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Review Article

Advances in the Pathogenesis of Perimenopausal Syndrome

Zhiyong Cao[1,2], Ke Lu[1,2], Jingqin Chen[1], Gang Fang[1]

[1]Guangxi Zhuang Yao Medicine Center of Engineering and Technology, Guangxi University of Chinese Medicine, Nanning 530200, China

[2]Department of Medicine, Hubei Minzu University, Enshi 445000, China

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Abstract: Perimenopause syndrome refers to the syndrome of the disorders of multiple systems of women around menopause caused by the reduction in secreted estrogen and is also known as menopause syndrome. Its pathogenesis involves increasing age, the abatement of ovarian function, and psychological change caused by the increasing life pressure. The above factors lead to physical and mental changes in postmenopausal women. This paper summarizes the pathogenesis of perimenopause from the perspective of gene studies and existing experimental studies and provide some ideas for clinical treatment and research.

Keywords: Perimenopausal period; Genes; Endocrine; Pathogenesis; Climacteric syndrome

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Corresponding author: Fang Gang, fglzyznn@yeah.net.

1 Introduction

Perimenopause refers to a series of neuroendocrine changes in the period from middle age to old age in women around menopause. With the increase in the age of a woman, the dysfunctions of gonads and other endocrine glands occur. These changes cause menstrual disorders and the imbalances in psychological, physiological and other aspects. In addition, with the rapid development of modern society, social factors also produce more mental and physical pressures on perimenopausal women. The troubles faced by perimenopausal women are caused by a combination of psychological, physiological and social factors, which are also the root cause for perimenopausal syndrome in most women[1]. The incidence of perimenopausal syndrome is accompanied by the changes in a large number of gene functions and its pathogenesis mainly involves endocrine, neurotransmitter, vascular factors, immune factors and free radicals.

2 Gene function changes of perimenopausal syndrome acquired based on bioinformatics

2.1 Methods

2.1.1 Acquisition of disease genes

In the website of Genecards (https://www.genecards.org/), the functional changes of those genes involved in the occurrence of perimenopausal syndrome were acquired.

2.1.2 Construction of PPI network diagram of disease genes

In the website (https://string-db.org/), the disease-related genes were imported to construct PPI network diagram.

2.1.3 Analysis of pathological gene data

In the website (http://www.webgestalt.org/), disease genes were imported for GO analysis and compared with the data in David Database. KEGG signal pathway analysis of genes was performed.

2.2 Results

2.2.1 Acquired disease genes

In the website of GeneCards (https://www.genecards.org/), the keyword of Perimenopausal syndrome was searched. The changes of the functions of a total of 157 genes are involved in Perimenopausal syndrome (Table 1).

Table 1. Diseased genes

BGLAP	SHBG	ESR1	LEP	VDR	IGFBP3	CYP19A1	CD36	APOE	CYP1B1	HMOX1
TNFRSF11B	PRL	CYP1A1	CALCA	COL1A1	IGFBP1	SLPI	ESR2	IL6	INS	PGR
MAPK2	DUSP1	BDNF	CGA	IL17A	ERBB2	IGF1	TNNT2	CRP	LEPQTL1	SLC6A4
CDKN1C	LGR6	SERPINE1	CTSK	AKR1C4	HSD17B1	ADIPOQ	PTH	IL6R	ALPP	IGFBP2
LEFTY2	IGF2	PAX5	GNRH1	APOA1	TNFRSF1B	EDN1	INHA	SOST	IFNG	IL4
APOC3	AMH	COMT	LRP5	PLAT	TPO	CCL2	IL1B	CCL4	GHRL	TNF
IL13	GAL	CXCL8	IL7	CSF3	PTEN	PPARG	PROC	F5	F11	NPPB
INHBB	IBSP	MTHFR	CDK4	CDK2	CYP3A4	CDC25A	STS	CYP1A2	NPY	SULT1E1
SULT1A1	CCK	RARRES2	MAOA	TFF1	VEGFA	DES	CETP	P2RX7	CSF1	VIP
TP53	AR	CTSD	TGFB1	LPL	TGFB2	VIM	CYP17A1	ACE	TNFRSF11A	SP1
GPER1	CSF1R	NGF	PTPRC	SPARC	BRCA1	KRAS	CAT	MLH1	NR1H2	FSHR
TNFSF11	NR1H3	TGFA	FST	CALCR	VEGFC	KLK3	SPP1	PON1	VCAM1	NR1I2
APOB	LIPC	SELE	CS	CRH	RBP4	TCIRG1	ALOX12	ADRB3	GIPR	IGFBP4
TSPO	COL14A1	KRT7	TEP1	TERC	LOC111589215	LOC110806262	IL10	IL5	THBD	RETN
ACTC1	GC	LIF								

2.2.2 PPI network diagram

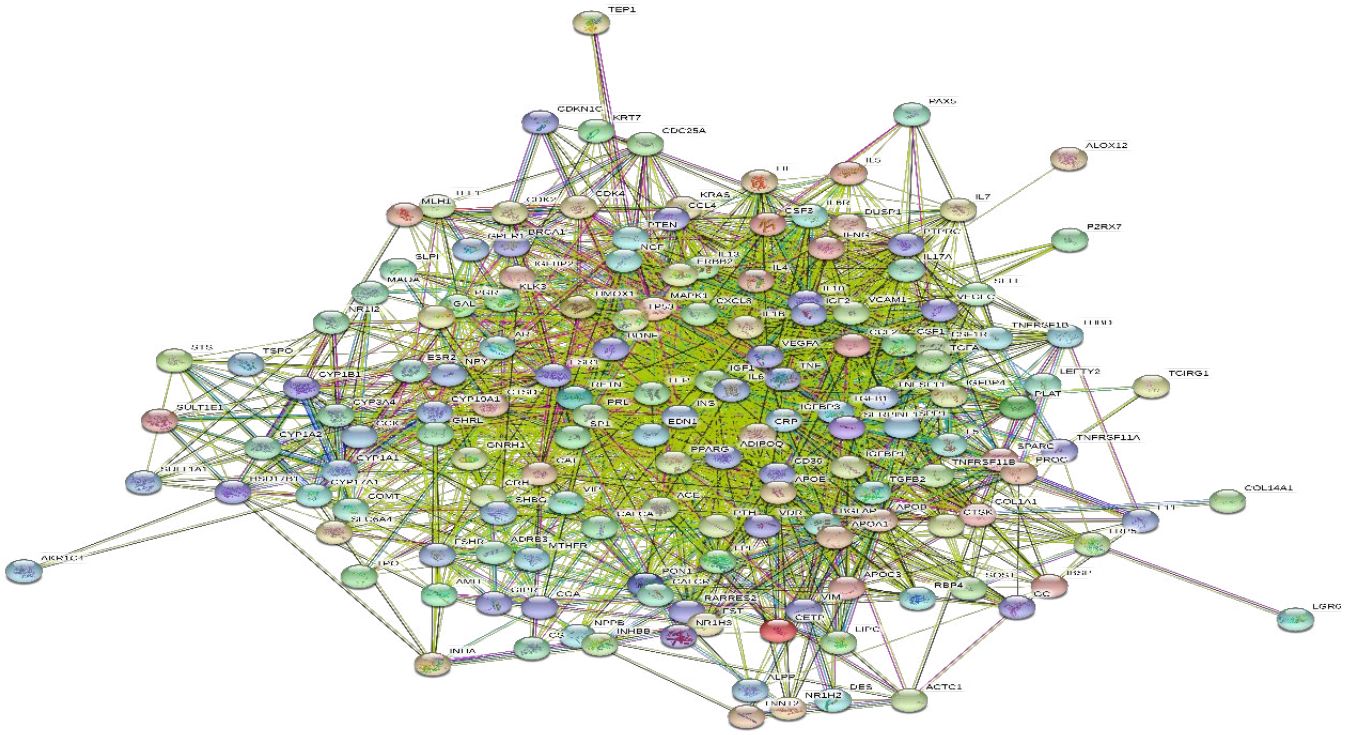

Figure 1. PPI network diagram.

The PPI network has 154 nodes, 2240 edges, an average node degree of 29.1, an average local clustering coefficient of 0.616, and a total of 606 expected edges (p <1.0e-16). In the whole PPI network diagram (Figure 1.), proteins such as ACE, APOE, APOB, APOA1, TGFB1, CXCL8, ESR1, VEGFA, TP53, TNF, TNFSH11, VCAM1, IGF1, PTEN, LEP, INS, MAPK2 and CRP interact closely with other proteins, indicating that they play an important role in the occurrence and development of perimenopause syndrome. In addition, cytokines IL-6, IL-6R, IL-4, IL-10, IL-5, IL-13, IL-7 and IL-1B are also closely related to the incidence of perimenopausal syndrome. In the perimenopausal period, the estrogen secretion, immunity, inflammatory response, angiogenesis and growth and development are significantly changed. These changes may be the causes for perimenopausal syndrome in women.

2.2.3 Pathological gene data analysis

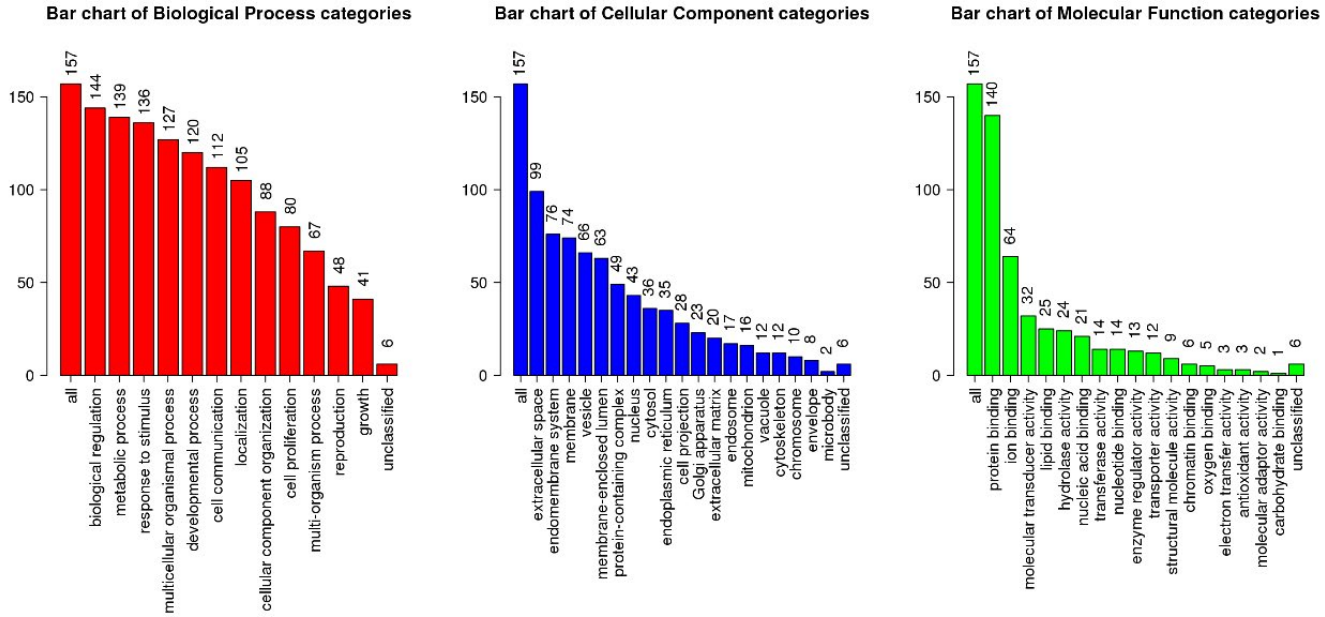

Figure 2. GO analysis diagram.

The disease genes are imported into the website (http://www.webgestalt.org/) for go analysis and compared with the data in DAVID Database (P<0.05, FDR<0.01). In total, 157 disease-related genes are closely related to growth, development, inflammatory response, aging, immune response, cell proliferation, cell association, estrogen metabolism, response to estradiol, and response to nutrients in the biological process (BP). The 157 genes that cause lesions in the perimenopausal period are closely related to the fever, estrogen secretion and senescence in perimenopausal period. In terms of cellular components (CC), 157 pathogenic genes are closely related to extracellular regions, extracellular matrix, outer plasmas, nuclei, endoplasmic reticulum lumen, cytokines and other factors. In terms of molecular function (MF), 157 genes are closely related to protein binding, cytokine activity, growth factor activity, hormone activity, receptor binding, enzyme binding, steroid hormone receptor and other factors (Figure 2.).

2.2.4 KEGG signaling pathway analysis

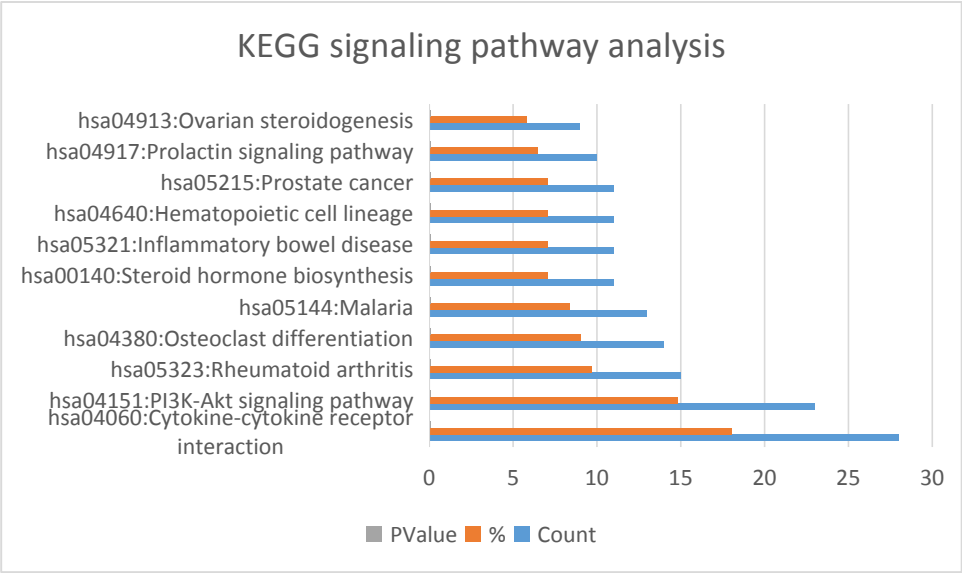

Figure 3. KEGG signaling pathway analysis (P<0.05, FDR<0.01).

The 157 genes are involved in cytokine-cytokine receptor interaction, PI3K Akt signaling pathway, rheumatoid arthritis signaling pathway, osteoclast differentiation, malaria (hsa05144: malaria), steroid biosynthesis (hsa00140: steroid hormone biosynthesis), inflammatory bowel disease (IBD), ovarian steroidogenesis (hsa04913: ovarian sterogenesis) and hematopoietic cell line (hsa04640: hematopoietic cell lineage) and these genes may lead to perimenopause syndrome through the above signal pathways (Figure 3.). It is worth mentioning that the pathological genes of perimenopause are also closely related to prostate cancer (hsa05215: prostate cancer), indicating that men in "perimenopause period" (40-60 years old) might have a high risk of prostate cancer. In the "perimenopause period", both women and men face the high risk of disease and need more care. The relationships between genes and pathways were imported into the software of Cytoscape 3.7.1 to construct the pathway gene relationship diagram (Figure 4.). Tumor necrosis factor (TNF), related TNF family genes, Interleukin-1B (IL-1B) and interleukin family genes are closely related to the pathways, indicating that inflammatory genes are highly expressed in perimenopausal syndrome.

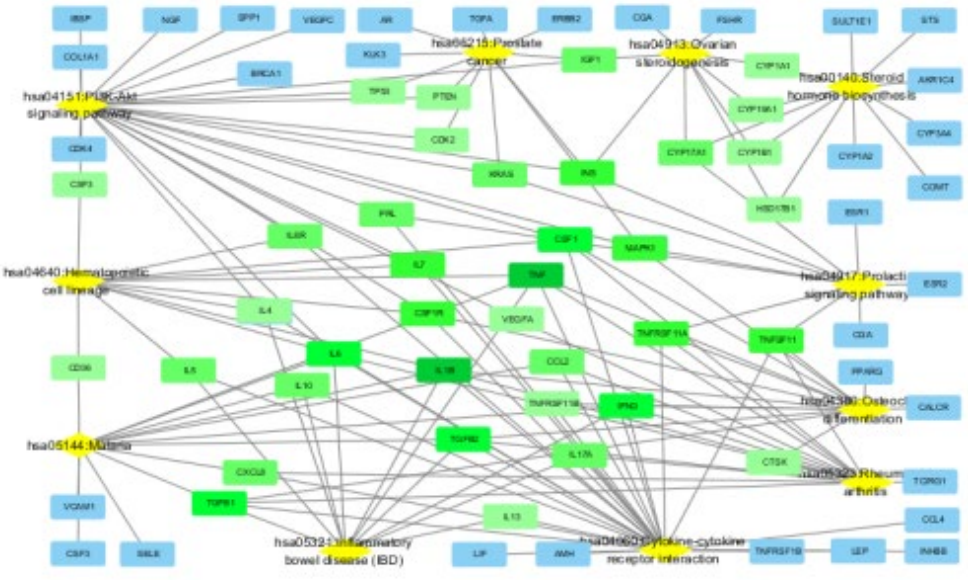

Figure 4. Pathway-gene relationship (yellow is the pathway; light blue is the independent gene-pathway, and the darker colors of other genes indicate the more related pathways).

The above analysis indicates that the occurrence of perimenopause syndrome is closely related to the body aging from the perspective of gene changes. Growth, development, abnormal estrogen, sterol hormone and other hormones, and immune response are closely related to the occurrence of the disease. The disease may be accompanied by inflammation. In this physiological stage, the risks of some diseases such as internal rheumatoid arthritis, intestinal inflammation and reproductive system diseases are high. Relevant prevention measures should be adopted in this stage.

3 Pathogenesis of perimenopausal syndrome

In 1994, World Health Organization introduced the term "perimenopause" instead of "menopause" to describe the normal transition from sexual maturity to old age. In 2012, the recommended reproductive senescence staging standard (STRAW+10) was approved again by the International Reproductive Senescence Staging Collaboration Group. In the standard, perimenopause starts from the menopause transition period and ends in 1 year after menopause (FMP)[2]. At present, perimenopause is recognized as an important life stage that cannot be ignored by women. In this stage of life, the onset of perimenopausal syndrome is related to hormonal, free radical, immune, neurotransmitter and vascular factors.

3.1 Hormones of the endocrine systems

In the perimenopausal period, the whole function of women declines. Especially, the ovarian function declines the most significantly, accompanied by the obvious change in the endocrine system, thus causing a series of physical, mental and psychological symptoms and even diseases and affecting the life quality of female in this stage. The changes in the endocrines systems during this period are mainly related to the endocrine changes of the hypothalamus-pituitary-ovarian axis, the hypothalamus-pituitary-thyroid axis and the hypothalamus-pituitary-adrenal axis, corresponding hormones and other endocrine organs and tissues. The synergistic changes of endocrine systems play an important role in the aging process of the physical function[3]. Among the available treatments, hormone replacement therapy (HRT) is the most effective and widely used. Hou Bo *et al*.[4] used estrogen to treat perimenopausal syndrome in clinical practice and achieved the good efficacy. Mussel Hu *et al*.[5] added progesterone on the basis of a small quantity of estrogen and achieved the significantly better efficacy than the control group. This indicated that the combination of estrogen and progesterone could improve the quality of life of patients, displaying the higher safety. Zhang Chenhong *et al*.[6] adopted the sequential treatment of estradiol valerate tablets and medroxyprogesterone acetate tablets and found that the method could effectively improve the serum estrogen level of patients and reduce the serum levels of FSH and LH. Some researchers believed that HRT should start as early as possible, so as to help women with early menopause and early ovarian dysfunction to relieve menopausal symptoms[7]. Although the effect of hormone replacement therapy is significant, slight adverse reactions often occur. The way to eliminate adverse reactions of the hormone replacement therapy is also the focus in the future study.

3.2 Neurotransmitters

In the perimenopausal period, the physical functions decline gradually and the nerve activity of cerebral cortex and hypothalamus is directly affected. Therefore, the neurotransmitter activity of the central nervous system further declines, displaying the abnormal mental mood and behaviors. The major neurotransmitters include serotonin (5-HT), norepinephrine (NE) and dopamine (DA). 5-HT can participate in the regulation of emotional disorders, sleep and ingestion behaviors[8]. NE is synthesized by nerve cells and can participate in emotion, consciousness, awakening, appetite, sexual desire and other activities[9]. DA may be involved in the inhibition of the secretion of gonadotropin releasing hormone (GnRH)[10]. GnRH is an important signal molecule interlinked with three main regulatory systems of nerve, immune and endocrine[11]. Deng Haifeng *et al*. believed that the decrease in 5-HT and NE concentrations might be the main reason for the onset of perimenopausal depression[12].

3.3 Free radicals

Free radicals are numerous, unpaired, and reactive atoms, ions, and chemical groups that are ubiquitous in the body. Free radicals are not always harmful to human body. Only abnormal or uncontrolled free radical reactions can cause the damage to the organization, body oxidation, or senescence. The cause for senescence in the perimenopausal period caused by free radicals might involve various mechanisms. Zhao Li *et al*.[13] believed that free radicals could oxidize a large number of unsaturated fatty acids in human body

and modify fatty acids to form peroxidation lipids and further produce aldehydes, which could cross-link with proteins, lipids and nucleic acids. Yadav *et al*.[14] found that free radicals could attack DNA in organisms, cause the denaturation of nucleic acids, affect their functions of transmitting information and their characteristics of transcription and replication, and lead to the decreased protein synthesis ability and synthesis errors. Asowata *et al*. believed that free radicals might cause the denaturation of proteins, thereby triggering their own immune responses. However, clavax could inhibit the denaturation of proteins by inhibiting free radicals[15]. E. d. *et al*.[16] believed that free radicals could cause the degradation of extracellular soluble components. In patients with rheumatoid arthritis, white blood cells entered the synovial fluid of the joint, and free radicals caused the oxidative degradation of glycosaminoglycan in the synovial fluid, which had the function of lubrication. In the normal living environment, the harm of free radicals is only chronic because of the existence of free radical scavenging defense system in normal human cells, including enzyme systems and non-enzyme systems as well as other endogenous antioxidants and antioxidant enzymes. Vitamin E is a non-enzymatic exogenous antioxidant that resists the oxidation of unsaturated fatty acids into lipofuscin. However, with the aging process, the concentration of this defense substance in the body decreases, thus weakening the defense against free radical damage[17] and accelerating the aging changes. The decrease in Vitamin E may also be a cause for perimenopausal syndrome. The exercise therapy could effectively improve the levels of serum sex hormones, free radicals and blood lipids in perimenopausal women[18].

3.4 Other factors

Existing studies suggested that multiple factors were involved in the onset of perimenopausal syndrome. Fu Ruiting *et al*.[19] believed that the onset of perimenopausal syndrome might be caused by the impaired immune response, which directly led to the proliferation of a large number of inflammatory cells. They found that perimenopausal female rats with hormone imbalance could affect the immune system, thus leading to a decrease in the proportion of T lymphocyte subsets, an increase in the released pro-inflammatory factors, and monocyte proliferation leading to a decrease in blood IL-2 and an increase in IL-6. Some researchers also believed that the onset of perimenopause was related to vascular factors. Shi Hongxia *et al*.[20] clinically selected 355 perimenopause female patients aged 45-60 with hypertension who underwent physical examination in the Second Hospital of Lanzhou University from October 2016 to October 2017 and found that the main receptor-mass index (BMI) of the heart structure in perimenopausal women with hypertension was affected by age, education, menopause and waist-hip ratio, whereas the vascular function was affected by age and menopause. Other researchers believed that the onset of perimenopause might be related to metabolic changes. Zhang Hongyan *et al*.[21] found that perimenopause and sleep state of postmenopausal women were affected by the metabolic rate. Białek-Gosk K *et al*. found that in chronic obstructive pulmonary disease (COPD) patients around the menopause period, the serum levels of vitamin D, a key factor to adjust a variety of metabolic processes, was significantly lower[22].

4 Conclusion

To sum up, the occurrence of perimenopausal syndrome involves not only a simple imbalance of estrogen secretion, but also the collaborative changes of multiple genes or even multiple systems. From the micro point of view, the genetic changes are caused by the aging of the physical functions, which finally changes the system functions. From the macro point of view, the endocrine system and the immune system are firstly changed. With the long-term physical fatigue, blood vessels begin to lose vitality and free radicals increased, thus accelerating the aging process. The perimenopause period is an inevitable stage from sexual maturity to senescence, a gradual adaptation process. However, the aging performance also causes the great psychological pressure to perimenopausal women and may be one of the reasons for the high incidence of perimenopause syndrome. Although its onset has various forms, perimenopause syndrome is accompanied by inflammatory response. This result is also consistent with the results of genetic research. The onset of the perimenopausal period is closely related to senescence. Although aging is irreversible, early prevention and exercise can slow the aging pace.

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