# The menopause disease

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**Abstract**

"Menopause" is not a disease as it is only the definitive stop of menstruations. The new concept of "menopause disease" results from a lack of androgens' production in woman after the definitive cessation of menstruations. This condition leads to functional symptoms, local consequences, and general ageing. Mesterolone is indicated for androgens' deficiencies in woman.

## Introduction

**Androgens in woman.** The technical term "androgen" includes *true androgens* such as *testosterone* and *dihydrotestosterone (DHT) active on their receptors*, but also *precursors* of androgens such as the dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (SDHEA) and A4-androstenedione, and androgens' *metabolites* among which androstanediol, androsterone and their glucuronides derivatives (which are the principal metabolites' representatives).

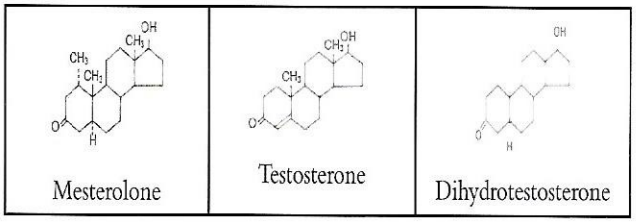
**Origin of androgen's production in woman.** Androgens' are produced daily in the ovaries, in the adrenals and in peripheral tissues constituting the total androgens' production. With ageing the daily androgen's production varies in those three pathways. When the ovaries' production of androgens decreases for one or another reason (ageing, oophorectomy, menopause) the total pool of androgens is diminished. When the total daily production is sufficient they are no symptoms of androgens' deficiencies. This explains why women don't suffer from androgens' deficiencies at the same age.

## Daily production of androgens during the normal menstrual cycle

| Androgens Productions in µg/day during the normal menstrual cycle | | | | | |
|---|---|---|---|---|---|
| | *Estra-diol* | *DHEA* | *DHEAS* | *Andro-stenedione* | *Testos-terone* |
| Proliferative phase | 40 | *5.000* | *15.000* | *4.000* | 200 |
| Secretory phase | 200 | *5.000* | *15.000* | *4.000* | 200 |

*Before menopause normal woman produces each day 5 fold more testosterone than estradiol in the proliferative phase and the same quantity in the secretory phase.*

## Mesterolone Testosterone and dihydrotestosterone




Depending from its *molecular structure* mesterolone has properties similar to those of testosterone and dihydrotestosterone.

## The clasical medical concept of menopause

The word "menopause" goes back to 1823. According to the dictionary this term means the end of the ovarian function characterized by the stop of ovulation and the menstrual hemorrhages (which are *physiological changes*). A second meaning means "the time when the menopause occurs (or more usually "the female climacteric". These vague definitions do not make possible to identify a disease and consequently its treatment.

The menopause presents obvious signs: the stopping of ovulation and the cessation of menses: *those conditions are physiological* and are not a disease.

The random administration of estrogens associated or not with progesterone or progestogens HRT (hormonal replacement therapy) is dedicated to failure and have even noxious effects.

The "Women's' health initiative" is a15-year project involves over 161,000 women ages 50-79, and is one of the most definitive, far reaching programs of research on women's health ever undertaken in the U.S. (www.whi.org). Results of the first HRT study on "Risks and Benefits of Estrogen plus Progestin in Healthy Postmenopausal Women" were published in 2002 (*JAMA. 2002; 288:321-333) (5)*. The conclusions about this randomized clinical trial of great scale relating to 16,608 old women from 50 to 79 years treated by Progestin (2.5 mg of medroxyprogesterone acetate) and estrogens (0,625 Mg of combined estrogens "equine") were:

| *Women taking estrogen plus progestin relative to placebo JAMA. 2002;288:321-333 (5)* |
|---|
| *Stroke rates increased by 41%* |
| *CHD (coronary heart disease) events was increased by 29%* |
| *Venous thromboembolism (VTE) 2-fold greater* |
| *Total cardiovascular disease increased by 22%* |
| *Breast cancer increased by 26%* |

The study was to proceed until 2005. It was stopped after a 5.2 years average of follow-up on July 9th, 2002. It was decided to continue the treatment containing estrogens alone among women with prior hysterectomy.

The Women's Health Initiative (WHI) Estrogen Alone (E-Alone) Trial was designed to assess the health benefits and risks of estrogen use in healthy postmenopausal women. In the WHI E-Alone Trial, 10,739 women with prior hysterectomy, aged 50-79 years, were assigned to take either estrogen alone (conjugated estrogens [Premarin®] or inactive (placebo) study pills. The National Institutes of Health stopped the E-Alone Trial ahead of schedule in February 2004 primarily because of an **increased stroke risk** for women taking study pills with estrogen alone.

Even after the Women's Health Initiative (WHI) found that the risks of menopausal hormone therapy (hormone therapy) outweighed benefit for asymptomatic women, about half of gynecologists in the United States continued to believe that hormones benefited women's health. The pharmaceutical industry has supported publication of articles in medical journals for marketing purposes (6).

In June 2011 the U.S. Supreme Court refused to hear a Pfizer Inc. unit's appeal of a $58 million award in a case against Premarin (estrogens) and Prempro (estrogens plus medroxyprogesterone acetate) menopause drugs.Three Nevada women who contracted breast cancer after taking the company's menopause drugs were awarded the amount in a 2007 case.

The rebuff leaves the amount as the largest to be upheld on appeal in thousands of hormone-replacement drug suits. Over six million women took Prempro and other menopause drugs before a 2002 study pointed out their links to cancer. At one point Pfizer and his units faced more than 10,000 claims, according to lawyers for former user.

## Androgens' deficiencies before menopause

Testosterone secretion decreases regularly from the age of 20 in woman: The expected Testosterone

concentration in the blood of a woman of 40 would be about half that of a woman of 21 (2).

***Oral contraceptive troubles***

| *Consequences of oral contraceptive troubles with Decrease of androgen ovarian synthesis Harrison's Principles of internal medicine – (endocrinology and metabolism), 1988.* | |
|---|---|
| *Thrombosis of the Deep Veins* | *Hypertension (14/9) after 5 years of continuous use ( 5% of the cases)* |
| *Pulmonary embolism (risks x 2 to 12)* | *Disturbances of the plasmatic lipoproteins.* |
| *Cerebral thromboembolism (risks x 3 to 9)* | *Resistance to insulin.* |
| *Cerebral hemorrhage (risks x 2)* | |

Women using OCs (OC=Oral contraceptive) had significantly lower serum androgen levels compared to naturally cycling women and free testosterone levels displayed an inverse relation to breast epithelial proliferation (3).

OC use, however, has been associated with women's sexual health complaints and androgen insufficiency. OC use is associated with a decrease of androgen ovarian synthesis and an increase in the production of sex hormone-binding globulin (SHBG) even months after the stop of OC. *Troubles may persist after stopping the OC(4).*

Bilateral oophorectomy: In this condition balance between estradiol and progesterone could be impaired leading to fibromyoma of the uterus, spotting and bleeding. Androgen's deficiency will be also considered in those cases.

Mesterolone therapy will benefit to all those cases with persisting troubles due to the decreased testosterone and dihydrotestosterone secretions.

**Androgens' deficiencies after menopause**

**The menopause disease**

To understand this disease of ageing it is advisable to establish a precise definition of it. I propound the following definition:The menopause disease is the whole of the physiopathological and psychopathological modifications brought out by the stop of the ovarian androgens' production.

**Cause**

The ovaries secrete estradiol, progesterone and testosterone. The cessation of estradiol and progesterone are linked with the stop of ovulation and of menstrual hemorrhages which are physiological changes. The drastic reduction in the secretion of androgens hormones by the ovaries (at an age where the production of androgens by the suprarenal glands is already decreased) is generally not taken into account and brings about the menopause disease.

**Blood rates of ovarian hormones in woman before menopause.** *Estradiol*: its blood rate varies from 0.06 nanograms per milliliter in the proliferative part of the menstrual cycle towards 0.2 nanograms per milliliter in the secretory part of the menstrual cycle. *Testosterone*: its rate is on average of 0.57 + 0, 19 nanograms per milliliter throughout all ovarian cycle and dihydrotestosterone levels are commonly the half of the testosterone rates in healthy women (1-p.432). *Progesterone*: its blood rate varies from 0.3 to 1.5 nanograms per milliliter (in the proliferative part of the menstrual cycle towards 3 to 20 nanograms per milliliter in the secretary part of the menstrual cycle.

| Woman before menopause : Plasmatic hormonal Concentrations in ng /ml (1) | | | | |
|---|---|---|---|---|
| | *Estradiol* | *Progesterone* | *Testosterone* | *Dihydrotestosterone (DHT)* |
| Proliferative phase | 0.06 | 0,3-1,5 | 0.57 ± 0,19 | 0,27± 0.06 |
| 24 hours before ovulation | 0.6 | | | |
| Secretory phase | 0.2 | 3-20 | 0.57 ± 0,19 | 0,27± 0.06 |

In woman concentration of testosterone in plasma is always greater than estradiol concentration (1). The plasma concentration of testosterone is + or – 10 fold the level of estradiol during the proliferative

phase and + or – 3 fold the level of estradiol during the secretory phase. Serum levels of testosterone increases during ovulation (Direct RIA) in normal menstrual cycle (7).

**Daily production of ovarian hormones.** Estradiol: its daily production varies from 40 micrograms per day in the proliferative part of the menstrual cycle around 200 micrograms per day in the secretary part of the menstrual cycle. Testosterone: its daily production is of 200 micrograms throughout all ovarian cycle. The progesterone: its daily production is of 4,200 micrograms during the proliferative phase of the ovarian cycle and of 42.000 micrograms in the secretary part of the menstrual cycle.

| *Woman before menopause : Normal daily hormonal production (µg/day) (1)* | | | |
|---|---|---|---|
| | *Estradiol* | *Progesterone* | *Testosterone* |
| Proliferative phase | 40 | 4.200 | 200 |
| Secretory phase | 200 | 42.000 | 200 |

**The secretion of these three hormones stops in the ovaries at the time of the menopause.** The secretory and proliferative cycle controlled by estradiol and progesterone intended to fertilize ovules does not exist any more after the "stop of the menses". One can logically wonder which reason would justify a systematic replacement of these hormones except the fact of wanting to prolong in time an ovarian cycle become useless in the absence of ovulation. The total production of testosterone during a menstrual cycle is more important in quantity compared with the production of estradiol. Consequently one is in right to ask for why estradiol substitution was proposed in the past by neglecting the production of testosterone? The sharp fall of front testosterone secretion at the time and after the stop of menses is responsible for most of the disorders caused by the menopause disease.

## CONSEQUENCES AND SYMPTOMS

The reduction in androgens' production causes in woman to different degree:

**Functional symptoms**: hot flashes, irritability, intestinal distension, swollen legs.

**Local consequences**:

**The masculine genitalia of woman are**: The clitoris and its foreskin, the labia majora, the bladder neck (= Inner part of urethra = Homology with the prostate musculature in man)

**Local symptoms** resulting from of masculine genitalia involutions are Chronic cystitis, incontinence, urgencies, (sclerosis of bladder neck); Painful or difficult copulation (sclerosis of vulva) as consequences of a lack of dihydrotestosterone production (lack of testosterone leads to a decreased production of dihydrotestosterone).

Balanced treatment with male hormones (mesterolone) is indicated in menopause disease as in andropause disease. This fact is generally ignored so that the administration of estradiol (or estrogens) associated or not with progesterone or progestogens doesn't constitute the treatment for the menopause disease whose I gave the definition (androgens' deficiencies). One can even wonder whether the "traditional" treatments of hormonal replacement therapy (HRT) do not worsen the state of good health. See: www.whi.org

**General consequences**: lipids' disorders, vascular disorders, weakness, hyper coagulation, venous thromboses, rheumatic problems, nervous breakdown, cerebral involution, and Alzheimer's disease. These consequences are wrongfully allotted to the lack of estradiol and progesterone (a polluted concept) whereas in fact they are the consequences of a lack of male hormones (*testosterone* for general consequences and *dihydrotestosterone* for local genital involution).

**General Symptoms** are the same in man suffering from andropause disease described for the first time in 1988. See: http://www. man.uk.georgesdebled. org/history andropause.htm

### Treatment of in androgens' deficiencies and of menopause disease with mesterolone

Orally administration of mesterolone in amounts between 5 milligrams and 25 milligrams per day constitutes the specific treatment. Each treatment is *unique* for each woman after complete biological check up. If there is no symptom, there is no disease.

If there is no disease no *curative* treatment is necessary. The treatment *covers all indications for androgens with women.*

Mesterolone is a hormone prescribed for man to compensate a lack of production of androgens. Used for man since 1967 it is henceforth in the public domain. Its manufacturing technique is known. No harmfulness was described to date. Before menopause woman secretes each day of the cycle 0.2 milligrams of testosterone = 200 micrograms or 200,000 nanograms or 200,000,000 picograms. Mesterolone makes it possible to replace androgens whose production is strongly decreased in woman with menopause disease. It requires a traditional compounding.

| **Testosterone and Dihydrotestosterone (DHT) deficiencies produce** | | |
|---|---|---|
| | **Symptoms** | **Pathology** |
| **Functional symptoms** | hot flashes<br>intestinal distension<br>swollen legs | weakness of all smooth musculatures of arteries, veins and bowel (6,5 meters of smooth musculature for the small intestine;1,5 meters of smooth musculature for the large intestine) |
| **Local consequences** | chronic cystitis, incontinence, urgencies incontinence)<br>dyspareunia (painful or difficult copulation) | sclerosis and inflammation of bladder neck<br>sclerosis of vulva |
| **Cardiovascular risk** | lipids' disorders<br>vascular disorders<br>hyper coagulation<br>venous thromboses<br>diabetes 2 | Low testosterone levels predict all-cause mortality and cardiovascular events in women: a prospective cohort study in German primary care patients (12). |
| **Loco motor system disabilities** | weakness<br>muscular atrophy<br>rheumatic problems | Women with higher free T levels have greater lean body mass consistent with the anabolic effect of T. Bone density is associated with T levels (13).<br>Connective Tissue Changes of Aging in postmenopausal woman (14). |
| **Cerebral consequences** | irritability<br>nervous breakdown<br>cerebral involution<br>Alzheimer's disease | Comparing women with and without AD (Alzheimer disease), *Female brains* levels of estrogens and androgens are lower in AD cases aged 80 years and older. Age-related depletion of androgens and estrogens in women may be relevant to development of AD (15) |

**Why is mesterolone the treatment for androgen's deficiencies in woman?** Mesterolone cannot be aromatized in estradiol (contrary to testosterone). Its methyl radical inserted on Carbon 1 of the testosterone confers this property. At physiological doses Mesterolone does not influence the secretion of the pituitary gland so that the secretion of LH is not modified (contrary to testosterone). Mesterolone prescribed in small amounts adds its effects to those of testosterone secreted by the organism. With the prescribed physiological pharmacological amounts doping is impossible and the overdose too. Mesterolone is prescribed orally in amounts varying between 5 milligrams and ten milligrams per day approximately. A substitution amount of 25 milligrams per day can be considered. The secretion of LH by the pituitary gland is not inhibited (contrary to testosterone). Mesterolone molecular structure has characteristics of dihydrotestosterone (DHT) which is directly effective on the masculine sex organs of women (clitoris, labia majora and bladder neck) and on brain tissue (preventing Alzheimer's disease) (15). Mesterolone can be prescribed alone.

No risks of virilism with mesterolone treatment. The treatment of androgen's deficiency simply consists in replacing missing secretions of testosterone (and dihydrotestosterone) thanks to mesterolone

properties. In this case the woman finds simply her former physiological state and prevents the disastrous consequences described above. Mesterolone used in small amounts allows that. Virilism secondary to an excessive administration of mesterolone should be the consequence of a doping which must be avoided in all cases.Virilism doesn't exist at physiological doses.

**Androgen's scientific biological deficit diagnosis background.** Concerning the determination of testosterone and dihydrotestosterone in serum, The GC-MS (Gas Chromatography- Mass Spectrometry) is the most precise method *(8)*. Direct RIA studies are significant *(9)*. Androgen glucuronides, instead of testosterone, are interesting markers of androgenic activity in women (10*)*.

In our study the scientific biological diagnosis of androgen's deficiencies is made on the total "pool" of androgens (RIA) in men since 1974 and in women since 1998 concluding that the level of androgens' daily production is a key diagnosis. This method led us to the concept of andropause disease (which is different from hypogonadism) which treatment is made with mesterolone. The 10 years' study on androgens' deficiencies in women is founded on RIA analyses made by a reference laboratory (Liege University, CHU, and Liege, Belgium).

The androgens' pool study reflects the daily production of androgens. Androgens in serum (RIA) are: Total testosterone, Dihydrotestosterone, Androstanediol glucuronide, Androsterone glucuronide, DHEA, DHEA Sulfate, Δ4-Androstenedione. Metabolites in urine over 24 hours are: Total 17 ketosteroids, Complete Chromatography of 17 ketosteroids, Androstanediol glucuronides.

**Clinical and biological diagnosis of androgen's deficit.** Our study concludes that symptoms of androgens' deficiencies in women are correlated with *a low daily production of androgens* reflected by low serum androgens' levels and low levels of metabolites in serum and urine over 24 hours (the androgens' pool study) leading to treat those women successfully with mesterolone since 1998 with spectacular results and without any side effect.

**The general practice for androgens' deficit in woman.** If there is no symptom there is no disease. And if there is no disease no treatment is necessary. More than 50 women are followed since 10 years. Our 10 years experience with mesterolone prescription for androgen's deficit in general practice will continue as an increased number of women ask to follow this treatment. Hormonal substitution is founded on the clinical story and on a simplified hormonal and biological check up (which is not expensive) for each case individually (11).

Each general practitioner, each gynecologist, each doctor will be aware of: The clinical diagnosis of androgens' deficiencies in women. The simplified and non expensive biological diagnosis of androgens' deficiencies in women. The successful and cheap treatment of androgens' deficiencies in women with mesterolone.

The global androgens' pool was evaluated for research purpose. A simplified biological diagnosis is often enough in general practice. The masculine genitalia of woman depend of the strong male hormone (dihydrotestosterone) like male genitalia. Difficult copulation, poor sensitivity of the clitoris and consequently lack of libido are the consequences of a lack of the strong male hormone (dihydrotestosterone) production which lack doesn't induces effects on the masculine genitalia of woman. Those sexual problems are improved with mesterolone which molecular structure is similar to the dihydrotestosterone structure.

Incontinence, urgencies, chronic cystitis and devastating disorder of interstitial cystitis can be the consequences of a bladder neck sclerosis and inflammation. Numerous bladder neck scleroses in women are the consequences of androgens' deficiencies (mainly dihydrotestosterone) before menopause (oral contraceptive) or after menopause (menopause disease: see above). Those bladder neck consequences (Incontinence, urgencies, chronic cystitis and devastating disorder of interstitial cystitis) due to androgens' deficiencies may improve with mesterolone. Results can be spectacular. Bladder neck fibrosis provokes hypertrophy of bladder musculature or weak bladder musculature. Bad opening of bladder

neck leads to secondary narrowing of terminal ureter, hypertension in upper urinary tract and bad function of the kidneys. In summary: destruction of the urinary tract (16).

Mesterolone treatment has cured spectacularly a woman with proved androgens' deficiency (The Georges Debled's study) whose bladder neck was congestive with abnormal sensitivity. Urologist of this woman had proposed an endoscopic surgery which was postponed thanks the mesterolone treatment. This woman is free of symptoms since 8 years. There exists no description of mesterolone effect on bladder neck in the world medical literature. Those findings are disclosed here for the first time.

We have an experience about bladder neck sclerosis (and its endoscopic surgery) in woman since 1974. The role of dihydrotestosterone on the woman's bladder neck and the benefit effect of mesterolone on this pathology need future investigations.

**About mesterolone in woman.** It was not possible to publish those conclusions before because consequences of menopause were wrongfully allotted to the lack of estradiol and progesterone. This polluted concept is still considered as a "dogma" by doctors in general. Even more import and prescription of mesterolone are not permitted by the US government. Manufacturers reserved mesterolone only for men. Our study was conducted during the last ten years after the first conclusions of the WHI study in 2002. The study was possible in Europe where mesterolone is available under traditional compounding. After the conclusions of the WHI study to date and the recent judgment (June 2011) of the U.S. Supreme Court *(17)* we disclose here for the first time in a medical review the conclusions of our study on mesterolone treatment for androgens' deficiencies in woman which is the real solution in the world for women with androgens' deficiencies before and after menopause.

## Conclusion

The menopause disease is a clinical entity with a specific cause, consequences and treatment. It is the consequence of a failure in androgens' productions which should be replaced. **With the help of governments and of manufacturers** exhaustive studies will be made to specify contours of mesterolone as treatment for androgens' deficiencies in women. These future studies on large scale will be conducted within the general framework of biology of ageing.

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www.woman.uk.georgesdebled.org/menopause disease.htm

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17. High Court Rejects Pfizer Hormone Therapy Lawsuit Appeal Date Published: Wednesday, June 22nd, 2011. The U.S. Supreme Court refused to hear a Pfizer Inc. unit's appeal of a $58 million award in a case against Premarin and Prempro menopause drugs. Three Nevada women who contracted breast cancer after taking the company's menopause drugs were awarded the amount in a 2007 case. The rebuff leaves the amount as the largest to be upheld on appeal in thousands of hormone replacement drug suits. Over six million women took Prempro and other menopause drugs before a 2002 study pointed out their links to cancer. At one point Pfizer and his units faced more than 10,000 claims, according to lawyers for former users. The Nevada Supreme Court concluded jurors properly held Pfizer's Wyeth unit responsible for hiding the breast cancer risks of Premarin and Prempro. The original 2007 case resulted in an award totaling $134.1 million to Arlene Rowatt, Jeraldine Scofield and Pamela Forrester. The trial judge later reduced the verdict to $57.6 million. Yearly sales of Wyeth's hormone replacement drugs exceeded $2 billion before a 2002 study, sponsored by the U.S. National Institutes of Health, suggesting that women using the medicines had a 24 percent higher risk of breast cancer. Pfizer, the world's largest drug maker, acquired Wyeth in 2009 settled a third of the pending cases over its Prempro menopause drug. The company said last month that it set aside $772 million to resolve claims over the medicine.