The Raise of Blood Pressure as One of Metabolic Syndrome Parameter in Post Surgical Menopausal Women

Efriyan Imantika[1]

[1]Fakultas Kedokteran, Universitas Lampung

Abstract

Background Natural menopause is the permanent cessation of menstrual period that is not caused by any type of surgical procedure or medical treatment, while post surgical menopause means surgical removal of both ovaries before the natural age of menopause.[1] Its estimated number of menopausal women in Indonesia reached 30.3 million in 2020 except post surgical menopause women. Reduction of estrogen production in oophorectomized women causes early menopause problems such as physical and physiological aspects. Physical aspect causes many reproductive disorders such as vasomotor disturbances , osteoporosis and metabolic disease that affect to the activities of women experiencing menopause. Metabolic syndrome (MS) is accompanying many factors such as hypertension, insulin resistance, obesity and lipid abnormalities and all these factors cause cardiovascular disease and diabetes [(10)]. The prevalence of metabolic syndrome in post menopausal women can change by the region or population but ovarian function is not well known. In this study we investigated blood pressure as one component of metabolic syndrome in post surgical menopause in our population based on indication of procedure. **Method** A cross sectional study using medical records of the post surgical menopause patient in Sardjito hospital Yogyakarta from January 2011- December 2016. It divided in to two groups based on the indication of surgical procedure. The first group was 31 women with history of bisalphingoooforectomy on indication ovarian cancer and second sub group was 31 women with history of bisalphingoooforectomy on indication endometriosis. **Objective** To analyse the raise of blood pressure as one of Metabolic Syndrome parameter in post surgical menopausal women. **Result** There was significant difference of systolic blood pressure between post surgical menopausal women statistically. The systolic blood pressure in malignancy group raised higher than benign group (141.9 ± 11.67 vs 129.67 ± 7.5; p=0.005). Diastolic blood pressure was not significant difference between post surgical menopause women based on indication of surgical procedure (74.5 ± 7.67 vs 72.9 ± 5.9; p=0.07) **Conclusion** The raise of systolic blood pressure in post surgical menopausal women due to ovarian malignancy was higher than benign then increased the risk of metabolic syndrome.

Keyword: Blood pressure, metabolic syndrome, post surgical menopause

Korespondensi: dr. Efriyan Imantika, M.Sc., Sp.OG , alamat Jl. Soemantri Brodjonegoro No. 1, HP 081279114343, e-mail rayan.rianto@gmail.com

Background

Menopause is reached upon exhaustion of the resting primordial follicle pool, occuring on average at 51 years of age (40-60 years). The process of reproductive ageing in women is characterized by gradual decline in both the quantity and the quality of the oocytes present in the primordial follicle pool resident within the ovarian cortex. [(1)(2)]

The World Health Organization (WHO) defines menopause as the permanent cessation of menses due to the loss of ovarian follicular activity. The final menstrual period is retrospectively assigned after 12 months of amenorrhea, in the absence of other pathological or physiological causes. [(3)] Natural menopause is the permanent cesssation of menstrual periods that is not brought on by any type of surgical procedure or medical treatment, while surgical menopause means surgical removal of both ovaries before the natural age of menopause.[(4)]

Objective

To analyse the raise of blood pressure as one of Metabolic Syndrome parameter in post surgical menopausal women.

Method

A cross sectional study using medical records of the post surgical menopause patient in Sardjito hospital Yogyakarta from January 2011- December 2016. It divided in to two groups based on the indication of surgical procedure. The first group was 31 women with history of bisalphingoooforectomy on indication ovarian cancer and second sub group was 31 women with history of bisalphingoooforectomy on indication endometriosis. Time interval of investigation was 6 months untill 1 year after surgical. Independent t-test was used to analyse the data.

Result

Surgical menopuse means early menopause period in womens undergone

surgical removal of both ovaries before the natural age of menopause. It could be accompany with hysterectomy or only bisalphingoooforectomy caused by malignancy or benign etiology. Infertility and ovarian cancer result from the same abnormal gonadal status. The theory of "incessant ovulation" suggests that the epithelial lining of the ovary may be sensitive to the events of ovulation. [12][13]

Table 1. Characteristics of patients

	Indication of surgical (Mean ± SD)		p value
	Ovarian Malignancy	Benign	
Age (years)	44.6 ± 5.8	40.3 ± 5.9	0.004*
Surgical Time Interval (months)	10.6 ± 2.7	10.7 ± 1.9	0.5
BMI (kg/m^2)	23.6 ± 3.8	23.9 ± 4.4	0.7

The characteristics of patients show that mean age of the cases group was 44.6 ± 5.8 years and in the control group was 40.3 ± 5.9 years. Table I summarises time interval calculated from surgical to the investigation time (time trade of examination) and average of Body Mass Index from each group. The mean time interval of investigation is 10.6 ± 2.7 months in the first group and 10.7 ± 1.9 months in the second group. The data was taken in interval 6-12 months in order to hinder bias from another complication of the disease. From the table in the figure 1, both of group have BMI more than 18 kg/m^2 (overweight categories).

Table 2. The systolic and diastolic Blood Pressure difference of post surgical menopausal women

Blood Pressure	Indication of surgical (Mean ± SD)		p value
	Ovarian Malignancy	Benign	
Systolic BP	141.9 ± 11.67	129.67 ± 7.5	0.005*
Diastolic BP	74.5 ± 7.67	72.9 ± 5.9	0.07

*p<0.05 (significant statistically)

Table 2 show that there was significant difference of systolic blood pressure between post surgical menopausal women statistically. The systolic blood pressure in malignancy group raised higher than benign group (141.9 ± 11.67 vs 129.67 ± 7.5; p=0.005). Diastolic blood pressure was not significant difference between post surgical menopause women based on indication of surgical procedure (74.5 ± 7.67 vs 72.9 ± 5.9; p=0.07).

Discussion

Both the ovary and the adrenal gland are responsible for androgen synthesis in women. Differentiating the quantitative and qualitative differences in the origin of the steroids requires an understanding of the steroidogenic capacity of each of these tissues. The adrenal gland produces predominantly the steroids, dehydroepiandrosterone (DHEA) and its sulphated form DHEA-S. These steroids are then converted to more potent androgens such as testosterone and dihydrotestosterone

(DHT), through peripheral metabolism. In contrast, the ovary synthesizes negligible amounts of DHEA and DHEA-S, but synthesize the androstenedione, testosterone and blood DHT which is primarily derived from androstenedione and partly from dehydroepiandrostenedione.

Haning *et al* compared the 5alpha-reductase activity at both pH 5.5 (optimum for 5alpha-reductase 2 activity) and 8.0 (optimum for 5alpha-reductase 1 activity). 5alpha-reductase activity of foreskin at pH 5.5 was 3900 times higher than small follicles, 1500 times higher than ovarian stroma, and 240 times higher than corpora lutea (all $P < 0.01$). 5alpha-reductase activity of corpora lutea at pH 5.5 was 17-fold higher than that of follicles ($P < 0.01$) and 6.5-fold higher than that of ovarian stroma ($P < 0.05$). 5 alpha-Reductase activity of foreskin at pH 8.0 was 93 times higher than small follicles, 51 times higher than corpora lutea, and 170 times higher than ovarian stroma (all $p < 0.01$). [7]

The post-menopausal ovary possessed the capacity to express the steroidogenic enzymes necessary for the initiation of ovarian steroidogenesis, but only ovaries from post-menopausal women with endometrial hyperplasia or cancer expressed all the enzymes necessary for androgen synthesis [8]. Post-menopausal women with intact ovaries have been shown to have 40% greater testosterone levels and 10% greater androstenedione levels than age-matched women who had previously undergone oophorectomy [9]

Metabolic disorders occurring in menopause, including dyslipidemia, disorders of carbohydrate metabolism (impaired glucose tolerance – IGT, type 2 diabetes mellitus – T2DM) or components of metabolic syndrome, constitute risk factors for cardiovascular disease in women. A key role could be played here by hyperinsulinemia, insulin resistance and visceral obesity, all contributing to dyslipidemia, oxidative stress, inflammation, alter coagulation and atherosclerosis observed during the menopausal period. Undiagnosed and untreated, metabolic disorders may adversely affect the length and quality of women's life. Prevention and treatment preceded by early diagnosis should be the main goal for the physicians involved in menopausal care.[4]

There was 3 or more of METS criteria (Based on Adult Treatment Panel III AHA) below:

- Abdominal obesity (waist circumference > 88cm).
- Increased serum triglycerides ≥ 150 mg/dL).
- Decreased of HDL < 50 mg/dL.
- High fasting glucose (≥ 100 mg/dL or the use of hypoglycemic agents) I.
- Increased of BP ≥ 130/85 mmHg or the use of antihypertensive medications).

Weight gain and obesity largely drive the increased prevalence of MetS in postmenopausal women. Menopausal transition is associated with significant weight gain (2 to 2.5 kg over 3 years on average). After menopause the incidence of obesity increases, including visceral (android) obesity. Such fat distribution fosters the occurrence of a number of metabolic disorders, including fully manifested metabolic syndrome, and enhances the development of atherosclerosis. The comparison of patients with normal BMI and those with high BMI showed that high BMI (> 30 kg/m) had a significant negative effect on blood pressure (as evidenced by the increased frequency of hypertension in overweight and obese patients) that it also negatively and significantly affected triglyceride and fasting glucose levels, and that it was linked significantly to low levels of HDL-C, therefore with CVD risk factors.[14]

The prevalence of MetS differs greatly in different populations. Amongst pre-and postmenopausal women. It ranges from 13.8% to more than 60.0%.[4] An increasing of abdominal adiposity and a decrease in energy expenditure in post menopausal women explain why it be the higher risk of metabolic syndrome. Higher level of cholesterol and triglycerides in menopause women is considered as a predictor of MetS, independent of women's age. [14] Other risk factors for MetS include menarche age. Menarche age showed a 'U'shaped relationship with MetS and oligomenorrhea in adulthood. Late menarche and early menarche are risk factors for adult oligomenorrhea, MetS, and cardiometabolic abnormalities.Therefore, girls with early (10 years old) and with late menarche (16 years old) represent a group at

high risk of adult cardiometabolic abnormalities and oligomenorrhea [15,16].

Also, in another study, irregular menses had been correlated with elevated levels of triglycerides and obesity. [17] The simultaneous occurrence of insulin resistance and obesity is the most detrimental for metabolic health, and is also associated with increased oxidative stress, inflammatory and prothrombotic processes as well as with postmenopausal alterations in adipocytokine production.[18,19]

Chedraui *et al*. reported that postmenopausal women with MetS showed higher interleukin 6 (IL-6) (inflammation) and lower urokinase-type plasminogen activator (uPA) levels (endothelial dysfunction). Moreover, IL-6 levels were higher among women with abdominal obesity, low HDL-C and high triglyceride levels. Women with low HDL-C and high triglyceride levels presented significantly lower uPA levels. These were mainly related to metabolic and lipid abnormalities. [20]

In women, increases in androgens are associated with increases in inflammatory cytokines, and reducing androgens reduces inflammation. Obese women have elevated levels of testosterone although the levels are only increased 2–3 fold and thus are still significantly lower than in men. Barrett-Connor and colleagues reported that serial measurements of testosterone in postmenopausal women over 9 years showed that testosterone levels decrease sharply after menopause transition along with estradiol levels, but increased slowly with age,such that by 70 years of age, the androgen levels were similar to levels found in premenopausal women. The difference between pre- and post-menopausal women was that the androgen levels were unopposed by estrogen levels in the post-menopausal women. The consequence of increasing levels of androgens in postmenopausal women is unknown. [21,22]

Multiple studies showed associations between serum testosterone and insulin resistance or metabolic syndrome/type 2 diabetes risk in women, but their cross-sectional nature did not allow conclusions about causality in three of the seven studies using euglycemic hyperinsulinemic clamps, reduction of androgen levels or blockade of androgen action improved insulin sensitivity. Testosterone induced insulin resistance in adipocytes of women *in vitro*. Direct effects of androgens on insulin action, especially insulin sensitivity in women. Indirectly through effects on lipid metabolism and body fat distribution, specifically the development of central obesity: these aspects have been relatively extensively investigated and are the subject of recent comprehensive reviews. Bioavailable testosterone refers to free testosterone plus albumin-bound testosterone. SHBG concentrations are decreased by insulin and androgens and increased by estrogens. SHBG regulates the bioavailability of testosterone, SHBG concentration is regarded as an indirect measure of androgenicity. [21]

Androgens are synthesized in the adipose tissue of women, primarily in the stromal fraction. Local concentrations of androgens in adipose tissue significantly exceed those in the systemic circulation. The concentration of testosterone in female adipose tissue is on average 2.5-fold higher than in serum and approaches the lower end of the male serum range in some women. Androgens have been shown to regulate lipolysis and lipogenesis in the adipose cells of women. In the subcutaneous adipocytes of women, testosterone inhibited catecholamine-stimulated lipolysis associated with decreased expression of hormone sensitive lipase (HSL) and ß2-adrenoceptors. DHT modulated expression of hormone sensitive lipase and lipoprotein lipase (LPL) in subcutaneous adipocytes of women. In ovariectomized female mice, DHT administration resulted in increased body weight and visceral fat mass, associated with increased expression of genes involved in lipogenesis in visceral fat and down-regulation of the activity of AMP activated protein kinase (AMPK), a key enzyme in the regulation of fat metabolism and energy balance. [23]

Conclusion

The raise of systolic blood pressure in post surgical menopausal women due to ovarian malignancy was higher than benign then increased the risk of metabolic syndrome.

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