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Review Article

Pregnancy outcomes in women diagnosed with Hodgkin lymphoma during pregnancy: a review of the literature

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ABSTRACT

Hodgkin's lymphoma (HL) is one of the most common haematological malignancies to complicate pregnancy due to its peak incidence in the reproductive age. Constitutional symptoms of the disease may be mistaken for early pregnancy symptoms, delaying diagnosis. Pregnancy neither affects the course nor is it associated with the recurrence of HL. HL has an excellent prognosis with 90% five-year survival if the disease is detected in the early stage and treated adequately. However, treating a pregnant woman with HL is challenging. A multidisciplinary approach is required to diagnose, stage, and start appropriate treatment at the proper gestation to achieve the best pregnancy outcome without compromising the status of the mother. Care should be taken to provide both psychological and emotional support to the couple throughout the pregnancy by a trained healthcare provider. This review offers insight into the presentation, management, and feto-maternal outcomes of pregnant women with HL over the last 15 years.

Keywords: Hodgkin disease, Pregnancy, Pregnancy outcome

INTRODUCTION

The incidence of malignancy diagnosed for the first time during pregnancy has increased in the last few decades, owing to the overall rise in the incidence of malignancy in the general population. Malignancy concurrent with pregnancy occurs in around 1/1000 women.[1]

Managing malignancy during pregnancy has always been a challenge despite advancements in modern medicine. Firstly, because the constitutional symptoms of disease, like easy fatigability, malaise, weight loss, generalized weakness, loss of appetite, or aversion to food, can be confused with the normal symptoms of early pregnancy, hence delaying the diagnosis. Secondly, most of the imaging modalities required to stage the disease, like contrast-enhanced computed tomography (CECT), positron emission computed tomography (PET-CT), and X-ray exposure, are not safe for the growing fetus.[2] Thirdly, most of the malignancies required chemotherapy or radiotherapy, which again can have teratogenic effects on the fetus and hence, should be avoided after weighing the risk and benefit of postponing the treatment. Lastly, because of the high rate of complications associated in mother (hypercoagulable state, thromboembolism, risk of post-partum hemorrhage, increased risk of infection due to immunocompromised state) and to the fetus (increased risk of miscarriage, congenital malformation, prematurity, small for gestational age fetus, infection, respiratory distress syndrome and mortality) due to malignancy.[3-5]

Hence, a multidisciplinary team, including a senior obstetrician, neonatologist, medical oncologist, anaesthetist, and radiologists, is required to manage such women to achieve a good feto-maternal outcome. Hodgkin lymphoma is the most common type of haematological malignancy affecting women during pregnancy.[6] We reviewed case reports published in the last fifteen years (2010-2024) to study pregnancy outcomes in Hodgkin lymphoma cases diagnosed during pregnancy, including the presentation, the latest updates in management, and how they affect the mother and baby.

METHODS

Type of study

This is a review that evaluates the pregnancy outcome in women diagnosed with Hodgkin lymphoma during pregnancy.

Selection criteria

We included case reports published in the last 15 years (2010-2024). All case reports/series, including those on pregnant women diagnosed with Hodgkin lymphoma during pregnancy, were included in the review. Studies related to HL-treated disease-free pregnant women were not included.

Search methodology

A systematic search of PubMed, MEDLINE, Web of Science, and Google Scholar was done. The reference and citation lists of published literature were also searched. The search was done using the following keywords and MeSH terms: ("Hodgkin's Disease" OR "Lymphoma" AND "Pregnancy Outcome" OR "Outcome" OR Obstetrics Outcome" AND "Complication" AND "Case Reports"). The case reports were checked by the authors for duplication and suitability. Conference papers and E-poster abstracts were not included. Figure 1 shows the flow chart of screened studies.

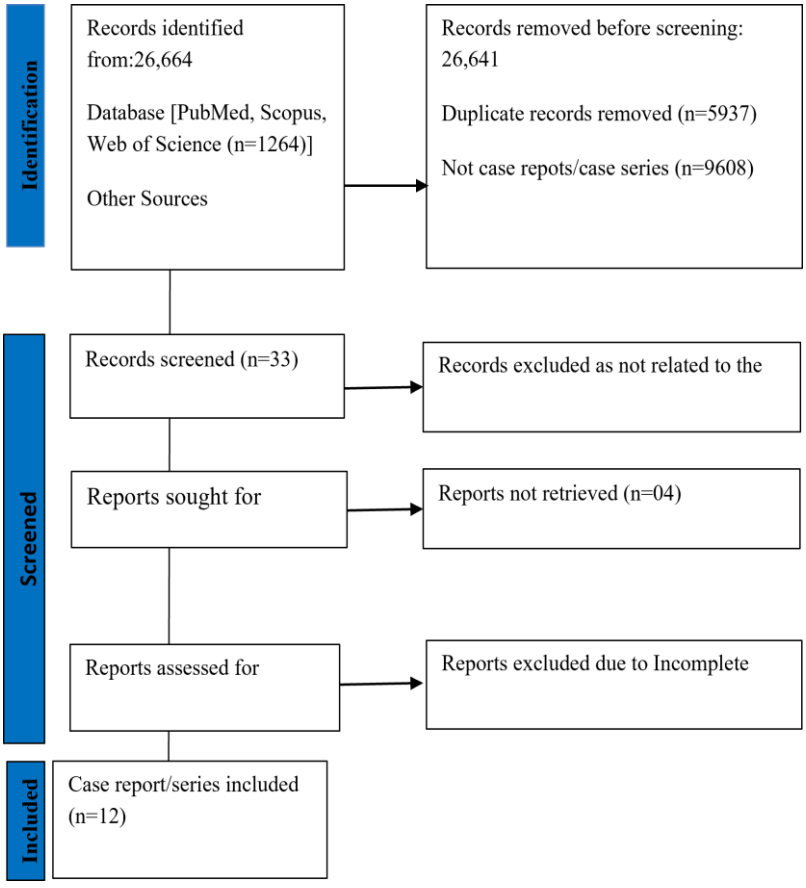


Figure 1: Flowchart of the screening process used for the present review.

RESULTS

A total of 12 case reports/series with 22 cases were found suitable and were included in the review Table 1 (Annexure 1). Twenty-two cases were diagnosed for the first time during pregnancy. Demographic data of the women are shown in Table 2 most of the cases were between 20 and 41 years of age. The majority of women presented during the second trimester.

Table 1: Annexure 1. Summary of cases of Hodgkin lymphoma diagnosed for the first time during pregnancy from 2009-2024.

Authors	No. of cases	Age (years)	Parity	Trimester	Presenting symptoms	Type of HL	Stage	Treatment received	Treatment	GA at delivery (weeks)	Maternal Outcome	Fetal Outcome
Israel R et al6	01	26	NA	I	Persistent & Progressive Lymphadenopathy	MC	IIIA	NA	AVD (8)	10	CR	A
Sagan D et al7	01	24	NA	II	NA	NS	IIA	II	Antenatal: EVA PP: ABVD (5)	36	CR	UN
Kassab C et al8	03	35	P2	III	Cervical ganglion at 23 weeks	NS	IIA	PP	Corticosetroids PP: ABVD	34	CR	Discrete hypoxia at birth (Apgar 6/8) Icterus neonatorum Discharged in satisfactory condition
		20	P1	III	Fever Cervical adenomegaly Symptomatic compression of the superior vena cava	NS	IIB	III PP	ABVD (1) PP: ABVD (6)	35	CR	UN
		29	P2	III	Recent onset of lymphadenopathy	NS	IIA	PP	ABVD (6)	38	CR	UN
Iriyana N et al9	01	34	P2	II	Enlarge bilateral neck lymph node, supraclavicular, & Axillary lymph nodes	NS	IVA	II PP	ABVD (3.5) PP: ABVD (6)	41	CR	UN
Sanchez et al10	01	33	NA	II	Bilateral inguinal lymphadenopathy	NS	IIA	II	ABVD (5)	37	CR	UN
Chunag FL et al11	01	25	NA	I	Cough Unintentional weight loss Right supraclavicular 2cm lymph nodes	NS	IIIB	NA	ABVD	FT	CR	UN

Continued.

Authors	No. of cases	Age (years)	Parity	Trimester	Presenting symptoms	Type of HL	Stage	Treatment received	Treatment	GA at delivery (weeks)	Maternal Outcome	Fetal Outcome
Khattak T et al12	01	25	P1	III	Fever Progressive jaundice Pruritis Abdominal distention Occasional night sweats Body aches Loss of appetite Weight loss Painless hepatospleenomegaly Nausea Generalized body weakness Anemia	MC	NA	NA	NA	NA	The patient died because of irreversible liver damage	NA
Kasonkanji E et al13	01	26	NA	II	Painless progressive cervical lymphadenopathy	NA	NA	NA	ABVD (6)	FT	CR	UN
Balcerzak RK et al14	09	28	NA	I	NA	MC	IIA		ABVD (4) ABVD (4) ESHAP (2) IVE auto -HSCT Relapse (2) GDP auto-HSCT (3)	40	RR Continued. CR CR	UN
		23	NA	II	NA	NS	IIIA		ABVD (8)	32	CR	PT
		22	NA	II	NA	MC	IIB		ABVD (7)	37	CR	UN
		24	NA	II	NA	NS	IIIB		ABVD (8)	36	CR	UN

Continued.

Authors	No. of cases	Age (years)	Parity	Trimester	Presenting symptoms	Type of HL	Stage	Treatment received	Treatment	GA at delivery (weeks)	Maternal Outcome	Fetal Outcome
		25	NA	II	NA	NS	IVA		ABVD (8) DHAP (2)	36	PR CR Continued.	UN
		26	NA	II	NA	NS	IVB		ABVD (6) ESHAP (3) Auto HSCT	36	R CR	UN
		25	NA	II	NA	NS	IVB		BEACOPP (4)	38	CR	UN
		24	NA	II	NA	NS	IVB		ABVD (8)	38	CR	UN
		20	NA	II	NA	LP	IVB		ABVD (8) BEACOPP (2)	38	PR CR	UN
Cotteret C et al15	01	41	NA	III	Right supraclavicular adenopathy upto 3 cm	NA	IIA	III PP	Corticosteroids ABVD PP: ABVD	33	CR	PT
Dunleavy K et al16	01	38	P2	I	Dull central chest pain	NA	NA	II	ABVD (5)	37	CR	UN
Delzotto J et al17	01	21	P0	II	Shortness of breath Facial swelling Lightheadedness Intermittent night sweats Syncopal event Enlarges the neck. Lymph node Swelling in the neck	NS	NA	II	Antenatal ABVD PP: ABVD + RT	28	CR	PT NICU admission Continued.

Table 2: Demographic Profile and pregnancy outcome of patients in previous studies.[7-18]

Variable	n=22
Median age (Range in years)	25 (20-41)
Parity	
P0	01
P1	02
P2	04
NK	15
The trimester in which presented	
1st	04
2nd	13
3rd	05
Presence of B symptoms	
Yes	04
No	09
NK	09
Type of HL	
NS	15
MC	04
LP	01
NK	02
Stage of disease	
I	01
II	06
III	04
IV	06
NK	05
Treatment received	
1st	02
2nd	14
3rd	03
PP	02
Not Known	01
Type of treatment	
Chemotherapy	21
Radiotherapy	0
Chemotherapy + Radiotherapy	01
NK	02
Maternal outcome	
Complete remission	22
Maternal death	01
Recurrence /Relapse	0
Pregnancy Outcome	
Mean gestation age of birth (Weeks)	37
Mean birth weight	
Spontaneous Abortion	01
Birth >37 weeks	09
Birth 34-37 weeks	08
Birth <34 weeks	03

Clinical presentation

Fever, night sweats, and unexplained weight loss, also known as B symptoms, were present in only four cases. One patient also presented with the symptoms of cholestatic jaundice (pruritus, jaundice, hepatosplenomegaly, abdominal distension, nausea, loss of appetite, generalised weakness, body aches). However, ten cases from two studies have not commented on the symptoms with which the patient presented.[7-10] Cervical lymphadenopathy, cervical ganglion, supraclavicular lymphadenopathy, axillary lymph nodes, inguinal lymphadenopathy, cough, dull chest pain, shortness of breath, neck swelling, facial swelling, light-headedness, anaemia, and syncopal event were some of the other presentations of the disease.[11-13] Figure 2 shows symptoms of Hodgkin disease in pregnancy.

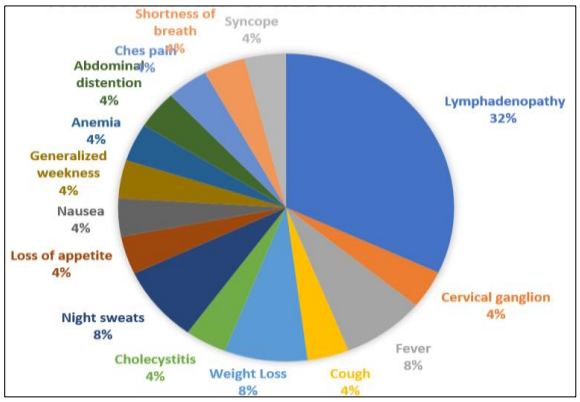


Figure 2: Symptoms of HL during pregnancy.

Diagnosis

Diagnosis of a chest X-ray with an abdominal shield (mediastinal mass) or abdominal and chest ultrasound were done to find any evidence of hepatosplenomegaly with discrete lesions or lymphadenopathy. However, the diagnosis was confirmed after a histopathological report of tissue biopsy. For staging workup, computed tomography (CT) or positron emission tomography (PET-CT) was done post-delivery, wherever possible. Where it was not possible to wait till delivery, Magnetic resonance imaging (MRI) of the whole body or neck, chest, abdomen, and pelvis was done. In a few patients, bone marrow aspiration was also done.

The type of HL is nodular sclerosis, the most common type of classical HL, followed by mixed cellularity. The stages of HL in women presented with stage II, III, or IV disease. Most of the women received chemotherapy (ABVD). None received radiotherapy.[14,15]

Pregnancy outcome

One woman had a spontaneous abortion at 10 weeks of pregnancy. The rest all had live births, out of which ten were full-term deliveries at or after 37 weeks, and eleven were preterm births. One preterm baby had discrete hypoxia at birth with an Apgar score of 6/8 and icterus neonatorum. Another baby born at 28 weeks through an electively planned birth was admitted to the neonatal intensive care unit (NICU) due to prematurity. However, both babies had an uneventful course thereafter. No case of congenital malformation, stillbirth, or intrauterine death was reported in these studies.[16-18]

Response to treatment of 21 cases achieved complete remission after treatment. One patient died because of irreversible liver failure.

DISCUSSION

Haematological malignancies are the fourth most common cancers affecting women during pregnancy after malignant melanoma, cervical cancer, and breast cancer. Hodgkin lymphoma (HL) is the most common haematological malignancy in pregnant women, with an incidence of around 1/1000-1/6000 deliveries. Hodgkin's lymphoma has a bimodal age distribution, and the peak incidence of the disease is seen at 15-35 and 50-70 years of age. Hence, the high incidence of Hodgkin lymphoma in pregnant women corresponds to its peak incidence during reproductive years.[19,20] Although the malignancy is said to be associated with low parity, there are no conclusive studies to prove this association. HL is of two main types: Classical HL (CHL) and Nodular lymphocyte predominant HL (NLP-HL). Classical HL comprises 95% of all HL cases and is mainly of the following four types: nodular sclerosis, mixed cellularity, lymphocyte predominant, and lymphocyte depletion type. Nodular sclerosis comprises 70% of all cases and is more commonly seen in women than in men.

The rest of the other variants of HL have male predominance.[21] Immunosuppression, infection with Human Immunodeficiency Virus (HIV), Epstein-Barr virus (EBV), HLA-A01* allele, and positive family history are known risk factors for HL.[22,23] HL lymphoma most commonly presents as peripheral lymphadenopathy (cervical, mediastinal, axillary, and para-aortic lymph nodes). Around 30-40% of cases can also present with B symptoms like fever, night sweats, weight loss, and pruritus. The spleen is the most common site of extranodal involvement, followed by the lung, liver, and bone marrow. Nodular sclerosis and lymphocyte-depleted HL usually present in early stages.

Since the most common type of Hodgkin's lymphoma during pregnancy is nodular sclerosis, we expect pregnant patients to report in the early stage of the disease. However, most of the constitutional symptoms like weakness, loss of appetite, easy fatigability, shortness of breath, and malaise can be easily mistaken for early symptoms of pregnancy, leading to late presentation and delay in diagnosis during pregnancy. History of fever and night sweats, if present during pregnancy, should be evaluated properly as they can be an early manifestation of

the disease in the absence of any visible or palpable lymph nodes and swelling.

A detailed general physical examination in these women may reveal cervical or axillary lymphadenopathy. Histopathological examination of tissue obtained through excisional biopsy is the gold standard for diagnosis. Fine needle biopsy or core needle biopsy may not be sufficient and should be avoided.[24-26] Tissue biopsy (excisional biopsy, core needle biopsy, and bone marrow biopsy) can be safely performed during pregnancy, and one should not hesitate to do it as HPE is a must for diagnosis.[27,28] Once the diagnosis is confirmed, further evaluation can be guided by imaging studies.

Chest X-ray, positron emission tomography-computer tomography (PET-CT) scan of chest, abdomen, and pelvis are usually preferred imaging modalities for further evaluation and staging of the disease in non-pregnant cases.[29] Since the radiation dose of these imaging modalities can be harmful to the growing fetus, it's better to avoid these imaging studies during pregnancy. The risk is higher in the first trimester and with the radiation dose of more than 100 mGy.[30] Wherever necessary, Chest X-ray with abdominal shield and MRI can be safely advised in pregnant women with HL.[31] HL has an excellent cure rate, with a cure rate of 80-90% with stage-adapted therapy.[32]

However, the prognosis depends upon several factors. Presence or absence of B symptoms, bulky disease, multiple lymph node involvement, stage of the disease, age of patient, suitability for treatment, raised erythrocyte sedimentation rate (ESR), age, sex, hematocrit, and extra-nodal site involvement are all important factors affecting the prognosis. In addition to all above factors gestational age at which the woman is diagnosed with HL also is very important as the treatment may affect the growing fetus adversely, hence when to start the treatment, which treatment is best for the mother and baby, timing of delivery to achieve best outcome for baby without compromising on mother's health requires meticulous planning.

An experienced team comprising of senior obstetrician, a senior neonatologist, a medical oncologist, a radiologist, senior anesthetist should be available while planning the management protocol for these women. Moreover, these women should receive treatment in centers equipped with facilities for a blood bank, adult intensive care unit, neonatal intensive care unit, facility for emergency surgery if needed. A detailed discussion regarding the diagnosis, course of disease, available treatments, risk versus benefits of each available treatment for the patient and baby, plan of management, complications, and follow-up should be discussed with the woman and family. Chemotherapy is the mainstay of treatment for HL. Most of the chemotherapeutic agents are teratogenic and should be avoided during the first trimester of pregnancy. Out of various chemotherapy regimens described for HL, combination chemotherapy with ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine) is considered to be safe during pregnancy beyond the first trimester.[33,34]

However, if the disease is diagnosed during the first trimester, the decision to start treatment will depend upon the stage of the disease (early or advanced) and the wishes of the patient to continue pregnancy. In the early-stage disease, if possible, treatment can be postponed till the second trimester, and the mother is kept under strict supervision. Steroids can be administered till this time, or if needed, the patient can be given single-agent chemotherapy with vinblastine.[35,36] However, in advanced disease where waiting is not an option, termination or pregnancy with the start of the full therapy ABVD regimen can be considered. If pregnant women need immediate treatment, combination chemotherapy should be started immediately after explaining the risk of treatment to the fetus and the need for immediate intervention as a life-saving measure.[37] If the disease is diagnosed in the second trimester, women can receive combination chemotherapy with ABVD. Delivery can be planned any time after 34 weeks of pregnancy, depending on the condition of the mother and fetus. In case the HL is diagnosed in the third trimester and there is no immediate threat to the mother and fetus, it is advisable to continue the pregnancy till 34-36 weeks so that the baby achieves lung maturity and neonatal morbidity due to prematurity is reduced. At 36 weeks, the patient's condition can be reviewed for continuation of pregnancy further till 37 weeks. Elective termination of pregnancy can be planned. Normal vaginal delivery is not a contraindication; hence labour can be induced unless there is any obstetric contraindication to vaginal birth or the lesion involves the inguinal area and lower abdomen and can lead to obstruction.

In such cases MRI pelvis is required to rule out the obstruction of the birth canal and the need for birth via cesarean section. Despite of high curability rate, 30% of patients with advanced disease and 5-10% of early-stage disease may relapse.[38] Pregnancy has no impact on the relapse of the disease.[39] Pregnant women who have received HL previously, if they present with relapse during pregnancy, need to be categorized as early (within 6 months) or late relapse cases (after 6 months). In cases of early relapse couple should be counselled regarding the prognosis and highly fetotoxic nature of second-generation drugs. In case the women are in early gestation elective termination of pregnancy should be advised followed by second generation chemotherapy with platinum-based agents followed by high dose therapy followed by autologous stem cell transplantation. In case termination of pregnancy is not an option, then second-line platinum-based or gemcitabine therapy may be given after explaining the fetal risk.

In cases of advanced gestation, planned delivery followed by the above-mentioned treatment is advisable. In cases of late relapse combination chemotherapy with ABVD can be tried during antenatal period followed by planned delivery

followed by high dose therapy and autologous stem cell transplant. As the chemotherapeutic agents cause temporary suppression of the fetal bone marrow, it is advisable to plan delivery at least 2- 3 weeks after the chemotherapy. This will allow the drugs to get excreted through the placenta and the recovery of fetal bone marrow. If the delivery takes place during the treatment or immediately after the completion of the cycle, the fetus will remain at risk of neutropenic sepsis.[40]

Placenta should be sent for histopathological examination in every woman with HL to rule out any placenta involvement.[41] In case placental metastasis is present baby should be thoroughly evaluated for any evidence of HL and should be kept under follow up. Breastfeeding is to be avoided in women who are on postpartum treatment with chemotherapeutic agents, as these agents are secreted in breastmilk and may lead to myelosuppression in the babies.[42] Venous thromboembolism prophylaxis with low molecular weight heparin is recommended for the first 6 weeks postpartum to reduce the risk of deep vein thrombosis and thromboembolic episodes in these women.[43] Getting to know that one has cancer is a very distressing time for the patient and family; hence, care should be taken to provide emotional and psychological support to the women throughout the antenatal period and for a few weeks post-partum period.[44]

CONCLUSION

Diagnosis of HL during pregnancy is challenging for the patient as well as the treating medical team. Most of the modern-day chemotherapeutic drugs for HL are found to be safe beyond the first trimester. With timely diagnosis and treatment, excellent outcomes are seen both for the mother and baby. A team comprising an experienced obstetrician, neonatologist, radiologist, and medical oncologist should be involved in the evaluation and management of the patient to provide the best fetal and maternal outcome. Pregnant women should receive psychological support from a trained health care provider throughout the antenatal and early postpartum period to avoid any short- or long-term psychological sequelae.

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