

# Pathogenesis and Treatment Progress of Precocious Puberty in Children

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**Abstract:** *This article reviews the pathogenesis and treatment methods of precocious puberty in children from both traditional Chinese medicine (TCM) and Western medicine perspectives. Precocious puberty refers to the development of secondary sexual characteristics in children before the normal age of puberty, and it is classified into central, peripheral, and partial types. TCM believes that the pathogenesis is related to the dysfunction of the kidney, liver, and spleen, with the main pathomechanisms being yin deficiency and fire, liver depression and fire transformation, and phlegm-dampness obstruction. The treatment focuses on nourishing yin and reducing fire, soothing the liver and resolving depression, and transforming phlegm and removing dampness. Western medicine, on the other hand, approaches the condition from the perspective of premature activation of the hypothalamic-pituitary-gonadal (HPG) axis, dividing precocious puberty into central and peripheral types, with treatment primarily using gonadotropin-releasing hormone analogs (GnRHa). This paper explores the integration of TCM and Western medicine treatments, which can significantly improve the symptoms and signs of children with precocious puberty and provide a milder and more personalized treatment plan.*

**Keywords:** Precocious puberty, Children, Traditional Chinese medicine, Western medicine.

## 1. Introduction

Precocious puberty refers to the developmental phenomenon of secondary sexual characteristics in children before the normal age of puberty [1][2], and is usually defined as the onset of sexual development characteristics before the age of 8 years in girls and 9 years in boys [3]. For girls, it may manifest as breast development, pubic hair growth, menarche, etc; Boys, on the other hand, may have symptoms such as testicular and penile enlargement, pubic hair, voice changes, and sperm loss. Precocious puberty is classified into three categories based on the pathogenesis and clinical manifestations: central precocious puberty, which is gonadotropin-releasing hormone (GnRH) dependent [4]; peripheral precocious puberty [5], which is GnRH independent; and partial precocious puberty, which is isolated premature thelarche [6]. In recent years, with the improvement of living standards and environmental pollution, the incidence of precocious puberty in children has increased significantly. Precocious puberty not only affects children's physical and mental health, but also may lead to premature epiphyseal fusion, short stature, and mental and care burden for parents. Therefore, it is of great significance to explore effective treatment methods for the clinical intervention of precocious puberty in children.

## 2. TCM Pathogenesis of Precocious Puberty in Children

In ancient Chinese medical literature, there is no specific term for "precocious puberty in children." [7], The main source of its understanding is the word "Tian Gui". There is a saying in "Shanggu Tianzhen Lunpian: Ancient Ideas on Preservation of Natural Healthy Energy": "A woman is seven years old, her kidneys are vigorous, and her teeth are longer; Twenty-seven and the day is to, Ren pulse is through, Taichong pulse is prosperous, and the moon is in the present, so there is a child; The transformation of Tian Gui from "arriving" to "exhaustion" reflects the physiological process of human birth, growth, maturation, and decline. The function of Tian Gui is

similar to that of the gonadotropins, growth hormone, and prolactin secreted by the anterior pituitary in modern medicine, which play a crucial regulatory role in the growth, development, and reproductive functions of the body [8].

Traditional Chinese medicine believes that the occurrence of precocious puberty is related to the dysfunction of the kidney, liver and spleen in children. If the kidney is deficient in yin and the phase fire is vigorous, it can lead to the early arrival of Tian Gui and the symptoms of precocious puberty; The liver is drained, the qi is regulated, and the liver is depressed and the fire will also promote the phase fire; The spleen is the foundation of nurture, the source of qi and blood biochemistry, the spleen is the main transport, and the diet is not modest, the spleen and stomach are damaged, the transport is lost, the spleen is deficient and phlegm and dampness are endogenous, and the phlegm and dampness accumulate and turn heat, which can promote phase fire and also cause precocious puberty. In short, the pathogenesis of precocious puberty is mainly yin deficiency and fire, liver stagnation and fire, phlegm and dampness stagnation. Therefore, the main clinical treatment is to nourish the kidney, yin and diarrhea, and for those who have liver depression and fire, it can clear the liver and diarrhea, and the phlegm and dampness content is supplemented by phlegm and dampness [9], aiming to improve symptoms and inhibit the rapid growth of bone age. The mechanism of modern Chinese medicine intervention in precocious puberty is mostly combined with epigenetics and metabolomics to explore the regulatory effect of traditional Chinese medicine on the HPGA axis and its molecular mechanism.

## 3. Traditional Chinese Medicine Treatment of Precocious Puberty in Children

According to the etiology and pathogenesis of precocious puberty in children, TCM often adopts the method of syndrome differentiation and treatment for precocious puberty in children, and clinically treats it from the syndrome types such as yin deficiency and fire, liver stagnation and fire,

phlegm and dampness stagnation. Professor Shi Yumin, the founder of Chinese integrative medicine, was the first to summarize the experience of Shanghai famous old Chinese medicine doctor Gu Wenhua in the treatment of precocious puberty, and proposed that the pathogenesis of precocious puberty is "kidney yin deficiency and phase fire". If children eat spicy, greasy, and high-calorie food for a long time, or due to diseases, emotions and other factors, it is easy to lead to the loss of yin fluid in the body, and the situation of yin deficiency and fire is vigorous. For the syndrome of insufficient kidney yin and phase fire, it is common for children to have symptoms such as hot flashes and night sweats, five heart irritability, dizziness and tinnitus. A nationwide population-based study showed that in Taiwan, 23.73% of children with precocious puberty used Zhibai Dihuang pills, Fangzhong Zhimu and Phellodendron phellodendron to clear heat and relieve fire, Rehmannia rehmannia, Cornus officinalis, and yam nourished kidney yin, peony skin cooled serum heat, and Poria cocos and Ze Epsom water infiltrated wet, so as to regulate the balance of yin and yang in the body and control the process of precocious puberty.

In modern society, children are under great pressure to learn, and parents have high expectations for their children, which is easy to make children in a tense and anxious mood for a long time. Traditional Chinese medicine believes that the liver is the ma in drain, happy and depressed. Long-term bad mood will lead to stagnation of liver qi, and gi stagnation will turn into fire over time. Liver fire can affect the endocrine system, leading to hormone imbalance and precocious puberty. Professor Xiong Lei believes that children with precocious puberty often have anxiety and fear at the beginning of the disease, which is easy to cause liver qi stagnation and depression to turn into fire [10]. Children with liver stagnation and fire syndrome often have symptoms such as irritability, chest tightness, sighing, and breast tenderness. The treatment should be to soothe the liver and diarrhea fire, and commonly use Dan Gardenia Xiaoyaosan plus or minus. Bupleurum soothes the liver and relieves depression, Angelica sinensis and white peony nourish blood and soften the liver, Poria cocos strengthens the spleen and dispels dampness, peony bark and gardenia clear heat and relieve fire, licorice reconciles various medicines, inhibits phase fire and irritation by clearing the liver meridian, and improves the signs related to precocious puberty caused by liver depression and fire.

Professor Zhao Jun, the fifth generation descendant of Xu's pediatrics in Shanghai, believes that the precocious puberty of children in the early stage of development is mostly characterized by liver meridian stagnation, which is prone to occur in spring: The progressive stage is mostly evidence of spleen loss and phlegm dampness [11]. Ye Jin, a famous pediatric physician in Jiangsu Provincial Hospital of Traditional Chinese Medicine, believes that the cause of childhood precocious puberty is insufficient congenital endowment and acquired care, with yin deficiency and fire prosperity as the basic pathogenesis, and spleen deficiency and phlegm accumulation [12]. For phlegm-dampness syndrome, children are often overweight, fatigued, and loose stools, and may be accompanied by premature breast development. The treatment is to strengthen the spleen, dissolve phlegm and dispel dampness, and use Erchen decoction to add or subtract. Banxia, tangerine peel dries and

dissolves phlegm, Poria cocos strengthens the spleen and infiltrates dampness, citrus aurantium husk dissipates phlegm, Atractylodes atractylodes dampness strengthens the spleen, dissolves phlegm and dispels dampness, eliminates the evil of phlegm and dampness in the body, prevents phlegm dampness and heat and fuels fire, and then alleviates the symptoms of precocious puberty.

Traditional Chinese medicine treatment is based on the principles of nourishing yin, reducing fire and soothing the liver, using herbs such as Zhimu, Phellodendron chinensis, Rehmannia rehmannia and Poria cocos [13]. One meta-analysis showed that NYPF therapy had a positive effect on central precocious puberty [14]. NYPF therapy significantly improved the clinical effectiveness and secondary sexual indicators (such as uterine volume, ovarian volume, breast nucleus diameter, follicle diameter), reduced TCM symptom scores and serum sex hormones (FSH, LH, E2), and slowed down the rate of bone age maturation [14]. Acupuncture and moxibustion have also been used as complementary treatments in the management of precocious puberty [15].

In recent years, the prevention of precocious puberty has attracted more and more attention as the medical model of children has gradually changed from traditional treatment to prevention-based health management. Relevant studies have shown that the prevention of precocious puberty in children can be started from many aspects, including adjusting work and rest, reasonable diet, strengthening exercise, using medicinal diet, ointment conditioning, and comprehensive exploration with the help of acupuncture, massage, auricular acupressure and other means. The TCM treatment of precocious puberty in children starts from the whole, adjusts the function of the body's internal organs and the balance of yin and yang, and combines the adjustment of lifestyle, providing a relatively gentle, comprehensive and fundamental treatment idea for children. It can help children to restore normal growth and development, reduce the adverse effects of precocious puberty on their physical and mental health, and escort the healthy growth of children.

#### 4. Pathogenesis of Precocious Puberty in Children

Western medicine mainly believes that the pathogenesis of precocious puberty in children is related to the early activation of the hypothalamic-pituitary-gonadal (HPGA) [16] axis. Genetic factors, environmental factors, lifestyle factors, and family factors can all lead to the early activation of the HPGA axis. Abnormal function of this axis prompts premature secretion of gonadal hormone-releasing hormone, which leads to the early appearance of secondary sexual characteristics. Western medicine divides precocious puberty into two categories: central precocious puberty and peripheral precocious puberty:

Central precocious puberty (CPP): Also known as true precocious puberty, it is caused by the premature activation of the function of the hypothalamic, pituitary gland, and gonadal axis [17]. This type of puberty is more common in women, with a ratio of about 20:1 [18] between girls and boys, and most of the central precocious puberty has no clear cause,

which is called idiopathic central precocious puberty. Other possible causes include central nervous system disorders that may irritate the hypothalamus and cause precocious puberty. Diagnosis is confirmed by measurement of basal luteinizing hormone (LH) levels or by gonadotropin-releasing hormone (GnRH) stimulation testing. Patients with central precocious puberty show elevated [19] levels of gonadotropins (LH and FSH), and gonadotropin-releasing hormone (GnRH) stimulation tests show markedly elevated levels of LH, which is a key indicator for diagnosing central precocious puberty [19]. It is characterized by a complete pubertal process, including breast development, pubic hair growth, menstrual cramps (in girls), and testicular enlargement [20] (in boys), with accelerated growth and advanced bone age [21].

Peripheral precocious puberty (PPP): Also known as pseudoprecocious puberty, it is not caused by the function of the hypothalamic-pituitary gland and gonadal axis, but by the abnormal secretion of sex hormones by peripheral glandular tissue [22]. For example, gonadal tumors, ovarian tumors, luteal tumors, testicular tumors, adrenal tumors, etc., as well as exogenous sex hormone-like substances (such as hormone ingredients in drugs, health products, and cosmetics) may cause pseudoprecocious puberty. Hormone tests, imaging tests, etc. are needed to determine the specific cause. In patients with peripheral precocious puberty, gonadotropin (LH and FSH) levels are usually suppressed or in the normal range, and sex steroid hormone (eg, estradiol, testosterone) levels are elevated. The development of only partial sexual characteristics is usually present, rather than the full course of puberty, and other symptoms may be associated with the specific cause, such as bone fiber dysplasia and skin pigmentation in patients with McCune-Albright syndrome [23]. Peripheral precocious puberty is relatively rare, accounting for 38.82% [24] of all precocious puberty cases in one study.

## 5. Western Medicine Treatment of Precocious Puberty in Children

At present, the goal of Western medicine for the treatment of precocious puberty is to control and slow down the maturity and speed of secondary sexual characteristics, slow down the progression of bone age, make the growth and development gradually consistent with the actual age, and restore the state of the child's actual age and life in terms of psychological behavior.

The treatment of central precocious puberty is a gonadotropin-releasing hormone analogue (GnRHa), which is considered the gold standard of treatment [25]. One study showed that patients treated with GnRHa had an increase in predicted height of  $1.73 \pm 0.29$  cm after treatment, compared with a  $0.52 \pm 0.23$  cm decrease in predicted height in the non-treated control group [8].

GnRHa inhibits the hypothalamic-pituitary hormone secretion by binding to the GnRH receptor, which can prevent the GnRH effect, inhibit the secretion of gonadotropins through the negative feedback pathway, delay the development of secondary sexual characteristics, and significantly reduce the peak values of follicle hormone (FSH), luteinizing hormone (LH), estradiol (E2) and testosterone (T), and even drop to

prepubertal levels. However, the long-term safety of GnRHa still needs to be evaluated and managed [25], such as limited improvement in height in children with older bone age, and may lead to slowed growth rate or even growth arrest [26], and it is expensive, and long-term use may cause side effects such as osteoporosis and weight gain [27]. In addition, some children did not respond well to GnRHa treatment, and there were individual differences in efficacy.

Peripheral precocious puberty is caused by exposure to exogenous sex hormones or abnormal synthesis and secretion of endogenous sex hormones, and the key to its treatment is also to treat the cause, which may include aromatase inhibitors and inhibitors of sex hormone action [28]. For precocious puberty caused by exposure to exogenous sex hormones, the cause should be identified and the contact should be stopped in time, and for precocious puberty caused by abnormal synthesis and secretion of endogenous sex hormones, the treatment method should be selected according to the specific disease. For example, ovarian and testicular tumors should be treated with surgery and chemoradiotherapy. In addition, there are some endocrine diseases that can cause sex hormone abnormalities, such as hypothyroidism, congenital adrenal hyperplasia, McCune-Albright syndrome, and familial hypertestosteronemia, which need to be treated with appropriate drugs.

## 6. Combination of Traditional Chinese and Western Medicine for the Treatment of Precocious Puberty

A clinical study investigated the effect of combining traditional Chinese medicine with megestrol in the treatment of idiopathic precocious puberty. The study included 106 girls, of whom 51 received a combination of traditional Chinese medicine and megestrol. The results showed that after an average of 2.7 years of treatment, the luteinizing hormone-releasing hormone stimulation test showed a significant decrease in the peak value of luteinizing hormone, a decrease in the size of the uterus and ovaries, a deterioration of secondary sexual characteristics, a decrease in the difference between bone age and chronological age, and an increase in the predicted final height from  $153.3 \pm 3.6$  cm to  $158.5 \pm 4.3$  cm ( $P < 0.001$ ) [29].

One study compared the effects of traditional Chinese medicine treatment, Western medicine treatment, and no treatment in people with precocious puberty. The results showed that the bone maturity rate of the Chinese medicine group ( $0.95 \pm 0.20$ ) and the Western medicine group ( $0.69 \pm 0.05$ ) was slowed down, while the bone maturity rate of the control group was accelerated ( $1.33 \pm 0.04$ ). The predicted height of both the Chinese medicine group and the Western medicine group increased after treatment ( $1.15 \pm 1.19$  cm vs.  $1.73 \pm 0.29$  cm), while the predicted height of the control group decreased ( $-0.52 \pm 0.23$  cm) [30]. Integrative medicine (ICIM) treatment is able to provide a gentler and more individualized treatment plan for patients with precocious puberty [31]. By combining traditional Chinese medicine, compound prescription, acupuncture, moxibustion and massage, adverse events and side effects of Western medicine can be compensated [31].

In recent years, the number of cases of precocious puberty in the treatment of traditional Chinese and Western medicine has gradually increased, and certain curative effects have been achieved. The combination of traditional Chinese medicine and Western medicine can give full play to the advantages of Western medicine in etiological diagnosis and drug treatment, as well as the expertise of traditional Chinese medicine in syndrome differentiation and treatment, and overall conditioning, so as to achieve better treatment results. However, it should be noted that integrative medicine treatment needs to be carried out under the guidance of a professional doctor to ensure the safety and effectiveness of the treatment. In addition, considering the individual differences of patients with precocious puberty, how to formulate individualized treatment plans based on the specific conditions of patients (such as age, gender, weight, symptom severity, etc.) is the focus of future research [32].

## 7. Summary

To sum up, precocious puberty is a phenomenon of abnormal growth and development, and Chinese and Western medicine have different understandings and treatment methods for it. Western medicine mainly treats secondary precocious puberty through the etiology from a physiological point of view, and there is no special treatment plan for idiopathic peripheral precocious puberty, and GnRHa is currently preferred. Traditional Chinese medicine believes that the pathogenesis of precocious puberty is yin deficiency and fire, liver depression and fire, phlegm and dampness stagnation, and the treatment is to nourish yin and reduce fire, relieve liver depression or dry and damp phlegm, pay attention to syndrome differentiation and treatment, improve symptoms by adjusting the balance of yin and yang in the child's body, and inhibit the rapid growth of bone age. The combination of traditional Chinese and Western medicine in the treatment of precocious puberty in children has certain clinical efficacy and advantages, which can significantly improve the symptoms and signs of children and provide better treatment options for children with precocious puberty.

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