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Original Article

Treatment of Early Stages Hodgkin Lymphoma During Pregnancy

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Abstract. ***Background:*** **To assess maternal and fetal outcome of women and newborns who received chemotherapy during pregnancy to treat Hodgkin lymphoma (HL)in early stages (IA, IIA), we performed a retrospective analysis of a cohort of 44 pregnant women with HL and early stages, diagnosed and treated between 1988 to 2013, at a tertiary reference cancer center.**
Methods: **We analyzed data on HL characteristics and treatment, with a particular attention to maternal and fetal complications; in children, we performed a longer follow-up to detect any anomaly in physical development, scholar performance, psychological, cardiac, neurological function, and intelligence tests.**
Results: **Median age was 29.4 (range 21-37) years; Most patients were stage IIA (86%), had M a bulky mediastinal disease (78%) and 60% had > 3 nodal sites involved; thus these patients were considered to have a not favorable condition. Abortion was refused when it was proposed. All patients received chemotherapy during pregnancy; ABVD (adryamicin, bleomycin, vinblastine, and dacarbazine) at standard doses and schedule, even during the first trimester. Radiotherapy, when indicated, was administered after delivery in 39 patients. No obstetrical complications were observed, delivery occurred between 33 to 36 weeks in 10 cases (22%); and >37 weeks in 34 cases (87%). Four newborns were low-weight: 2012 g median (range 1750 – 2350 g). No clinical malformations were observed, and development of newborns was physiological without evidence of cardiac and neurological damage, behavior, intelligence, and scholar attendance were normal. At median follow-up range of 120.4 (48-299) months, the progression-free survival and overall survival of patients were 95% and 93%respectively**
Conclusion: **Combined chemotherapy, as initial therapy appears to be the best approach in this setting of patients, with an excellent outcome to both mothers and children. If radiotherapy is necessary, it could be administered after delivery.**

Keywords: Hodgkin and pregnancy, Chemotherapy and pregnancy, Radiotherapy and pregnancy, Hematological malignancies and pregnancy.

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Introduction. Cancer is a leading cause of death in women of childbearing age. Although simultaneous occurrence during pregnancy is uncommon with a reported incidence of 0.07 to 0.8%, it is evident that in the last years an increment in reported cases was observed. The coincident occurrence of cancer and pregnancy presents complex therapeutic problems for the patient, family, oncologist, obstetricians, pediatricians, and neonatologist. The potential

effects of therapeutic interventions on the developing fetus influence both physicians recommendations and patients decision; regarding the choice of chemotherapy or radiotherapy, the timing of their administration, and whenever a pregnancy should be continued or treatment is deferred after delivery. Most of these problems concern the risks to the fetus and the best therapeutic schedule to treat with curative attempt to the mother.[1-3] Hodgkin lymphoma (HL) is the most common hematological malignancy associated with pregnancy. Treatment of advanced stages (IIB, III and IV) during pregnancy has well defined, and ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) is considered the best therapeutic option, with a very good response and overall survival, and minimal toxicity to the fetus,[4-11] even administered during the first trimester.[12] However, treatment during early stages (IA and IIA) remain controversial, while some oncologist suggested that chemotherapy administration will be deferred until after delivery,[4-6,8-10] and suggested that the use of single agent: vinblastine, could be administered, but, no precise schedule; dose, timing, time; has been considered.

Adjuvant Radiotherapy (RT) is an excellent option in early HL, without pregnancy associated, with overall survival (OS) > 95% at more than ten years.[13,14] RT during pregnancy remains to be controversial, some authors suggested that RT can be employed with adequate protection,[6,9.10,15] but, concern about late toxicities,[16-18] will be considered and RT has been suggested that will be administered after delivery, it is necessary. Thus, we retrospectively analyzed our cohort of pregnant patients with early stage HL that were treated with a uniform schedule, and with a longer follow-up, to observe the impact on OS in mothers and to assess the outcome of the children.

Material and Methods. We conducted a retrospective analysis of patients who had a diagnosis of HL on early stages, from 1988 to 2013. The diagnosis was established by biopsy that was revised for two pathologists . All patients were staged with physical examination, complete blood counts, serum chemistry, serum determinations of lactic dehydrogenase and beta-2 microglobulin, also tests to virus immunodeficiency virus, hepatitis B and C; aspirate and biopsy of bone marrow, X-ray of the thorax, ultrasound of abdomen and pelvis were performed. Pregnancy was carefully examined by two obstetricians in an obstetric high-risk clinic; fetal ultrasound was performed at diagnosis, and every month until delivery. All cases, we informed to the patient, family, lawyer, religious people, about the risks of began treatment with chemotherapy or deferring treatment after delivery, also, the options of treatment of single agent: vinblastine, 6 mg/m^2, every two weeks until delivery. When curative chemotherapy was the election, we administered the ABVD regimen at standard doses and schedule. Chemotherapy was stopped between week 35 to 37 to avoid the risk of hematological toxicity. Delivery was performed according to the obstetrics indications.

Abortion was not accepted by any of the women. Six patients preferred to defer the treatment and received single agent, but, in all cases clinical progression of the tumor was observed: a cough, fatigue, dyspnea (that were considered as increased in oppression of the respiratory tract) and increase in tumor mass, measured with clinical or radiologically studies; and complete chemotherapy regimen was administered. The delay in treatment was 8.9 (3 to 12) weeks.

If the patient did not complete the six cycles of chemotherapy during pregnancy, it was restarted after two weeks of delivery to complete the schedule. If RT, was considered necessary, it was four weeks after chemotherapy was completed.

At birth, the newborns were carefully examined by neonatologist team, to detect any congenital abnormalities, height and weight were considered, complete blood counts and serum chemistry were performed. Subsequently, the children were carefully evaluated at 3, 6, 12 and moths, and annually until now. At each visit, biometric data were obtained and compared with normal children of the same, economic and social status.

Psychological test, behavior development and scholar attendance, were performed every three years. Neurological examination was conducted annually. Cardiac evaluation with ultrasound was performed from the 5-year, every 5 years, or when any clinical suspicious.

The mothers were evaluated with respect to response type, duration of progression-free survival and OS. Also fertility after chemotherapy, to observe if the new pregnancies could affect the possibility of relapse.[19]

The study was approved by the Scientific and Ethical Committee of our Institution, and all

mothers, and children (< 18 years) for the legal custodian, gave a written consent to publish the results.

Results. Forty-four women fulfilled the criteria entry. **Table 1**, shows the mother clinical characteristics; most patients were stage IIA, (86%); 27 have > 3 nodal sites involved (60%), 38 have a bulky mediastinal disease (86%); nodular sclerosis was the most frequent histology presentation (84%). All patients received chemotherapy during pregnancy, including four patients during the first trimester. Twenty-four patients (55%) received more than three cycles of chemotherapy before delivery. At the time of delivery, 28 patients (63%) had a complete clinical response. Two patients (both deferred treatment for 5 and 8 weeks) were on partial response after chemotherapy and were converted to complete response after radiotherapy.

Table 1. Mothers. Clinical characteristics.

	No	**%**
Number	44	100
Age(years) range	21 – 37	
Median	29.4	
First pregnancy	13	29
Stage IA	6	13
IIA	38	86
Histology:		
Nodular sclerosis	37	84
Mixed cellularity	5	11
Not classified	2	4
Mediastinal bulky disease	38	86
> 3 nodal sites	27	60
Chemotherapy during pregnancy	44	100
First trimester	4	9
Second trimester	32	72
Number of cycles during pregnancy		
1	2	4
2	8	18
3	10	22
4	10	22
6	14	32
Status at delivery		
Complete Response	44	54
Radiotherapy after Delivery	39	80
*After completion of treatment: 6 cycles of ABVD and radiotherapy when necessary		
Current status		
Alive free-disease	42	95
Lost to follow-up	1	2
Died, relapsed and/or tumor progression	1	2

Chemotherapy was well tolerated, only seven cases of moderate granulocytopenia were observed (3.4%). No anemia, thrombocytopenia or other abnormal laboratory tests were observed. Delay on treatment was minimal, and the dose-intensity was > 96%. 42 patients (95%) are alive-free disease and could be considered cured, with an OS of 5.6 to 22.4 (median 11.5) years. One patient relapses and was refractory to salvage therapy, including stem cell transplant.

No obstetrical complications were observed, delivery was without complications. Eight patients were pregnant after chemotherapy, and no evidence of relapse has been observed.

Table 2 show the clinical characteristics of newborns, the 4 newborns that received chemotherapy during the first trimester had low-weight: 1950 to 2100 (median: 2010) g, these fetuses began ABVD regimen at 12, 13, 16, and 16 weeks of pregnancy, but, all recovered the normal weight at a median of 7.4 weeks.[3-10] No congenital abnormalities were observed. Psychological, physical, neurological and cardiac tests were normal. Physical development was according to the standard of the Mexican population. Academic development was similar to children of the same economic and social status. Intelligence tests, including verbal and performance IQ, were within normal ranges, as compared with 77 children of the same age, that were the control group. The children that received chemotherapy during the first trimester had a healthy physical development.

Table 2. Newborns. Clinical characteristics

Delivery: weeks of gestation	**No**	**%**
33 to 36	10	22
> 36	34	77
Weight (g)		
< 2500	4	9
2600 – 3000	17	38
> 3000	23	52
Median 3125		
Range 2150 – 3900		
Congenital malformations 0		
Current status	No	%
Alive, normal life	43	97
Died, home accident	1	2

Also, no cardiac, neurological deficiencies were found, and the academic approach was normal without any difference between the children that

received chemotherapy during the second or third trimester. A child died at nine years age, for a home accident. No evidence of second neoplasms and acute leukemia have been documented. No statistical differences were observed when univariate tests observed the impact on outcome in these patients (data not shown).

Discussion. Treatment of cancer during pregnancy remains a challenge because the common treatment included chemotherapy, which has been considered to produce detrimental effects on a fetus, including congenital malformations, mutations, carcinogenesis, intrauterine growth restriction, mental retardation and low-weight. These side-effects limited the use of chemotherapy during 30 years; actually it is considered that chemotherapy could be safely administered during the second and third trimester,[2-11] and eventually, according to the aggressiveness the hematological malignancy, during first trimester,[12] but, considering that certain drugs, like methotrexate, idaurubicin, 6-mercaptopurine, should always be avoided.

At present, chemotherapy is accepted to be administered in HL during second and third trimester of pregnancy, because of the ABVD regimen, that is the best therapeutic approach in the neoplasm, appear to be safe to the fetus, and the prognosis of the women remain to be excellent with minimal complications.[3,7-10,11,12,15] But, most of the reported cases were mothers with advanced stages (IIB, III, IV) and organ-failure secondary to tumor infiltration and needing a prompt treatment.

Treatment of early stages remains to be defined; some reports suggested that chemotherapy in this condition could be deferred, because the prognosis in this stage remain good, and the growth of the tumor until delivery did no affected the possibility of response,[2,3,9,10] or well indicated a single agent, as vinblastine; but, the doses, the schedule, and the growth of the tumor was not reported. However, some patients even in early stage, have some adverse prognostic factors, as bulky mediastinal disease and > 3.

Nodal involvement sites and mediastinal bulky disease, and in this condition no has been addressed the use of a single agent. In the present study, we agree to offer the possibility of deferred treatment, and the six patients who accepted were included in an intensive vigilance. The six patients showed dates of progression of the tumor: increase in the volume of the clinical lymph nodes, and the increased in no-specific symptoms: a cough, dyspnea, fatigue, that we interpreted as compression of the airways. Taking into consideration our results, the treatment with chemotherapy should not be deferred, because mothers have an excellent obstetrical course, no complications during the delivery and 95% of the patients are alive and possibly cured. Also, the newborns did no-show any severe problems, only four children had low-weight that was quickly recovered, and the development of children was normal. Thus, our results confirm that good prognosis of HL during pregnancy.

Some concerns about the patients who were treated for HL during pregnancy regard the relapse that could be most frequent. However, the large study of Weisbull et al.,[19] and our data show that no a major risk of relapse of HL exist in patients treated in pregnancy and in the subsequent pregnancies.

The best treatment of early-stage HL and bulky disease is the use of chemotherapy and RT. In some cases, RT has been administered during pregnancy, and apparently without damage to the fetus, but the follow-up is very short to observe the possibility of a carcinogenetic effect and apparition of acute leukemia or solid tumors[16,17] will have to be considered. Taking into consideration these concerns we decided to avoid the use of RT during pregnancy and employed RT after delivery. Our data show that the prognosis is good and RT remains useful when employed after delivery.

Conclusions. The best approach to treat early stages HL, is the use of standard chemotherapy, that is well tolerated, retains an excellent outcome and the newborns did not show any abnormalities secondary to employ chemotherapy.

We agree that definitive conclusions cannot be drawn, because it a single center report, but, controlled studies are not possible in this setting, and taking into consideration the low number of cases reported, we wait that more people report patients in this clinical condition to have the best information to define the treatment in this group of patients.

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