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Anti-Müllerian Hormone is a Useful Marker of Gonadotoxicity in Girls Treated for Cancer: A Prospective Study

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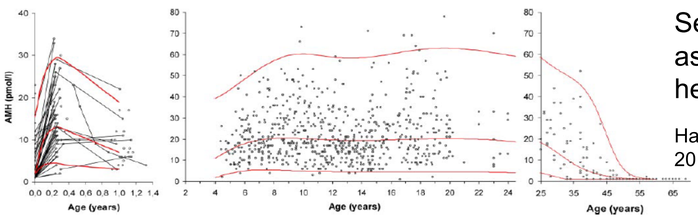
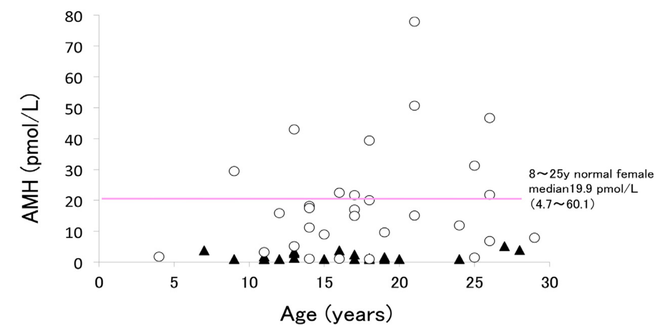
Background: Gonadal dysfunction is one of the major endocrinological late effects among childhood cancer survivors (CCS). Measurements of anti-Müllerian hormone (AMH) concentration are useful as markers of ovarian reserves in female CCS.
Objective: To investigate variations in serum AMH levels to determine the acute and chronic effects of cancer therapy
Method: A prospective study in three female patients with hematological diseases
Results: <Case 1> Patient with myelodysplastic syndrome. Received chemotherapy and reduced intensity stem cell transplantation (SCT) at 10 years old, AMH (ng/mL): 1.48 (pre) → <0.10 (1-9 months post-SCT) → 0.9 (12m) → 0.34 (15m) → <0.1 (18-36m). Breast development and menarche occurred spontaneously after SCT.
<Case 2> Patient with acute lymphocytic leukemia. Chemotherapy: 11y8m~, AMH: 1.85 (pre) → <0.10 (0m post-tx) → 1.46 (3m) → 0.6 (6-18m) → 1.24 (24m) → 1.55 (30m). Menstruation continued regularly.
<Case 3> Patient with acute myelocytic leukemia. Cancer therapy: 13y11m~, Chemotherapy and myeloablative stem cell transplantation, AMH: 1.41 (pre) → 0.88 (during therapy) → <0.10 (0-24m post-SCT). Became amenorrheic post-treatment.
Conclusion: Different patterns of AMH during the recovery phase supported the significance of longitudinal studies. AMH levels after cancer treatment were low in tthe patient with spontaneous puberty, whereas gonadotropin did not increase. The timing of measuring AMH should not be just after the end of therapy for the CCS.

Previous reports



Serum levels of anti-Müllerian hormone as a marker of ovarian function in 926 healthy females from birth to adulthood

Hagen CP *et al*. J Clin Endocrinol Metab 95:5003–10, 2010.



Triangles and circles indicate patients who underwent (n = 23) and did not undergo (n =30) HSCT, respectively.

Serum AMH levels in female CCS

These values were measured more than two years after cancer therapy.

Among 53 female CCS, 28 (53%) had decreased AMH levels, while only 16 (30%) had increased FSH levels.

Miyoshi Y, *et al*. Horm Res Paediatr 79:17-21, 2013.

Background and Aim

- An increasing number of pediatric and adolescent patients with cancer survive and treatment-related infertility is one of the most important issues among late treatment-related complications (late effects). We previously reported endocrinological abnormalities in 82 (67%) out of 122 survivors and gonadal dysfunction in 60 (49%) patients in our hospital [Endocr J, 2008]. It is difficult to predict reproductive capacity in childhood, because gonadotropins are not informative before puberty.
- In this regard, the plasma concentration of **anti-Müllerian hormone (AMH)** may be helpful. AMH is secreted by ovarian granulosa cells. The levels of this hormone remain stable between puberty and perimenopause but decreases with aging, reflecting the number of follicles, i.e., ovarian reserves. AMH levels decrease after chemotherapy and radiotherapy; therefore, AMH is currently considered to be a useful indicator of long-term impact of cancer therapy on reproduction capacity in female childhood cancer survivors (CCS) [Horm Res Paediatr, 2013].
- The aim of this study was to investigate **variations in serum AMH levels** to determine the acute and chronic effects of cancer therapy.

Patients and Methods

- We conducted a prospective, longitudinal study before and after different cancer therapies from January 2012. The ethical committee of Osaka University Hospital approved this study. Written informed consent for evaluation was obtained from the parents of the patients.
- The medical records of three female patients with hematological diseases were reviewed. Patients were questioned regarding age at the time of breast development and details regarding menstruation.
- We measured basal plasma concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2). The concentrations of AMH were measured using highly sensitive ELISA assays (AMH Gen II).
(AMH Gen II (ng/mL)＝0.189 × EIA AMH/MIS (pmol/L) -0.334 : SRL)
- We did not perform trans-vaginal ultrasounds to measure ovary antral follicle count because of the young age of the patients or because consent was not obtained.

Results

<Case 1> Pt w/ myelodysplastic syndrome (MDS)
Chemotherapy and reduced intensity stem cell transplantation (SCT) at 10y0m
Fludarabine (FLU) 150 mg/m²
Melphalan (L-PAM) 180 mg/m²
Thelarche: 11y1m (12 months after SCT)
Menarche: 12y5m (28 months after SCT)

Age		FSH mIU/mL	LH mIU/mL	E2 pg/mL	AMH ng/mL	AMH pmol/L	Breast Tanner
10y0m	pre-SCT	5.5	0.4	14	1.48	9.6	1
10y4m	3m	2	0.2	<10	<0.1	<10	1
10y6m	6m	28	7.8	<10	<0.1	<10	1
10y10m	9m	0.4	<0.2	<10	<0.1	<10	1
11y1m	12m	9	1.1	<10	0.9	6.5	2
11y3m	15m	3.1	1.2	<10	0.34	3.6	3
11y6m	18m	12	3.9	25	<0.1	<10	3
11y10m	21m	12	4.9	19	<0.1	<10	3
12y0m	24m	9.4	5.6	15	<0.1	<10	4
12y6m	30m	9.7	1.4	69	<0.1	<10	menarche
13y0m	36m	2.6	0.5	18	<0.1	<10	4

<Case 2> Pt w/ acute lymphocytic leukemia (ALL)
Chemotherapy: 11y8m~
Cyclophosphamide (CPA) 3350 mg/m²
Pirarubicin (THP) 120 mg/m²
Etoposide (VP-16) 1200 mg/m²
Vincristine (VCR) 7 mg/m²
Methotrexate (MTX) 20 g/m², Ara-C 32 g/m²
Menstruation continued regularly from 9y of age.

Age		FSH mIU/mL	LH mIU/mL	E2 pg/mL	AMH ng/mL	AMH pmol/L	Breast Tanner
11y8m	Pre-tx	4.1	0.9	13	1.85	11.6	4
11y11m	On tx	22.6	19.1	27	0.31	3.4	4
12y2m	0m post-tx	38.1	7.8	<10	<0.1	<10	4
12y5m	3m	8.4	5.2	29	1.46	9.5	4
12y8m	6m	11.4	3.1	50	0.72	5.6	4
12y11m	9m	6.4	5.3	43	0.61	5	4
13y2m	12m	5.3	4.5	30	0.66	5.3	4
13y9m	18m	4.7	6	35	0.68	5.4	4
14y2m	24m	8.7	5.1	29	1.24	8.3	4
14y8m	30m	6.1	7.8	109	1.55	9.9	4

<Case 3> Pt w/ acute myelocytic leukemia (AML)
Chemotherapy: 13y11m~
Myeloablative stem cell transplantation: 14y6m
Total body irradiation 12 Gy
Melphalan (L-PAM) 180 mg/m²
Etoposide (VP-16) 1250 mg/m², Mitoxantrone (MIT) 70 mg/m²
Idarubicin (IDA) 10 mg/m², Cytarabine (Ara-C) 69.4 g/m²
Gemtuzumab ozogamicin (GO) 3mg/m²
Menarche at 12y0m. Estrogen replacement therapy (ERT) was started at 16y5m due to the post-treatment amenorrhea.

Age		FSH mIU/mL	LH mIU/mL	E2 pg/mL	AMH ng/mL	AMH pmol/L	Breast Tanner
13y11m	Pre-tx	9.5	9.7	30	1.41	9.22	4
14y4m	On tx	156.7	48.7	<10	0.88	6.42	4
14y5m	Pre-SCT	173.2	72	<10	<0.1	<10	4
14y9m	3m post-SCT	192.1	114.7	<10	<0.1	<10	4
15y0m	6m	162.4	49.2	<10	<0.1	<10	4
15y3m	9m	192.4	56.9	<10	<0.1	<10	4
15y8m	14m	175	66.9	<10	<0.1	<10	4
16y0m	18m	142.4	64.2	<10	<0.1	<10	4
16y6m	24m	97.9	35.7	85 (ERT)	<0.1	<10	4
17y1m	31m	93.6	29.9	33 (ERT)	<0.1	<10	4

Conclusion

- A marked and prompt decrease in AMH levels was observed. Post-treatment AMH was low in the patient with spontaneous puberty, whereas gonadotropin levels did not increase.
- Different patterns of AMH during the recovery phase supported the significance of longitudinal studies. The optimal timing for measuring serum AMH levels is not just after the end of cancer therapy for CCS.
- This study may help to better understand ovarian toxicities associated with cancer therapy and may help predict the needs for hormone replacement therapy and fertility counseling in the future.

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Estimated risk of gonadal dysfunction with cytotoxic drugs

High risk	Medium risk	Low risk
Cyclophosphamide	Cisplatin	Vincristine
Ifosfamide	Carboplatin	Methotrexate
Chlormethine	Doxorubicin	Dactinomycin
Busulfan		Bleomycin
Melphalan		Mercaptopurine
Procarbazine		Vinblastine
Chlorambucil		

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