Prevention of Chemotherapy-Induced Ovarian Failure with Goserelin in Premenopausal Lymphoma Patients

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ABSTRACT

Purpose: To determine the effectiveness of gonadotropin-releasing hormone agonist (GnRHa) (Goserelin acetate) in preserving ovarian function in premenopausal women undergoing combined chemotherapy for Hodgkin or non-Hodgkin lymphoma by documenting the changes in hormonal levels.

Design: Prospective randomized controlled study.

Setting: Oncology Department, Beni-Suef University Hospital, Beni-Suef, Egypt.

Methods: Fifty-two females aged 17–40 years old were assigned at random to receive combined GnRHa (Goserelin acetate) and standard chemotherapy for 6 months (goserelin group, n = 26), or standard chemotherapy alone (control group, n = 26). Goserelin (3.6 mg) was given subcutaneously at the start of chemotherapy every 4 weeks for 6 months. The levels of follicle stimulating hormone (FSH) and Estradiol (E2) were measured at 3 and 6 months (6–8 cycles) during the chemotherapy regimen and 3 months after, AMH anti-Mullerian hormone was measured at base line and end of follow up, also assessment of clinical history (menstrual rhythm). In addition, side effects were observed and recorded during therapy and overall response to the treatment.

Results: The goserelin group showed significantly lower FSH levels compared to the control group at 3 and 6 months of treatment and after 3 months of chemotherapy, and higher menstrual recovery percentage after completion chemotherapy, also better higher ovarian reserve. However, the E2 level was not significantly different between groups. The occurrence of adverse events was similar in both groups, and there was no significant difference in overall response to the treatment at the end of follow-up.

Conclusion: In young females, concurrent administration of goserelin acetate during chemotherapy may preserve ovarian function, with a mean FSH level < 10 IU/L and protect from premature ovarian failure (POF). However, a long-term study is required to further validate these findings.

Key words: Premature ovarian failure, Goserelin, GnRHa, Premenopausal women, Lymphoma

INTRODUCTION

Chemotherapy has improved the life expectancy of reproductive-age patients treated for Hodgkin or non-Hodgkin lymphoma, both of which are now considered as highly curable[1,2]. Nevertheless, chemotherapy often causes infertility or premature ovarian failure due to chemotherapy-induced ovarian follicular damage, which is the main long-term consequence of combination chemotherapy used for the treatment of lymphoma[3,4]. Ovarian dysfunction and damage result in a menopause-like state in patients younger than 40 years of age reflective of the gonad toxicity of chemotherapy[5]. Since fertility is a critical issue affecting female quality of life, investigators and clinicians have attempted to understand ways to preserve fertility in this population[6]. There are several methods of fertility preservation for female lymphoma patients who have been exposed to chemotherapy. One such method is the administration of gonadotropin releasing hormone agonist (GnRHa) during chemotherapy. Although the mechanism of GnRHa is poorly understood, it may involve a decrease in utero-ovarian perfusion due to the hypoestrogenic milieu, which subsequently leas to a decrease in the cytotoxic penetration of ovaries, suppression of endometrial growth and thinning of the endometrial mucosa. Moreover, this process also results in a decrease in follicular apoptosis, together with the inhibition of chemotherapy-induced ovarian follicular depletion by inhibiting the follicles from entering the growing stage[7,8]. GnRHa has a sustained action that results in the downregulation of GnRH-receptors. Thus, GnRHa eventually creates a hypogonadotropic state, with low follicle stimulating hormone (FSH) and estradiol (E2) concentrations causing decreased recruitment of follicles and low estrogen levels, respectively. Within 1–3 weeks after administration, the hypogonadotropic state is established and estradiol is reduced to levels similar to those occurring after menopause or after surgical oophorectomy[9]. At present, scientific evidence from several studies does not established yet and still debated[10-15]. Therefore, in the current study, we aimed to determine the effect of GnRHa, goserelin, on the ovarian function of young female lymphoma patients < 40 years of age during and after combined chemotherapy treatment, (Goserelin has minimal invasive technique in preservation ovarian function which may help in various future implications).

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PATIENTS AND METHODS

Subjects: The present study is a randomized-control, parallel, open-label study designed by block randomization. We included 52 eligible (Figure 1) premenopausal women < 40 years, with a history of normal menstrual rhythms, and newly diagnosed with lymphoma, either Hodgkin or non-Hodgkin (any stage), confirmed by pathology, radiology, and Immunophenotyping (IPT). Twenty-eight patients were randomly and equally assigned to the goserelin group and control group. The reproductive functions of the patients were assessed by measuring the serum levels of FSH and E2 at the start of the treatment (baseline), 3- and 6-months during chemotherapy treatment, and 3 months after chemotherapy. AMH anti-Mullerian hormone was measured at base line and end of follow up. The regimens consisted of six to eight cycles of polychemotherapy received. The sample size was calculated based on previous studies in the field to ensure a power of 80% and a type I error probability of 5%, by calculating the following using statistical G*Power software version 3[16,17]:

Effect size d = xt – xc/S pooled

where d = Cohen's d effect size = mean (average of treatment or comparison conditions), s = standard deviation, t refers to the treatment condition, and c refers to the comparison condition (or control condition)[18].

In addition, relatively small numbers of women recruited in the study due to the cancer incidence in Egypt from the national population-based cancer registry program, which shows a low lymphoma incidence in females[19], and as far as we know, the largest RCT in young female lymphoma patients conducted in 15 oncologic centers in France, Belgium, and Italy, which analyzed 84 patients[7] (In addition high exclusion criteria, young age, female and fertile, so it is difficulty to involve participant with this particular condition). All patients were recruited from the Oncology Department at Beni-Suef University Hospital, Beni-Suef, Egypt. Written informed consent was obtained from all patients prior to their participation in the study. The study was performed according to the guidelines of the Declaration of Helsinki, and the study protocol was approved from an ethical point of view[20] and registered under Federal Wide Assurance (FWA) for Protection of Human Subjects. The study was granted Local Ethics Committee approval, from the Ethics Committee, Faculty of Medicine, Beni-Suef University, FWA#: FWA 00015574. Data on the complete medical and fertility history, and demographics were collected for all included patients.

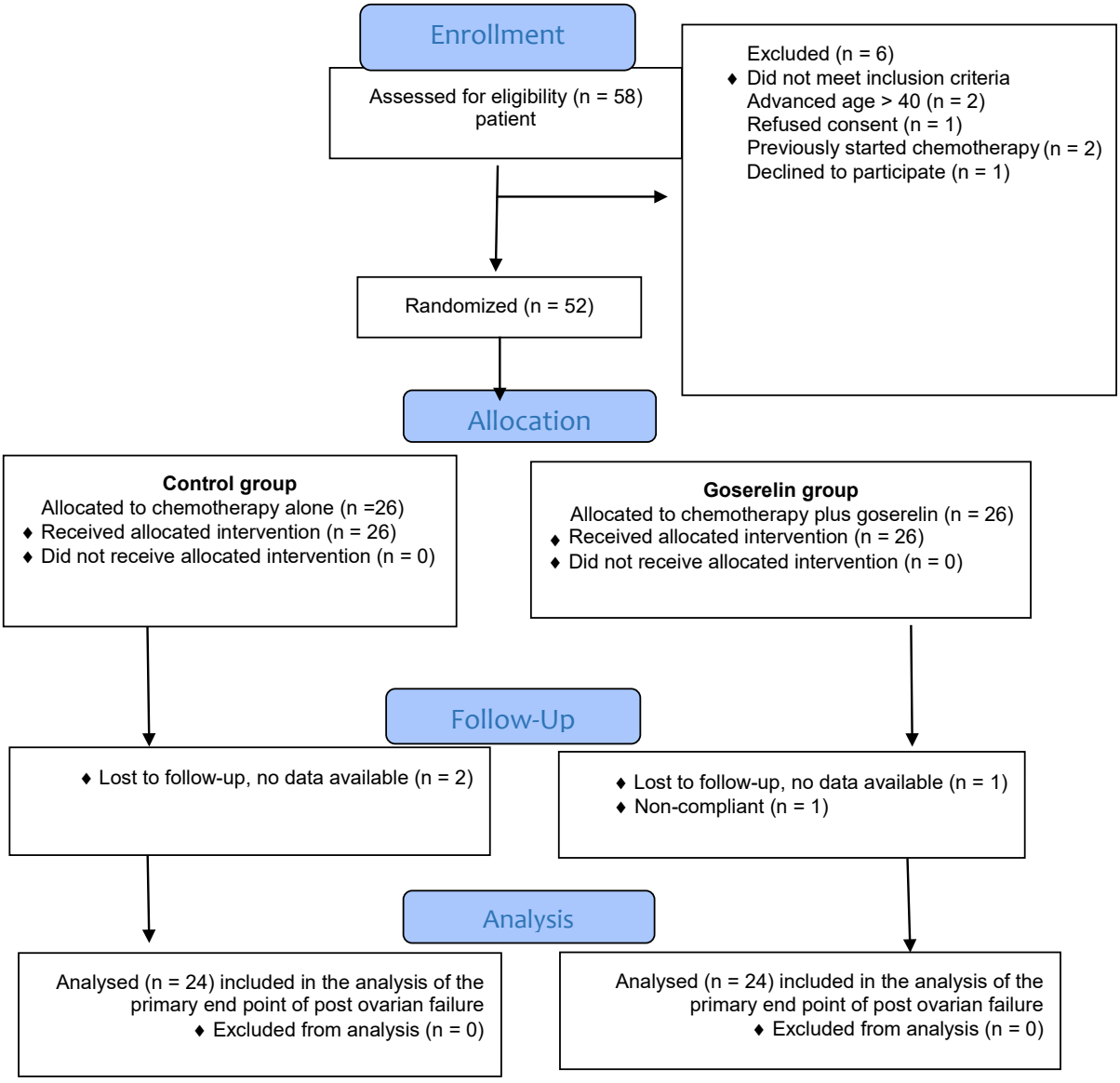

Figure 1: CONSORT Flow Diagram

Inclusion Criteria: The inclusion criteria were as follows: All lymphoma types, stages I–IV, premenopausal female patients between 17 and 40 years old, with normal menstruation and normal FSH levels (< 10 IU/L)[7,21]. Patients of childbearing potential were required to have a negative pregnancy test (urine or serum) in the 14 days prior to starting the study, and had to implement adequate non-hormonal contraceptive measures with an intrauterine device during the study period. Any use of hormonal contraceptives had to be discontinued in the month before enrollment and prior to the first goserelin injection[22].

Exclusion Criteria: Patients with primary ovarian dysfunction, a previous history of amenorrhea, and patients who were unlikely to comply with trial requirements (e.g., those with confusion, psychological or mood disturbances, alcoholism, vaginitis, vaginal bleeding, and cardiac arrhythmia) were excluded. Furthermore, patients who underwent hysterectomy or bilateral oophorectomy were categorized as "unable to be evaluated".

Study Design: Twenty-six eligible patients (Figure 1) received goserelin (Zoladex) 3.6 mg subcutaneous injection in the abdominal wall every 4 weeks (28 ± 3 days) plus standard chemotherapy at the start of the regimen for 6 months (goserelin group). The first dose was administered 10–14 days before the initiation of chemotherapy[23]. The other 26 eligible patients were administrated standard chemotherapy only for 6 months (control group). All of the patients in both groups received one of the standard chemotherapy protocols (Table 1)[24].

Table 1: Chemotherapy regimen

	Treatment regimen
ABVD	Doxorubicin 25 mg/m^2, IV, D1, D15 Bleomycin 10 units/m^2, IV, D1, D15 Vinblastine 6 mg/m^2, IV, D1, D15 Decarbonize 375 mg/m^2, IV, D1, D15 Repeat cycle every 4 weeks for 6–8 cycles
R+/R- CHOP	Rituximab 375 mg/m^2, IV, D1 Cyclophosphamide 750 mg/m^2, IV, D1 Doxorubicin 50 mg/m^2, IV, D1 Vincristine 1.4 mg/m^2, IV bolus (max dose 2 mg), D1 Prednisone 100 mg orally, D1–5 Repeat every 3 weeks for 6–8 cycles
CVP	Cyclophosphamide 750 mg/m^2, IV, D1 Vincristine 1.4 mg/m^2, IV bolus (max dose 2 mg), D1 Prednisone 100 mg orally twice daily, D1–5 Repeat every 3 weeks for 6–8 cycles

None of the patients received radiotherapy as a cotreatment. Blood sampling was performed, and FSH and E2 levels were measured before starting the treatment (baseline), for further follow-up every 3 cycles at 3 and 6 months (6–8 cycles), and 3 months after the completion of chemotherapy, AMH measured baseline and 3 months after the completion chemotherapy[7,25]. Blood samples were collected in venipuncture tubes without additives or anticoagulants; the samples were allowed to clot before being centrifuged to separate the serum from the cells. The serum FSH, E2 and AMH levels were evaluated by commercially available enzyme-linked immunosorbent assay kits (ST AIA-PACK; TOSOH Corporation, Tokyo, Japan)[26]. The overall response evaluation criteria in lymphoma (RECIL 2017) by[27] were followed and confirmed by computed tomography and positron emission tomography at 3 and 6 months of treatment. According to RECIL 2017, the disease response is divided into main five categories: complete response, partial response, minor response, stable disease, and progressive disease. Forty-eight patients completed the study, and two patients in the control group and one patient in the goserelin group were lost during the follow-up, with no available data. In addition, one patient in the goserelin group exhibited noncompliance relating to the invasive procedure of subcutaneous goserelin injection.

Outcomes

Primary Outcome: To measure ovarian function by evaluating hormonal changes in FSH and E2 levels, and assessment of clinical history (menstrual rhythm) 3 and 6 months during and after chemotherapy treatment, in addition AMH level was measured which is suitable marker of ovarian reserve in women treated for lymphoma[7]. In the current study, premature ovarian failure (POF) was defined as a serum FSH level > 30 IU/mL[28].

Secondary Outcome: To document the adverse effects during the study; only adverse events related to goserelin, or chemotherapy were routinely assessed, with assessment according to the Common Terminology Criteria for Adverse Events, version 5.0[29]. In addition, the study document disease overall response in both groups.

Statistical Analysis: Data analysis was performed using the Statistical Package of Social Science (SPSS) software version 22 in Windows 7. Simple descriptive analysis in the form of numbers and percentages was performed for qualitative data, and arithmetic means, as a central tendency measurement, and standard deviations (SD) were performed as a measure of dispersion for quantitative parametric data. Prior to selecting inferential statistic tests, the quantitative data were first tested for normality by the One-Sample Kolmogorov–Smirnov test in each study group. The Mann–Whitney test was used in comparing two independent groups. Kruskal-Wallis test was used to compare more than two independent groups, the chi-square test was used to compare between two or more qualitative groups, and the Mc-Nemar was used to test for paired dependent qualitative data. The general linear model was used to compare repeated measures, and the bivariate Pearson correlation test was used to test the association between quantitative parametric variables. P-values < 0.05 were considered to be statistically significant.

RESULTS

Patient Demographics and Obstetric History: The results of the current study showed there were no significant differences between the two study groups in terms of age, anthropometric measurements, and fertility history (Table 2). There was no correlation in anthropometric measures in different final hormonal levels at 3 and 6 months regarding FSH and E2 between all subjects. Moreover, there was no significant difference between the study groups with regards to the type and subtypes of lymphoma (Hodgkin HL or non-Hodgkin NHL), tumor staging, and chemotherapy regimen at baseline (Table 2).

Table 2: Comparisons of patient demographics, age, anthropometric measures, fertility history, tumor characteristics, and chemotherapy treatment in both study groups

Variables	Goserelin group (n = 24)	Control group (n = 24)
	Mean ± SD	Mean ± SD
Age (years)	28.7 ± 8.2	29.8 ± 8.3
Anthropometric measures		
Weight (kg)	61.5 ± 6.9	66.7 ± 18
Height (cm)	155.6 ± 4.1	160.3 ± 8.7
BMI (kg/m^2)	25.5 ± 2.9	25.6 ± 5.5
BSA (m^2)	1.6 ± 0.09	1.7 ± 0.23

Type of lymphoma					
NHL		14	58.3%	10	41.7%
HL		10	41.7%	14	58.3%
Diagnosis					
NHL	Diffuse large B cell	12	50%	10	41.7%
	Follicular T cell	2	8.3%	0	0%
HL	Mixed cellularity	6	25%	10	41.7%
	Nodular sclerosis	2	8.3%	4	16.7%
	Nodular lymphocyte predominant	2	8.3%	0	0%
Ann Arbor stage					
Stage I		0	0%	2	8.3%
Stage II		14	58.3%	16	66.7%
Stage III		4	16.7%	6	25%
Stage IV		6	25%	0	0%
Regimen of treatment					
ABVD		8	33.3%	14	58.3%
R/R CHOP		14	58.3%	10	41.7%
CVP		2	8.3%	0	0%

IUD: Intrauterine device; GnRHa: Gonadotropin-releasing hormone agonist; ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine; RCHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP: Cyclophosphamide, vincristine, and prednisone; GnRHa: Gonadotropin-releasing hormone agonist; NHL: Non-Hodgkin lymphoma; HL: Hodgkin lymphoma.

Ovarian Function Parameters: The present study revealed there were no significant differences between the two study groups regards to the basal level of FSH and E2. Chemotherapy treatment led to a significant elevation in FSH 3 and 6 months after the initiation of treatment, and after 3 months end of chemotherapy. Treatment with goserelin significantly alleviated this elevation nearly to the basal level value compared to the chemotherapy control group (Figure 2). In the control group, the percentage of females with a FSH level > 30 IU/L was 41.6% (n = 10) after 3 months and increased again after 6 months to 75% (n = 18). In the goserelin group, the percentage of females with a FSH level < 10 IU/L was 91.7% (n = 22) after 3 months and increased again after 6 months to 100% (n = 24) at end of chemotherapy treatment (Table 3). After 6 cycles of chemotherapy all patients in both groups developed amenorrhea, and menstrual recovery 3 months after chemotherapy was reported in only 25% (n = 6) of the control group patients compared to 83% (n = 20) in the goserelin group. Serum E2 at 3 and 6 months and after chemotherapy treatment showed no significant difference between groups, while E2 was significantly lower compared to baseline in both the control and goserelin groups (Figure 3). The mean AMH values were higher in the goserelin group compared with the control group 3 months after completion of chemotherapy treatment (Figure 4). The present study revealed there was no correlation between patient age at the random assignment for FSH values at the start of the study between the goserelin and control groups (r = -0.19 versus r = 0.04, respectively) and at 6 months follow-up (r = -0.02 versus r = - 0.29 respectively).

Table 3: Comparisons of FSH level in different study groups

FSH level	Goserelin (n= 24)		Control (n= 24)	
	No.	%	No.	%
Basal				
<10 IU/L (%)	24	100%	24	100%
11 to 29IU/L (%)	0	0%	0	0%
>30 IU/L (%)	0	0%	0	0%
After 3 months				
<10 IU/L (%)	22	91.7%*	4	16.7%*
11 to 29IU/L (%)	2	8.3%*	10	41.66%*
>30 IU/L (%)	0	0%	10	41.66%*
After 6 months				
<10 IU/L (%)	24	100%*	0	0%
11 to 29IU/L (%)	0	0%	6	25%*
>30 IU/L (%)	0	0%	18	75%*

*Significant difference at P-value < 0.05 between control group and goserelin group

Moreover, there was no significant difference regarding the effect of goserelin on FSH and E2 in different types of lymphoma, HL/NHL, as well as the tumor staging (I–IV) (Table 4). With regard to the degree of toxicity of the chemotherapeutic regimen, it was found that ABVD and R+/R-CHOP showed a similar effect on FSH and E2 in both groups during the follow-up period. Besides, there was no significant difference in disease response (Table 5).

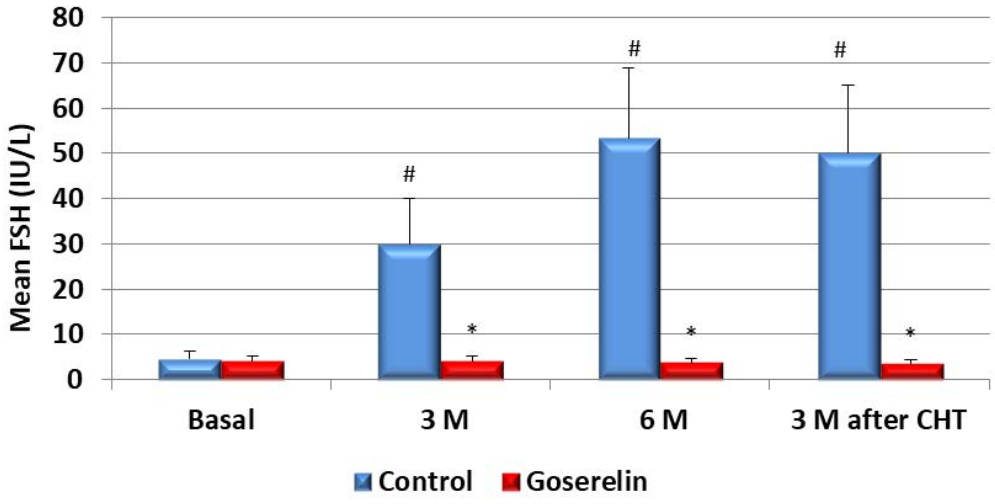

Figure 2: Follicle-stimulating hormone (FSH) levels in both study groups. Values are expressed as mean ± SD (standard deviation). *Significant difference at P-value < 0.05 compared to control group, #significant difference at P-value < 0.05 compared to basal level.

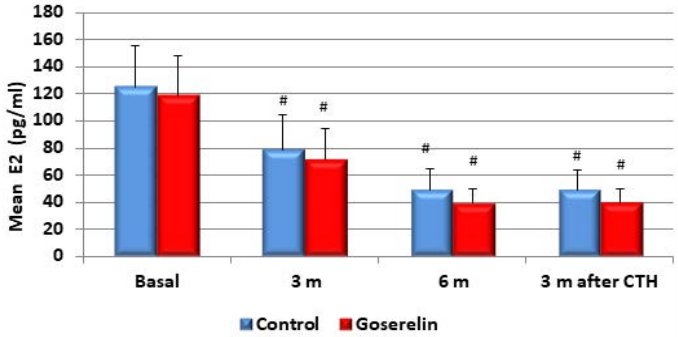

Figure 3: Estradiol (E2) level in both study groups. Values are expressed as mean ± SD (standard deviation) reveals no significant difference at P-value < 0.05 compared to control group. #Significant difference at P-value < 0.05 compared to basal level.

Table 4: Comparisons of hormonal levels in different types of lymphoma in the two groups

Control group	NHL (n = 10)	HL (n = 14)
	Mean ± SD	Mean ± SD
FSH level (IU/ml)		
Basal	3.7 ± 1.8	5.5 ± 1.9
After 3 months	34.9 ± 1.9	26.3 ± 9.9
After 6 months	58.2 ± 18.9	49.7 ± 14.3
3 months after end of CTH	56.2 ± 17.6	45.7 ± 13.2
E2 level (pg./ml)		
Basal	167.4 ± 48.3	118.4 ± 28.8
After 3 months	105.2 ± 37.9	70.6 ± 25.6
After 6 months	53.5 ± 11.5	45.5 ± 17.6
3 months after end of CTH	54 ± 11.2	45 ± 16.9
Goserelin group	NHL (n = 14)	HL (n = 10)
	Mean ± SD	Mean ± SD
FSH level (IU/ml)		
Basal	4.4 ± 1.3	3.5 ± 1.4
3 months	4.6 ± 0.99	3.5 ± 0.76
6 months	4.1 ± 1.2	3.04 ± 1.1
3 months after end of CTH	4.1 ± 1.15	3.1 ± 1
E2 level (pg./ml)		
Basal	136.1 ± 45.5	105.6 ± 30.6
After 3 months	79.5 ± 28	60.6 ± 27.7
After 6 months	32.8 ± 10.7	48.5 ± 13.7
3 months after end of CTH	34.7 ± 10.3	48 ± 13.1

Table 5: Comparisons of hormonal levels in different chemotherapy treatment regimens, and disease response

Control group	ABVD (n = 14)	R+/R- CHOP (n = 10)
	Mean ± SD	Mean ± SD
FSH level (IU/ml)		
Basal	5.5 ± 1.7	3.7 ± 1
After 3 months	26.3 ± 10.23	34.9 ± 9.4
After 6 months	49.7 ± 9.3	58.2 ± 12.9
3 months after end of CTH	45.7 ± 13.2	56.2 ± 17.6
E2 level (pg./ml)		
Basal	118.4 ± 28.8	167.4 ± 48.3
After 3 months	70.6 ± 25.6	105.2 ± 37.9
After 6 months	45.5 ± 17.6	53.5 ± 11.5
3 months after end of CTH	45 ± 16.9	54 ± 11.2
Disease response after 3 months		
Complete	0 0%	0 0%
Partial	14 100%	10 100%
Disease response after 6 months		
Progressive	2 14.3%	0 0%
Complete	8 57.1%	4 40%
Partial	4 28.6%	6 60%
Goserelin group	ABVD (n = 8)	R+/R- CHOP (n = 14)
	Mean ± SD	Mean ± SD
FSH level (IU/ml)		
Basal	3.1 ± 1.2	4.4 ± 1.3
After 3 months	3.5 ± 0.9	4.6 ± 0.99
After 6 months	3.5 ± 1.1	4.1 ± 1.2
3 months after CTH	3.5 ± 1.1	4.1 ± 1.1
E2 level (pg/ml)		
Basal	102.5 ± 25.4	136.1 ± 45.5
After 3 months	60.1 ± 18.1	79.5 ± 28.5
After 6 months	44.2 ± 17.4	32.8 ± 10.7
3 months after end of CTH	45 ± 17	34.7 ±10.3
Disease response after 3 months		
Complete	0 0%	0 100%
Partial	8 100%	14 100%
Disease response after 6 months		
Progressive	0 0%	2 14.3%
Complete	2 25%	6 42.9%
Partial	6 75%	6 42.9%

Disease Overall Response: The response was classified into three categories: progressive disease, partial response, and complete response. Neither group showed a significant response 6 months (6–8 cycles) after the end of chemotherapy (Figure 5). In addition, both groups reported the same final response, irrespective of the type of lymphoma (HL or NHL) and type of chemotherapy protocol.

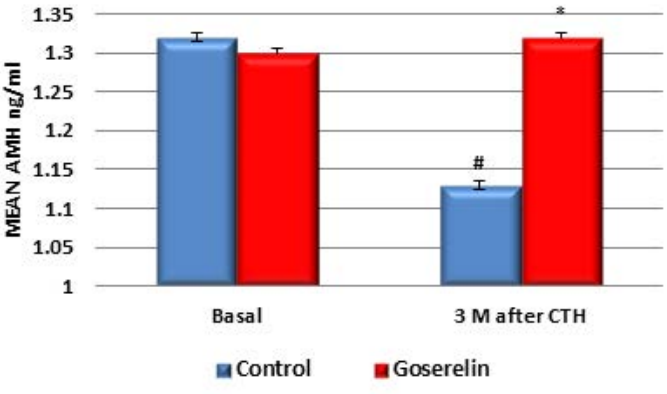

Figure 4: AMH anti-Mullerian hormone level in both study groups. Values are expressed as mean ± SD (standard deviation) reveals significant difference at P-value < 0.05 compared to control group. # Significant difference at P-value < 0.05 compared to basal level.

Adverse Effects: Symptoms associated with estrogen deficiency were observed during treatment, and both groups reported similar side effects, including hot flushes 75% (n = 18) (goserelin group) compared to 50% (n = 12) (control group). Vaginal bleeding was observed in the control group only (16.7%, n = 4), while headache was more common in the goserelin group than in the control group (50%, n = 12 versus 16.7%, n = 4, respectively) (Table 6). No severe or life-threatening toxicities occurred as a result of goserelin treatment, and no grade 3 or 4 toxic effects were reported (Table 6).

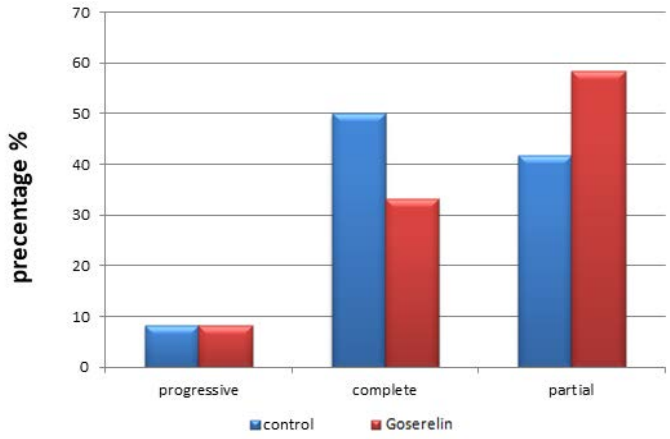

Figure 5: No significant difference at P-value < 0.05 between the control and goserelin groups in (progressive-complete-partial) responses after 6 months (6–8 cycles) follow up.

Table 6: Comparisons of treatment side effects in both study groups

Variables	Goserelin group n = 24				Control group n = 24			
	No.	%	Grade I %	Grade II%	No.	%	Grade I%	Grade II%
Sweating	12	50%	83%	17%	12	50%	100%	0
Hot flushes	18	75%	78%	22%	12	50%	83%	17%
Vaginal bleeding	0	0%	0	0	4	16.7%	50%	50%
Vaginal dryness	0	0%	0	0	0	0%	0	0
Headache	12	50%	66%	34%	4	16.7%	100%	0
Vaginitis	8	33.3%	75%	25%	8	33.3%	50%	50%

DISCUSSION

Many studies have demonstrated that young adult females with hematological malignancy who are treated with different regimens of chemotherapy experience ovarian failure and infertility[5,30]. This is in accordance with the results of the present study, which revealed that chemotherapy induced ovarian failure 3 and 6 months after treatment. Ovarian failure in the present study was evident by an elevation in FSH, which is used to evaluate the ovarian function[21]. We demonstrated that treatment with goserelin in addition to chemotherapy significantly alleviates this elevation compared to the control group, with no significant differences in the E2 levels at end of the 6 months during chemotherapy treatment and after chemotherapy, 3 months follow up period. In addition, we showed that the rate of POF in the control group was 75%, which is matched with previous studies that revealed a POF rate of 53.3% and 76.9% in chemotherapy-treated patients[11,31]. Similarly, Zhang et al. (2013) and Clowse et al., (2009)[32] confirmed the protective effect of GnRHa on ovarian functions in a meta-analysis study. The POF rate after Hodgkin's lymphoma ranges from 0% to 50%, depending on the woman's age and the chemotherapeutic protocol[33]. The current study reported higher ovarian reserve in goserelin group which matched previous study[34].

The current study observed no correlation between the patient age and the FSH levels at random assignment and at the end of the trial; this finding is in agreement with the previous study by Demeestere et al. (2013) but is in contrast to a previous study in breast cancer[35]. This difference may be due to a higher median age at the time of hormonal measurement, at 40 years (range, 32 to 49 years) versus the current study which was 30 years (range, 17 to 40 years). Furthermore, the adverse effects in the present study were similar in both groups, except for vaginal bleeding, which was more common in the control group. Indeed, this finding is in accordance with the results of Demeestere et al. (2013) and may confirm the role of goserelin in the reduction of uterine bleeding and in the control of the menstrual cycle[36]. Moreover, hot flushes and headache were reported more frequently in patients treated with goserelin, which is similar to a previous study in breast cancer (Moore et al., 2015). Besides, the current study reported the protective role of GnRHa, goserelin, in patients with Hodgkin's disease similarly to the results of Leonard et al., (2017), Castelo-Branco et al., (2007)[11,25].

The primary goal of lymphoma treatment is to achieve a high cure response with a low risk of infertility. The current study may go some way to confirm the safety and efficacy of goserelin related to different chemotherapeutic regimens, R+/R-CHOP and ABVD, as well as in patients with HL and NHL which shows no significance difference in both groups in ovarian function or disease response. We were unable to evaluate the CVP regimen in the current study because it was only given to two patients in the goserelin group[24,36] matched with the conclusion of the present study in that GnRH-a cotreatment may preserve ovarian function; however, Huser et al. (2015) and Blumenfeld et al. (2008) found that the decrease in the incidence of POF was only in the more aggressive protocols containing alkylating agents BEACOPP and MOPP/ABVD, but not in ABVD-treated patients. These differences may be explained by the differences in the design of both studies, as Huser et al. (2015) enrolled patients with advanced stages of HL (stage IV) and used high-dose and combination chemotherapeutic regimens (BEACOPP regimen), while Blumenfeld et al. (2008) enrolled a small series of ABVD-treated patients; thus, it is possible that a larger series may demonstrate such a difference. Moreover, the present study a revealed similar effect of goserelin in both subgroups with different tumor stages (I–IV) on ovarian functions; this subgroup analysis had some limitations as the study population were mainly in stage II (62.5% n = 30). In contrast to the current study, there is a proof incidence of ovarian damage in Hodgkin's lymphoma patients irrespective of GnRHa co-treatment[8]. This was a case control study which is limited by the lack of accurate matching of patients and controls in relation to the chemotherapy, and the small number of treated patients. The current study assess the resumption of menses, which found higher menstrual recovery percentage in goserelin group which matched with a previous study[21]. However, recovery of menses may require a longer follow-up after the completion of chemotherapy because menstrual activity may not the best surrogate of ovarian function, and FSH and E2 measurements may be more suitable[37]. The results of the present study are in contrast with the previous study in breast cancer[38], which demonstrated that GnRHa does not preserve the ovarian function as measured by the resumption of menses.

The impact of goserelin on the overall response in lymphoma is very crucial, and few studies have measured the overall response in hematological malignancies. The current study may confirm that goserelin had no effect in the overall disease response with no significant difference between both groups according to RECIL 2017 criteria at

the end of the trial period. Besides, the current study may confirms the safety of concurrent administration of goserelin with chemotherapy in patients with lymphoma, which is in accordance with a previous study that reported that goserelin administration did not adversely impact survival[39,40]. In addition, a systematic review by[41] showed that 20 studies were in support, and another 8 studies were against the use of GnRHa for fertility preservation. Blumenfeld and Evron, (2015) meta-analysis concluded that GnRHa cotreatment appears to improve the ovarian function and may decrease the risk of POF in most female patients exposed to gonadotoxic chemotherapy. This is similar to the present study and also matched with previous publications[42,43]. The main limitations of the present study are the small number of patients and the short duration of follow up.

CONCLUSION

Here in, we demonstrate that treatment of premenopausal young lymphoma patients with goserelin during cancer therapy may preserve the ovary from the gonadal toxic effect of chemotherapy regimens. However, further studies with a larger scale and a longer follow-up are required to fully validate our findings.

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