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Fertility after Treatment of Pediatric Hodgkin's Lymphoma [HL]

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ABSTRACT

To identify the long-term effect of chemo-radiotherapy on fertility in Hodgkin's disease (HD) patients regularly attending the pediatric oncology clinic of NCI, 42 long-term survivors (LTS) (33 males & 9 females) were studied, together with 26 newly-diagnosed (ND) HD patients (15 males & 11 females) and 28 healthy controls. During 3 years period, all patients subjected to through clinical history/ examination. Files of LTS were revised for date of diagnoses, original site(s), stage, histopathological subtypes and dose/ duration of therapy. Clinical examination was done with laying stress on visceromegaly and the presence of lymphadenopathy. Lab investigations included CBC, ESR, bone marrow biopsy and fertility hormones. Radiodiagnostic studies (plain X-ray, abdominal sonography, and chest/ abdominal/ pelvic CT scans) were done whenever indicated. In LTS the mean age was 14.9±3.4 yrs. (median 15.5 yrs) versus 9.5±3.7 yrs. (median 8.5 yrs) in ND patients. In LTS, treatment modalities included radiotherapy [RT] alone (2.4%), chemotherapy [CTH] alone [MOPP, ABVD, OPPA, and COPP] (26.2%) or combination chemo-radiotherapy (71.4%). The mean follow-up time was 7.47±2.19 yrs. (median 6.75 & 6.75 yrs.).

Increased incidence of high luteinizing hormone (LH) & follicle-stimulating hormone (FSH) and testosterone levels was found in patients who received therapy for one year versus those who received longer period, with no statistically significant difference. However, the mean values of pre-pubertal male LH and post- pubertal male LH& FSH were statistically significant difference among the three groups. Azoospermia was seen in 10/11 of LTS, with low testosterone in 2 only. Finally, the study documented that there is Azoospermia with affection of fertility hormones (in males) in LTS-HD patients. Recommendations regarding the comprehensive follow-up of therapy for HD were discussed. Endocrine consultation is needed for Survivors with concerns regarding fertility. Intervention strategies and new evidence-based surveillance of the long-term effects like screening for early detection of late effects, and chemoprevention are needed for dealing with HD, especially in children.

Keywords: Hodgkin's Lymphoma / Fertility

INTRODUCTION

The development of curative therapy for most pediatric malignancies has produced a growing population of childhood cancer survivors who are at increased risk for a variety of health problems resulting from their cancer or its treatment [35]. Many treatment-related sequelae may not become clinically apparent until the survivor attains maturity or begins to age [34, 68]. Contemporary, combined-modality therapy for pediatric HL, results in greater than 85% LTS [25]. Nearly 2/3rd of all of childhood

cancer survivors will suffer some late effect, and the endocrine system is commonly involved [65, 47, 44]. Reduced-intensity protocols for pediatric HL are aimed at preserving excellent relapse-free survival while decreasing the incidence of late effects [13]. Numerous investigators have reported the use of multiagent chemotherapy with or without low-dose (ie, less than 35 Gy) extended- or involved-field irradiation [55]. A common goal is to combine effective agents with non overlapping toxicities to optimize survival while minimizing therapy-related sequelae. Although most studies have achieved desired survival outcomes, data on late effects of therapy were waiting for LT follow-up studies [13]. As many as 40% of childhood cancer survivors may have endocrine disturbances related to their underlying malignancy, surgery, RT, or CTH [19, 65]. These factors are further modified by the age at which treatment was initiated, the length of time since treatment, and gender [39, 41, 44].

All therapeutic modalities [radiation (RD), surgery, or CTH] cause both germ cell depletion and abnormalities of gonadal endocrine function among male cancer survivors. RD to the testes is known to result in germinal loss with decreases in testicular volume and sperm production, and increases in FSH. Effects are dose-dependent, following fractionated exposures of 0.1 to 6 Gy. RT may also be toxic to Leydig cells, although at doses higher than those which are toxic to germ (Sertoli) cells [33]. As summarized by ***Sklar*** [62] Leydig cell damage is dose-dependent and inversely related to age at treatment. Boys treated pre-pubertally or peri-pubertally with > 20 Gy for testicular leukemia, in addition to suffering germ cell depletion, are at high risk of delayed sexual maturation associated with decreased testosterone levels, despite increased LH levels. Adolescent and young adult male testes are relatively radio-resistant, and fractionated doses greater than 30 Gy to the testes may induce Leydig cell failure in only about 50% of patients [4, 33]. Bilateral orchiectomy will, of course, result in infertility, as well as testosterone deficiency requiring ongoing hormonal replacement therapy beginning during puberty. These patients should be managed in collaboration with an endocrinologist [33]. In contrast to the process in male survivors, germ cell failure and loss of ovarian endocrine function occur concomitantly in females. RD effects are both age- and dose-dependent. In women older than 40 years at the time of treatment, irreversible ovarian failure is an almost universal result of 4 to 7 Gy of conventionally fractionated RD delivered to both ovaries. In contrast, prepubertal ovaries are relatively radio-resistant, and despite higher doses (12–50 Gy), primary amenorrhea and delayed puberty eventually occurred in only 68% of patients treated at a mean age of 6.9 years [66]. Secondary amenorrhea resulting from such modest doses appears to be reversible within several months to 4 years in 50% to 60% of patients [48]. Total body irradiation [TBI] (10 Gy single fractions) has been associated with primary amenorrhea and absent secondary sexual characteristics in most patients treated prior to puberty and followed for as long as 10 years [37]. However, others have reported normal pubertal progression although with elevated FSH levels following total body irradiation during early childhood [40]. As with standard RD, increasing age at the time of TBI has been found to predict ovarian failure [15]. Premature menopause has also been reported in the setting of hematopoietic cell transplantation [37,4].

In recent years there has been a significant increase in both acute and chronic toxicity associated with the more successful but now highly intensive CTH regimens used to treat childhood cancers [60]. Alkylating agents decrease spermatogenesis in a dose-dependent manner. Gonadal damage following cumulative doses of cyclophosphamide lower than 7.5 g/m^2 (or 200 mg/kg, as used in hematopoietic cell transplantation) have been shown to be reversible in up to 70% of patients after therapy-free intervals of several years. In contrast to their prominent effects on germ cell epithelium, chemotherapy effects are less striking on slowly dividing Leydig cells and may be age-related. Following exposure to alkylating agents in pre pubertal boys, normal pubertal progression and normal adult levels of

testosterone are the rule; gynecomastia with low testosterone and increased LH have been reported in patients treated during adolescence, and compensated Leydig cell failure (increased LH with low normal testosterone levels or exaggerated FSH and LH responses to LH-releasing hormone) without gynecomastia is common in adults [59, 4]. Although chemotherapy-related gonado-toxicity is seen less frequently in females than in males, ovarian failure has been associated with CTH, especially the alkylating agents, and the gonado-toxicity is dose-and age-dependent. Following myeloablative doses of alkylating agents, including busulfan and cyclophosphamide, permanent ovarian failure can be expected at all ages [53]. For survivors who retain normal ovarian function after cancer therapy, there is an increased risk of premature menopause later in life [63]. The risk factors associated with an early menopause include exposure to high doses of alkylating agents and abdomino-pelvic RD [4].

AIM OF THE WORK

The present study aimed to identify the late effects of RD and/or CTH on fertility of HD- LTS regularly attending the pediatric oncology clinic of National Cancer Institute (NCI), Cairo University, during 3 years period (inclusive).

PATIENTS AND METHODS

- The patients were classified into two groups:
  - ***1st group [LTS]:*** 42 patients (33 males and 9 females) who completed therapy for HD and off therapy more than 5 years. Their ages ranged from 9-22 years with a mean of 14.9±3.4 years and median age of 15.5 years. The mean follow up time was 7.47±2.19 years [median 6.75 & 6.75 years].
  - ***2nd group [ND]:*** 26 patients (15 males and 11 females) prior to any type of treatment. Their ages ranged from 4-15 years with a mean of 9.5±3.7 years and median age of 8.5 years.
  - ***The control group:*** 28 healthy age and sex matched normal children (15 males and 13 females).

- All patients were subjected to:
  - **Thorough clinical history/ examinations:** Files of the LTS were revised for the date of diagnosis and end of treatment, original site(s), staging, histopathological subtype and dose & duration of therapy. Clinical examinations were done laying stress on visceromegaly and the presence of lymphadenopathy.
  - Lab investigations included :
    - ***a-*** CBC and ESR done for all patients groups and controls.
    - ***b-*** Bone marrow aspirate and / or biopsy were done for ND and LTS only.
    - ***c-*** Fertility hormones:

    - Male fertility hormones: Testosterone hormone was measured in 35 LTS, [26 males & 9 females], 23 ND patients [15 males & 8 females] and 24 controls [13 males & 11 females].
    - Female fertility hormones:

    i- *Estrogen (E2):* was measured in 35 LTS, [26 males & 9 females], 20 ND patients [13 males & 7 females] and 27 controls [15 males & 12 females].

    ii- *Progesterone:* was measured in 34 LTS, [25 males & 9 females], 22 ND patients [14 males & 8 females] and in all controls.

    iii- *Follicle stimulating hormone [FSH]:* was measured in 32 LTS, [23 males & 9 females], 21 ND patients [14 males & 7 females] and 18 controls [9 males & 9 females].

iv- *Luteinizing hormone [LH]:* was measured in 33 LTS, [24 males & 9 females], 22 ND patients [14 males & 8 females] and 21 controls [10 males & 11 females].

- All hormones were done by RIA technique using MEDGENIX- DIAGNOSTICS kit and Gamma Counter.

d- Semen analysis: was performed in 11 LTS.

- Radiodiagnostic studies (plain X-ray, abdominal sonography, and chest/ abdominal/ pelvic CT scans) were done whenever indicated.
- **Ann Arbor Stage/sub-stage Classification for HD according to Hays** [22] was performed. Staging laparotomy was done in 15 LTS (5 were positive) and in 14 ND patients (7 were positive) to confirm the diagnosis and allow proper pathological staging.
- **Treatment modalities** are illustrated in tables (1&2). The chemotherapeutic regimens used alone or in combination were *MOPP* [Mechlorethamine, Oncovin, Procarbazine& Prednisone], *ABVD* [Adriamycine, Bleomycin, Vinblastine & Dacarbazine], *OPPA* [Adriamycine, Vincristine, Procarbazine & Prednisone], *COPP* [cyclophosphamide, Vincristine, Procarbazine & Prednisone].
- **Statistical analysis** was done using Statistical Package for Social Sciences (SPSS). Mean and standard deviation, Chi-square and Fisher exact test, t-test or Mann Whitney, ANOVA or Kruskal Wallis ANOVA was applied whenever indicated. P value was always two-tailed and is significant ≤ 0.05 **Winters et al** [71].

Table (1): Treatment modalities in LTS.

Type	No.	%	Total	%
Radiotherapy alone: (IF)			1	2.4
Chemotherapy alone:			11	26.2
MOPP	8	19.0		
MOPP + ABVD	1	2.4		
MOPP + Others	2	4.8		
Chemo-radiotherapy:			30	71.4
MOPP	12	28.5		
MOPP + ABVD	4	9.5		
OPPA	4	9.5		
MOPP + OPPA	2	4.8		
MOPP + OPPA + ABVD	2	4.8		
Other regimens	6	14.3		

Table (2): Radiotherapy schedule of LTS

Types of radiotherapy	No (%)	Dose of fractionated irradiation (Gy)
-Involved Field (IF)		
* Whole neck	18(58.1)	25-40
* Mediastinal	3 (9.7)	22-26
* Inguinal	2 (6.5)	22-40
-Mantle	1 (3.2)	23.5
-Inverted Y (IY)	4(12.9)	25-30
-Whole neck + Whole abdomen + IY	1 (3.2)	30 + 15 + 15
-Cranial irradiation + IY	1 (3.2)	24 + 25.2
-Whole neck + IY	1 (3.2)	34 + 36
Total	31 (100)	

RESULTS

The results of the present work are presented in tables (3-4).

- The presenting stage of the disease was stage I & III (35.7% for each) followed by stage II in LTS, versus stage I (34.6%) followed by stage II (30.8%) and III (30.8%) in ND patients.
- The predominant subtype of HD was similar in LTS and ND patients: mixed-cellularity (54.8%, 53.8%, respectively) followed by nodular sclerosis (21.4%, 26.9%, respectively).
- Increased incidence of elevated LH, FSH and testosterone levels was found in patients who received therapy for one year, when compared to those who received longer period, with no statistically significant difference. Moreover, there was no statistically significant difference, as regards the type of therapy, on the levels of sex hormones in LTS. However, statistically significant difference were established among the 3 groups, regarding the mean values of the pre-pubertal and post- pubertal male LH levels [p= 0.002 & p= 0.02, respectively], male post- pubertal testosterone [p= 0.02] (table 3&4).
- Azoospermia was seen in 10/11 of LTS [all were > 13 years], with low testosterone in two of them. All received chemo-radiotherapy, except one patient who had chemotherapy alone (MOPP).
- For the female sex hormones (table 3), statistical analysis could not be evaluated because of the small sample size.

Table (3): Hormonal profiles in the 3 groups

	Hormones Mean±SD	LTS Mean ±SD	ND Mean ±SD	Control Mean ±SD	P value
Male Sex Hormones	**Pre-pubertal**				
	Estrogen	11 (21.1±16.0)	9 (48.7±42.9)	11 (33.6±26.3)	0.27 N.S.
	Progesterone	10 (1.0±0.2)	10 (1.0±0.2)	11 (0.9±0.8)	0.06 N.S.
	FSH	8 (144±80.2)	10 (136.5±82.2)	6 (438.2±610.2)	0.9 N.S.
	LH	9 (165.7±65.8)	10 (275.5±89.8)	6 (336.5±141.1)	0.002 H S
	Testosterone	11 (1.0±2.8)	11 (0.1±0.1)	9 (0.3±0.4)	0.5 N.S.
	Post-pubertal				
	Estrogen	15 (40.9±26.2)	4 (52.2±7.0)	4 (18.9±13.8)	0.6 N.S.
	Progesterone	15 (1.0±0.4)	4 (1.2±0.1)	4 (0.7±0.3)	0.09 N.S.
	FSH	15 (18.8±25.6)	4 (29.3±0.9)	3 (75.6±73.3)	*
	LH	15 (45.7±39.9)	4 (285.5±19.7)	4 (519.2±629.3)	0.02 S
	Testosterone	15 (3.4±1.7)	4 (0.4±0.2)	4 (1.8±1.3)	0.02 S
Female Sex Hormones	**Pre-pubertal**				
	Estrogen	2 (45.5±14.2)	6 (47.1±5.9)	5 (38.7±8.6)	--------
	Progesterone	2 (2.0±2.0)	7 (1.1±0.7)	5 (0.6±0.4)	
	FSH	2 (20.7±9.7)	6 (180.9±258.3)	5 (59.2±18.0)	
	LH	2 (54.4±53.9)	7 (306.4±83.8)	5 (293.6±134.2)	
	Testosterone	2 (0.2±0.2)	7 (0.1±0.1)	5 (1.0±1.7)	
	Post-pubertal				
	Estrogen	7 (202.8±210.5)	1 (56.0)	7 (152.0±169.3)	--------
	Progesterone	7 (5.8±12.0)	1 (0.8)	8 (14.7±25.2)	
	FSH	7 (19.9±19.1)	1 (39.1)	4 (207.8±294.2)	
	LH	7 (41.5±57.7)	1 (273.3)	6 (100.3±103.7)	
	Testosterone	7 (0.3±0.1)	1 (0.03)	6 (0.5±0.3)	

* Comparison between groups could not be done because of small number of patients.
Comparison between female groups could not be done because of small number of subgroups

NS= not significant HS= highly significant S= significant

Table (4): Effect of duration and type of therapy on sex hormone long-term survivors

	< 1 year No. (%)	1-3 years No. (%)	> 3 years No. (%)	X^2 value	Chemo-radio-therapy No. (%)	Chemo-therapy No. (%)	X^2 value
Estrogen							
Normal	16 (76.2%)	3 (50.0%)	7 (87.5%)	N.S.	18 (75.0%)	7 (70.0%)	0.590
high	2 (9.5%)	2 (33.3%)	1 (12.5%)		4 (16.7%)	1 (10.0%)	N.S.
low	3 (14.3%)	1 (16.7%)	0 (0.0%)		2 (8.3%)	2 (20.0%)	
Progesterone							
Normal	8 (38.1%)	2 (40.0%)	5 (62.5%)	N.S.	11 (47.8%)	4 (40.0%)	0.678
High	13 (61.9%)	3 (60.0%)	3 (73.8%)		12 (52.2%)	6 (60.0%)	N.S.
Low	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
FSH							
Normal	8 (40.0%)	2 (40.0%)	5 (71.4%)	N.S.	12 (57.1%)	3 (30.0%)	0.157
High	12 (60.0%)	3 (60.0%)	2 (28.6%)		9 (42.9%)	7 (70.0%)	N.S.
Low	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
LH							
Normal	5 (23.8%)	0 (0.0%)	1 (14.3%)	N.S.	6 (27.3%)	0 (0.0%)	0.067
High	16 (76.2%)	5 (100%)	6 (85.7%)		16 (72.7%)	10(100%)	N.S.
Low	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Testosterone							
Normal	11 (50.0%)	4 (66.7%)	3 (42.9%)	N.S.	12 (50.0%)	5 (50.0%)	0.801
High	1 (4.5%)	0 (0.0%)	0 (0.0%)		1 (4.2%)	0 (0.0%)	N.S.
Low	10 (49.5%)	2 (33.3%)	4 (57.1%)		11 (45.8%)	5 (50.0%)	

N.S = Not significant.

DISCUSSION

Effective risk-based therapy for the management of childhood cancer in the setting of clinical trials has been the cornerstone of the tremendous progress in overall survival seen over the last four decades, with 5-year survival rates now at 80% [28, 33]. The use of cancer therapy at an early age can produce complications [33]. It has been demonstrated quite conclusively that LTS of childhood cancer carry a high burden of morbidity, with one third of survivors reporting severe or life-threatening complications 30 years after their primary diagnosis [46]. Furthermore, these long-term sequelae can potentially have an adverse effect on the overall quality of life of the survivors [33], such as impairment

in growth and development, cardiopulmonary compromise, endocrine dysfunction, renal impairment, gastrointestinal dysfunction, musculoskeletal sequelae, and subsequent malignancies, and, not only related to the specific therapy employed, but may also be determined by individual host characteristics [5].

Survivors from HD are at high risk of late complications. Reduced fertility can follow exposure to cyclophosphamide, especially in the male. RT to the para-aortic and iliac lymph nodes can affect gonadal function both in males and females; concomitant CTH with alkylating agents like cyclophosphamide and especially procarbazine have a synergistic action and can lead to premature menopause as well as infertility [67]. Impaired fertility is most profound in survivors of HD compared to survivors of other types of malignancy [14]. Disruption of sexual activity occurred in 25.8% of treated early-stage HD patient [10]. Testicular injury included damage to the germinal epithelium and the Leydig cells [23]. In the present work, a statistically significant difference was established between the 3 studied groups, regarding pre-pubertal and post-pubertal male LH levels, and male post-pubertal testosterone. ***Bramswing et al*** [8] studied 75 boys treated with 0-6 courses of OPPA and COPP- CTH, all had normal pubertal development. However, 24% had elevated basal LH, and 88% had elevated stimulated LH, indicating CTH-induced Leydig cell damage. Additionally, 41% showed indicating severe spermatogenesis impairment. ***Bramswig et al*** [8] and ***Heikens et al.*** [23] reported elevated basal LH levels (in 24%) despite apparently normal pubertal development and testosterone levels in all patients. This was comparable with the present study, with 31.3% and 22.6% elevation of LH and FSH, respectively. The devastating effects of CTH are mainly attributable to Mechlorethamine and Procarbazine, which form a part of MOPP combination therapy [23]. The ABVD regimen has proved to be superior in disease control without permanent gonadal damage [11]. However, some reports suggested that the pre-pubertal testis was less sensitive than the post-pubertal testis to damage by chemotherapy [59, 51], but others have questioned this observation [27, 3, 14, 21].

In the present work, increased incidence of elevated LH, FSH, and testosterone levels was found in patients who received therapy for one year, when compared to those who received longer period, with no statistically significant difference. None of the patients who received CTH alone had raised serum testosterone level. ***Kinsella et al.*** [32] reported no evidence of Leydig cell injury [as measured by LH & testosterone level] following low-dose scatter irradiation (0.2-0.7) on testicular function of adult males treated for HD. However, the same workers detected a dose- dependant rise in serum FSH values, with a maximum at 6 months after irradiation that returned to normal in all patients within 12-24 months following irradiation. At higher doses of scatter irradiation (0.5-25 Gy) in adult men treated for soft tissue sarcoma, a dose-dependant elevation of both LH and FSH was demonstrated. A gradual decline without normalization was seen 30 months after doses >2 Gy to testis with no alteration in testosterone levels. Following BMT, individuals who received RD were more likely to develop an elevated FSH level over time than those who had, received no preparative RD treatment [42].

In the current work, 10/11 of LTS who had semen analysis showed azoospermia for 5-9 years. Ten patients received chemo-radiotherapy; the remaining LTS had CTH alone. However, low testosterone was documented only in two patients. It seemed that the germinal epithelium is more sensitive than Leydig cells [2]. This was in agreement with ***Shafford et al.*** [57] and ***Mustieles et al.*** [43] they indicated that the prepubescent testes are not protected from the greater risk of permanent damage to germinal epithelium as pubescent ones. However, preservation of spermatogenesis is age-related. Since chemotherapeutic agents generally affect the more

metabolically active cell-lines, CTH-induced damage is proportional to gonadal activity at the time of treatment [23]. Severe damage to the testicular germinal epithelium frequently follows treatment which includes an alkylating agent and procarbazine [57, 14, 38, 29]. Azoospermia was present in all men by the start of the third cycle of nitrogen mustard, vinblastine, or vincristine, procarbazine, and prednisone CTH (It occurred less frequently following treatment with two, rather than six, cycles). Less than 20% had recovery of spermatogenesis when evaluated 37 to 48 months after treatment [21,29]. The combination of doxorubicin, bleomycin, vinblastine, and dacarbazine produced oligo- or azoospermia frequently during the course of treatment, but recovery of spermatogenesis occurred after treatment was completed [70]. The administration of cyclophosphamide has been associated with impaired spermatogenesis after treatment of children for nonmalignant [69, 21], and malignant [49, 50] diseases. Azoospermia was reported after cumulative cyclophosphamide doses as low as 6.0 g/m^2 [31] whereas spermatogenesis was preserved after cumulative doses as high as 16 g/m^2 [3]. Impaired spermatogenesis was more likely after cumulative doses exceeding 7.5 to 9.5 g/m^2 [49, 21]. Furthermore, a cumulative cyclophosphamide doses used in contemporary regimens for HD is (3.2 to 4.8 g/m^2). [56, 21] However, men who are azoospermic after CTH can be treated with microdissection testicular sperm extraction (TESE) and intracytoplasmic sperm injection (ICSI) [24]. Unfortunately, the recovery of spermatogenesis following CTH is generally poor, partial recovery was seen at 10 years in a range of 0-20% [14]. ***Santoro et al.*** [54] reported azoospermia in all patients treated with MOPP- CTH with recovery of spermatogenesis occurring in 1/10 patients 36 months after first semen analysis. Recovery of azoospermia was linked to the dose of the maximum dose compatible with it [14]. On the other hand, the Stanford series, where 10/12 (83%) of boys treated with 6 MOPP cycles with or without irradiation were azoospermic with no evidence of recovery after 11 years of follow-up [48]. Moreover, ***Charak et al.*** [12] reported azoospermia in 100% of the male patients treated by 6-10 cycles of COPP, 97% had testicular atrophy and 100% of testicular biopsies showed germinal aplasia. Serum FSH showed 3-fold rise, while serum LH had moderate rise. In the present work, serum LH showed 2-3 fold rise in all azoospermic patients, FSH was high in 7/ 10(70%) of the patients.

The dose of fractionated irradiation given in the present work was 4-40 Gy. This was in agreement with ***Shalet et al.*** [58] who reported oligo- or azoospermia in 8/10 of men treated by doses of 2.68- 9.83 Gy at the age of 1-11 years. Only one had elevated LH with low plasma testosterone level. Also, ***Green et al*** [21] demonstrated impaired fertility of male childhood cancer survivors in who received a testicular RD- dose of more than 7.5 Gy, and were treated with procarbazine or cyclophosphamide, or had a summed alkylating agent. On the other hand, ***Donaldson and Kaplan*** [17] reported that 3 out of 5 boys, who received pelvic irradiation without CTH at the age of = 15 years, had fathered normal children. The effect of testicular irradiation is highly dose-dependent. At doses of 1-3 Gy, azoospermia may be reversible; at 3-6 Gy, this reversibility is much less likely. Over 6 Gy, the patient is likely to suffer from permanent azoospermia. Doses >20 Gy may cause Leydig cell damage and affect production of testosterone [44]. Previous studies reported that recovery of spermatogenesis was unlikely after single-dose exposures exceeding 4.0 Gy [52, 30] or low-dose fractionated exposures [9, 6]. Loss of both spermatogenesis and androgen secretion occurred at high doses (= 24.0 Gy); [9, 6, 36, 61] lower-dose exposures may not produce azoospermia [57, 14]. Leydig cell function may be preserved when the testicular dose is = 20.0 Gy [64,30,21].

Risks of adjuvant therapy depend on age of the patient at treatment, as well as dose, site, and type of treatment given. Additionally, although CTH and RTH potentially impart individual risks, a combination of both may be additive. With CTH regimens, alkylating agents such as cyclophosphamide seem to present the greatest risk of ovarian failure, likely because they are non–

cell-cycle specific and can damage even "resting" oocytes and their support cells in the ovary [29]. Ovarian dysfunction is rare in pre-pubertal and pubertal girls given intensive CTH without pelvic irradiation [7]. The chance of maintaining gonadal function following combined modality treatment appears to be much greater among girls than boys [1]. Meanwhile, following BMT (for pediatric and adult hematological malignancies including HD), 92% of males and 99% of females developed evidence of gonadal dysfunction [42]. Females were more likely to develop earlier elevated gonadotrophin levels while males were more likely to experience gonadal recovery [42]. In the present work, comparing the female sex hormones between the 3 groups could not be done because of the small number of patients. Meanwhile in the Stanford series, none of the girls who had pelvic irradiation without oophoropexy has maintained ovarian function [1]. In fact, the effect of RD on ovarian function is related to both RD-dose and age at treatment. Some premenstrual girls treated with doses as high as 20-30 Gy may express subsequent ovarian function, although most, if not all, will experience premature ovarian failure [18]. Unfortunately, Gonadotropin deficiency that leads to secondary deficits in estrogen and testosterone occurs with high-dose RD (=40 Gy) to the neuroendocrine axis [26]. Hypogonadism caused by gonadal RD occurs at much lower RD-doses, and as with alkylator therapy, the risk varies with gender and pubertal status [62]. Ovarian dysfunction and premature menopause are associated with RD-doses of =10 Gy to the ovaries in prepubertal females and =5 Gy in pubertal females [62, 26]. In males, although small doses (1–6 Gy) of RD to the testes are associated with germ-cell failure, higher doses (=20 Gy) are required to cause Leydig cell dysfunction with associated androgen insufficiency [62, 26, 68]. However, acute ovarian failure (AOF) occurred in 6.3% of eligible survivors. Exposure of the ovaries to high-dose RD (especially over 10 Gy), alkylating agents and procarbazine, at older ages, were significant risk factors for AOF. Premature nonsurgical menopause (PM) occurred in 8% of participants versus 0.8% of siblings. Risk factors for PM included attained age, exposure to increasing doses of RD to the ovaries, increasing alkylating agent score, and a diagnosis of HL [20].

Finally the present study concluded that, after a mean follow-up time of 7.47 ± 2.19 years, there is a significant impairment in fertility in Egyptian HD-LTS. Azoospermia with affection of the fertility hormones was seen in males as a late effect of therapy. Predicted disruption of sexual activity and financial loss are of major concern has been reported in the study of ***Brierley et al.*** [10]. The growing population of childhood cancer survivors carries a significant burden of morbidity, necessitating comprehensive long-term follow-up of these survivors. This follow-up should ideally begin at the completion of active therapy, with a documented summarization of therapeutic exposures [33, 47]. Particular attention should be paid to the irradiated sites in post treatment follow-up [45]. On the other hand, Survivors of pediatric HD require cancer screening [16, 72]. Hormonal evaluation, including at least a single measurement of serum LH, FSH, and testosterone levels, is recommended as a baseline at age 14 years and in boys in whom puberty appears to be delayed. Males at risk of infertility may benefit from semen analysis. When abnormalities in testicular function are detected, close cooperation with an endocrinologist is essential in planning hormonal replacement therapy or in monitoring patients for spontaneous recovery [4]. The diagnostic evaluation of ovarian dysfunction relies on history. Serum gonadotropin (FSH, LH) and estradiol levels should be obtained as a baseline at age 13 years and as clinically indicated, in the absence of clinical evidence of puberty, in order to assess the need for hormone therapy to induce puberty. Survivors with concerns regarding fertility are urged to seek consultation with reproductive endocrinologists [4].

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