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BACKGROUND: The survival rate of young patients with cancer has greatly improved in the last decades, in part due to the introduction of new therapeutic agents and protocols.

Chemotherapy during puberty has been associated with permanent or transient amenorrhea, symptoms of ovarian insufficiency or infertility. The rates of ovarian dysfunction range from 11-37%. It has been reported that prepubertal ovary is less susceptible to the deleterious effect of chemotherapy.

Pre-clinical studies suggested that hormonal suppression of the hypothalamic-pituitary-ovarian axis could minimize the impact of cytotoxic agents on the ovary. The effectiveness of gonadotropin-releasing hormone agonists (GnRHa) in preventing the impairment of ovarian function due to exposure to cytotoxic agents in pubertal girls is still controversial.

AMH is expressed by the ovarian granulosa cells of primary, preantral and small antral follicles. It is independent of gonadotropins, representing an ideal surrogate for ovarian reserve. AMH has been employed as a useful marker of ovarian damage in girls treated for cancer.

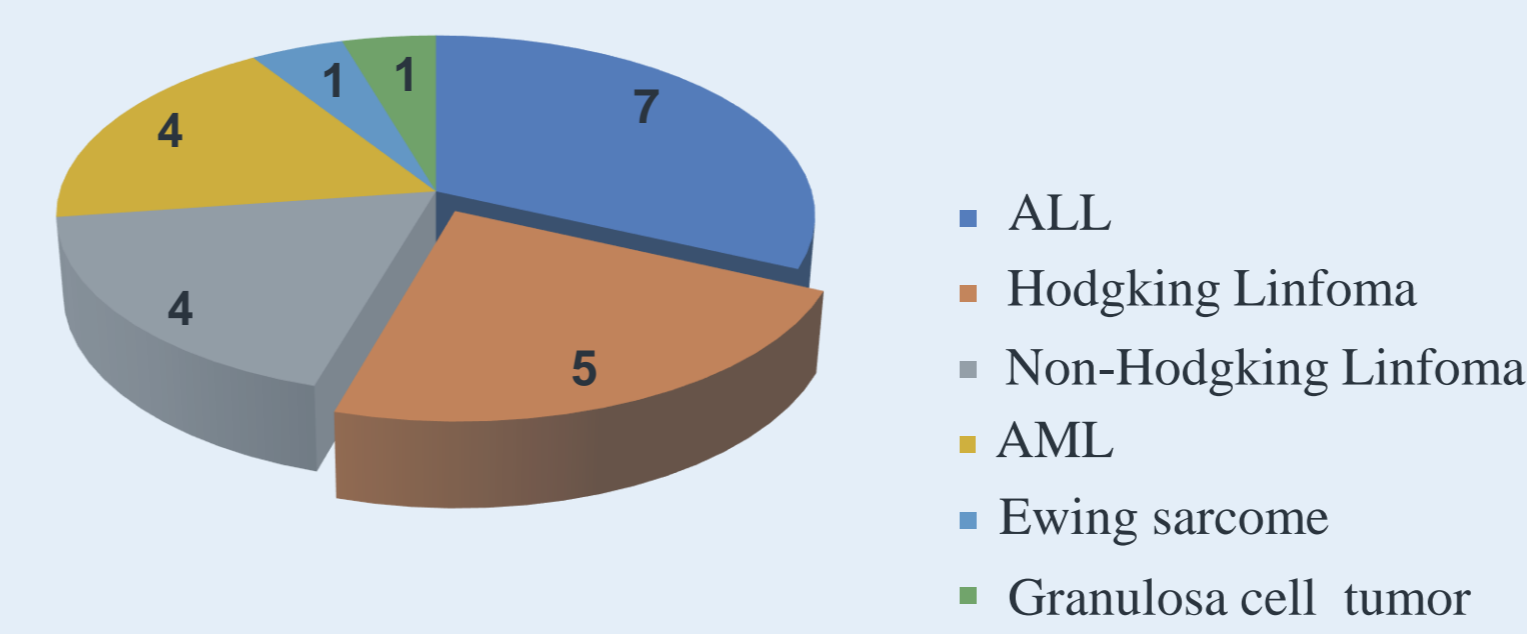
OBJECTIVE: To evaluate long-term ovarian function specially by AMH measurement in female adolescents with history of malignant diseases treated with chemotherapy at prepubertal or pubertal stage.

MATERIAL AND METHODS

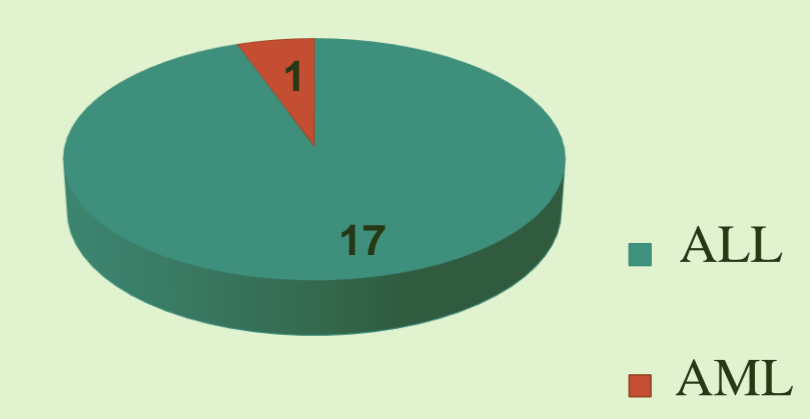
A transversal study was conducted. Female adolescent patients with history of malignancy who received chemotherapy were evaluated at least two years after menarche. Gonadal function evaluation was done by a questionnaire, clinical examination, gonadotropins (ECLIA) and AMH (ELISA) levels after at least two-years of treatment withdrawal.

RESULTS

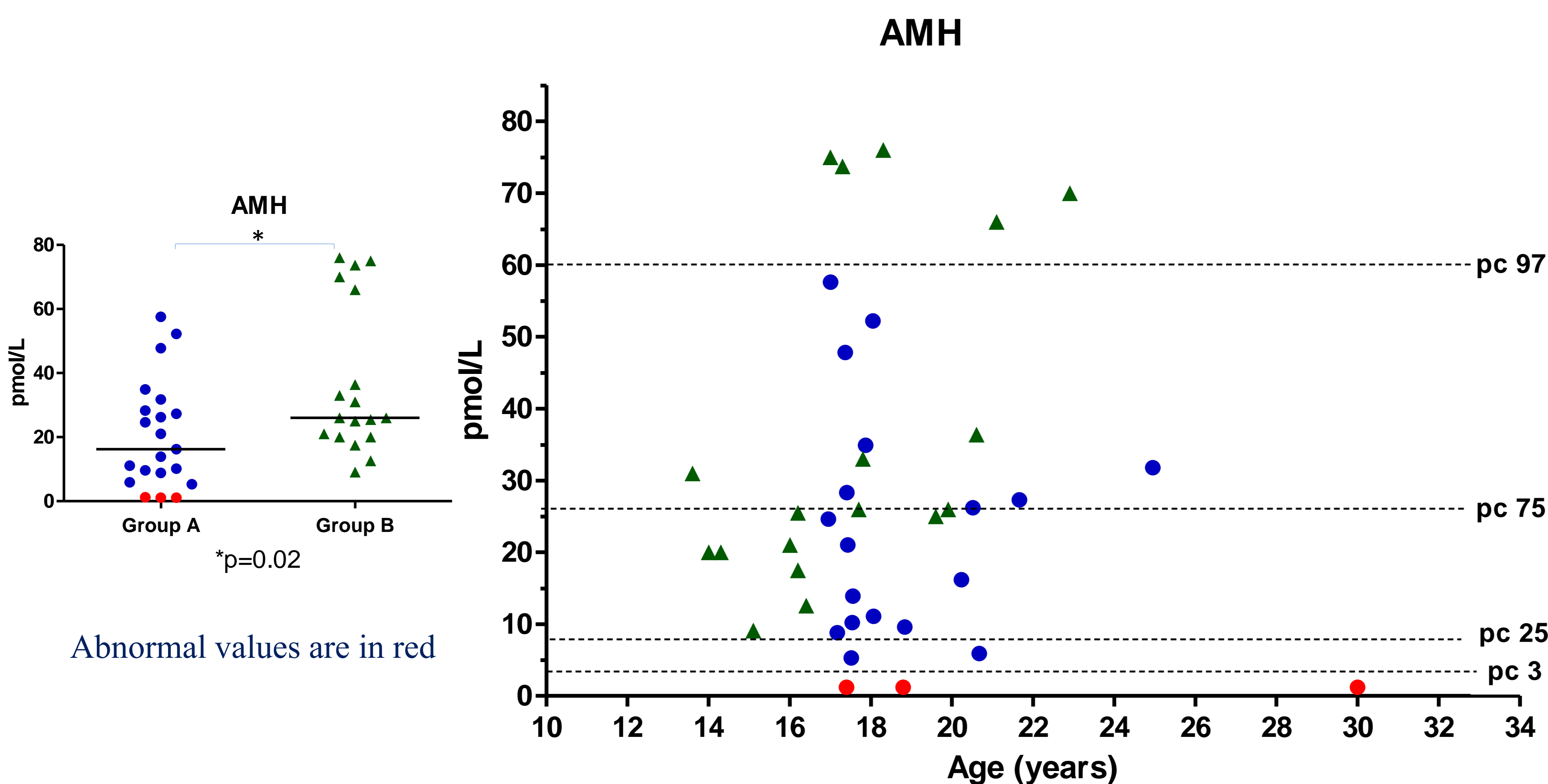
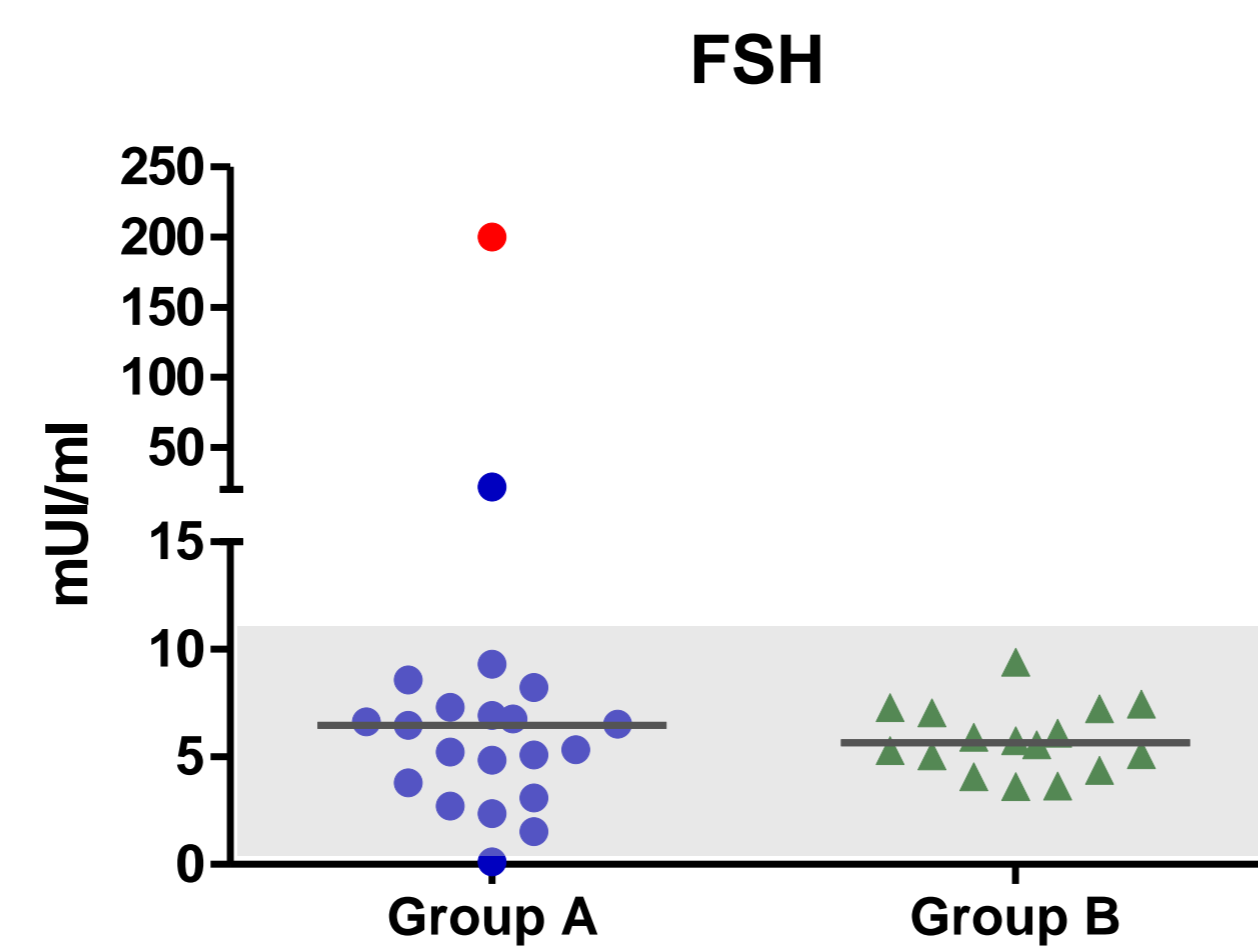
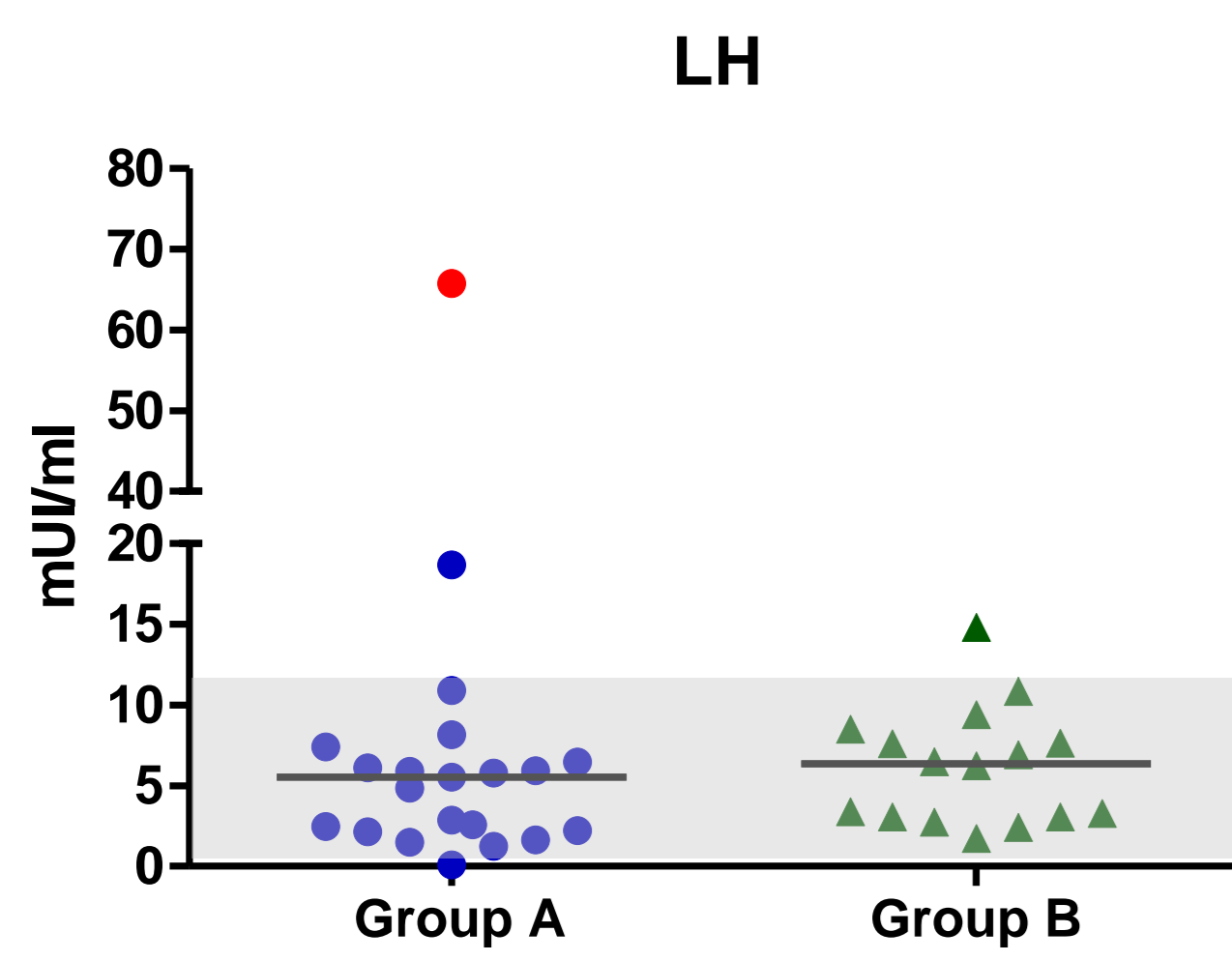
Group A: n=21 Patients treated throughout puberty who received chemotherapy concomitant with GnRHa



Group B: n= 18 Patients treated at Prepuberty only with chemotherapy.



ALL: Acute lymphoblastic leukemia; ALM: Acute myeloid leukemia



	Group A (n=21)	Group B (n=18)	P
Chronological age at diagnosis (years, y)	14.3 (9.2-18.1)	6.0 (0.5-10.5)	<0.001
Age at evaluation (y)	17.5 (17.0-30.0)	17.0 (13.6-22.9)	ns
Menarcheal age (y)	12.4 (10.0-15.0)	12.0 (10.2-14.7)	ns
Regular menses (n)	20/21	18/18	ns
Hot flushes (n)	1/21	0/18	ns
LH mIU/ml	5.7 (1.2-65.7)	6.4 (6.8-14.8)	ns
FSH mIU/ml	6.5 (0.11-200)	5.7 (3.6-9.4)	ns
AMH (pmol/L)	16.2 (1.2-57.6)	26.0 (9.1-76)	0.02

Data are expressed as median and range. Statistics: Mann Whitney test was used.

Most patients in our cohort had AMH within normal levels according to age, except for 3 in group A who showed undetectable AMH levels representing a rate of 7.7% with ovarian dysfunction.

AMH levels were significantly lower in group A in comparison with group B. Serum LH and FSH were within normal levels in both groups except in one patient from group A, who had primary ovarian insufficiency. Three patients from group A achieved fertility.

CONCLUSION

In this long term evaluation study, prepubertal girls who received chemotherapy and pubertal girls who received chemotherapy concomitantly with GnRHa showed low rates of ovarian dysfunction. AMH levels were lower in patients who received chemotherapy in pubertal stage than in those treated in prepubertal stage. This finding could be explained as a consequence of different treatments employed, although a physiological decrease of follicular reserve by effect of age cannot be ruled out.

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