

Hormone replacement therapy regimens in chemotherapy-induced premature ovarian failure and the subsequent correction of hormone levels

Klaudia STANGEL-WÓJCIKIEWICZ¹, Alexander ZDEBIK², Robert JACH¹, Hubert HURAS³, Katarzyna WADOWSKA-JASZCZYŃSKA¹, Małgorzata RADOŃ-POKRACKA³, Ewa KEMPISTY-ZDEBIK⁴, Artur LUDWIN¹, Inga LUDWIN¹

1 Department of Gynecology and Oncology, Collegium Medium Jagiellonian University of Kraków, Poland

2 School of Medicine in English, Faculty of Medicine, Jagiellonian University Medical College Kraków, Poland

3 Department of Obstetrics and Perinatology, Collegium Medium Jagiellonian University of Kraków, Poland

4 Family Practice Office, Frankfurt am Main, Germany

Correspondence to: Klaudia Stangel-Wójcikiewicz
Department of Gynecology and Oncology,
Collegium Medium Jagiellonian University of Kraków,
Ul. Kopernika 23, 31-501 Kraków, Poland.
TEL: +48 12 424 85 60; E-MAIL: ksw@cm-uj.krakow.pl

Submitted: 2012-05-24 *Accepted:* 2012-09-02 *Published online:* 2012-12-01

Key words: **premature ovarian failure; gonadotoxic therapy; hormone replacement therapy; menopause; infertility**

Neuroendocrinol Lett 2012; **33**(7):697-702 PMID: 23391877 NEL331012A03 © 2012 Neuroendocrinology Letters • www.nel.edu

Abstract

OBJECTIVES: Premature ovarian failure (POF) is a consequence of gonadotoxic chemoradiotherapy given in antineoplasia treatment. In young women it will correlate with menopausal symptoms which tend to appear due to depleted ovarian follicle reserve.

DESIGN: It was a case series study that included women 18–50 years old who were treated for malignancy with gonadotoxic chemioradiotherapy. We have measured blood hormonal levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) and progesterone within one month of various hormone replacement therapy (HRT).

RESULTS: We have observed different kind of hormonal reaction according to FSH, LH, estradiol and progesterone levels due to various hormonal replacement therapy. The administration of various HRT regimens presented with a decrease in the blood concentration of estradiol E2 and progesterone and a concomitant increase of FSH and LH. These findings demonstrate a shift to physiological ranges and a simultaneous improvement of symptoms associated with CI-POF.

CONCLUSIONS: The most appropriate therapy needs to be selected according to the patient's alleviation of symptoms and correction of blood hormone levels.

INTRODUCTION

Chemotherapy for hematological cancers is associated with Premature Ovarian Failure (POF). The gonadotoxic effect may be temporary or permanent. Women who were administered high doses of antineoplastic treatment experience so-called Chemotherapy-induced Premature Ovarian Failure (CI-POF) (Beard *et al.* 1984; Wang *et al.* 2010) due to depleted ovarian follicle reserve. The estrogen and progesterone depleted patient suffers from premature menopause with hot flashes (Heinz 2010), osteoporosis (Amarante *et al.* 2011), vaginal dryness, amenorrhea (Tfayli & Arslanian 1998), dyspareunia, infertility (Moline *et al.* 2005) and psychological disturbances (De Vos *et al.* 2010; Maclaran *et al.* 2010). POF is often treated with hormone replacement therapy (HRT) (Cartwright *et al.* 2010; Mulder 1999). The purpose of this study was to measure hormonal levels of patients who underwent chemotherapy for various hematological disorders. Various HRT plans were used for the correction of hormone levels and symptoms of CI-POF (Verschuuren *et al.* 2006).

MATERIALS AND METHODS

This was a case series study that included women 18–50 years of age who were treated with gonadotoxic chemotherapy at the Hematology Department of the University Hospital in Kraków, Poland between June 2003 and December 2009.

33 patients were included in the study. Diagnoses, various treatment regimens and duration of treatment were evaluated. Inclusion criteria of patients were being female, 18–50 years old, treated for malignancy with various gonadotoxic chemotherapy regimens (Kreuser *et al.* 1992). For Hodgkin lymphoma (Chapman *et al.* 1979; Haukvik *et al.* 2006; Verschuuren *et al.* 2006) BEACOPP (Grigg 2004) (Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procar-

bazine and Prednisone) and ABVD (Lee *et al.* 2008) (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) was administered (Mackie *et al.* 1996; Clark *et al.* 1995). For non-Hodgkin lymphoma (Lee *et al.* 2008) CHOP (Kreuser *et al.* 1992) (Cyclophosphamide, Hydroxydaunorubicin, Vincristine and Prednisone) and for essential thrombocytosis hydroxyurea were given, respectively. In some cases radiotherapy (Larsen *et al.* 1988; Kreuser *et al.* 1992) was necessary. Radiation therapy doses were between 20–35 Gy. Consistent loss of ovarian function may result from single doses of 8 Gy or fractionated doses of 15 Gy. Patients were also required to have completed a minimum duration of one year after the treatment without any relapses of their primary hematological disease.

Clinical evidence of ovarian failure was conducted. Estradiol (E2) and progesterone were evaluated as well as follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels. Blood hormone levels were drawn at first patient presentation and at one month of hormonal replacement therapy (HRT).

Various types of HRT were administered according to the patient's main complaint.

Patients without any contraindications to HRT were given orally administered HRT. In cases of contraindications to oral HRT intake (history of hepatic dysfunction or dyspepsia), transdermal and subcutaneous administration were considered. In women complaining of vaginal dryness and concomitant dyspareunia as well as frequent urinary tract infections (UTI), intravaginal forms of HRT (estradiol or estriol) were the choice of treatment.

Patients have been evaluated according to the following measures (Table 1):

1. Demographic information
2. menopausal symptoms
3. Estriol E2 (estradiol), progesterone, FSH, LH
4. HRT type
5. Time of treatment (1 month)

In 33 patients hormone Levels of FSH, LH, E2 (estradiol) and progesterone were measured. The data were collected upon first visit and after one month. All serum measurements were performed in the same laboratory using the same assays.

The patients presented with various types of POF symptoms. The most common hot flashes, vaginal dryness, amenorrhea, dyspareunia and signs of osteoporosis. We have also observed affective symptoms such as depression and mood disorders. Due to hormonal imbalances patients have experienced infertility.

Gynecological examination and transvaginal ultrasound were performed in all patients. The myometrium was normal. There were no repository follicular structures in the ovarian tissue. The endometrium remained atrophic.

All 33 patients have elevated FSH and LH levels at the beginning of the study. Estradiol levels were between

Tab. 1. Demographic and clinical information

| | |
|--|------------------------------|
| Number of Patients (n) | 33 |
| Mean age, years \pm 1 SD | 32.96 \pm 11.87 |
| Mean age at diagnosis, years \pm 1 SD | 26.67 \pm 9.6 |
| Mean time since end of treatment, months \pm 1 SD | 23.54 \pm 8.47 |
| Previous pregnancies | 20/33 women |
| Chemotherapy type | See Materials and Methods |
| Radiotherapy (radiation doses between 20-35 Gy in all patients) | 6/3 women |
| Hematopoietic stem cell transplantation (subsequent immunosuppressive therapy with prednisone) | 31/33 women |

<5.0–110.9 pg/ml (mean level: 21.07 ng/ml). Progesterone levels were between 0.3–1.87 pg/ml (mean level: 0.8 ng/ml).

FSH levels were very variable and between 5.0–187.4 mIU/ml (mean level: 90.65 mIU/ml). LH levels were between 2.6–128.2 mIU/ml (mean level: 60.97 mIU/ml).

Only two patients presented with regular cycles despite the above-mentioned results. Mean age at the diagnosis of hematological disease was 26.67 years and the mean time since the end of radio- and chemotherapeutic treatment was 23.54 months.

20 patients delivered more than once. All of those pregnancies took place before the presentation of the hematological disease.

Various hormonal replacement therapy (HRT) regimens were prescribed in all patients. This included combinations of oral and transdermal HRT, only transdermal HRT, only oral HRT, subcutaneous HRT and other combinations as well as intravaginal administration of HRT.

The aim was to decide which drug regimen provides the fastest correction of hormone concentration and best improvement in symptoms characteristic of CI-POF.

The following 22 drug regimens were used:
Categories of drug administration:

I. Transdermal and oral combinations:

1. Climara® 50 mg (transdermal), Provera® 5 mg (oral)
2. Climara® 50 mg (transdermal), Provera® 10 mg (oral)
3. Climara® 50 mg (transdermal), Duphastone® 10 mg (oral)
4. Evra® (transdermal), Gynofer® (oral)
5. Femostone 7 Combi® (transdermal)
6. Oesclim® 25 mg (transdermal), Provera® 5 mg (oral)
7. Oesclim® 50 mg (transdermal), Provera® 5 mg (oral)
8. Oesclim® 50 mg (transdermal), Duphastone® 10 mg (oral)
9. Femostone® 2/10 mg (oral)
10. Oesclim® 50 mg (transdermal), Lutein 3® (oral)

II. Only transdermal combinations:

1. Oesclim® 25 mg
2. System Sequi®
3. System Conti®

III. Only oral combinations:

1. Diane® 35 mg
2. Duphastone® 10 mg
3. Lutenyl® 5 mg (Nomegestrol), Tri-Minulet®
4. Provera® 5 mg, Gynofer®
5. Orgametril® (Lynestrenol)

IV. Subcutaneous combinations:

1. Depo-Provera® (subcutaneous)

V. Intravaginal and other combinations:

1. Ovestin® (intravaginal ovula), Depo-Provera® (subcutaneous)
2. Provera® 5 mg (oral), Menofemme® (oral), Ovestin® (intravaginal ovula)
3. Vagifem® (intravaginal pill)

Changes in hormone concentrations of estradiol, progesterone, FSH and LH were measured with various above-mentioned drug regimens. 31 of 33 patients reported a subjective improvement in at least one of the CI-POF symptoms. All patients reported to be compliant with the treatment regimen.

Six out of 33 patients have taken the drug regimen with 50 mg Oesclim® (Estradiol), Provera® (Medroxyprogesterone). 2 patients have been administered Depo-Provera® (Medroxyprogesterone) alone.

2 patients have taken 25 mg of Oesclim® and Provera®, and 2 patients have taken Oesclim® 50mg and Duphastone® (Dydrogesterone). All other individual patients have taken one of the remaining drug regimens.

Figure 1 depicts the results for the concentration of estradiol in the beginning of the study (red column) and its concentration after one month (blue column). The shaded green area describes the normal serum concentration of estradiol of healthy women during reproductive age.

The results show that various drug regimens present with variable final results in the concentration of estradiol. Elevation of this hormone from “below normal” levels to over 100 pg/ml was observed.

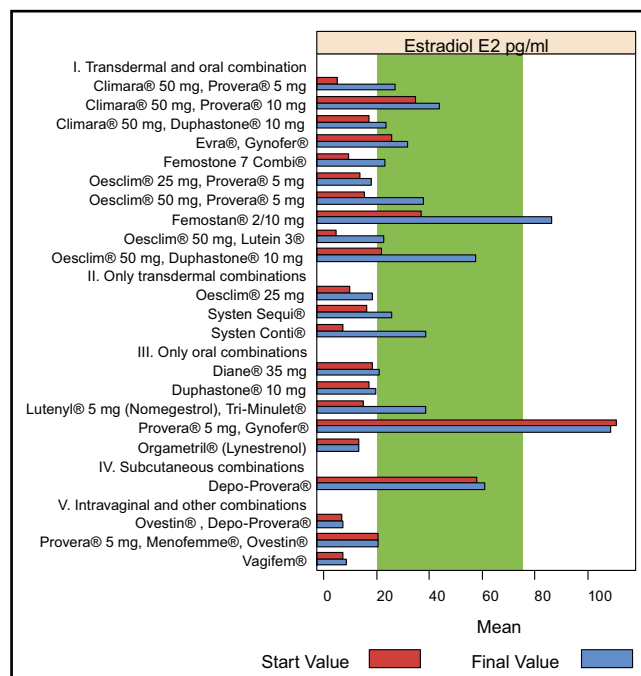


Fig. 1. Effects on estradiol E2.

A drug regimen showing a rise of <20% in the measured estradiol concentration may be designated as mildly effective in CI-POF, a drug regimen showing a rise of 20–50% as moderately effective and a rise of >50% within a month is highly effective in the correction of estradiol levels.

The following list presents which drug regimen has the best measurable efficacy in elevating the serum concentration of estradiol within one month of daily drug intake:

Mild Efficacy:

- Depo-Provera®
- Diane® 35
- Duphastone® 10 mg
- Evra®, Gynofler®
- Oesclim® 25 mg, Provera® 5 mg
- Ovestin®, Depo-Provera®
- Vagifem®

Moderate Efficacy:

- Climara® 50 mg, Provera® 5 mg
- Climara® 50 mg, Duphastone® 10 mg
- Oesclim® 25 mg

High Efficacy:

- Climara® 50 mg, Provera® 5 mg
- Femoston 7 Combi®
- Lutenyl® 5 mg, Tri-Minulet®
- Oesclim® 50 mg, Duphastone® 10 mg
- Femoston® 2/10 mg
- Oesclim® 50 mg, Lutein 3®
- Oesclim® 50 mg, Provera® 5 mg
- System Conti®

The best improvement was observed with the administration of the drug Femoston® 2/10 mg. This drug combination attained an improvement of approximately 133.5% above baseline in the serum estradiol concentration. The measured starting value rose from 37 pg/ml to 86.4 pg/ml throughout the study.

Therefore, the drug regimen of choice for a quick relief in CI-POF was oral Femoston® 2/10 mg.

Similar to estradiol E2, the results show an elevation of progesterone (Figure 2).

A drug regimen <20% in the measured hormone concentration may be designated as mildly effective, a rise of 20–50% as moderately effective and a rise of >50% as highly effective. The following list presents which drug regimen has the best measurable efficacy in elevating the serum concentration of progesterone:

Mild Efficacy:

- Diane® 35 mg

Moderate Efficacy:

- Lutenyl®, Tri-Minulet®

High Efficacy:

- Climara® 50 mg, Provera® 5 mg
- Climara® 50 mg, Duphastone® 5 mg
- Femoston 7 Combi®
- Oesclim® 50 mg
- Oesclim® 50 mg, Provera® 5 mg
- Orgametril® (Lynestrenol)
- System Conti®
- Provera® 5 mg, Menofemme®, Ovestin®
- System Sequi®

The best and fastest improvement in blood progesterone concentration was achieved with the oral drug Orgametril®. This drug attained an improvement of approximately 196% in the blood progesterone concentration within one month of administration. The measured starting value rose from 0.54 pg/ml to 1.6 pg/ml throughout the study. Other highly effective drug regimens were Femoston 7 Combi® with a blood progesterone concentration elevation of 178% from 0.57 pg/ml to 1.59 pg/ml and Provera® 5 mg, Menofemme®, Ovestin® with a blood progesterone concentration of 154% from 0.67 pg/ml to 1.7 pg/ml.

Therefore, the drug regimen of choice for relief in the treatment of CI-POF with focus on below normal values of blood progesterone concentration is Orgametril®. The second-line drug regimen is the combination of orally given Provera® 5 mg and Menofemme® with intravaginal Ovestin® in ovular form.

Drug regimens used for the alleviation of symptoms of CI-POF present with a negative feedback effect on the gonadotrophic hormones FSH (Figure 3) and LH (Figure 4). Most of the drug regimens used do not reduce elevated FSH levels in CI-POF to normal values of <20 mlU/ml (Day 3). The only drug combinations

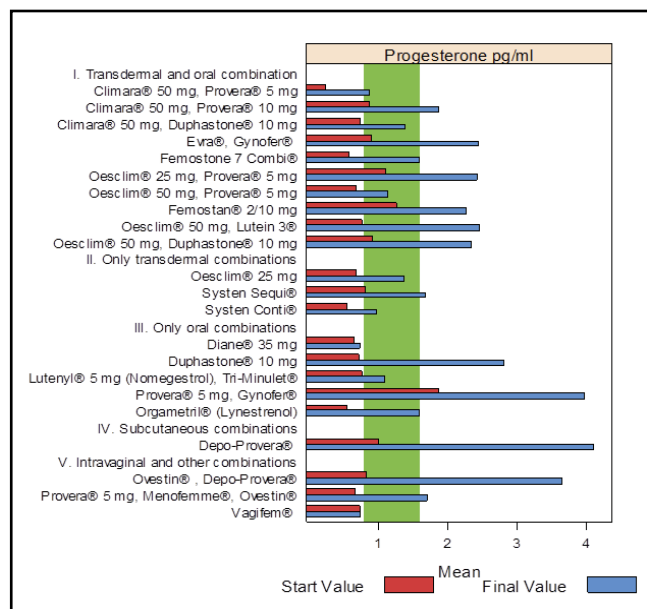


Fig. 2. Effects on Progesterone.

showing a reduction of elevated FSH to normal values, which is observed in healthy women during day 3 of the menstrual cycle, consist of Climara® 50 mg with Provera® 5 mg, Luteryl® with Tri-Minulet® and System Sequi®. All other drug regimens, although reducing elevated levels of FSH, could not reach normal blood FSH levels.

The most effective drug regimen in reducing FSH levels within one month of treatment was oral Femostone® 2/10 mg showing a drop of 70.3% from 107 mlU/ml down to 31.8 mlU/ml.

Similarly to FSH, drug regimens used for the improvement of symptoms of CI-POF present with a negative feedback effect on LH (Figure 4). Besides Vagifem®, all other drug regimens have shown a reduction of elevated LH blood concentration. No drug regimen has been shown to reduce elevated LH levels in CI-POF to normal values of <7 mlU/ml (Day 3) within one month of treatment.

The most effective drug regimen in reducing LH levels within one month was Orgametril® showing a drop of 73.1% from 65.5 mlU/ml down to 17.6 mlU/ml. The desired LH blood concentration of <7 mlU/ml was not reached within one month.

RESULTS AND DISCUSSION

The decision about which is the best and fastest treatment option in a patient with CI-POF, one has to ponder on the patient's main presenting complaint and other comorbidities. While choosing from a multitude of hormone replacement plans, the most appropriate therapy needs to be selected according to the patient's alleviation of symptoms and correction of blood hormone levels (Mulder 1999).

The best and fastest HRT option for patients with below normal values of blood estradiol concentration was orally administered Femostone® 2/10 mg.

For those patients with below normal values of blood progesterone concentration orally administered Orgametril® was most effective.

Patients with a diagnosis of CI-POF also show elevated concentrations of FSH and LH well above physiological levels due to the loss of negative feedback from estradiol and progesterone, respectively.

The administration of various HRT regimens causes a decrease in FSH levels to normal physiological levels. A decrease to normal physiological levels of FSH could only be achieved in patients with the HRT regimens consisting of Climara® 50 mg with Provera® 5 mg, Luteryl® with Tri-Minulet® and System Sequi®.

The most effective drug regimen in reducing FSH levels within one month of treatment was Femostone® 2/10 mg.

The administration of various HRT regimens has shown that no drug regimen was effective enough in reducing elevated LH levels in CI-POF to normal values (<7 mlU/ml on Day 3) within one month of treatment.

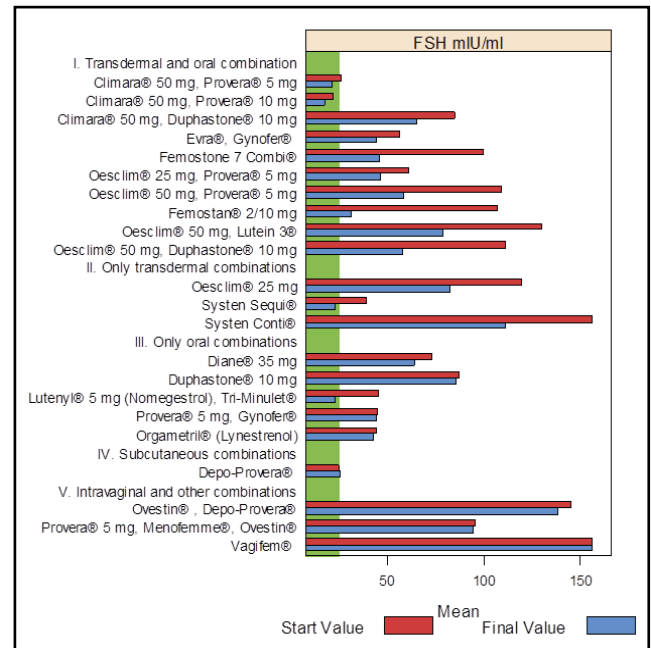


Fig. 3. Effects on FSH.

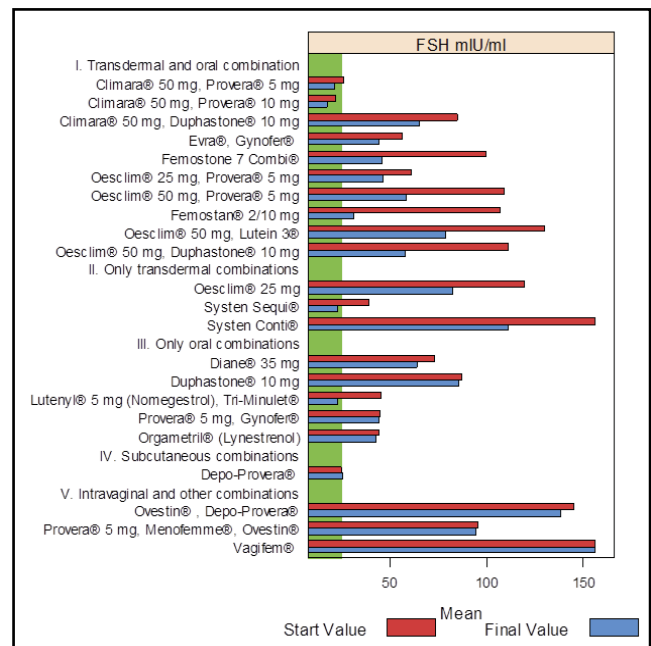


Fig. 4. Effects on LH.

The most effective drug regimen in reducing LH levels within one month of treatment was orally administered Orgametril®.

More research needs to be conducted whether other drug regimens are more effective in causing elevated FSH and LH levels to decrease to normal physiological values and if long-term elevated FSH and LH levels may have a detrimental health effect in CI-POF.

REFERENCES

- 1 Amarante F, Vilodre LC, Maturana MA, Spritzer PM (2011). Women with primary ovarian insufficiency have lower bone mineral density. *Braz J Med Biol Res.* **44**(1): 78–83.
- 2 Beard ME, Conder JL, Clark VA (1984). Ovarian failure following cytotoxic therapy. *N Z Med J.* **97**(767): 759–762.
- 3 Cartwright B, Robinson J, Rymer J (2010). Treatment of premature ovarian failure trial: description of an ongoing clinical trial. *Menopause Int.* **16**(1): 18–22.
- 4 Chapman RM, Sutcliffe SB, Malpas JS (1979). Cytotoxic-induced ovarian failure in women with Hodgkin's disease. I. Hormone function. *JAMA.* **242**(17): 1877–1881.
- 5 Clark ST, Radford JA, Crowther D, Swindell R, Shalet SM (1995). Gonadal function following chemotherapy for Hodgkin's disease: a comparative study of MVPP and a seven-drug hybrid regimen. *J Clin Oncol* **13**(1): 134–139.
- 6 De Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency (2010). *Lancet.* **376**(9744): 911–921.
- 7 Grigg A (2004). The impact of conventional and high-dose therapy for lymphoma on fertility. *Clin Lymphoma.* **5**(2): 84–88.
- 8 Haukvik UK, Dieset I, Bjoro T, Holte H, Fossa SD (2006). Treatment-related premature ovarian failure as a long-term complication after Hodgkin's lymphoma. *Ann Oncol.* **17**(9): 1428–1433.
- 9 Heinz M (2010). Hormonal development therapy (HDT) in hypogonadism in long-term view. *Best Pract Res Clin Obstet Gynaecol.* **24**(2): 149–155.
- 10 Kreuser ED, Klingmuller D, Thiel E (1992). [Diagnosis and prognosis of gonadal damage after chemotherapy and irradiation]. *Dtsch Med Wochenschr.* **117**(47): 1810–1817.
- 11 Larsen EC, Muller J, Schmiegelow K, Rechnittzer C, Andersen AN (1988). Reduced ovarian function in long-term survivors of radiation- and chemotherapy-treated childhood cancer. *J Clin Endocrinol Metab* **88**(11): 5307–5314.
- 12 Lee JS, Bracci PM, Holly EA (2008). Non-Hodgkin lymphoma in women: reproductive factors and exogenous hormone use. *Am J Epidemiol.* **168**(3): 278–288.
- 13 Mackie EJ, Radford M, Shalet SM (1996). Gonadal function following chemotherapy for childhood Hodgkin's disease. *Med Pediatr Oncol.* **27**(2): 74–78.
- 14 Maclaran K, Horner E, Panay N (2010). Premature ovarian failure: long-term sequelae. *Menopause Int.* **16**(1): 38–41.
- 15 Molina JR, Barton DL, Loprinzi CL (2005). Chemotherapy-induced ovarian failure: manifestations and management. *Drug Saf.* **28**(5): 401–416.
- 16 Mulder JE (1999). Benefits and risks of hormone replacement therapy in young adult cancer survivors with gonadal failure. *Med Pediatr Oncol.* **33**(1): 46–52.
- 17 Tfayli H, Arslanian S (1998). Menstrual health and the metabolic syndrome in adolescents. *Ann N Y Acad Sci.* 1135: 85–94.
- 18 Wang PH, Chao HT, Chao KC (2010). Chemotherapy-induced gonadotoxicity. *Taiwan J Obstet Gynecol.* **49**(1): 1–2.
- 19 Verschuuren SI, Schaap JJ, Veer MB, Stijnen T, Burger CW, Ansink AC (2006). Optimal treatment of premature ovarian failure after treatment for Hodgkin's lymphoma is often withheld. *Acta Obstet Gynecol Scand.* **85**(8): 997–1002.