DEFINITION AND PATHOPHYSIOLOGY

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DEFINITION

The definition of menopause is still relatively new and originates from the 19th century. Menopause designates that point of time at which the last menstrual cycle, that is the last uterine bleeding under ovarian hormonal control, ceases. However, this can only be recognized in retrospect when no further bleeding occurs during the course of the following year and thus still includes that year.

Whilst the menopause is clearly defined as the point in time, or more precisely as a period of time, the definition of the time periods prior to and following this are from the linguistic usage point of view frequently indistinct and inhomogeneous [1]. Hence it is understandable that today we use these terms rather generously, which sometimes can give rise to misunderstandings. For this reason an attempt is being made in this chapter to list and define the more commonly used expressions and thus try to create more clarity.

Menopause: The period of time from the last spontaneously occurring menstrual bleeding controlled by the ovaries and a year thereafter (which however can only be determined after one year has elapsed).

Perimenopause: This term is used to describe a variable period of time of some years prior to but also after the menopause during which time the characteristic symptoms pointing to a declining ovarian function already manifest themselves.

Premenopause: This, in the narrower sense, is the period of time spanning some years before the onset of the menopause which is characterised by progesterone and oestrogen deficiency. During this time both vegetative symptoms and also bleeding irregularities may become manifest. In the wider sense the premenopause encompasses the entire period of the fertile phase prior to the menopause, that is the time from the menarche to the menopause.

Postmenopause: This is the overall period of time starting after the menopause (12 months of amenorrhoea), which also can be defined as extending from the end of the menopause to the senium.

Senium: This is the phase of life which in the past started from approximately 65 years of age, and nowadays has shifted more towards the age of 70 years and upwards.

Climacteric: Generally speaking this means the change of life, that is a period of time during which hormone deficiency (progesterone, estrogen) along with menstrual irregularities and various symptoms related to a lack of hormones are noticed. The climacteric begins in the premenopause and extends over a variable period of time up to some years into the postmenopause.

Climacterium praecox *(premature menopause, preterm or early onset of the menopause)*: This terms describes the premature onset of the last menstrual bleeding, which individual au-

thors assess very differently in terms of age, and occurs in women between the age of 35 to 45 years.

Climacterium tardum: Menopause which sets in late after the age of 54 years.

Iatrogenic menopause: It occurs as a result of radiological, cytostatic or surgical interventions which have to be undertaken prior to reaching the natural menopause. In this context, hormone withdrawal symptoms occur which are substantially more abrupt and thus are experienced much more intensely and severely.

Pathophysiology

FSH and LH levels in the serum significantly increase in and after the menopause, due to the subsiding ovarian function, compared to the levels in sexually mature women. These high values remain at about this level until the onset of the senium when they start to drop again due to an age related involution of the pituitary gland. They then remain more or less steady at a slightly increased level until the end of life.

The hormonal characteristics of the menopause or postmenopause respectively are an increase of LH and FSH levels accompanied by a **decrease of estrogens and progesterone** which is partly associated with a **relative androgen predominance**. There are increasingly more anovulatory cycles and menstruation becomes more irregular until it finally ceases altogether. This relative general failure of ovarian steroid production affects above all the hypothalamo-pituitary axis via the negative feedback mechanism. Hence the onset of the climacterium can be determined comparatively easily by monitoring serum FSH and E_2 at the beginning of the cycle on days 3–6 (FSH > 30 mU/ml). However, there should be at least 2–3 control measurements at intervals of 3 months in order to obtain a reliable diagnosis.

The main reason for the occurrence of the various climacteric symptoms can be attributed to the ceasing of hormone production by the ovaries. The ovaries are among the few glands which cease to function prematurely, that is a comparatively long time before the end of life, when reduced hormone production starts with a decrease in progesterone and progresses through the ceasing of estrogen production to finally reach a point when no more androgen is produced, which can continue until an age of sixty or above when its function completely stops. Androgens, in particular androstendione and testosterone, continue to be produced in the hilum and interstitial cells even after the menopause. However, conversion of androgens into estradiol in the ovary is lost because the aromatase enzyme system is closely connected with and dependent on the granulosa cells [3].

The suprarenal cortex function only reveals much later, that is in the senium, markedly smaller decreases in dehydroepiandrosterone, androstendione, androsterone-3β, 17β-diol and testosterone secretion, which are recognized as the precursors of estrogen production [4].

During the menopausal and postmenopausal periods the thyroid gland does not show any significant changes in its hormone production, that is thyroid disorders on the whole do not occur more frequently in the climacteric than in younger years.

The cause for the onset of the menopause is an increasing decline of ovarian function due to follicle degeneration (atresia). As life progresses there

is a continuing reduction of a large number of preformed follicles, so that at around the age of 50 years only few primordial ovarian follicles remain which still respond to gonadotropin secretion and are able to mature into a follicle. With the onset of the climacteric the number of primordial ovarian follicles present in the ovary has dropped from about 500,000 in puberty to only a few thousand. Due to the declining number of ovulations and hence the lack of luteal production in the second half of the cycle, progesterone levels drop followed by tempo abnormalities and irregularities in the intensity of bleeding. In addition there is also a decrease in estrogen production [5–7].

The steady decrease of organ weight presents an additional limiting factor for ovarian function. The maximal ovarian weight peaks between 25 and 30 years of age after which time it slowly but regularly decreases. Hence an atrophic ovary in the senium merely weighs about a third of that of a fully functional one. The decrease in weight is triggered by the sclerosing hilum vessels with a subsequently reduced perfusion as well as increased connective tissue deposits and thickening of the capsule.

It is interesting that these changes in the ovaries show only slight variations between the races in the age when they occur. Thus the age when the menopause sets in only presents with insignificant variations between black and white women throughout America [8]. On the other hand socio-economic differences are discussed. Women of a low social standing and low income experience an earlier onset of the menopause than women of a higher social status. In a comparison of development countries with western industrialized nations differences also appear to exist both in the age when the menarche first occurs and the age when the menopause sets in. Due to a better nutritional status in industrialized nations, in addition to the body growing taller there is also an earlier occurrence of the menarche and a later onset of the menopause [9].

On the other hand, however, the life-style in the western hemisphere also has an increasingly negative effect on the menopausal age. In a multicentre study Kaufmann could demonstrate that increased nicotine consumption can bring forward the menopausal age by up to two years [10]. Consumption of nicotine results in greater ovarian vasoconstriction which in turn leads to reduced oxygen transport by bound haemoglobin and thus an insufficient blood supply to and restricted estrogen production in the ovary. In addition, aromatising of androgens as precursors of estrogen is inhibited by other components contained in cigarettes. Moreover, the resulting insufficient production of estrogen can also be considered as a contributory factor of an increased osteoporosis risk in women who smoke.

The climacteric syndrome, which is implied in the collective term of "climacteric problems" through a number of signs and symptoms, represents as such the typical pattern of complaints as a sequelae of relative estrogen deficiency, starting in the perimenopause,

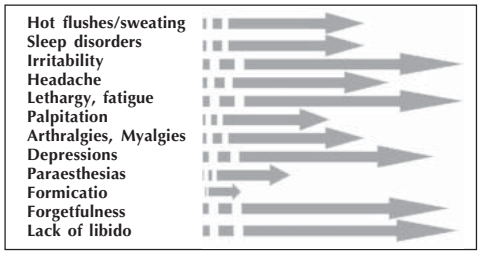

Figure 1. Frequency of climacteric symptoms in women between 45 and 54 years of age.

which can extend over a variable period of time and even span several years until the postmenopause is reached. This comprises several hormone related components such as the estrogen deficiency syndrome, problems associated with a relative excess amount of estrogen and lack of progesterone (all these occur at the start of the climacterium) and problems which can result from estrogen/gestagen replacement therapy [11]. These can be classified as:

- Vasomotor-vegetative disorders such as hot flushes, sweating, circulatory instability;
- psychological disorders such as lack of motivation, lack of concentration, depressive mood, insomnia, increasing nervousness;
- organic disorders such as local atrophy in the region of the urogenital tract associated with atrophic colpitis, discharge, incontinence and cohabitation problems, dyspareunia; generalised atrophy of the skin accompanied by dehydration and wrinkling, hirsutism and effluvium; occurrence of osteoporosis in approximately one third of all climacteric women,
- disturbance of the fat metabolism: decreased HDL-lipoproteins and increased LDL-lipoproteins promoting arteriosclerosis accompanied by an increased risk of myocardial infarction and a stroke [12].

Despite all our knowledge to date, climacteric problems which women experience in great variety and the signs and symptoms as well as their intensity which can vary considerably between individuals could so far not be completely investigated and explained. The occurrence of these problems appears to be influenced by several factors:

1. The level of estrogen loss and the rate of estrogen drop.
2. A genetically related or acquired tendency to resist more easily, or with greater difficulty, the ageing process in psychological as well as physical terms.
3. Effects of a racial, sociocultural and educational nature which determine how to deal with and overcome any occurring problems.

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