Review Article

MENOPAUSE: A NEGLECTED REPRODUCTIVE HEALTH CONCERN IN CAMEROON

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ABSTRACT
Introduction: Menopausal medicine is an outstanding problem in health care systems in Africa as a whole and in Cameroon in particular. Most menopausal women tend to seek medical attention in various medical specialties because of the polymorphous clinical features of menopause, yet its origin is gynaecological. This may be due to the lack of knowledge on menopause by health practitioners and decision makers.
Methods: In this complete literature review, we carried out a meta analysis of menopause through its definition, age of onset, pathophysiology, clinical presentation, complications, diagnosis and management.
Conclusion: Adequate provision of knowledge to medical practitioners and decision makers on this natural ageing phenomenon with emphasis on the creation of menopausal clinics as an integral part of reproductive health delivery system appears necessary for the appropriate management of the many menopausal women in Cameroon.

KEY WORDS: Menopause- Clinical features- Management- Complications- Menopausal clinics

RESUME
Introduction : La ménopause est un problème majeur de santé publique en Afrique en général et au Cameroun en particulier. Les femmes ménopausées ont tendance à consulter dans diverses spécialités médicales, certainement à cause du polymorphisme des signes cliniques de la ménopause, bien que la cause soit purement gynécologique. Ceci s'expliquerait par le manque de connaissances appropriées des praticiens sur la ménopause.
Méthodes : Nous faisons une revue complète de la littérature sur la ménopause en allant de la définition, l'âge d'apparition, la physiopathologie, la présentation clinique, le diagnostic, la prise en charge, jusqu'aux complications.
Conclusion: Les connaissances appropriées sur la ménopause, ce phénomène de vieillissement naturel, aideront d'une part les décideurs dans la création des unités de la femme ménopausée comme une part entière de la santé de reproduction et d'autre part les praticiens dans la prise en charge au Cameroun des nombreuses femmes ménopausées.
MOTS CLES : Ménopause- Présentation clinique- Prise en charge- Complications- Clinique de la ménopause.

I- INTRODUCTION

Menopause, the terminal phase in a woman's reproductive life, has long been neglected by gynaecologists and physicians until fifty years ago in the western world. It is continuously being neglected in our reproductive health delivery system in Africa in general and in Cameroon in particular, to the detriment of the so many menopausal women who constitute a significant proportion of the population and deserve appropriate medical care.
In the absence of a well-defined intervention strategy, coupled with the increasing number of menopausal women developing severe disabling symptoms necessitating medical attention[1], it is becoming necessary to rebuild our reproductive health policy including the management of menopause. Specific management of these "third age" women is probably ignored in Cameroon because of our poor understanding of menopause

unlike in the developed world. In Africa, in the absence of menopausal clinics, menopausal women seek medical care in all the medical disciplines because of the polymorphous clinical picture of the menopause which cuts across all the different specialties[2], even though the aetiology of menopause is principally gynaecological. A better understanding of menopause in all its aspects, as part of reproductive health, will therefore provide a proper management to this huge population of women in the terminal phase of reproductive health in Cameroon.

The objective of this review therefore, was to comprehensively update our knowledge on menopause in order to provide appropriate care to menopausal women as part of our reproductive health delivery system. Consequently, the specific variables reviewed included the definition, age of onset, the pathophysiology, clinical features, complications, and management of menopause.

II- CLINICAL REVIEW OF MENOPAUSE

II.1. Definition

Menopause is defined as the cessation of menses for twelve consecutive periods caused by the almost complete absence of follicles in the ovaries. Menopause is a natural ageing phenomenon. The first menstruation called menarche, is a single clearly demarcated event that occurs during the development of reproductive maturity (puberty), while the last menstrual period (menopause) serves as an objective sign of reproductive senescence. The climacteric and the menopause are often used synonymously yet they refer to different conditions. Climacteric is the period during which the genital organs involute in response to the cessation of gonadal activity, and menopause refers to the cessation of menses. Menopause, therefore, is merely one of the manifestations of the climacteric and precedes complete cessation of ovarian function by several months. Menopause and climacteric are peculiar to the human race; in lower animals ovulation and fertility continue into old age.

II.2. Age

The mean age of the menopause is fifty-one years in the western societies, as it occurs between forty-five and fifty-five years[3]. In Cameroon, the average age of occurrence of menopause is forty-eight years[1]. The age of menopause doesn't depend on the age of menarche, type of menstrual cycle, number of previous pregnancies, marital status, climate, nor the environment[4]. In the absence of general or pelvic diseases the only known factors governing menopause are familial and racial[5].

II.3. Physiology of Menopause

In the human, folliculogenesis begins in the ovary around the third week of gestation. Primordial germ cells appear in the yolk sac, migrate to the germinal ridge, and undergo cellular divisions. It is estimated that the foetal ovaries contain approximately 7 million oogonia at 20 weeks' gestation. After 7 months' gestation, no new oocytes are formed. At birth, there are approximately 1–2 million oocytes, and by puberty this number is reduced to 300,000–500,000[6]. Continued reduction of oocyte numbers occurs during the reproductive years through ovulation and atresia. Nearly all oocytes vanish by atresia, with only 400–500 actually being ovulated. Very little is known about oocyte atresia. Accelerated follicular depletion begins at age 37-38, and menopause follows 10 years later[7]. Menopause occurs when the number of follicles falls below a critical threshold, about 1000, regardless of age.

Table I- Effects of maternal age on number of oocytes (BLOCK 1952)

Age (Years)	N° of oocytes
At birth	733,000
4-10	499,200
11-17	389,300
18-24	161,800
25-31	80,500
32-38	60,200
39-45	10,900

Source: Hsueh AJW [8]

Menopause apparently occurs in the human female because of two processes. First, oocytes responsive to gonadotropins disappear from the ovary, and second, the few remaining oocytes do not respond to gonadotropins. Isolated oocytes can be found in postmenopausal ovaries on very careful histologic inspection. Some of them show a limited degree of development, but most reveal no sign of development in the presence of excess endogenous gonadotropins.

Spontaneous cessation of menses before the age of 40 years is called premature menopause, or premature ovarian failure. It appears that approximately 0.9% of women in the United States may experience this early cessation of function [9]. Cessation of menstruation and the development of climacteric symptoms and complaints can occur as early as a few years after menarche. The reasons for premature ovarian failure are unknown.

Disease processes, especially severe infections or tumours of the reproductive tract, can occasionally damage the ovarian follicular structures so severely as to precipitate the menopause. The menopause can also be hastened by excessive exposure to ionizing radiation, chemotherapeutic drugs, particularly alkylating agents, and surgical procedures that impair ovarian blood supply[10]. The possibility of associated endocrine or chromosomal abnormalities should also be considered.

The permanent cessation of ovarian function brought about by surgical removal of the ovaries or by radiation therapy is called artificial menopause. Irradiation to ablate ovarian function is rarely used today. Artificial menopause is employed as a treatment for endometriosis and rarely may be used to treat oestrogen-sensitive neoplasms of the breast and endometrium. More frequently, artificial menopause is a side effect of treatment of intra-abdominal disease; eg, ovaries are removed in premenopausal women because the gonads have been damaged by infection or neoplasia. When laparotomy is being performed for intra-abdominal or pelvic disease (ie, hysterectomy for leiomyomata), elective bilateral oophorectomy is sometimes employed to prevent ovarian cancer. In some women who are genetically predisposed to ovarian cancer, elective laparoscopic oophorectomy is also performed.

II.4. Hormonal production at menopause

II.4.1. Gonadotropins

With menopause, both LH and FSH levels rise substantially, with FSH usually higher than LH (Table 2). This is thought to reflect the slower clearance of FSH from the circulation. The reason for the marked increase in circulating gonadotropins is the absence of the negative feedback of ovarian steroids and inhibin on gonadotropins release (Figure1). As in young women, the levels of both gonadotropins are not steady, but instead show random oscillations. These oscillations are thought to represent pulsatile secretion by the pituitary. In older women, these pulsatile bursts occur every 1–2 hours, a frequency similar to that seen during the follicular phase of premenopausal subjects. Although the frequency is similar, the amplitude is much greater. This increased amplitude is secondary to increased release by the hypothalamic hormone, gonadotropin-releasing hormone (GnRH), and enhanced responsiveness of the pituitary to GnRH because of low oestrogen levels.

Table II- Gonadotropins values at different ages

Young children, male and female	0.5-2.0 IU 2nd IRP
Adult non-pregnant women	5.0-25.0 IU 2nd IRP
Women at the climacteric	30.0-160.0 IU 2nd IRP

When contradictory or uncertain clinical findings make the diagnosis of the postmenopausal state questionable, measurement of plasma FSH, LH, and estradiol levels may be helpful. This situation occurs frequently in women following hysterectomy without oophorectomy. The findings of plasma estradiol below 20 pg/ml and elevated FSH and LH levels are consistent with cessation of ovarian function [12]. In practical terms, it is not necessary to measure LH.

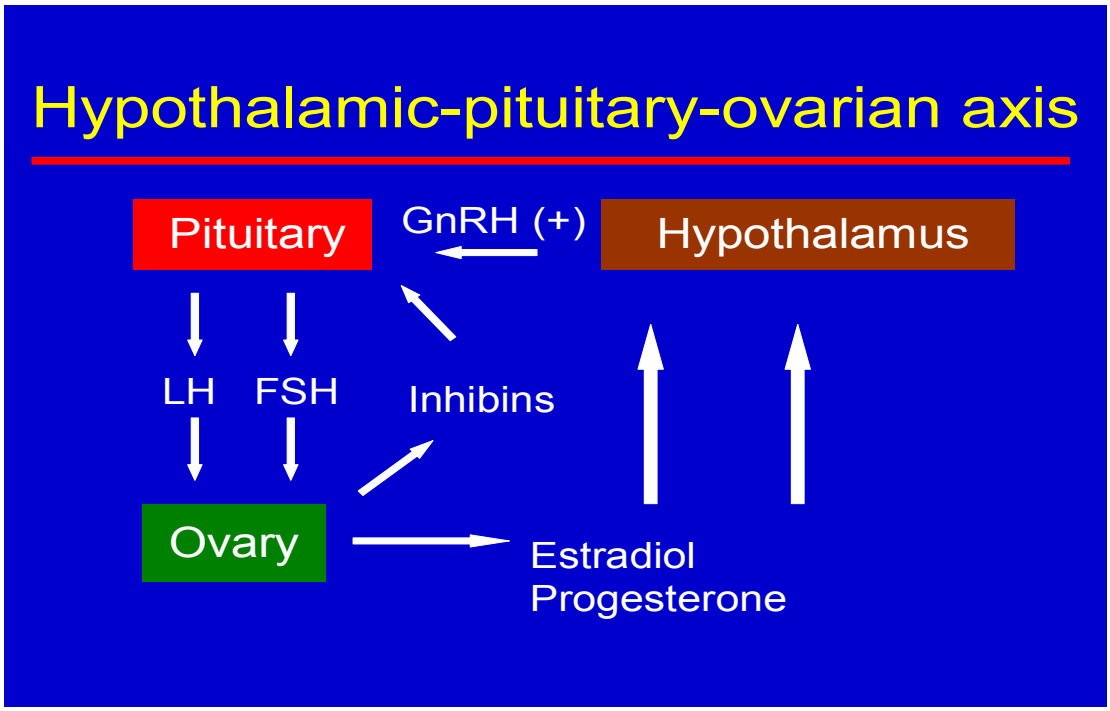

Figure 1: Hormonal cycle of a Woman. *Source: JoAnn V.P.*[13]

II.4.2. Oestrogens

After a woman has passed the menopause, there is good clinical evidence of reduced endogenous oestrogen production in most subjects (Table 3). When circulating levels have been assessed, the greatest decrease is in oestradiol. Its concentration is distinctly lower than that found in young women during any phase of their menstrual cycle and is similar to the level seen in premenopausal women following oophorectomy. A decrease of this oestrogen occurs up to 1 year following the last menstrual period. There does not appear to be a circadian variation of the circulating concentration of oestradiol following the menopause.

The source of the small amount of oestradiol found in older women has been established. Direct ovarian secretion contributes minimally, but the adrenal glands are the major source. Investigators who have examined the concentrations of oestradiol in adrenal veins have reported minimal increments, arguing against direct adrenal secretion being a major contributor. Although both oestrone and testosterone are converted in peripheral tissues to oestradiol, it is conversion from oestrone that accounts for most oestradiol in older women[14].

After menopause, circulating level of oestrone decreases, not as much as that of oestradiol, and overlaps with values seen in premenopausal women during the early follicular phase in menstrual cycles.

Most oestrone results from the peripheral aromatization of androstenedione. The average percent conversion is double that found in ovulatory women and can account for the total daily production of this oestrogen. Aromatization of androstenedione occurs in fat, muscle, liver, bone marrow, brain, fibroblasts, and hair roots. Other tissues may also contribute but have not been evaluated. To what extent each cell type contributes to total conversion has not been determined, but fat cells and muscle may be responsible for only 30–40%. This conversion correlates with body size, with heavy women having higher conversion rates and circulating oestrogen levels than slender women.

Table III- Oestrogens values at different ages

Young female children	1.0-3.0µg
Female aged 9-12 years	3.0-50µg rising with age
Adult non-pregnant woman follicular phase	5-25µg (mean=15)
Ovulation peak	30-100µg (mean=60)
Luteal phase	15-80µg (mean=35)
Post-menopausal woman	3-12µg (mean=6)
Adult men	7-20µg (mean=11)

Source: Sherman BM [11]

II.4.3. Progesterone

In young women, the major source of progesterone is the ovarian corpus luteum following ovulation. During the follicular phase of the cycle, progesterone levels are low. With ovulation the levels rise greatly, reflecting the secretory activity of the corpus luteum. In postmenopausal women, the levels of progesterone are only 30% of the concentrations seen in young women during the follicular phase. Because postmenopausal ovaries do not contain functional follicles, ovulation does not occur and progesterone levels remain low. The source of the small amount of progesterone present in older women is felt to be caused by adrenal secretion, as dexamethasone suppresses its level, adrenocorticotropic hormone (ACTH) increases its level, and human chorionic gonadotropin (hCG) administration has no effect[15].

II.4. Clinical Presentation and Complications

More than 50 symptoms have been identified to be associated with menopause, with prevalence and severity varying among individuals. As high as 76.23% of the women have symptoms but do not seek medical advice in Cameroon while 31.9% have severe disabling symptoms necessitating medical attention[1].

II.4.1. Changes associated with Oestrogen Decline

Numerous physical and psychological symptoms have been attributed to the decline and discontinuance of ovarian function in midlife. These symptoms include vasomotor symptoms, genital atrophy, osteoporosis, menopausal skin changes, cardiovascular disease, psychiatric disorders, and changes in libido.

II.4.1.1. Vasomotor Symptoms

Vasomotor symptoms are the most common perimenopausal symptoms that compel women to seek medical attention. Fifty percent of Cameroonian women experience hot flushes[1]. The average duration of these symptoms is two to three years. These symptoms, which include sudden increases in central skin temperature as well as perspiration, are apparently due to deregulation of the temperature-regulating centre in the hypothalamus. Both peripheral vasodilatation and perspiration occur. The flush, which generally lasts from a few to 20 minutes, typically is preceded by a premonition - a flash. It is apparently related to decreases in oestrogen and inhibin levels, not to absence of oestrogen. About one-third of women with vasomotor symptoms find these symptoms severe enough to require medical assistance[16]. Hot flushes may begin before menopause, but generally are more severe after cessation of menses (fig 2). Exogenous oestrogen therapy, progestogen therapy, and, to a lesser extent, vasodilator therapy have been shown to decrease the incidence of vasomotor symptoms[17]. Flushes may not respond optimally to oestrogen replacement therapy for up to one month.

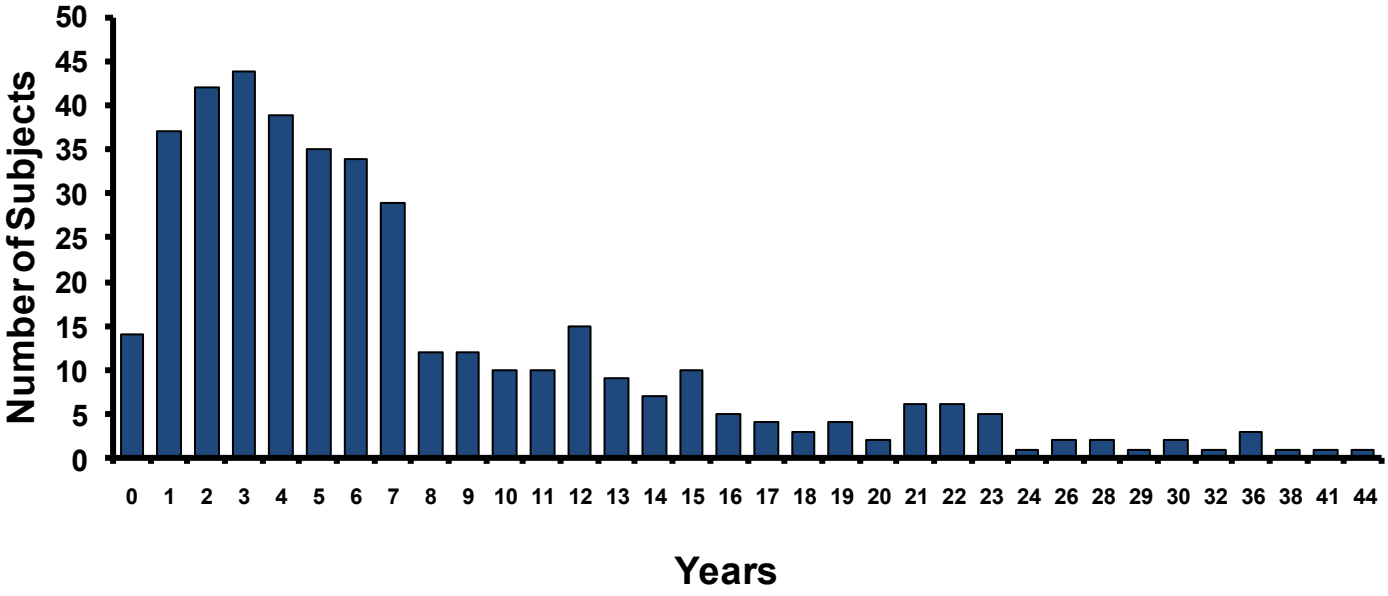

Figure2: Number of years women reported having hot flushes as estimated by a survey of 501 women. *Source: Kronenberg F[18]* .

II.4.1.2. Genital Atrophy

Genital atrophic changes associated with hypoestrogenism are a significant problem for many women. Clinically, the atrophic vagina has a pale appearance and loses its elasticity. The epithelium is thin and friable, and with the lack of colonization by acidophilic bacteria, it no longer produces glycogen necessary for the natural acidic vaginal protection.

The symptoms related to genital atrophy include vaginal and vulvar itching and burning, dyspareunia, vaginal bleeding, dysuria, urinary frequency, and urinary urgency. The most effective therapy for atrophic vaginitis or urethritis is oestrogen, which increases the local blood supply and in part reverses these changes.

II.4.1.3. Osteoporosis

Osteoporosis, defined as a reduction of bone mass per unit volume, significantly affects more than one-third of older women[19]. Bone strength or bone mineral content is a function of numerous factors that, when deficient, may predispose one to osteoporosis.

Osteoporosis is rare in African-American women, and it is more common in thin Caucasian or Asian women[20]. Osteoporosis may be somewhat less common in women who have maintained healthy lifestyles. Smoking, excessive alcohol use, sedentary lifestyle, and steroid use appear to be contributing factors in women who develop osteoporosis. There is well-documented accelerated bone calcium loss beginning prior to the time of ovarian failure[21]. The calcium loss is primarily from the trabecular (spongy) bone of the vertebral bodies, long bone shafts and heads, and the pelvis. Abundant evidence indicates that exogenous oestrogen therapy reduces the risk of postmenopausal osteoporosis and fractures[22]. Serial bone densitometry studies show a halt in bone density loss in oestrogen-treated patients but not in untreated controls[23].

II.4.1.4. Menopausal Skin Changes

The skin changes associated with aging include increased fragility and wrinkling, as well as some changes in sensation. These changes may increase around the time of menopause. A decline in skin collagen content paralleling the decline in bone density in postmenopausal women has been illustrated with a loss of up to 3 percent per year. Oestrogen therapy slows the loss of collagen[24].

II.4.1.5. Cardiovascular Disease

Heart disease, specifically coronary artery disease, is the leading cause of death for postmenopausal women[25]. Numerous epidemiologic studies indicate that hormone replacement, particularly oestrogen replacement, after ovarian failure substantially reduces the

incidence of coronary artery disease[26]. Ovarian failure may also be an important determining factor in coronary artery disease in women. The incidence of the disease in women prior to menopause is much lower than that in men of the same age[27].

II.4.1.6. Psychological Disorders

A number of symptoms (anxiety, depression, irritability, fatigue, insomnia, emotional liability, and changes in libido) may occur around the time of menopause. The aetiology of these symptoms is incompletely understood and appears to be multifactorial. Oestrogen decline may indirectly cause or worsen these symptoms by increasing the risk of developing a sleep disturbance and adversely affecting overall feelings of well-being. The use of hormone replacement therapy (HRT) in menopausal patients has been demonstrated to help improve symptoms such as nervousness, depression, anxiety, and insomnia[28]. In addition, progestin therapy may increase depressive symptoms. As longevity of women increases, so does the prevalence of senile dementia. It is estimated that up to 50 percent of women 85 years or older may suffer from Alzheimer's disease[29]. Overall, patients with mild to moderate dementia have demonstrated improvement of memory, orientation to place and time, and mental calculations. Oestrogen replacement therapy has also been demonstrated to reduce the number of women who develop Alzheimer's disease.

II.4.2. Other Menopausal pathologies Not Directly Related to Estrogen Depletion

II.4.2.1. Libido

When a woman complains of decreased libido, more than androgen levels need to be considered. There is decrease in libido in 38.16% of menopausal Cameroon women[1]

II.4.2.2. Cancer Risks

Cancer of the breast is the most frequent cancer in women, and the second leading cause of cancer death[30]. The median age at which breast cancer develops is 69, but 80 percent of women are affected after the age of 40. There is an abundance of indirect evidence that estrogen and/or progesterone have roles in breast cancer aetiology[31].

The FDA Advisory committee has agreed that long-term use of oestrogen is associated with a modest increase in breast cancer risk of a magnitude of 1.3 to 1.5; however the risk may be significantly lower if lower doses of oestrogen are used consistently. In addition, the risk may increase further when women already at high risk for breast cancer take exogenous oestrogen[32].

II.4.2.3. Benign Breast Problems

Fibrocystic breast changes respond variably to menopausal hormone replacement. As with other hormone-related effects, breast symptoms usually are dose-related, and mastalgia frequently worsens during the oestrogen/progestin days of cyclic therapy.

II.4.2.4. Other menopausal effects (Coagulation defects, Hypertension, Vascular Disease, and Gallbladder Disease)

By directly or indirectly stimulating liver enzymes, oestrogen may increase the production of serum globulins, including angiotensinogen, sex hormone binding globulin, and others. It favorably affects fat and cholesterol metabolism in the liver, tilting the balance toward increases in high-density lipoprotein cholesterol and triglycerides, and decreases in total cholesterol and low-density lipoprotein cholesterol[33].

Oestrogen also increases the cholesterol content of bile, and may increase the incidence of cholesterol-containing gallstones in some individuals.

II.5. Diagnosis of Menopause

The diagnosis of menopause is essentially clinical. Some clinicians at times carry out hormonal analysis with an increase in gonadotropins (FSH, LH) and a decrease in oestrogens, progesterone, and androgens. There is a decrease in the ratio of oestrogen to androgen with a decrease in sex hormone-binding globulin secretion and also the peripheral aromatization of DHEA to oestrone. Also is observed a reversal of E2 to E1 ratio. No significant change in testosterone levels has been observed.

II.6. Management

The management of menopause consists essentially of the following:

II.6.1. Advice on a healthy life style

The advice on a healthy life style is one of the main axes on the management of menopause. This helps in the prevention of certain complications like osteoporosis and cardiovascular diseases. It includes essentially avoidance of spicy food, alcohol, strong tea and

coffee, exercises, adequate calcium and vitamin D intake, avoidance of smoking and control of hypertension, diabetes and hyperlipidaemia

II.6.2. Psychological support

This includes the understanding of menopause and the strengthening of self image. Patients who understand that menopause is a natural ageing phenomenon usually accept it without much apprehension.

II.6.3. Hormone replacement therapy (HRT).

Hormone replacement is the key to the management of menopause. This helps in reducing menopausal symptoms and complications like osteoporosis and cardiovascular diseases, and therefore improving life quality during menopause.
Since menopausal symptoms are mainly due to oestrogen depletion, oestrogen replacement will help reduce these symptoms, but an influx of oestrogen is usually accompanied by certain side effects. This is the reason for the introduction of progesterone combinations.
Contra indications of HRT include existing breast cancer, existing endometrial cancer or hyperplasia, venous thrombo-embolism, acute liver disease, hypertension and diabetes.

The routes of administration of oestrogen are: oral, transdermal, implants, or local vaginal preparation

For oral oestrogen therapy we have:

- Natural occurring oestrogens: Inoclim® and various oestradiol preparations. These phyto-oestrogens are metabolised in the liver to the weaker metabolite oestrone and then converted to oestradiol in the peripheral circulation and in the target tissue. The natural oestrogens are nowadays in vogue in the management of severe cases of menopause because they are associated with minimal side effects unlike the synthetic ones[34].

- Tibolone: is a steroid hormone that has oestrogenic, progestogenic and androgenic properties, which can be used as an alternative to natural oestrogen in cases of contra indication of oestrogen therapy[35].

- Synthetic oestrogens: such as mestranol or ethinyl oestrodiol are not generally prescribed for older women for HRT because of their side effects.

Transdermal preparations are patches (oestrogen only or combined preparation) or oestrogen gels. They are preferred by most women. Skin irritation may be a problem but new matrix patches and the gels are usually well tolerated .It is the route of choice for women with risk factors for venous thrombo-embolism, liver disease or gastro-intestinal problems. Oestrogen implants are now less widely used

Progesterone preparations are oral or transdermal form and the levo-norgestrel releasing intra-uterine system.

Oral progestogens are:

- C21 progesterone derivatives : dydrogesterone or medroxyprogesterone acetate

- C19 nor-testosterone derivatives: norethisterone acetate or levonorgestrel

HRT regimens [36]

- Women who have had hysterectomy only need to take oestrogen.

- Women with an intact uterus must take progestogen to prevent endometrial cancer or hyperplasia.

- Regular surveillance of endometrium is required for women (extreme intolerance of progestogen) on unopposed oestrogen.

Risks and contraindications of HRT

- Breast cancer.
- Endometrial cancer : if oestrogen-only pills are used
- Thrombo-embolism.
- Cardiovascular diseases.

In the absence of risk factors, HRT can be stopped progressively after two years.

II.7. Conclusion/Recommendation

We have presented a clinical review of menopause, bringing out its polymorphism in clinical presentation. This is why in the absence of an appropriate patient's guide, most of these women turn to seek medical attention from several medical specialists and are at times mismanaged.

Due to the absence of this sector of reproductive health care in Cameroon, a large number of Cameroonian women in the menopausal group are completely neglected.

Therefore, the creation of menopausal clinics as an integral part of reproductive health delivery system appears necessary for the appropriate management of the many 'third age' women with severe menopause in Cameroon.

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