Maturitas 67 (2010) 91–93

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

EMAS position statement: Managing women with premature ovarian failure

Svetlana Vujovic*, Marc Brincat, Tamer Erel, Marco Gambacciani, Irene Lambrinoudaki, Mette H. Moen, Karin Schenck-Gustafsson, Florence Tremollieres, Serge Rozenberg, Margaret Rees

Institute of Endocrinology, Clinical Center of Serbia, Belgrade School of Medicine, Dr Subotica 13, 11000 Beograd, Serbia

ARTICLE INFO

Article history:
Received 21 April 2010
Received in revised form 22 April 2010
Accepted 22 April 2010

Keywords:
Premature ovarian failure
Menopause
Fertility
Osteoporosis
Estrogen deficiency

ABSTRACT

Introduction: Premature ovarian failure (also known as premature menopause) is defined as menopause before the age of 40. It can be "natural" or "iatrogenic" such as after bilateral oophorectomy. It may be either primary or secondary. In the majority of cases of primary POF the cause is unknown. Chromosome abnormalities (especially X chromosome), follicle-stimulating hormone receptor gene polymorphisms, inhibin B mutations, enzyme deficiencies and autoimmune disease may be involved. Secondary POF is becoming more important as survival after treatment of malignancy through surgery, radiotherapy and chemotherapy continues to improve.
Aim: To formulate a position statement on the management of premature ovarian failure.
Materials and methods: Literature review and consensus of expert opinion.
Results and conclusions: Diagnosis should be confirmed with an elevated FSH greater than 40 IU/L and an estradiol level below 50 pmol/L in the absence of bilateral oophorectomy. Further assessment should include thyroid function tests, autoimmune screen for polyendocrinopathy, karyotype (less than 30 years of age) and bone mineral density. Untreated early ovarian failure increases the risk of osteoporosis, cardiovascular disease, dementia, cognitive decline and Parkinsonism. The mainstay of treatment is hormone therapy which needs to be continued until the average age of the natural menopause. With regard to fertility, while spontaneous ovulation may occur the best chance of achieving pregnancy is through donor oocyte in vitro fertilization. It is essential that women are provided with adequate information as they may find it a difficult diagnosis to accept. It is recommended that women with POF are seen in a specialist unit able to deal with their multiple needs.

1. Introduction

Premature ovarian failure (POF) (also known as premature menopause) is defined as menopause before the age of 40 [1]. It can be "natural" or "iatrogenic" such as after bilateral oophorectomy. The condition is common. It affects 1% of women under age 40 years and 0.1% of women under age 30 years [2]. The aim of this position statement is to provide evidence-based advice for health professionals on its management.

2. Aetiology

It may be either primary or secondary [3]. In the majority of cases of primary POF the cause is unknown. Causes of premature ovarian failure are shown in Table 1. Chromosome abnormalities (especially X chromosome), follicle-stimulating hormone receptor gene polymorphisms, inhibin B mutations, enzyme deficiencies and autoimmune disease may be involved. Secondary POF is becoming more important as survival after treatment of malignancy through surgery, radiotherapy and chemotherapy continues to improve. Uterine artery embolisation may also cause POF [4].

3. Presentation and assessment

The most common presentation is secondary amenorrhoea or oligomenorrhoea which may be accompanied by vasomotor symptoms, vaginal dryness, lack of libido and arthralgia. Investigation should include an endocrine screen to diagnose other causes of oligo/amenorrhoea. Co-existing disease must be detected, particularly hypothyroidism, Addison's disease, diabetes mellitus and any chromosome abnormalities in women with primary ovarian failure – especially those who have not achieved successful pregnancy or younger than 30 years (Table 2). The diagnostic usefulness of ovarian biopsy outside the context of a research setting is unproven.

4. Consequences of estrogen deficiency

Women who experience POF are now recognized to be at increased risk for premature morbidity and mortality. Women

* Corresponding author.
E-mail address: vujovics@EUnet.rs (S. Vujovic).

0378-5122/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.maturitas.2010.04.011

Table 1
Known cases of premature ovarian failure.

Primary
Chromosome abnormalities
Follicle-stimulating hormone receptor gene polymorphism and inhibin B mutation
Enzyme deficiencies
Autoimmune disease
Secondary
Chemotherapy and radiotherapy
Bilateral oophorectomy or surgical menopause
Hysterectomy without oophorectomy/uterine artery embolisation
Infection, e.g. mumps

Table 2
Investigation of premature menopause.

Estimates of levels of follicle-stimulating hormone
Luteinsiing hormone, prolactin, estradiol, progesterone, testosterone
Thyroid function tests
Autoimmune screen for polyendocrinopathy
Chromosome analysis, especially in women younger than 30 years
Estimates of bone mineral density through dual X-ray absorptiometry (DXA) (optional)
Adrenocorticotrophic hormone stimulation test if Addison's disease is suspected (optional)

with untreated POF are at increased risk of developing osteoporosis, cardiovascular disease, osteoporosis, dementia, cognitive decline and Parkinsonism [5–7].

5. Management

Women must be provided with adequate information and counseling as they may find this a difficult diagnosis to accept. Ideally these women should be managed in specialist menopause centres able to deal with their multiple needs. In the absence of oophorectomy, POF is associated with intermittent ovarian function in nearly half of the women affected [8]. This return of ovarian function is unpredictable and may result in menstrual bleeding or even pregnancy.

6. Hormone therapy

Hormone therapy (HT) is the mainstay of treatment for women with POF. It is recommended until the average age of the natural menopause. HT or the combined estrogen/progestogen contraceptive pill may be used. The latter may be more acceptable in younger women. There is a lack of comparative data. The only direct comparison of ethinylestradiol and conjugated equine oestrogen is a study of 17 women with Turner syndrome [9]. In this short study, no difference was seen between the two oestrogens with respect to effect on the endometrium, hyperinsulinaemia or lipid profile. Ethinylestradiol had a more potent effect on markers of bone turnover and suppression of gonadotrophins. Women with POF who take HRT may need a higher dose of estrogen to control vasomotor symptoms than women in their fifties.

No evidence shows that estrogen replacement increases the risk of breast cancer to a level greater than that found in normally menstruating women, and women with POF do not need to start mammographic screening early [10].

Some patients report reduced libido or sexual function despite apparently adequate doses of estrogen replacement. This may be more common in oophorectomized women, and consideration should be given to additional treatment with testosterone. This may be administered with either patches or subcutaneous implants depending on availability [11].

7. Non-hormone therapies and herbal remedies

There have been no clinical trials which have examined the efficacy or safety of the use of non-estrogen based treatments, such as bisphosphonates, strontium ranelate or raloxifene, in these women. Should pregnancy occur, there are no long-term studies on the effect of bisphosphonates or strontium ranelate on the skeleton in fetal or later life. There is no evidence that herbal remedies can be used instead of estrogen [12].

8. Fertility and contraception

Women with POF have a 5–15% chance of spontaneous conceiving at sometime after confirming diagnosis. Therefore it is essential to find if women wish to become pregnant or not. A number of ovarian reserve tests (ORTs) have been designed to determine oocyte reserve and quality [13,14]. These include early-follicular-phase blood values of FSH, estradiol, inhibin B, anti-Müllerian hormone (AMH), the antral follicle count (AFC), the ovarian volume (OVVOL) and the ovarian blood flow, and furthermore the Clomiphene Citrate Challenge Test (CCCT), the exogenous FSH ORT (EFORT) and the gonadotrophin agonist stimulation test (GAST). However they have only modest-to-poor predictive properties.

9. Fertility

Donor oocyte in vitro fertilization (IVF) is the treatment of choice for women with primary and secondary POF. Women with spontaneous, karyotypically normal POF have similar success rates to women who undergo conventional IVF. Patients can be reassured that there is no urgency for treatment after a diagnosis of POF.

In women having chemotherapy or radiotherapy, IVF with embryo freezing prior to treatment currently offers the highest likelihood of a future pregnancy should they experience premature ovarian failure as a result of their treatment [15,16]. However this depends on having a partner with whom the woman wishes to have a family and whether awaiting ovulation induction and delaying cancer therapy will adversely affect survival. Technical advances in oocyte preservation have improved live birth rates following freezing of mature eggs. It is still less successful than embryo freezing. Cryopreservation and transplantation of fresh ovarian tissue is still largely experimental, although pregnancies have been reported [17]. This technique would be an option for prepubertal girls where ovulation induction is not possible.

10. Contraception

Women who do not wish to have children need to consider using an effective form of contraception. The next issue will be how long contraception should be continued. Traditionally, women have been advised that contraception can be stopped if they have been amenorrhoeic for 2 years before the age of 50 years and 1 year above that. However, the menstrual pattern is difficult to establish in HT users and one may advise using contraception until the age of 55 years [18]. Women must be advised that HT is not contraceptive.

11. Summary recommendations

- POF (also known as premature menopause) is defined as menopause before the age of 40. It may be either primary or secondary. In the majority of cases of primary POF the cause is unknown.

- Diagnosis is confirmed with an elevated FSH >40 IU/L and an estradiol level below 50 pmol/L.
- Untreated early ovarian failure increases the risk of osteoporosis, cardiovascular disease, dementia, cognitive decline and Parkinsonism.
- The mainstay of treatment is estrogen replacement which needs to be continued until the average age of the natural menopause. Hormone therapy is not contraceptive.
- In the absence of oophorectomy POF is associated with intermittent unpredictable ovarian function resulting in menstrual bleeding or even pregnancy.
- Ideally women with POF are seen in a specialist unit able to deal with their multiple needs.

Competing interests

None declared.

Provenance

EMAS position statement.

Acknowledgements

SV prepared the initial draft which was circulated to all EMAS board members for comment and approval, production was coordinated by Margaret Rees.

References

[1] International Menopause Society. http://www.imsociety.org/menopause_terminology.php, accessed 1 March 2010.
[2] Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. Obstet Gynecol 1986;67:604–6.
[3] Rees M, Stevenson J, Hope S, Rozenberg S, Palacios S. Management of the menopause. 5th ed. RSM Press; 2009.
[4] Hehenkamp WJ, Volkers NA, Broekmans FJ, et al. Loss of ovarian reserve after uterine artery embolization: a randomized comparison with hysterectomy. Hum Reprod 2007;22:1996–2005.
[5] Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. Premature menopause or early menopause: long-term health consequences. Maturitas 2010;65:161–6.
[6] Rivera CM, Grossardt BR, Rhodes DJ, et al. Increased cardiovascular mortality after early bilateral oophorectomy. Menopause 2009;16:15–23.
[7] Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton 3rd LJ. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol 2006;7:821–8.
[8] Nelson LM. Clinical practice. Primary ovarian insufficiency. N Engl J Med 2009;360:606–14.
[9] Guttman H, Weiner Z, Nikolski E, et al. Choosing an oestrogen replacement therapy in young adult women with Turner syndrome. Clin Endocrinol 2001;54:159–64.
[10] Ewertz M, Mellemkjaer L, Poulsen AH, et al. Hormone use for menopausal symptoms and risk of breast cancer. A Danish cohort study. Br J Cancer 2005;92:1293–7.
[11] Kingsberg S. Testosterone treatment for hypoactive sexual desire disorder in postmenopausal women. J Sex Med 2007;4(Suppl 3):227–34.
[12] Herbal medicines for menopausal symptoms. DTB 2009;47:2–6, doi:10.1136/dtb.2008.12.0031.
[13] Lambalk CB, van Disseldorp J, de Koning CH, Broekmans FJ. Testing ovarian reserve to predict age at menopause. Maturitas 2009;63:280–91.
[14] Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. Hum Reprod Update 2006;12:685–718.
[15] Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 2006;24:2917–31.
[16] Anchan RM, Ginsburg ES. Fertility concerns and preservation in younger women with breast cancer. Crit Rev Oncol Hematol 2010 [March 4; Epub ahead of print].
[17] Silber S, Kagawa N, Kuwayama M, Gosden R. Duration of fertility after fresh and frozen ovary transplantation. Fertil Steril 2010 [February 18; Epub ahead of print].
[18] Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. Contraception for women aged over 40 years. J Fam Plann Reprod Health Care 2005;31:51–64.