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SPECIAL SECTION: CANCER IN PREGNANCY

Imaging evaluation of lymphoma in pregnancy with review of clinical assessment and treatment options

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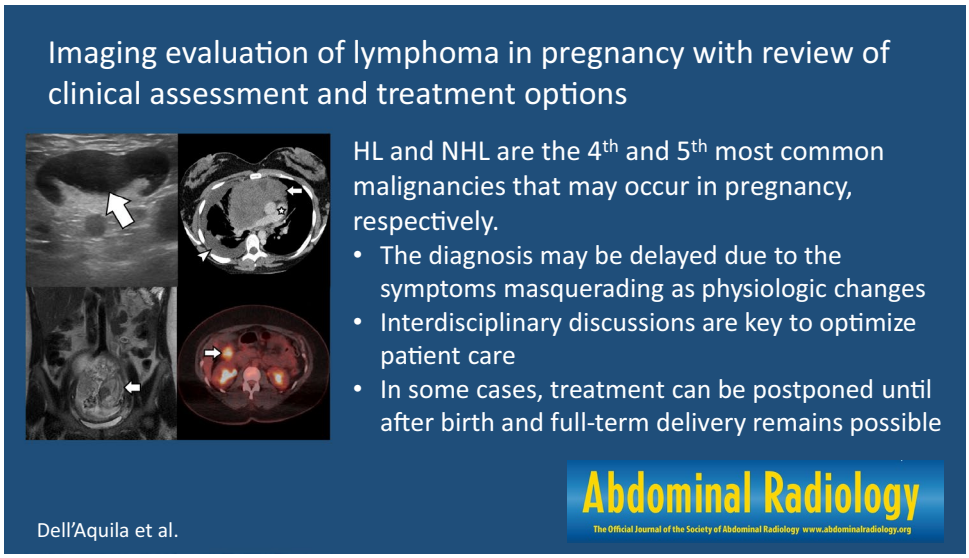
Abstract

Lymphoma-related malignancies can be categorized as Hodgkin's lymphoma (HL) or non-Hodgkin's lymphoma (NHL) based on histologic characteristics. Although quite rare during pregnancy, HL and NHL are the fourth and fifth most common malignancies during the pregnancy period, respectively. Given the rarity of lymphoma among pregnant patients, radiologists are usually unfamiliar with the modifications required for staging and treatment of this population, even those who work at centers with busy obstetrical services. Therefore, this manuscript serves to not only review the abdominopelvic imaging features of lymphoma in pregnancy, but it also discusses topics including birthing parent and fetal lymphoma-related prognosis, both antenatal and postpartum, current concepts in the management of pregnancy-related lymphoma, as well as the current considerations regarding birthing parent onco-fertility.

Graphical abstract



Keywords Pregnancy · Lymphoma · Oncology · Cross-sectional oncologic imaging

Introduction

The diagnosis of "lymphoma" broadly encompasses hematologic malignancies derived from lymphocytes and lymphoblasts. These malignancies can be categorized as Hodgkin's

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lymphoma (HL) or non-Hodgkin's lymphoma (NHL) based on histologic characteristics. The age-standardized global incidence of HL in 2020 has been estimated to be 0.98 cases per 100,000 individuals per year among adult and pediatric patients [1], whereas NHL has an estimated age-standardized global incidence in 2020 of 7 cases per 100,000 individuals per year [2]. Although quite rare during pregnancy, HL and NHL are the fourth and fifth most common malignancies that may occur during the pregnancy state, respectively [3]. It has been previously estimated that lymphoma can complicate approximately 1 in 6000 pregnancies [4].

Hodgkin's lymphoma has a bimodal distribution with peak incidences in the mid-to-late 20s, and after age 50 [5, 6]. Therefore, this is the most common lymphoma type among those diagnosed during pregnancy. To date, no definitive causal relationship between pregnancy and HL has been established, to our knowledge [6]. While there is growing evidence that sex hormones play a role in lymphoid cell proliferation, these studies suggest a potential protective role of sex hormones against the development of HL [7, 8].

The incidence of NHL increases with age, reaching upwards of 150 cases per million individuals in the adult population [9]. Out of many types of NHL, B-cell lymphoma is the most common type reported among pregnant patients [6]. Risk factors for the development of NHL are a history of human immunodeficiency virus, solid organ transplantation, and X-linked lymphoproliferative syndrome, as well as those with prior successful treatment of HL [9]. Sex hormones may have an influence on the development of NHL-follicular lymphoma, but have not been found to have an association with other NHL-subtypes [10].

Both HL and NHL most commonly originate from within lymph nodes. Lymphomatous involvement of sites other than lymph nodes is termed extranodal lymphoma, which can be primary or secondary. In primary extranodal lymphoma, disease originates in an organ (not lymph nodes) such as in primary central nervous system lymphoma. In secondary extranodal lymphoma, there is extension from a site of lymph node disease into an adjacent organ. In general, HL is considered a lymph node disease (i.e., lymph nodes and spleen) with extranodal disease only uncommonly encountered. When primary and secondary extranodal disease is present, it is most often related to NHL (i.e., pleura, liver, kidneys, and bowel, among other potential sites) [11–16]. Interestingly, pregnant patients with NHL have a high rate of extranodal lymphoma at presentation, reported at 26% of subjects in a study conducted by Evens et al., but to our knowledge, the cause for this increased incidence remains unknown [17].

The diagnosis of lymphoma may be delayed in the context of pregnancy given that the symptoms of lymphoma may masquerade as physiologic changes due to pregnancy. Symptoms which are considered suspicious for lymphoma among the general population, which mimic physiologic changes in pregnancy, include fatigue, profuse sweating, and dyspnea on exertion [6]. Unfortunately, lymphoma in pregnancy is more likely to be aggressive on presentation than in non-pregnant women, and is often Stage IV at the time of diagnosis.

After a thorough literature search, the authors could not find any references that would address whether the radiologic features of lymphoma in the abdomen and pelvis could be affected specifically by pregnancy.

Although hormonal influence may play a role in the development of lymphoma, an increased risk for the development of lymphoma in pregnancy (initial lymphoma diagnosis or relapse of lymphoma while pregnant) has not yet been identified, to our knowledge. At present, potential relapse is not typically a consideration in reproductive planning for patients with a history of lymphoma, whether cured or in remission [18].

In this review, we discuss the imaging options of pregnant patients that become diagnosed with lymphoma or surveillance of those who are in remission, including US, CT, MRI, and nuclear imaging, as well as tissue diagnosis. The staging and prognosis are discussed with management, treatment, and surveillance of lymphoma in pregnancy. Additionally, the risks of the fetus through treatment are discussed. This review also touches on the current considerations regarding birthing parent onco-fertility. To ensure that this review is supportive and inclusive of the transgender population, the term "birthing parent" will be used in place of "maternal" [19].

Imaging of lymphoma in pregnancy

Ultrasound

Ultrasound is utilized as an initial imaging modality for assessment of the pregnant patient with suspected abdominal pathology, such as urinary obstruction or appendicitis [20]. Benefits of ultrasound examinations include widespread availability and absence of ionizing radiation. A disadvantage of ultrasound lies in the fact that it is sonographer dependent. Ultrasound is also limited by depth and spatial resolution, and therefore, is best to evaluate superficial lymphadenopathy and solid organs, particularly the liver, kidneys, and spleen, with otherwise limited utilization in the chest and abdomen.

Lymphomatous disease on ultrasound can have variable appearances depending whether it is an indolent or a more aggressive subtype. Classic HL and low-grade NHL may only appear as enlarged lymph nodes (> 1 cm short axis), which are rounded, and possibly hypoechoic with a "pseudocystic appearance" (Fig. 1) [15, 21]. The presence

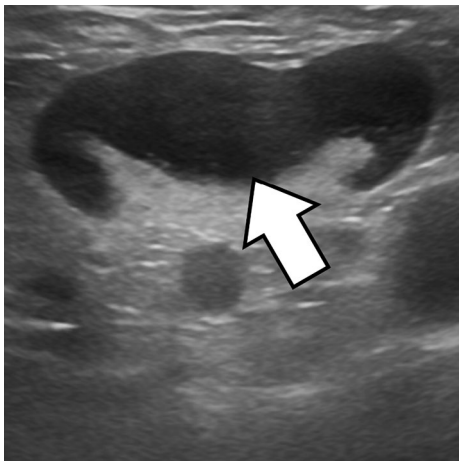

Fig. 1 21-year-old woman at 8 weeks gestation with bilateral breast nodularity. Gray-scale ultrasound of the left axilla demonstrates an enlarged lymph node that measures 3.5 × 1.4 cm in long and short axis. The lymph node fatty hilum is maintained; however, the eccentric cortical thickening is present (arrow). This patient was subsequently diagnosed with diffuse large B-cell lymphoma

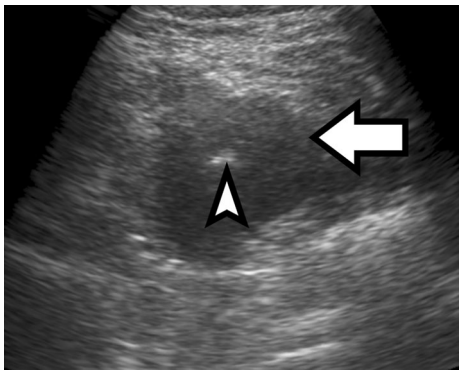

Fig. 2 40-year-old Latina woman at 23 weeks gestation with abdominal fullness. Gray-scale abdominal ultrasound demonstrates a lobulated 6 cm hypoechoic mesenteric mass (arrow). This patient was subsequently diagnosed with diffuse large B-cell lymphoma. The hyperechogenic focus within the central aspect of the mass (arrowhead) likely represents an artifact related a site of cystic change when correlating with the subsequently obtained magnetic resonance imaging examination shown in Fig. 6

of a lymph node fatty hilum does not necessarily indicate benignity, as this feature can be maintained in some cases of metastatic disease, such as micro-metastases, which are defined as conglomerations of tumor cells between 0.2 and 2 mm on pathologic assessment [22, 23]. Focal or diffuse eccentric cortical thickening can indicate the presence of malignant tumor infiltration in spite of a normal lymph node size and maintained fatty hilum, and these features should be reported when identified [24].

Lymphomatous involvement of the spleen can have a variable appearance ranging from diffuse enlargement without the presence of a solitary nodule or mass, or multiple focal nodules [25]. Involvement of the spleen in HL is considered as nodal disease, but in the case of NHL the spleen is regarded as an extranodal site [26]. On ultrasound, the involved spleen may appear hypoechoic with scattered vascularity [25].

Extranodal lymphomatous disease can appear as a soft-tissue mass with irregular contours (Fig. 2) without much vascularity on Doppler interrogation [27]. Ultrasound can be used to identify soft tissue encasing the aorta and/or inferior vena cava in some cases of lymphoma. Hydronephrosis related to encasement of the ureters may also be identified (Fig. 3).

Computed tomography (CT)

Trauma is one of the primary indications for obtaining a CT examination of the abdomen and pelvis during pregnancy. Otherwise, ultrasound and magnetic resonance imaging are the typical preferred examinations since they do not expose the birthing parent or fetus to ionizing radiation. Although trauma and other emergent conditions are justifications for CT of the abdomen and pelvis in pregnancy, to our knowledge there is no published data addressing the rate of incidental lymphoma detected on emergency CT examinations.

The CT appearance of lymphoma can range between isolated nodal enlargement to extranodal disease with or without adjacent structural infiltration (Fig. 4) [21]. The lymph nodes that are involved with lymphomatous disease may appear enlarged (> 1 cm short axis), rounded, and predominantly homogenous in attenuation [21]. Lymphoma of abdominal solid organs can appear as discrete solid masses, or can be diffusely infiltrative [21]. The infiltration of adjacent structures can potentially lead to vascular occlusion (Fig. 5), bowel obstruction, or urinary obstruction, and may invade the reproductive organ.

Splenic lymphomatous foci are typically hypoattenuating and hypoenhancing compared to the normal splenic parenchyma [25]. The gastrointestinal system is the most common site of extranodal lymphoma, and can present as bowel wall thickening, polyps/masses, and "aneurysmal" luminal bowel dilatation [21]. Osseous lymphomatous involvement can be lytic, sclerotic, or mixed [13]. In cases of osseous disease, evaluation for extraosseous soft-tissue extension is important since this feature is associated with more aggressive lymphomas [13, 21].

In a study by Maggen et al. in a study of 80 subjects showed 26.5% extranodal lymphoma involvement in the reproductive organs [28]. They hypothesized that the involvement of reproductive organs may be due to the increased blood supply to these reproductive organs that occurs during pregnancy, or possibly by the presence of

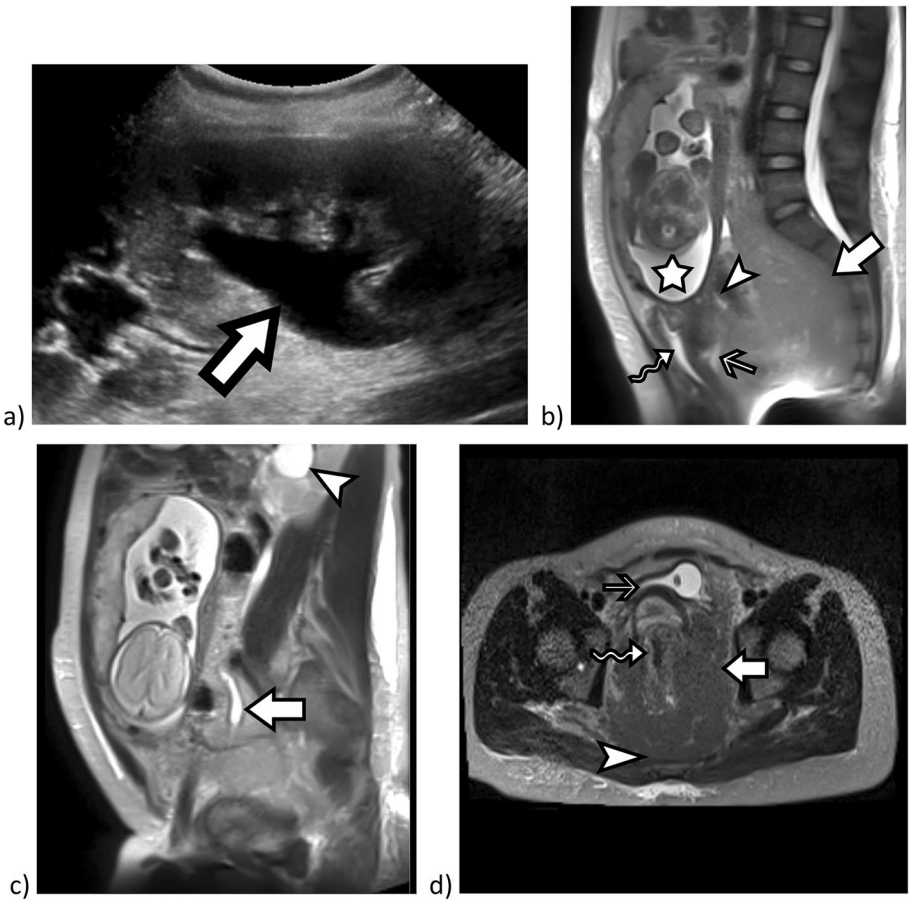

Fig. 3 28-year-old woman at 25 weeks gestation with flank pain and urinary retention. **a** Gray-scale renal ultrasound demonstrates mild right-sided hydronephrosis (arrow). Mild left-sided hydronephrosis was present as well (not shown). A follow-up abdominal magnetic resonance imaging examination was obtained to assess for urinary obstruction. **b** Sagittal T2-weighted MR image demonstrates an infiltrative retroperitoneal/extraperitoneal mass beginning at the level of the aortic bifurcation and extending to the level of the anorectum (arrow). The mass also abuts portions of the gravid uterus (star), cervix (arrowhead), and vagina (thin arrow) as well as portions of the bladder (curved arrow). **c** Parasagittal T2-weighted MR image demonstrates the mass encasing the dilated right ureter (arrow). The hydronephrotic right kidney is partially imaged (arrowhead). **d** Axial T2-weighted MR image demonstrates the infiltrative mass invading the mesorectal space (arrow), encasing the rectum (curved arrow), and involving the presacral space (arrowhead). Bladder (small arrow)

gestational hormonal receptors on malignant lymphocytes, although further research on this topic is required [28].

Lastly, the currently available research does not support withholding administration of iodinated contrast during pregnancy from birthing parents when its use is appropriately indicated. While there are rare reports of newborn hypothyroidism following the administration of iodinate contrast to the birthing parent, the routine evaluation of thyroid-stimulating hormone in all infants at the time of birth to specifically assess for contrast-induced thyroid dysfunction is not required [29].

Magnetic resonance imaging

The features of lymphoma on MRI are variable and depend on the involved organ as well as the degree of disease aggressiveness. There are no absolute MRI signal features that can be used to unequivocally suggest a diagnosis of lymphoma prospectively, and soft-tissue sampling is ultimately required to confirm the diagnosis. Similar to other imaging modalities, the involved lymph nodes may be enlarged. In cases of splenic lymphomatous disease, the foci may demonstrate increased restricted diffusion compared to adjacent normal splenic parenchyma. Post-contrast images may show mild enhancement, although the focal nodules are typically hypoenhancing relative to normal spleen.

Extranodal lymphomatous masses can be solid or necrotic, hypointense on T1-weighted imaging, hyperintense on T2-weighted imaging, and appear hyperintense on diffusion-weighted imaging (DWI), with hypointense signal on apparent diffusion coefficient (ADC) maps (Fig. 6) [15, 30]. Comparing adjacent normal tissue to that of an abnormal soft-tissue focus signal features can help raise the level of suspicion for lymphomatous involvement,

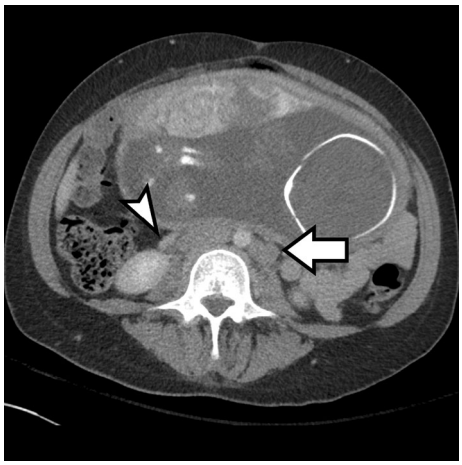

Fig. 4 21-year-old woman at 12 weeks gestation with known diffuse large B-cell lymphoma and worsening tachypnea, same patient as Fig. 1. IV contrast-enhanced axial computed tomography image of the mid abdomen demonstrates multifocal peri-aortic lymphadenopathy (arrow), with mass effect displacing the inferior vena cava laterally (arrowhead)

or increase the level of confidence. On MRI, lymphoma is usually T1 hypointense with variable appearance on T2-weighted imaging.

In recent years, MRI has become more routinely used in the staging and monitoring of lymphoma, while non-PET whole-body MRI (WB-MRI) has demonstrated comparable capability for lymphoma detection, staging, and treatment response assessment to that of PET-CT [31]. A benefit of WB-MRI is lack of ionizing radiation; however, some of the key limitations include lack of wide availability and limited billing/reimbursement. Additionally, MRI is limited in its ability to image the mediastinum due to cardiac motion artifact [30, 31]. Unfortunately, there are no standardized "optimal" MRI protocols used for the evaluation of lymphoma, to our knowledge. Sequences that can be used for tissue signal and size assessment of lymphatic and non-lymphatic organs include non-contrast enhanced T1- and T2-weighted MRI (with and/or without fat-saturation) and short tau inversion recovery.

DWI can increase tumoral tissue conspicuity in some cases with lymph nodes appearing hyperintense on high B-value sequences. DWI data can also be used quantitatively to generate ADC maps providing functional information that can potentially be trended for assessment of treatment response [30–32]. Unfortunately, both normal lymph nodes and the normal spleen will demonstrate restricted diffusion at baseline, which can make suggestion for lymphomatous involvement difficult in the absence of structural abnormalities such as enlargement [31]. Additionally, there are no

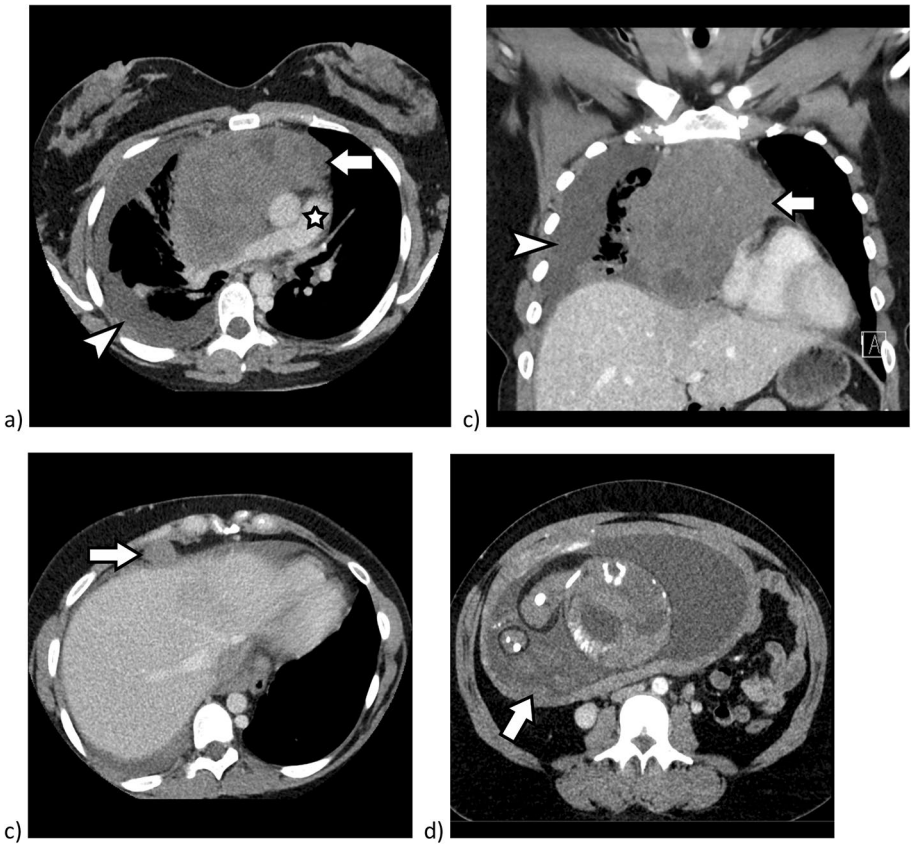

Fig. 5 30-year-old woman at 34 weeks and 5 days gestation presenting with mediastinal mass. **a** Axial and **b** coronal contrast-enhanced CT images of the chest show a large anterior mediastinal mass (arrow) compatible with biopsy proven primary B-cell lymphoma, and a right-sided pleural effusion (arrowhead). The axial image also demonstrates features of mass effect related to mediastinal mass, including: leftward deviation of the mediastinal contents (star) and absent visualization of the superior vena cava due to occlusion by the mass. **c** Axial contrast-enhanced CT image through the upper abdomen shows an enlarged pre-phrenic lymph node (arrow). **d** Axial contrast-enhanced CT image through the lower abdomen shows a gravid uterus with embryo (arrow). No findings of lymphomatous disease were demonstrated below the diaphragm

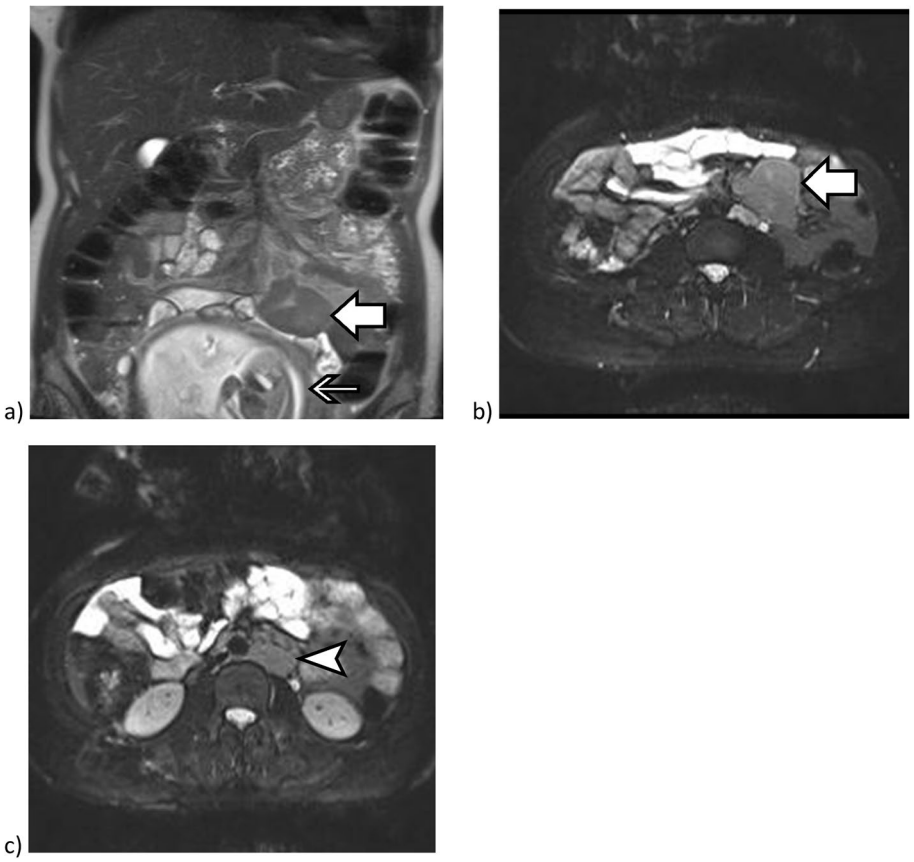

Fig. 6 40-year-old Latina woman at 23 weeks gestation with abdominal fullness and known intra-abdominal mass demonstrated on prior ultrasound, same patient as Fig. 2. **a** Coronal T2-weighted non-fat saturated MR image demonstrates a mildly T2-hyperintense 6 cm mesenteric mass (arrow) that abuts the gravid uterus (thin arrow). **b** Axial T2-weighted fat- saturated MR image demonstrates that the mass is mildly T2-hyperintense (arrow). **c** Enlarged retroperitoneal lymph nodes are present as well (arrowhead), which were contiguous with the mesenteric lymphadenopathy. This patient was subsequently diagnosed with diffuse large B-cell lymphoma

definitive ADC maps values that can be used to confidently differentiate a normal lymph node from lymphoma, to our knowledge [30]. In a meta-analysis of 338 non-pregnant patients comparing WB-MRI to FDG-PET-CT in pre-therapeutic staging of lymphoma, WB-MRI was superior to PET-CT for assessment of indolent disease, but both had 98% accuracy for the detection of HL and aggressive NHL with FDG-avidity [32]. Studies have also found that PET-CT is less accurate than WB-MRI in the diagnosis of indolent NHL due to the lack of FDG avidity in those patients. Lin G et al. conducted a systematic review in 457 patients with either lymphoma, multiple myeloma, or sarcoma, and compared PET-CT to WB-MRI with diffusion-weighted imaging and WB-MRI without DWI [33]. They found that WB-MRI with diffusion-weighted imaging had a sensitivity of 94% for the detection of the aforementioned diseases, which was statistically significantly higher than the 88% sensitivity of WB-MRI without DWI [33].

Latifoltojar et al. attempted to determine the optimal MRI sequence for staging in 22 patients with HL and DLBCL [34]. This study evaluated four combinations of WB-MRI protocols, and compared them to baseline PET-CTs. The investigators used pre-contrast modified Dixon (mDixon), T2-weighted turbo-spin-echo (TSE), diffusion, dynamic-contrast-enhanced (DCE) liver/spleen, IV contrast-enhanced (CE) lung MRI, and CE whole-body mDixon. The sequences were then divided into groups: (1) WB-MRI DWI in-phase, (2) WB-MRI T2-TSE, (3) WB-MRI CE mDixon + DCE liver/spleen and CE Lung mDixon, and (4) WB-MRI All. The primary conclusion of the study was that "WB-MRI All," which combined all sequences, had the highest sensitivity and specificity for the assessment of lymphoma when comparing to PET-CT, by 100% [34]. Further review of this publication is beyond the scope of this manuscript; however, the study contains additional details that may be of interest to the reader. Practically, obtaining multiple MRI sequences requires a relatively substantial allotment of time that may be difficult for pregnant patients to tolerate, and radiology departments to accommodate.

As more research comparing WB-MRI to PET-CT is becoming available, it seems that WB-MRI offers competitive performance over PET-CT. While the optimal WB-MRI protocol for lymphoma is not yet known, to our knowledge, diffusion-weighted imaging and ADC maps are seemingly likely to play a role.

As the safety of IV gadolinium use during pregnancy is still not well established to date, the generally accepted practice is to not administer gadolinium to pregnant patients [35]. The 2022 American College of Radiology Manual on Contrast Media emphasizes that gadolinium contrast should be

administered cautiously in pregnant patients, and it should only be used if the potential information gained from the use of the contrast is considered beneficial and would justify the potential risks to the fetus [36]. To our knowledge, there have been no studies published demonstrating an increased risk of fetal anomalies when IV gadolinium contrast has been administered to pregnant patients when compared to patients who have not received gadolinium contrast while pregnant [36]. Since gadolinium agents may cross the placenta, enter the fetal circulation, and accumulate within the amniotic fluid, there is a potential risk of gadolinium dissociation which could in theory result in nephrogenic systemic fibrosis (NSF). However, to our knowledge there have been no published cases of birthing parent or fetal NSF resulting from the administration of gadolinium contrast during pregnancy [36].

Positron emission tomography (PET)

18F-Fluorodeoxyglucose positron emission tomography/CT (PET-CT)

Although the fetal radiation exposure associated with PET-CT has been shown to be below the deterministic effect threshold, physicians and patients may remain understandably apprehensive in obtaining this examination during the antepartum period [37]. PET-CT may be rarely indicated during pregnancy as a troubleshooting procedure to better localize or stage the lymphomatous disease, especially if the PET-CT findings are expected to have an effect on disease management during pregnancy, or may be inadvertently obtained in the setting of a false negative pregnancy [37–40]. Radiation to the fetus with PET-CT results from external irradiation from radiotracer activity within adjacent maternal organs (for e.g., bladder and bowel), internal irradiation from F-18-FDG crossing through the placenta, and from the ionizing radiation related to the CT component [37, 40]. In rare situations in which PET-CT is to be performed during pregnancy, using a lower dose of radiotracer, compensated for by increased image acquisition time, along with frequent urinary bladder emptying can help minimize fetal dose [37–41].

On PET-CT, degree of organ involvement with lymphoma can be evaluated by semi-quantitatively measurement of the site's standard uptake value (SUV). Before raising concern that a finding is lymphomatous disease, it must first be compared to the physiologic background (normal mediastinal blood pool, and liver), as well as assessed to ensure that it does not correspond to a normal anatomic finding (i.e., normal bowel activity, or brown fat) [21]. There is no absolute/specific SUV for lymphoma; however, higher SUV measurements can be seen with more aggressive disease [21]. In general, a potential lymphoma focus with an SUV greater than the reference background would be considered PET positive for disease involvement [21, 42].

18F-FDG-PET-Magnetic resonance imaging (PET-MRI)

PET-MRI is an emerging technology that is not yet widely available. These examinations offer the combined benefits of tumor metabolic assessment from the PET, as well as the non-ionizing radiation benefits of MRI, which would eliminate the extra radiation dose from CT to the fetus [41]. Heacock et al. previously demonstrated the comparability of PET-MRI to PET-CT in 24 lymphoma patients with a 96.4% staging concordance [43]. PET-MRI can be used to upstage patients by identifying sites of marrow disease that were not depicted on PET-CT due to absence of hypermetabolic activity [44]. Compared to MRI alone, PET-MRI has a greater ability to depict nodal disease, thus improving staging [45]. Aside from the limited availability of PET-MRI scanners, another potential limitation is the extended time by 30 min to an hour for a complete examination [30].

Chest radiographs

Chest radiographs are no longer utilized as the primary means of evaluating for features of thoracic lymphoma as they are not sensitive for depiction of all sites of thoracic lymphomatous disease when compared to CT [46, 47]. However, chest radiography can provide a general, limited, assessment for presence of intra-thoracic lymphomatous disease (Figs. 7, 8) [44, 48]. A non-contrast chest MRI could be obtained for a more detailed evaluation of the chest.

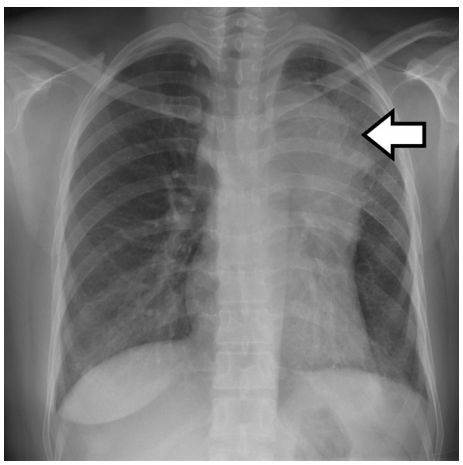

Fig. 7 21-year-old woman at 8 weeks gestation with dyspnea, same patient as Fig. 1. Posteroanterior chest radiograph demonstrates a large left-sided mediastinal mass (arrow), indicating presence of intra-thoracic lymphomatous disease

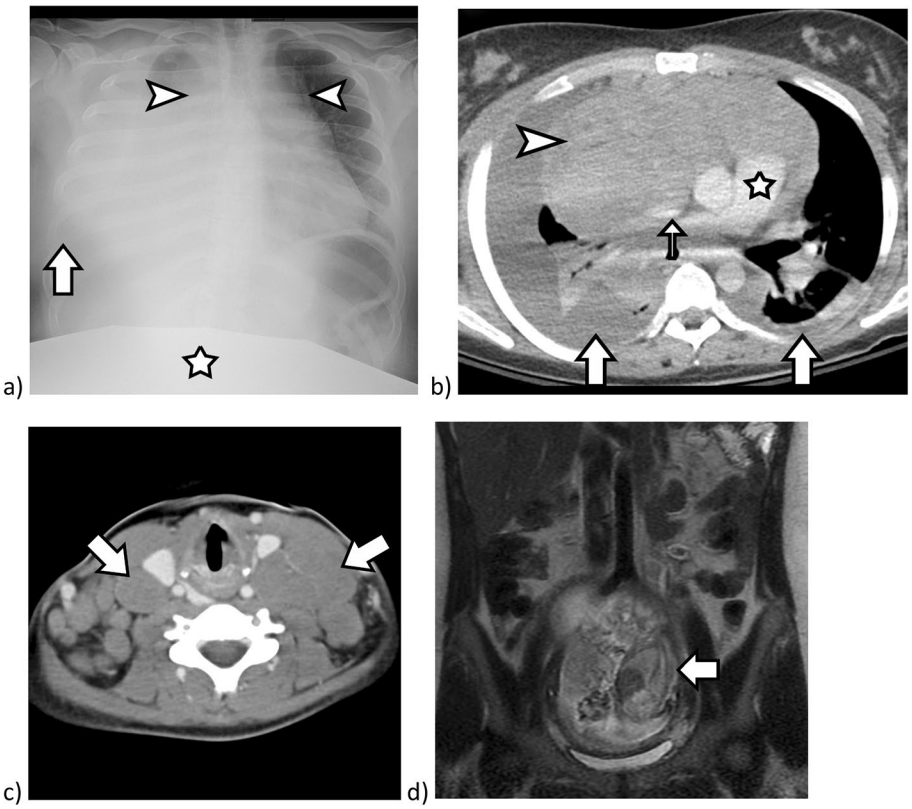

Fig. 8 23-year-old woman at 22 weeks gestation presenting with neck fullness and shortness of breath. **a** Portable anteroposterior chest radiograph demonstrates an enlarged cardiomediastinal silhouette (arrowheads) and right pleural effusion (arrow). Abdominal lead shielding was utilized (star). **b** Axial contrast-enhanced CT chest image shows large anterior mediastinal mass (arrowhead), compatible with biopsy proven Hodgkin's lymphoma. The mass causes leftward deviation of the mediastinal contents (star), and compresses the superior vena cava (thin arrow). Bilateral pleural effusions are also present (arrows). **c** Axial contrast-enhanced CT neck image demonstrates enlarged bilateral cervical lymphadenopathy (arrows). **d** Coronal T2-weighted abdominal MR image of the abdomen and pelvis shows a gravid uterus (arrow), but without evidence of lymphomatous disease below the diaphragm

Mimics of lymphoma on imaging

Non-lymphomatous lymphadenopathy

To the authors' knowledge, pregnancy in and of itself has not been a previously reported cause for lymph node enlargement. As such, when lymphadenopathy is encountered in a pregnant patient the potential etiology should be sought, such as history of recent viral infection or features of infection on imaging. Considering the on-going COVID-19 pandemic, cases of axillary lymphadenopathy warrant correlation with history of recent COVID-19 vaccination as this is a known cause of ipsilateral lymphadenopathy [49, 50]. Lymphadenopathy resulting from COVID-19 infection has also been reported, which may be due to a humoral immune response to the SARS-CoV-2 virus [51].

Lymph node features that are suspicious for malignancy are discussed in the previous sections of this manuscript. When a cause for lymphadenopathy is not elicited, follow-up imaging and/or physical examination may be required to ensure interval resolution. If there is substantial concern that the lymphadenopathy reflects a neoplastic etiology, tissue sampling may be required to further evaluate (Fig. 9).

Splenic enlargement

In adults, the spleen is considered enlarged when it measures > 13 cm in craniocaudal dimension. Splenomegaly in and of itself is non-specific, and in pregnant patients it can reflect physiologic change related to the increased blood volume [52]. Studies have previously observed a linear splenic growth pattern throughout pregnancy that can reach up to 13 cm in length [52, 53]. Isolated/primary splenic lymphoma is rare, occurring in < 1% of lymphoma cases [25]. Splenomegaly is more likely to reflect lymphoma when findings of lymphomatous disease, such as lymphadenopathy, are identified elsewhere. Therefore, if isolated splenic enlargement is identified in a pregnant patient, it would seemingly most likely reflect a non-lymphomatous process.

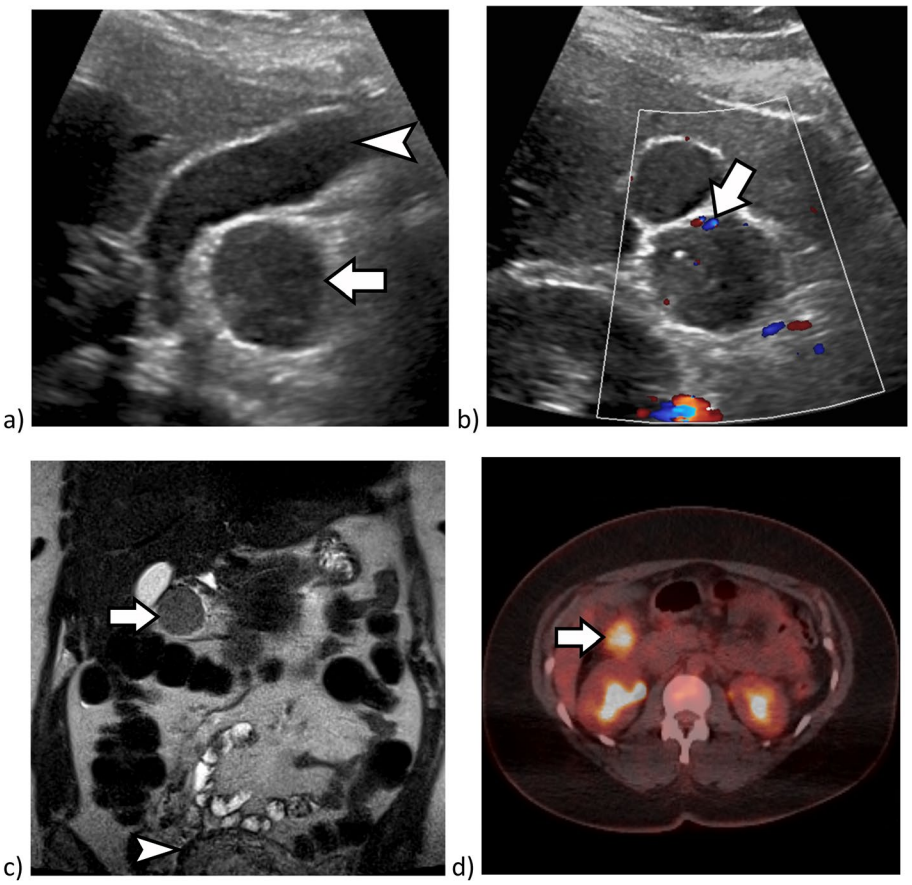

Fig. 9 29-year-old woman at 12 weeks gestation presenting with hyperemesis gravidum, elevated liver function tests, and epigastric pain. **a** Sagittal ultrasound image of the gallbladder fossa demonstrates a 3 cm hypoechoic mass (arrow) posterior to the gallbladder (arrowhead). **b** Transverse color Doppler image shows possible trace vascularity (arrow) within the hypoechoic lesion. **c** Coronal T2-weighted MR image of the abdomen demonstrates a mildly T2-hyperintense 3 cm mass in the right upper quadrant that corresponds to the ultrasound finding (arrow). The gravid uterus is partially visualized (arrowhead). A suspicion for possible lymphoma was raised. Subsequently, tissue sampling of the mass was performed, and the histopathology revealed reactive lymphoid tissue without evidence of lymphoma. **d** Axial fused image from follow-up PET-CT obtained after delivery demonstrates hypermetabolic activity within the right upper quadrant mass, but the mass was stable size compared to the prior examinations. The mass remained stable in size on follow-up examinations that were over multiple years

Splenic abnormalities

The majority of splenic focal abnormalities are benign (i.e., hemangiomas, sarcoidosis), and a review of such lesions is beyond the scope of this manuscript; however, there are several more recently published review articles on this topic that are available to the reader (Fig. 10) [25, 54].

Thymus

The thymus normally involutes as patients enter into adulthood. During times of stress, including pregnancy, the thymus usually decreases in size; however, in postpartum period, the thymus may return to its original size, or become larger in a phenomenon termed "thymic rebound hyperplasia" [55]. Radiologically, thymic rebound hyperplasia can be suggested based on the presence of smooth contours, variable amounts of fat, and normal traversing vessels in the mediastinum [55]. By comparison, thymic neoplastic processes, including lymphoma, are usually associated with a nodular contour which may be accompanied by necrotic or calcified components [55]. An enlarged thymus in the presence of thoracic lymphadenopathy should raise concern for lymphoma [55]. When necessary, a non-contrast chest MRI can be obtained to differentiate thymic rebound hyperplasia from a thymic neoplasm by calculating the thymic chemical-shift-ratio [56]. On in- and out-of-phase MR sequences, the normal thymus and rebound hyperplasia should lose signal on out-of-phase imaging due to the presence of interspersed fat amidst the non-malignant thymic tissue [56]. Quantitative assessment of the thymic tissue can also be performed by comparing the signal intensity change

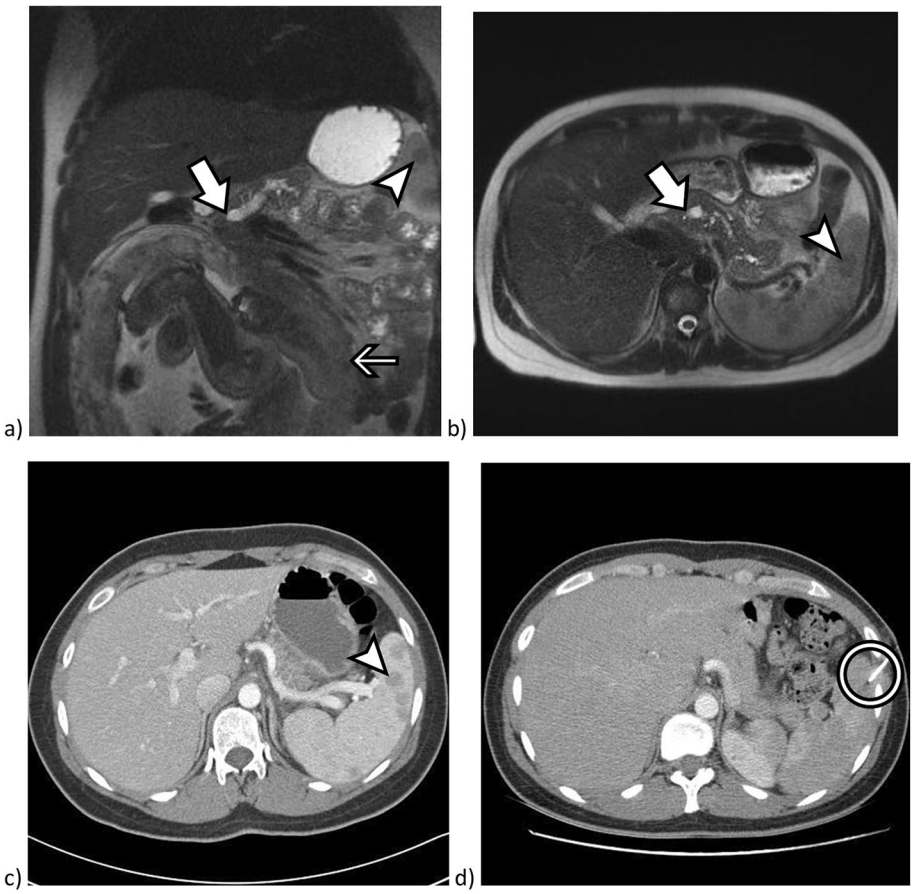

Fig. 10 31-year-old woman at 36 weeks gestation with severe abdominal pain. An initial abdominal ultrasound was remarkable for cholelithiasis and pancreatic ductal dilation (not shown). Non-contrast abdominal magnetic resonance imaging was obtained to evaluate the pancreas. **a** Coronal and **b** axial T2-weighted non-fat-saturated MR images demonstrate main pancreatic ductal dilation abruptly terminating at the pancreatic head (arrow). The spleen is enlarged measuring 15 cm craniocaudal, and it contains multiple 1–2.5 cm hypodense nodules (arrowhead). Gravid uterus (thin arrow). **c** On follow-up IV contrast-enhanced abdominal computed tomography, hypoenhancing splenic nodular foci are present (arrowhead). An obstructing calculus at the duodenal ampulla causing biliary and pancreatic ductal dilation is not shown. **d** IV contrast-enhanced CT-guided percutaneous biopsy at one of the splenic foci was performed (circle indicates biopsy needle). On subsequent histopathology, non-caseating granulomas were present, consistent with sarcoidosis

of the thymus to skeletal muscle between in- and out-of-phase with a ratio < 0.5–0.6 [56]. Lack of uniform signal suppression and elevation of the chemical-shift-ratio should be considered suspicious for a neoplastic process, including lymphoma [56].

Staging of lymphoma in pregnancy

Tissue sampling

While imaging features can raise concern for lymphoma, biopsy is ultimately required to establish the diagnosis. Pathological assessment also allows for lymphoma subtyping, which influences staging and treatment planning.

There are multiple factors that radiologists must consider when performing an image-guided biopsy in a pregnant patient, including modality (CT, US, MRI), disease site to target and approach, as well as type of anesthesia to be utilized. When the targeted structure is superficial, such as an axillary or inguinal lymph node, local anesthesia can often be safely achieved with cutaneous lidocaine. However, when an intra-abdominal or intrapelvic structure is the target, an interdisciplinary discussion may be needed with the patient's care team and an anesthesiologist to determine whether procedural sedation may be required. A multidisciplinary approach is needed to review topics including the target site location, potential procedural complications, required patient positioning and its potential effect on the birthing parent and/or fetal vitals, as well as whether an obstetrician should be present during the procedure. The physician performing the procedural sedation should be knowledgeable about pregnancy physiology, as well as the administered medication

pharmacological profiles and their effects on both the birthing parent and the fetus [57, 58].

Lymphoma staging

A discussion on the various lymphoma staging systems (i.e., Ann Arbor, Lugano, St. Jude's) is beyond the scope of this manuscript. The primary role of the diagnostic radiologist is to provide key anatomical information to allow for accurate staging, including the sites/regions of lymphadenopathy (i.e., exclusively above or below the diaphragm, or lymphadenopathy on both sides of the diaphragm), the presence of bulky disease (lymph node conglomerate ≥ 10 cm or 1/3 of the transthoracic diameter), single or multiple sites of extranodal disease, features of bone marrow disease, and features of central nervous system disease. In cases where PET is performed, reporting metabolic activity is also helpful.

Prognosis and treatment of pregnancy-related lymphoma

Hodgkin's lymphoma

HL tends to have a more indolent course, and is often diagnosed with early-stage disease IA/B or IIA. It has a similar 3-year survival prognosis as in non-pregnant patients of approximately 97% [59]. Therefore, treatment of early stages of HL may be deferred until the patient is postpartum. If the disease is discovered in more advanced stages, the treatment option depends on the pregnancy trimester (or gestational age of the fetus).

Traditionally, HL is treated with one of the two chemotherapy regimens (Table 1) plus radiotherapy [6]. During the 1st trimester the embryo is most vulnerable to teratogens, and usage of chemotherapeutic agents can cause spontaneous pregnancy loss. Thus, multi-agent chemotherapy regimens are contraindicated. In some advanced cases of lymphoma, combination therapy becomes unavoidable and therapeutic termination of pregnancy is generally suggested [6]. In some first trimester advanced lymphoma cases, a bridging therapy approach using vinblastine or steroids could be considered with the goal of reaching the second trimester to then initiate a multi-agent regimen. With regards to radiotherapy during the 1st trimester (weeks 1–8), dose-related teratogenic effects are possible; however, multiple studies have demonstrated that in select cases of localized supradiaphragmatic lymphomatous disease, radiation can be administered without adverse fetal outcomes so long as proper abdominopelvic shielding is utilized.

In the second and third trimesters when organogenesis is complete, the risk of congenital malformations related to chemotherapy is ≈3%, similar to the risk among the general population; thus, ABVD chemotherapy is considered to be safe or of low risk [6].

Non-Hodgkin's lymphoma

NHL, specifically diffuse large B-cell lymphoma (DLBCL), runs a more aggressive clinical course compared to HL, more frequently involving reproductive organs, and is more often discovered at an advanced stage when patients present [6]. The 3-year survival in NHL is approximately 82% [59]. Depending on pregnancy status and stage there are different treatment options for management of the DLBCL.

Similar to HL, if a NHL patient requires a multi-drug regimen in the first 2–10 weeks of gestation, then pregnancy termination is recommended [6]. When a pregnant patient with lymphoma becomes symptomatic in the late first trimester, a short course of cyclophosphamide and steroids could be used as a treatment bridge until week 12 gestation is reached, at which time a chemotherapy regimen can be initiated (Table 2) [6].

Table 1 Hodgkin's lymphoma chemotherapy regimen [6]

	1st trimester	2nd and 3rd trimester
Chemotherapy Regimen	Multiagent chemotherapy regimens are contraindicated	• Considered safe/low-risk: Doxorubicin hydrochloride (Adriamycin), bleomycin sulfate, vinblastine sulfate, and dacarbazine (ABVD) • Discouraged during pregnancy due to insufficient data regarding potential fetal toxicity: Bleomycin sulfate, etoposide phosphate, doxorubicin hydrochloride (Adriamycin), cyclophosphamide, vincristine sulfate (Oncovin), procarbazine hydrochloride, and prednisone (BEACOPP)
General oncology therapy recommendations	• Delay treatment if possible • Possible bridging therapy with vinblastine and steroids • Therapeutic termination if multiagent combination therapy must be used	• See above

Table 2 Non-Hodgkin's lymphoma chemotherapy regimen [6]

	1st trimester (0–12 weeks)	2nd and 3rd trimesters
Regimen	Multiagent chemotherapy regimens are contraindicated	• R-CHOP: rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride, vincristine, and prednisone) • Cyclophosphamide has been studied in pregnant patients with autoimmune diseases, and was found to be safe after the completion of organogenesis
General oncology therapy recommendations	Symptomatic pregnant patients: • Therapeutic termination if multiagent chemotherapy is immediately required • Late first trimester (12–13 weeks): Cyclophosphamide and steroid bridging therapy could be considered until the 12th week of gestation is complete, at which time a full anthracycline regimen can be initiated Asymptomatic patient and without critical disease (i.e., airway compromise, CNS compression): • Chemotherapy initiation should be delayed until the 2nd trimester to allow for the completion of organogenesis	See above

In the second and third trimesters the administration of R-CHOP is considered safe; however, there is an increased risk of pre-term birth [6]. Delivery should be scheduled at least 2–3 weeks after cycle completion to allow for bone marrow recovery and fetal drug excretion [6].

Transplacental transmission of lymphoma

Transplacental transmission of birthing parent malignancy to the fetus is exceptionally rare [60]. In theory, the transplacental transmission of malignant lymphocytes is possible, but they would normally be removed by the fetus's immune system [61]. A proposed reason for occurrence of transplacental transmission of lymphoma involves failure of fetal immune response, either from immaturity, immunodeficiency, or shared HLA haplotype between the mother and the fetus [61]. As of the time of this writing, the authors located two case reports within the last 50 years of transplacental lymphoma transmission, both NHL of natural killer cell T-cell lymphoma and B-cell lymphoma [60, 61]. In both case reports, the infants were diagnosed with lymphoma before 1-year-of-age, and neither survived long after diagnosis.

Fetal biometry and neonatal prematurity

In a multicenter, retrospective cohort study published in 2019, Maggen et al. evaluated the outcomes of 134 patients diagnosed with HL while pregnant, and found that there was no difference in birthing parent survival when compared to non-pregnant patients with HL [62]. However, the study did note that pre-term labor and rupture of membranes were higher in HL patients who received antenatal therapy compared with cases where chemotherapy was deferred until postpartum [48, 62].

In cases of HL, there are some reports mentioning higher rates of infant prematurity and low birth weight when birthing parents received ABVD chemotherapy, but these findings may be related to elective pre-term deliveries as opposed to direct effect of the chemotherapy [6, 48].

In cases of NHL, the administration of R-CHOP has been shown to have a slight increased risk of pre-term delivery and low birth weight [6].

Other considerations

Treatmen of Extranodal lymphoma involving reproductive organs

Treatment strategies for cases of reproductive organ infiltrative lymphoma are similar to those described for other cases of lymphoma in pregnancy. In 2013, Horowitz et al. performed a systematic review of reproductive organ involvement in pregnant patients with NHL and identified 121 patients among 74 papers that were published between 1967 and 2011 [63]. In their review, the 6-month mortality for patients who received antepartum chemotherapy was 21.4% compared to 43.9% in those who did not [63]. Therefore, delaying initiation of chemotherapy can result in adverse maternal outcomes in such patients.

Interdisciplinary approach to care

The care of pregnancy-associate lymphoma patients is complex. Specialists from several fields of medicine are required to weigh in on topics including imaging, chemotherapy, birthing plan, and surgical intervention. As such, these patients should be discussed in a multidisciplinary tumor

board setting, which in general have been shown to improve oncologic patient management [64].

Family planning

Onco-fertility

Onco-fertility is a rapidly developing medical specialty that combines the knowledge bases of oncology and fertility medicine. These specialists are uniquely qualified in their ability to provide patients with fertility counseling and management options before, during, and after oncologic treatments. The chemotherapy and radiation therapy used for treatment of lymphoma can be gonadotoxic, which would then lead to premature ovarian insufficiency and loss of fertility [65, 66]. Therefore, when considering the high 5-year survival rate in cases of lymphoma, infertility is a real possibility, and a discussion regarding potential gonadotoxicity related to anticancer treatments should be undertaken with all reproductive age patients [65]. Fertility preservation and restoration options can be categorized as: established, debatable, and experimental. Established options include embryo freezing and egg freezing [65]. Debatable options include fractional radiation therapy dosing, oophoropexy, and use of ovarian protection techniques (i.e., reproductive hormonal suppression) [65]. Lastly, experimental options include ovarian tissue freezing for future autotransplantation, and oocyte in vitro maturation [65]. Ultimately, these patients can be best served in a multi-disciplinary setting to align their reproductive health goals with the available treatment options, and to then set realistic expectations.

Birth control recommendations

Implementation of contraception is not a requirement for those undergoing cancer treatments [67]. Therefore, clinical recommendations for usage of contraception should occur during a shared decision-making visit with the patient. Considerations included in the discussion are risks for thromboembolism development, as well as desire for maintained fertility [67].

Breastfeeding considerations

Breastfeeding has immediate and long-term benefits for both the nursing infant and the mother. However, chemotherapeutic agents often used to treat lymphoma can be excreted into breast milk. Therefore, cessation of breastfeeding during chemotherapy is recommended. Additionally, some of the chemotherapeutic agents can persist in the breast milk even after completion of a chemotherapy cycle, and parents may need to wait 3–6 weeks post-treatment before resuming breastfeeding [68–70].

18F-FDG PET-CT is commonly used for the staging of lymphoma. The nuclear regulatory commission advisory committee on medical uses of isotopes (ACMUI) recommends breastfeeding discontinuation for 4 h following F18-FDG PET-CT [71]. 18F-FDG can become concentrated in breast tissue and be excreted into the breast milk. Therefore, to limit an infant's radiation exposure through contact with the imaged parent's breast tissue, it is recommended that holding the infant be ceased for 12 h following 18F-FDG administration [72].

Conclusion

Lymphoma in pregnancy is rare, and the radiologist may be the first physician to suggest the diagnosis. Although a diagnosis of lymphoma may be suspected based on the combination of patient's age, symptoms, and radiologic findings of lymphadenopathy and splenomegaly, these features may be non-specific, and tissue sampling is required to establish the diagnosis. Interdisciplinary discussions are key for optimizing the patient's care, including review of institutionally available radiologic examinations for staging (i.e., low-dose CT and whole-body MRI), available clinical and surgical oncologic expertise, as well as determination of the need for immediate pregnancy intervention. With current medical therapies, lymphoma in pregnancy patients do not necessarily require rapid initiation of chemotherapy or radiation, and treatment can be postponed to after birth. In some cases, full-term delivery remains possible.

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