The Management of Hodgkin Lymphoma During Pregnancy

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18.1 Introduction

The peak incidence of Hodgkin lymphoma (HL) coincides with reproductive years, and about 0.5–1% of all HL patients present with concurrent pregnancy. Lymphoma is the most common hematologic malignancy complicating pregnancy, with an estimated incidence of HL-associated deliveries of between 1 in 1000 and 1 in 3000 pregnancies [1, 2]. The medical challenge of concurrent HL and pregnancy stems from the need to manage the potentially life-threatening malignancy while giving the

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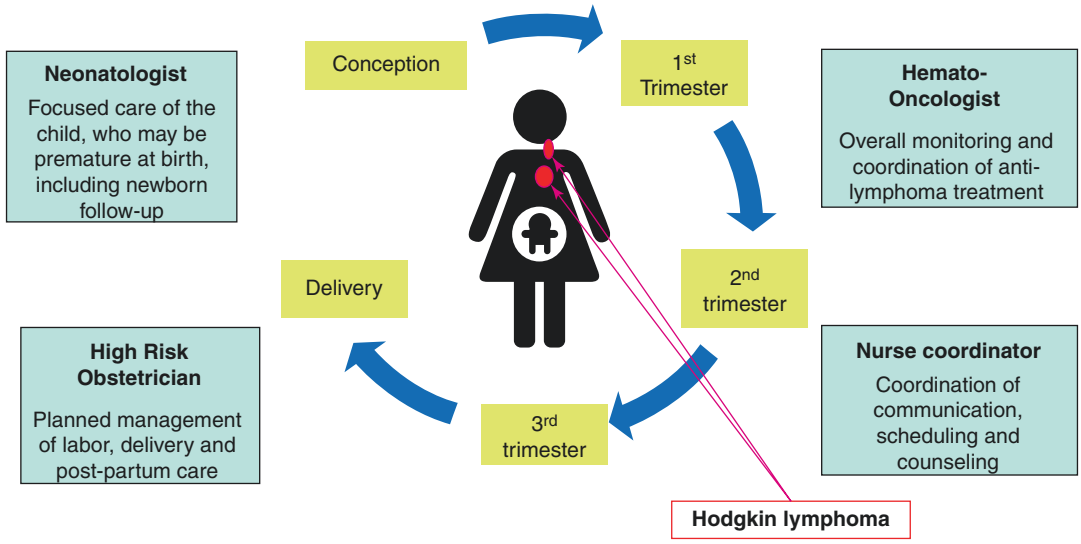

Fig. 18.1 Recommended algorithm for treatment of pregnancy-associated Hodgkin lymphoma (*HL*). *ABVD* doxorubicin, bleomycin, vinblastine, dacarbazine

developing fetus the best chance of reaching term fully intact. Essentially, two patients need to be managed: one with lymphoma and the other without, both of whom will be affected by the toxicity of any treatments. Religious, ethical, psychological, social, and cultural beliefs and attitudes of the patient and her partner, family, and physicians all can affect decision-making. Thus, management of the disease and pregnancy not only involves the therapeutic approach but also requires attention to alleviating fear and anxiety and supporting the patient's emotional and social well-being. Current clinical practice for treating HL during pregnancy is based largely on case series, retrospective reports, and expert opinions. Therefore, management of HL during pregnancy requires that the advising clinician must balance the provision of expertise and knowledge about treatment options and prognosis with respect for ethical principles, compassion, and acceptance of patient autonomy.

One of the main principles in treating patients with HL discovered during pregnancy is to provide care under the direction of a multidisciplinary team composed of a hemato-oncologist knowledgeable in the treatment of HL, an obstetrician experienced in the management of high-risk pregnancy, a pediatrician/neonatologist familiar with hematologic problems in the neonate, and a nurse coordinator who augments the communication and delivery of care (Fig. 18.1). The best results are possible if the decision-making is guided by a judicious mix of careful clinical judgment, the experience of involved team members, knowledge of the natural history of HL, and consideration of the patient's personal beliefs and desires [2–4]. A comprehensive review of the management of HL and coincident pregnancy recently published by Eyre et al. validates the effectiveness of this team approach and the specific recommendations described below [5].

18.2 Diagnostic Approach to HL during Pregnancy

Planning the diagnostic evaluation of HL in a pregnant patient should balance accurate disease assessment with the need to limit invasive procedures. The histopathologic diagnosis of HL should be based on tissue examination obtained by excisional or incisional tissue biopsy. The most common subtype encountered in pregnancy is nodular sclerosing HL. Following diagnosis, the initial evaluation should include a complete history and physical examination with thorough

palpation of all node-bearing areas and the abdomen, as well as careful documentation of B symptoms. Despite a higher rate of extranodal involvement of genital organs in non-Hodgkin lymphoma during pregnancy [6], non-lymphatic spread in the pregnant HL patient is rare and usually limited to the lung or liver [7]. Often complete staging is not necessary, and the guiding principle in managing the pregnant patient should be to restrict investigations to determining the cause of patient symptoms, noting the bulk and anatomic location of the dominant tumor masses, and estimating lymphoma stage. Standard laboratory tests should include hemoglobin, complete differential white blood cell count, platelet count, erythrocyte sedimentation rate (ESR), liver and renal function assessment, lactate dehydrogenase, and serum protein electrophoresis including albumin level. It is important to recall that pregnancy can affect the results of some of these tests, particularly ESR and alkaline phosphatase, and therefore, these tests must be interpreted carefully.

Radiologic staging should be limited to the minimum necessary to identify disease that seriously threatens the immediate well-being of the mother or child. Combined F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) scan is a standard imaging modality for staging HL under ordinary circumstances, but it employs ionizing radiation that is potentially harmful to an unborn fetus and should be avoided in pregnancy [7]. A single posteroanterior radiograph of the chest, with proper shielding, should be obtained to characterize the extent of mediastinal and pulmonary disease because overall radiation exposure is much lower than the dose associated with malformation during organogenesis [8]. Abdominal ultrasonography should be used to identify the extent and size of retroperitoneal nodal disease and provides sufficient detail for proper management [3]. Magnetic resonance imaging (MRI) without use of gadolinium has been used in place of CT scan with no potential toxicity to the fetus [9]. A recent study on 90 patients with lymphoma coincidental with pregnancy reported that MRI staging was performed on most patients without obvious negative consequences [2]; however, the amount of detail provided in excess of what can be found with ultrasonography is not necessary, and the safety of the intensive magnetic fields required and the exposure to gadolinium for contrast enhancement is not fully established. Bone marrow biopsy should be performed in patients with B symptoms or abnormalities in blood counts such as anemia, thrombocytopenia, or leukopenia; however, only 1 out of 40 had marrow involved in a recently published large case series [2]. For those patients in whom chemotherapy is planned, echocardiography may be used to assess left ventricular function. The goal of clinical and radiologic staging is to provide guidance about the pace of disease progression, to determine the cause of any specific symptoms such as cough, and to evaluate whether treatment can be deferred or whether immediate treatment is required because of symptomatic disease or organ dysfunction. Hence, tests should only be performed if decisions regarding immediate management will be influenced.

18.3 Outcomes of Mother and Child in HL Coincident with Pregnancy

The complexity of caring for pregnant patients with HL requires a multidisciplinary team of experts working together to develop an individualized management plan (Table 18.1). The therapeutic options for pregnant patients with HL depend on stage, symptoms, gestational age at diagnosis, fetal risks, and the patient's wishes regarding the continuation of pregnancy. Useful lay language explanations and guidance for patients have been developed by several advocacy groups and can be recommended to patients (e.g., https://lymphoma-action.org.uk/about-lymphoma-treatment-lymphoma/treatment-during-pregnancy). Although the evidence for managing pregnant HL patients comes from a few published case series and anecdotal descriptions, this evidence can provide useful guidance when complemented by careful clinical judgment and knowledge of the natural history of HL. The

Table 18.1 Characteristics of an ideal multidisciplinary team treating the pregnant patient with concomitant Hodgkin lymphoma

Obstetrician	Usually makes the diagnosis, arranges referral to hematologist/oncologist
	Brings experience in high-risk pregnancies (patients with active malignancy)
	Provides counseling regarding pregnancy termination (if recommended by the team and chosen by the patient)
	Establishes the timing and method of delivery
	Supervises effective postpartum contraception for a minimum of 2 years (greatest risk of relapse)
Hematologist/ medical oncologist	Performs oncologic history and physical examination and plans staging
	History searching for B symptoms or other symptomatic problems suggesting more advanced disease
	Physical examination for lymphadenopathy or organomegaly
	Complete blood cell counts
	Serum creatinine, alkaline phosphatase, lactate dehydrogenase, bilirubin, and protein electrophoresis (including albumin level)
	Chest radiograph, posteroanterior view only, with appropriate shielding
	Abdominal ultrasound for retroperitoneal lymphadenopathy
	Formulates overall therapeutic plan
	Administers chemotherapy if deemed necessary
	Provides supportive care for patients treated with chemotherapy to keep Hgb $\geq$100 g/L and platelet count $\geq 30 \times 10^9$/L and reviews safety of medications used for supportive care during pregnancy
	Coordinates delivery planning and chemotherapy administration to ensure that platelet count is $\geq 50 \times 10^9$/L at the time of delivery
	Arranges oncology follow-up after pregnancy to complete appropriate staging
Neonatologist	Has experience in high-risk pregnancies
	Has experience in childhood hematologic disorders
	Examines placenta and arranges histopathologic evaluation for presence of metastasis
	Coordinates newborn care at the time of delivery
	Delivers early postnatal care of newborn
	Registers newborn to central registry of children born to pregnant mothers with HL
	Counsels about breastfeeding
	Schedules long-term follow-up of newborn
Nurse coordinator	Coordinates communication among subspecialists
	Helps interpret complex communication with the patient

clinical challenge of managing pregnant HL patients lies in determining the effect of treatment delay on maternal survival versus the risk of previously undesired abortion, fetal malformation, and adverse perinatal outcomes associated with the use of chemotherapy and radiotherapy. Frequent communication with the patient and her family is crucial to ensure understanding and alleviate anxiety and fear.

A critical question to be considered when caring for a pregnant patient with HL is the effect of pregnancy on the survival of mother and infant. Evens et al. published one of the largest series, which included 40 HL and 50 non-HL cases occurring during pregnancy [2]. Data on the clinical course of the disease and pregnancy outcomes were gathered from 11 institutions that had treated these patients during the past decade. HL was diagnosed at a median of 23 weeks' gestation. Of the six patients diagnosed in the first trimester, three elected to terminate the pregnancy and three elected to defer treatment until later. Most patients were diagnosed in the second or third trimester, and all patients who decided to keep the pregnancy successfully reached term delivery. In a study by Lishner et al., 48 pregnant women with HL were matched to nonpregnant controls with HL [10]. They found that stage and clinical presentation, course of the disease, response to therapy, and overall survival were similar when

compared to age- and stage-equivalent nonpregnant controls. These findings are consistent with previous analyses in which no difference in survival was found among women who did not have a therapeutic abortion and those who did [11–13]. Several authors have observed that HL by itself does not appear to have an adverse effect on the course of pregnancy, fetal development, labor, or puerperium [2, 14, 15]. The primary conclusion to be drawn from these observations is that pregnancies encountered coincident with HL do not need to be terminated [16].

18.4 Treatment of Hodgkin Lymphoma during Pregnancy

18.4.1 General Therapeutic Principles

Most patients with HL and concomitant pregnancy require no immediate intervention. As a general rule, any treatment, such as radiation or chemotherapy, should be avoided during the first trimester unless severe symptoms are present or organ function is seriously compromised or threatened. Almost all chemotherapy agents have been documented to be teratogenic in animals or humans, although for some drugs only experimental data exist. Chemotherapy during the first trimester may increase the risk of spontaneous abortion, fetal death, and major malformation; the fetus is extremely vulnerable from the second to eighth week of gestation during which time organogenesis occurs. Even after primary organogenesis, several organs including the eyes, genitalia, hematopoietic system, and central nervous system remain vulnerable to chemotherapy and radiation therapy.

18.4.2 Early-Stage HL during Pregnancy

The majority of HL patients diagnosed during pregnancy have stage IA or IIA disease and are asymptomatic or minimally symptomatic. Treatment for these patients can be deferred, but close monitoring and follow-up through the entire pregnancy has to be ensured. In a recent multicenter series, 75% of patients had early-stage HL and more than a third deferred treatment until the postpartum period resulting in good outcomes for both the mother and child [2]. In the Stanford series, 11 out of 17 patients required no immediate treatment for HL concomitant with pregnancy [17]. The approach of watchful waiting has also been demonstrated to be safe in a small case series of 19 patients from Royal Marsden Hospital [18]. Many patients can be monitored throughout pregnancy until normal full-term delivery without treatment for lymphoma. Nevertheless, therapy is required if severe symptoms or organ dysfunction develops. Patients with stage IA–IIA HL with localized or stable disease who have chemotherapy safely deferred can complete appropriate staging and initiate treatment soon after delivery. In two recent studies, among HL patients opting to delay treatment until after delivery, the birth weight, mean gestational age, and method of delivery were similar to normal pregnancies [10, 15].

Based primarily on experience acquired prior to the development of highly effective chemotherapy, several studies demonstrated the efficacy of irradiation for symptomatic patients with cervical adenopathy, stage IB or IIB, or respiratory symptoms due to enlarging mediastinal masses. However, at most, radiation should be reserved for cases where it is absolutely necessary, and extreme caution should be taken to provide special shielding of the fetus with ten half-value layer shields [10, 12, 19, 20]. An inverted Y field is not an option at any time during pregnancy. Radiation therapy to lymph nodes in the axilla, mediastinum, and neck-mediastinum could lead to a dose of >10 cGy and therefore should not be recommended in the first trimester [21, 22]. It is important to recall that use of any therapeutic radiation during pregnancy, especially in advanced gestational age, results in direct or scattered exposure. The effects of fetal irradiation may become evident only many years later. For example, a known risk for the fetus from radiation in the second half of gestation is acquisition

of blood dyscrasias or leukemia later in life [23]. In addition, irradiation encompassing the mediastinum exposes breast tissue to scatter radiation and potentially increases the risk of later secondary breast cancer and other secondary malignancies [24].

Because radiation unnecessarily endangers the fetus, a better choice, if treatment is necessary, is systemic chemotherapy. If intervention is required, especially after the first trimester, selected symptomatic patients can be treated with single-agent vinblastine (Fig. 18.1). Vinblastine, first described for this use more than 40 years ago [25, 26], is a particularly attractive agent because of its high level of effectiveness against HL in treatment-naïve patients (>75% response rate) and modest acute toxicity. Although teratogenic effects have been reported in mice, neither teratogenic nor carcinogenic effects are apparent in humans at doses therapeutic for lymphoma. The combination of a high level of effectiveness, minimal acute toxicity, and low likelihood of a negative effect on the fetus makes vinblastine an attractive agent to suppress HL during pregnancy. Single-agent vinblastine used as monotherapy does not cross the placenta and has been safely used in patients in all trimesters, including during early gestation when the use of other agents is more often associated with fetal malformations and increased risk of spontaneous abortions and stillbirths [11, 12, 27–30].

18.4.3 Use of Chemotherapy for Symptomatic or Advanced-Stage HL in Pregnant Patients

Management of HL with advanced stage, bulky disease, visceral involvement, B symptoms, subdiaphragmatic disease, or rapid disease progression remains challenging during pregnancy. A recent large collection of cases of coincident HL and pregnancy demonstrated that this presentation is rare, and good outcomes for both the mother and fetus were achieved in most patients [2]. Alkylating agents (mechlorethamine, cyclophosphamide, procarbazine, and chlorambucil), antimetabolites (methotrexate), and multiagent regimens including these agents (e.g., MOPP [mechlorethamine, vincristine, prednisone, and procarbazine]) should be avoided during pregnancy because of a reported increased risk of spontaneous abortion, teratogenicity, carcinogenicity, and fetal malformations [10, 11, 17, 18, 27–30]. Rather than expose the fetus to the potential adverse effects of multiple agents, an alternative approach for advanced-stage symptomatic HL is to employ single-agent chemotherapy with vinblastine. Infrequent doses at intervals of several weeks or longer can be given to control HL until delivery at term, minimizing risks to the mother and child. Standard dosing of 6 mg/m^2 is unlikely to cause significant myelosuppression, but careful timing to avoid a blood cell count nadir near delivery is prudent. Progression despite vinblastine, which occurs infrequently, should be treated with full-dose ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, dacarbazine) because evidence of vinblastine resistance signifies aggressive disease requiring multiagent chemotherapy (Fig. 18.1). ABVD, the current standard of care in North America, has been used during pregnancy. Although experience is limited, obvious negative effects on the fetus have not been observed [3–5]. The largest US retrospective analysis on 40 HL patients reported 21 subjects treated with ABVD or AVD in the second and third trimester [2]. Overall, the response to therapy was excellent with a 96% overall response rate and 83% complete remission rate. Multiple variables were examined in this series to predict outcomes. For HL patients, multiparous status predicted improved progression-free survival (hazard ratio 0.07), and the presence of B symptoms at diagnosis predicted inferior progression-free survival (hazard ratio 10). No variable was predictive of overall survival.

We have managed 18 pregnant patients with coincident HL at the British Columbia Cancer Agency during the past 23 years using the approach described above. Eleven patients remained off treatment through term delivery, and 6 required vinblastine to control the disease. Fourteen of the 18 patients are still alive and

well, while 4 have died, 2 from HL and 1 each from acute myeloid leukemia and retroperitoneal sarcoma. All 18 delivered normal children who now range in age from 2 to 23 years (median 17). Although these children have not been systematically assessed, no overt abnormality has become apparent [3]. The conservative use of single-agent vinblastine, which has allowed normal-term delivery of children and effective management of the mother's HL and psychological stress, appears to be a reasonable approach to this rare problem of coincident pregnancy and HL.

Data on the use of more intensive regimens such as Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, and prednisone) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine) during pregnancy are not available; however, because both contain alkylating agents, they should be avoided. Recently, novel agents including the antibody-drug conjugate brentuximab vedotin and the checkpoint inhibitors nivolumab and pembrolizumab have been shown to be highly effective for classic Hodgkin lymphoma; however, no experience with administration of these agents during pregnancy has been reported. Thus, they are included in US FDA category D, possibly harmful in pregnancy. Until evidence of their safety becomes available, it is best to avoid their use in pregnancy, especially with acceptable, effective alternatives available.

18.5 Fetal Outcomes

Patients with HL in whom gestation progresses to term need planning of the timing and mode of delivery. Fetal maturity should preferably be the criterion to induce delivery. In a multidisciplinary setting, maximal effort should be made to delay delivery until at least 35–37 weeks. A coordinated, detailed peripartum plan developed by a neonatologist, an obstetrician with experience in high-risk pregnancies, and an oncologist/hematologist is required to minimize complications. In a recent large retrospective study from Evens et al., preterm complications among 31 patients with HL included induction of labor (40%), preterm delivery in 14 patients, C-section in six, low gestational age in four patients, and postpartum hemorrhage in two patients [2]. The median gestational age at delivery was 37 weeks (range 31–40 weeks). Preeclampsia and fetal demise or malformations were not observed in this retrospective series. Thus, there appeared to be no impact of antenatal chemotherapy on the frequency of these complications. The median birth weight of infants was 2688 g (range 1005–3628 g) with no difference based on receipt of antenatal chemotherapy. No malformations were detected in babies exposed to ABVD or ABV chemotherapy [2]. In a smaller series of 26 children with HL with a long follow-up of 3–19 years, children born to women who received chemotherapy for HL in the second and third trimesters are delivered healthy newborns without short-term or long-term neurological, developmental, or infectious complications or secondary malignancies [15]. However, the use of anthracyclines at doses exceeding 70 mg/m^2 per cycle has been associated with a 30-fold increase in severe fetal toxicity including death, malformations, and cardiac toxicity [31]. The ABVD regimen contains doxorubicin at a lower dosage (25 mg/m^2 per dose); however, caution and careful counseling are always required when ABVD is administered in the second and third trimester. For example, one series reported stillbirth of twins in an HL patient who started the ABVD regimen at 14 weeks of gestation [31]. In addition, multiagent chemotherapy used in the last trimester of pregnancy may often result in prematurity, lower birth weights, and neonatal myelosuppression, although none of these complications were reported in the 21 patients included in the most recently reported series [2, 32, 33]. In a recent European series of 176 neonates born to mothers with malignancy, of whom 13 had HL, binomial testing revealed a significant increase in small-for-gestational-age children in the group receiving treatment during pregnancy versus those not treated during pregnancy [34]. Therefore, caution has to be taken because the adverse outcomes associated with chemotherapy are likely

underreported and available evidence comes from limited, small, and heterogeneous clinical series and anecdotal descriptions [2, 10–13, 15, 17, 20, 25–27, 32, 35–37].

18.6 Planning the Delivery and Managing the Postpartum Period in Patients with HL

Postdelivery oncologic care is a critical step in managing HL in pregnancy. Breastfeeding must be discouraged in those patients who continue chemotherapy postpartum as most cytotoxic agents can be excreted into the breast milk. In the perinatal period, patients who had not received any therapy for HL during pregnancy should be fully restaged after delivery including PET/CT staging. Patients treated with radiation, single-agent vinblastine, or other chemotherapy can no longer be accurately staged and therefore should be treated with a full course of six to eight cycles of multiagent chemotherapy. Posttreatment PET/CT imaging has a strong predictive value for overall survival and should be considered to assess the depth of post-therapy remission.

18.7 Relapsed HL and Concomitant Pregnancy

Occasionally, the patient with history of HL presents with relapsed lymphoma and concurrent pregnancy. There are limited data to guide the therapeutic decisions for such a rare clinical situation (five cases reviewed in Eyre et al. [5]); however, we advise that care be guided by principles similar to those recommended for newly diagnosed HL and concurrent pregnancy. Individualized recommendations will depend on the initial HL stage, type of primary therapy used in the past, and the time from remission to relapse, as well as current symptoms, stage, and gestational age. Patients with minimal disease burden in the second or third trimester can often be managed by careful watching. Most patients who relapse with advanced HL or those who had received prior chemotherapy would be considered for treatment with salvage multiagent chemotherapy followed by high-dose myeloablative chemotherapy and autologous hematopoietic stem cell rescue. Brentuximab vedotin should be avoided in pregnancy because there is no experience with this agent during pregnancy and it caused embryo-fetal lethality in pregnant female rats [38]. Conservative management that allows the pregnancy to develop to term is often possible, and interventions for definitive therapy, such as autologous stem cell transplant, can be planned for soon after delivery. The decision to initiate treatment rests on careful and frequent monitoring of the patient and the pace of disease progression. If rapidly symptomatic disease develops in the first trimester, planned pregnancy interruption and subsequent standard treatment should be considered. Coordination of care with a transplant team is necessary to ensure timely postdelivery interventions.

18.8 Conclusions

The diagnostic and therapeutic approach to the patient with concurrent HL and pregnancy presents the challenge of managing two lives. The goal is to give the mother with HL the best chance of cure while preserving the healthy development of the fetus. The management of a pregnant patient with HL requires a multidisciplinary approach combining expertise in medical oncology, high-risk obstetrics, and neonatology, as well as effective communication with the patient and her family. A pregnant patient with HL should be staged by clinical examination and judicious use of nonradiation imaging such as ultrasound or MRI, balancing the need for accurate disease assessment with the need to minimize invasive procedures. The treatment strategy should be individualized based on symptoms, lymphoma stage, gestational age, and the patients' wishes [36]. Therapeutic options include treatment deferral or single-agent vinblastine with reservation of multiagent chemotherapy until the second or third trimester for those patients with advanced-stage disease and B symptoms. Finally, establishment

of a prospective central registry for patients with concurrent HL and pregnancy to allow data collection on long-term follow-up of children born to HL patients would enhance the care of patients with this uncommon complication of pregnancy and that of their children by providing a larger database of relevant information than is currently available.

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