30 grays (Gy) in 15 fractions.

Patient 3, also diagnosed with Hodgkin lymphoma, received six cycles of ABVD chemotherapy. She also had radiotherapy.

Patient 4, diagnosed with plasmablastic lymphoma, received six cycles of CHOP chemotherapy (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone).

Patient 5, diagnosed with primary mediastinal large B-cell lymphoma, underwent R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone), DepoCyte, ESHAP therapy and radiotherapy (36 Gy in 18 fractions). ASCT was also performed in this case.

Detailed information is presented in Table 2.

The International Prognostic Index (IPI) was assessed for patients 1, 2, 3, 4, 6, and 7, all of whom scored one point. For Patient 5, diagnosed with primary mediastinal large B-cell lymphoma, the Revised

Table 2. Treatment Details of Pregnant Patients Diagnosed with Lymphoma

Patient number	Treatment used during pregnancy	Week of pregnancy when treatment started	Treatment used after pregnancy ended	Total number of treatment cycles
1	–	–	2 cycles of escalated BEACOPP, 4 cycles of ABVD	6
2	ABVD chemotherapy for 6 cycles and consolidation irradiation to the area of residual mediastinal invasion: 30 Gy in 15 fractions to the area of residual mediastinal invasion and 20 Gy in 10 fractions to the remaining bilateral supraclavicular and cervical mediastinal lymph nodes	20	–	6
3	–	–	6 cycles of ABVD, IFRT consolidation radiotherapy	6
4	–	–	6 cycles of CHOP chemotherapy	6
5	–	–	CHOP–R VI, DepoCyte IV, ESHAP, ASCT IFRT 36 Gy in 18 fractions	6
6	ABVD chemotherapy for 3 cycles	32	After pregnancy, second-line ESHAP treatment with stem cell mobilization and ASCT consolidation	3 + ESHAP
7	–	–	2 cycles of chemotherapy escalated BEACOPP, 4 cycles of ABVD, consolidation radiotherapy 30 Gy in 15 fractions	6

ABVD – doxorubicin, bleomycin, vinblastine, dacarbazine
ASCT – Autologous stem cell transplantation
BEACOPP – bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
CHOP-R – rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone
CHOP – cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone
ESHAP – etoposide, cytarabine, cisplatin, methylprednisolone
IFRT – Involved-field radiotherapy

International Prognostic Index (R-IPI) – appropriate for diffuse large B-cell lymphoma – was applied, yielding a score of 1 point as well.

Hematological toxicity was monitored by measuring the neutrophil counts, platelet counts and hemoglobin levels. Platelet counts and hemoglobin counts were discussed above. In two patients, the neutrophil counts dropped below the normal reference range during treatment. The lowest neutrophil counts recorded during therapy are presented graphically in Figure 4. The median lowest neutrophil count was 1,85 G/L.

Prophylaxis for febrile neutropenia was administered to 4 patients after chemotherapy.

Pregnancy and Delivery

All patients were carrying singleton pregnancies and it was their first pregnancy, with no prior history of miscarriage. Five patients had cesarean birth (four due to hematological indications and one due to threatened intrauterine fetal demise), while two patients delivered vaginally. Deliveries occurred between the 33rd and 39th weeks of gestation, with a median gestational age of 36 weeks. Newborns were assessed using the Apgar score. The lowest recorded Apgar score at 1 minute was 4. Three newborns received 10 points. Detailed information is presented in Table 1.

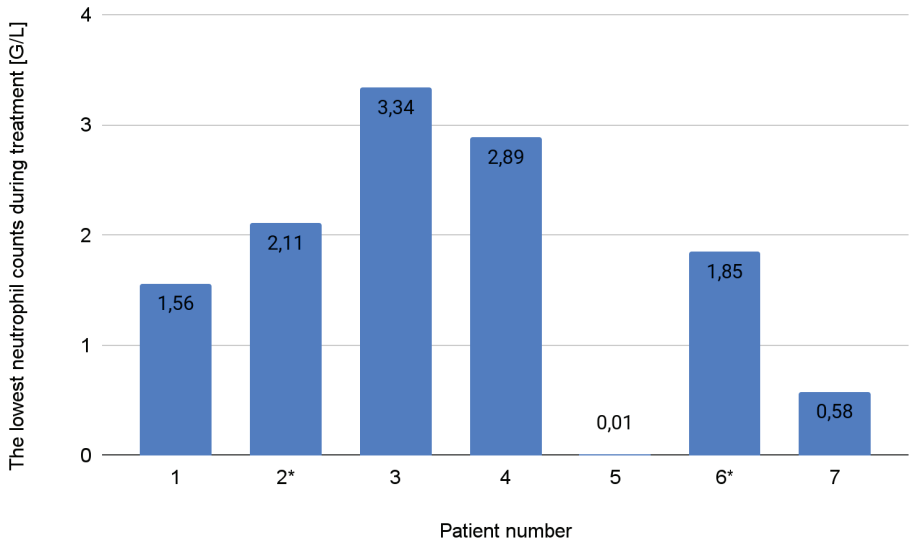
In pregnant patients with lymphoma, more frequent medical appointments, even monthly, with specialists such as a gynecologist and a hematologist, are very important. A neonatologist should also be involved in the decision-making process.

Follow-up

After treatment, patients remained under hematological follow-up. One patient (Patient 4) experienced disease relapse and died 6 years after the initial diagnosis. Five women delivered healthy children, while two children were diagnosed with abnormalities: Duchenne muscular dystrophy and immune disorders. The first of these diseases is a genetic disease, X-linked, recessive, so there is no relationship with the treatment.

DISCUSSION

The incidence of cancer during pregnancy is increasing due to the trend of delayed pregnancies [3]. As maternal age rises, especially in Western countries, the incidence of lymphomas is also on the rise [4]. Diagnosing cancer during pregnancy presents a significant challenge for medical teams. One of the major issues during this period is the limited capacity for imaging diagnostics. Computed tomography (CT) and positron emission tomography (PET) are generally avoided during pregnancy because of the risks associated with radiation exposure [1]. Magnetic resonance imaging (MRI) is typically avoided in the first trimester. However, it may be considered in the second and third trimesters when clearly indicated and if the findings are expected to significantly influence clinical decision-making. Gadolinium-based contrast agents should be avoided during the first trimester due to their ability to cross the placenta and potential risk of fetal developmental abnormalities. In the second and third trimesters, their use may be considered if strongly indicated [1, 4]. While ultrasound is the safest imaging modality during pregnancy, it is also the least sensitive [10]. The analyzed data confirm these findings. All patients underwent an ultrasound during pregnancy, and three patients additionally underwent MRI. No patient had a CT scan or PET during pregnancy.



*Patients who received chemotherapy during pregnancy

Fig. 4. The Lowest Neutrophil Counts during Treatment [G/L]

Laboratory investigations are a vital component of diagnosis, particularly in pregnant patients. It should be emphasized that the analysis of laboratory results in pregnant patients is difficult to interpret due to the physiological changes occurring in their bodies. Some tests may be helpful in assessing health status and may provide indirect indicators of malignancy. Basic laboratory tests, including complete blood count (CBC), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), as well as kidney and liver function panels (e.g., alkaline phosphatase), may offer valuable diagnostic insights. However, it should be noted that alkaline phosphatase levels may be significantly elevated during the third trimester, limiting its diagnostic utility [1, 4]. In pregnant patients, anemia is diagnosed when hemoglobin (Hb) levels fall below 11 g/dL, because during pregnancy the mass of red blood cells increases, but to a relatively lesser extent compared to the increase in plasma volume, with the final result being a decrease in hemoglobin concentration [13]. Anemia was present in six out of the seven patients treated in this department at the time of diagnosis, based on blood count results.

The treatment of pregnant patients with lymphoma is a considerable challenge for healthcare providers. The timing of therapy depends on the type of cancer, its aggressiveness, the gestational age, and the patient's preferences [10]. Drugs used in systemic chemotherapy regimens are cytostatic and cytotoxic, posing a potential risk to the developing fetus. If immediate treatment is required during the first trimester, rituximab monotherapy may be considered a relatively safe option. In the second and third trimesters, combination regimens such as R-CVP (rituximab, cyclophosphamide, vincristine, prednisone) or R-CHOP (R-CVP with the addition of doxorubicin) can be administered. However, fludarabine-based therapies are generally avoided during pregnancy [1, 14]. Several reports have shown that the administration of R-CHOP in pregnant patients with DLBCL (diffuse large B-cell lymphoma) has been linked to a higher risk of preterm delivery and low birth weight, although no fetal developmental abnormalities have been observed [4].

Many case reports have described the use of rituximab during pregnancy without significant teratogenic risks [1, 15]. Rituximab is not recommended during the first trimester of pregnancy [1]. Exposure to rituximab during early pregnancy may cause a temporary decrease in fetal B-cell counts, which typically resolves spontaneously. A retrospective analysis of 153 pregnant patients treated with rituximab documented pregnancy outcomes. In 90 cases, live births were recorded, with no significant malformations or delivery complications. Neonatal complications observed included transient leukopenia, occasionally accompanied by infections. Overall, in cases of aggressive lymphomas during the second or third trimester, the potential benefits of rituximab therapy may outweigh the associated risks to the fetus. Available data and studies on the safety of rituximab in pregnant women are limited [1, 15].

The ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine), the most commonly used chemotherapy regimen for treating Hodgkin lymphoma, is not recommended during the first trimester due to limited safety data. There is a lack of available data on the safety of other chemotherapy regimens for HL during pregnancy, such as Stanford V (mechlorethamine hydrochloride, doxorubicin hydrochloride, vinblastine sulfate, vincristine sulfate, bleomycin, etoposide phosphate, prednisone) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone) [16, 17]. In cases of early-stage Hodgkin lymphoma diagnosed during the first trimester, careful monitoring for disease progression is recommended, with chemotherapy typically deferred until the second trimester. In selected cases, localized radiation therapy to the cervical and/or axillary regions with appropriate abdominal shielding may be considered during the first trimester. For most women diagnosed with HL in the second or third trimester, treatment with the ABVD regimen is generally appropriate. However, in patients with localized disease (stage IA or IIA) diagnosed later in pregnancy, it may be possible to delay chemotherapy until after delivery in order to better evaluate disease progression and tailor postnatal treatment accordingly. Currently, no randomized controlled trials are comparing the outcomes of early versus delayed treatment in this patient population. The 20-year survival rate for pregnant women diagnosed with Hodgkin lymphoma is comparable to that of non-pregnant women with the same disease. Furthermore, the incidence of preterm birth and intrauterine growth restriction (IUGR) is not increased in pregnant patients with HL [1]. After the first trimester, ABVD administration is considered safe. In the third trimester, there are two treatment options: delaying treatment until postpartum or starting ABVD treatment, especially in patients with massive disease diagnosed early in the third trimester. For NHL, different clinical approaches are used depending on the subtype and gestational age. For indolent lymphomas, such as follicular lymphoma or marginal zone lymphoma, a watchful waiting approach may be appropriate. In contrast, most cases of aggressive non-Hodgkin lymphomas, including diffuse large B-cell lymphoma

(DLBCL) and primary mediastinal B-cell lymphoma, require prompt initiation of treatment [4].

Neutropenia is a common complication of treatment in patients with hematological malignancies. It is defined as a neutrophil count below 1.5 G/L [18]. Particularly dangerous is febrile neutropenia, which can lead to severe complications such as infections, the need for hospitalization, delays in chemotherapy administration, and poor treatment outcomes. In some cases, it can be fatal [19, 20]. The risk of neutropenia depends on factors such as the treatment protocol used, disease stage, initial neutrophil count, comorbidities (e.g., liver or kidney failure), and the patient's age [19-21]. Neutropenia was identified in 2 of the patients, with one patient's neutrophil count being just above the lower normal limit (1.56 G/L).

There are two main strategies to reduce the risk of neutropenia: prophylaxis with growth factors and reducing myelotoxicity, for example, by dose reduction of cytotoxic agents. Identifying patients at high risk of febrile neutropenia is crucial. Guidelines recommend granulocyte colony-stimulating factor (G-CSF) administration when the risk is >20% [19-21]. A meta-analysis of 3,493 patients treated in 17 centers showed that G-CSF prophylaxis effectively reduces the incidence of febrile neutropenia and mortality during chemotherapy [19].

Managing lymphoma during pregnancy requires a multidisciplinary team that includes a hematologist, an obstetrician, a neonatologist, a radiologist, and, in many cases, a psychologist. A collaborative, individualized treatment strategy is essential to balance maternal and fetal risks. Patients should be informed of potential treatment complications, options, and outcomes at various gestational stages to support shared decision-making. A cancer diagnosis during pregnancy imposes a profound emotional burden on the patient. Anxiety about the fetus's well-being, treatment-related risks, and the unpredictability of the disease course contribute to psychological distress. Studies highlight that maternal stress can influence pregnancy outcomes and fetal development [22]. Therefore, psychosocial support and counseling should be considered integral to care.

Given the rarity of lymphoma during pregnancy, available data are limited to case series and retrospective analyses. There is a pressing need for large, multicenter registries and prospective cohort studies to establish standardized treatment protocols and assess long-term outcomes, particularly for children exposed to chemotherapy or monoclonal antibodies in utero. Current data support the safety of ABVD after the first trimester and rituximab after organogenesis. However, additional controlled studies are needed [23].

In our cohort, Hodgkin lymphoma was the most frequently diagnosed malignancy (71.4%). In a study conducted in Australia and New Zealand, which included patients diagnosed with lymphoma during pregnancy or within the first 12 months after childbirth, this was also the most common lymphoma, accounting for 54.8%. Among the analyzed group of patients treated in the Krakow hospital, 1 patient died as a result of recurrence of the neoplastic process after 6 years from the initial diagnosis. In the previously mentioned study, the 5-year survival rate for patients with Hodgkin lymphoma was 82% [24]. Another multicenter retrospective study of 90 patients with Hodgkin and non-Hodgkin lymphoma diagnosed during pregnancy showed that the 3-year survival rate for patients with Hodgkin lymphoma was 97% and for non-Hodgkin lymphoma was 82% [25].

It should be emphasized that the study is limited by the small patient population. A retrospective analysis of pregnant patients diagnosed with lymphoma treated in other hospitals would be necessary to better understand the subject.

CONCLUSIONS

Patients diagnosed with lymphoma during pregnancy require a tailored approach to therapy, balancing the risks and benefits to both the mother and the fetus. The treatment must be carefully timed to minimize potential harm to the fetus while ensuring optimal maternal outcomes. The combination of a multidisciplinary approach, careful monitoring, and appropriate treatment strategies offers the best chance for maternal and fetal outcomes.

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