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ARTICLE

RESEARCH PROGRESS ON PRECOCIOUS PUBERTY TREATMENT

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ABSTRACT

Precocious puberty is a common pediatric endocrine disorder characterized by early onset of puberty. Current research suggests that the occurrence of this condition is related to multiple factors such as genetics, diet, and environment. Children with precocious puberty experience advanced bone age development, early closure of epiphyseal plates, and shortened growth periods. Since children's intellectual and psychological development levels remain at their actual age, but their physical development is advanced, this can cause significant adverse effects on their physical growth and psychological health in the short term. In the long term, it may result in shorter adult height, reproductive health issues, and increased risks of breast cancer, metabolic diseases, and cardiovascular diseases. In terms of treatment, Western medicine primarily uses gonadotropin-releasing hormone analogues (GnRHa), while traditional Chinese medicine (TCM) focuses on syndrome differentiation and treatment. In recent years, discussions on treatment options for precocious puberty have gained traction. This paper comprehensively elaborates on the progress in treatment options for precocious puberty, aiming to provide reference and guidance for future clinical diagnosis and treatment.

KEYWORDS

Girls, Precocious Puberty, Treatment

Precocious puberty refers to the development of secondary sexual characteristics in children earlier than the typical age. It usually denotes the onset of breast development, pubic hair, axillary hair, or menarche before the age of 8 in girls (Xiong et al., 2023; Yu et al., 2024). This condition is related to various factors, including genetics, environment (social and living environment), diet, physical constitution (e.g., obesity), and exercise. Clinically, precocious puberty is usually classified into central precocious puberty (CPP), peripheral precocious puberty (PPP), and partial precocious puberty, based on whether the hypothalamic-pituitary-gonadal axis (HPGA) is prematurely activated (Yu et al., 2024).

CPP refers to the premature secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus, which stimulates the secretion of gonadotropins by the pituitary gland, thereby activating the HPGA and initiating early sexual development. This type of precocious puberty mimics the normal maturation process, hence it is called GnRH-dependent precocious puberty, complete precocious puberty, or true precocious puberty. Based on etiology, CPP can be further divided into idiopathic precocious puberty and secondary precocious puberty. Idiopathic precocious puberty, also known as constitutional precocious puberty, has an unclear specific etiology and is more common in girls, accounting for over 80% of female CPP cases (Aguirre and Eugster, 2018). Secondary precocious puberty is often caused by tumors, infections, and trauma.

PPP refers to the secretion of gonadotropins or sex hormones from locations other than the pituitary gland, promoting gonadal development without GnRH secretion. This type of precocious puberty is not due to normal HPGA activity, hence it is referred to as incomplete precocious puberty, GnRH-independent precocious puberty, or pseudo precocious puberty (Wu et al., 2018). Common causes include McCune-Albright syndrome, ovarian tumors (such as granulosa cell tumor, mixed germ cell tumor, gonadoblastoma, and choriocarcinoma), feminizing adrenal cortical tumors, Peutz-Jeghers syndrome, primary severe hypothyroidism, exogenous sex hormones, food, drugs, and cosmetics.

Partial precocious puberty refers to the early appearance of only some sexual characteristics, mainly presenting as isolated premature thelarche, isolated premature pubarche, or isolated early menarche. It is also known as incomplete precocious puberty and variant puberty, with a few cases developing into CPP. From the perspective of pathogenesis, partial precocious puberty can be regarded as a variant of CPP (Yu et al., 2024). This paper reviews the progress in treatment options for precocious puberty, hoping to contribute to the treatment of this condition.

1. Etiological Treatment

Since idiopathic precocious puberty (CPP) is more common and its cause is unknown, etiological treatment mainly targets peripheral

precocious puberty (PPP). For instance, exogenous estrogen sources should be removed for cases of exogenous precocious puberty (Yu et al., 2024). Tumors causing precocious puberty should be surgically removed (Yu et al., 2024), and thyroid hormone should be supplemented for hypothyroidism-induced precocious puberty (Yu et al., 2024; Huang, 2003). When hypothalamic hamartomas manifest solely as precocious puberty, medication is effective, but surgical removal is preferred for patients with gelastic seizures or other types of epilepsy (Wang et al., 2022).

2. Western Medicine Treatment

2.1 GnRHa

GnRHa is the first-choice drug for treating CPP and is ineffective for PPP. Commonly used drugs include triptorelin and leuprorelin. They bind to the GnRH receptors on pituitary gonadotroph cells, initially promoting the release of LH and FSH, known as the "flare effect". Subsequently, GnRHa reduces the number of corresponding receptors on target cells, inhibiting the hypothalamic-pituitary-gonadal axis, reducing the secretion of LH, FSH, and sex hormones, thus controlling the progress of sexual development, delaying bone maturation, and preventing premature closure of the epiphyses (Shen et al., 2023; De Sanctis et al., 2019). The inhibitory effect of GnRHa does not persist after discontinuation, with few side effects, and does not affect the child's future growth and development (Wu et al., 2018). Shen et al. (2023) treated 49 CPP girls with triptorelin acetate for one year, finding that it effectively inhibited the gonadal axis and gonadal development, delaying bone age progression. Li et al. (2023) treated 100 CPP girls with leuprorelin acetate microspheres for one year, finding that the microspheres improved sex hormone levels and promoted healthy growth.

2.2 High-Dose Sex Hormones

Before the widespread use of GnRHa, traditional treatment drugs were sex hormones. High-dose sex hormones inhibit hypothalamic FSH and LH secretion through negative feedback mechanisms and directly inhibit sex hormone synthesis, thus reducing breast size and stopping menstruation. Medroxyprogesterone acetate is commonly used clinically; it is a potent progestin that does not significantly inhibit epiphyseal growth and cannot effectively control bone age and height growth (Lu et al., 2014). Han et al. (2023) used Ziyin Xiehuo Fang combined with medroxyprogesterone acetate to treat 123 rapidly progressing precocious girls for six months, finding that the combination therapy inhibited breast development, delayed uterine and ovarian development, suppressed bone age advancement, but did not significantly slow growth.

2.3 Calcium and Vitamin D

Studies have shown that vitamin D deficiency is prevalent in children with precocious puberty, with serum vitamin D levels significantly lower than peers (Sun, 2020; Xu et al., 2023). After GnRHa treatment, bone density may decrease, and calcium and vitamin D supplementation can prevent and treat this decrease (Cai et al., 2005). Johnson et al. (2014) found through mouse models that vitamin D deficiency leads to mammary alveolar growth and early gland development. Lou et al. (2024) compared serum 25-hydroxyvitamin D3 levels in CPP girls and healthy girls, finding that vitamin D deficiency might lead to an earlier onset of precocious puberty, affect HPGA function, alter reproductive hormone indicators, and increase ovarian volume. Cui et al. (2023) used GnRHa combined with vitamin D to treat CPP children, finding that vitamin D helps improve bone age and growth conditions, inhibit sex hormone expression, reduce the impact of GnRHa treatment on vitamin D levels, and enhance treatment efficacy. Therefore, children with precocious puberty who have lower bone mineral content and bone density than their peers should be promptly given sufficient calcium and vitamin D treatment.

2.4 Combined Use of GnRHa and Recombinant Human Growth Hormone (rhGH)

GnRHa temporarily inhibits height growth in the short term. For CPP children whose growth rate is too slow after treatment, whose wrist bone epiphyses are close to closure but have not yet reached the ideal height, or who are dissatisfied with their final adult height, rhGH combined with GnRHa can be considered. Many studies have shown that the combined effect of these two drugs is better than GnRHa alone, reducing psychological problems caused by insufficient height, with no increase in adverse reaction incidence (Zang et al., 2022). However, rhGH combination therapy requires attention to its side effects, such as glucose metabolism abnormalities, hypothyroidism, and increased tumor incidence (Seminara et al., 2005). Monitoring blood glucose, thyroid function, and serum insulin-like growth factor 1 (IGF-1) levels can evaluate drug safety. Yuan et al. (2023) treated 82 large bone age CPP girls with triptorelin acetate combined with rhGH, finding that the combined treatment was more effective, improving growth conditions, reducing sex hormone levels, and inhibiting secondary sexual characteristics, with good safety. Zang et al. (2022) treated 96 CPP girls with triptorelin combined with rhGH, finding that the combined treatment reduced sex hormone levels, slowed gonadal development, improved IGF-1 and IGFBP-3 levels, delayed epiphyseal maturation, and improved final adult height with certain safety.

3. Traditional Chinese Medicine Treatment

For children with short disease duration and mild precocious puberty, traditional Chinese medicine (TCM) treatment often yields satisfactory results. TCM believes that the condition may arise due to congenital deficiencies in the parents' essence (Yin Jing), environmental influences, inappropriate dietary supplements, or medication use leading to an imbalance of Yin and Yang. The undeveloped kidney Yin cannot control fire, resulting in hyperactivity, internal disturbance of deficient fire, and premature sexual maturity due to the early arrival of Tian Gui. This can cause Qi to accumulate in the chest, leading to breast pain and triggering precocious puberty (Shao and Ye, 2020; Hu, 2008). Based on the analysis of the etiology and pathogenesis, the clinical approach often focuses on nourishing Yin and tonifying the kidneys, as well as clearing and draining the ministerial fire, aiming to restore the body's balance to a healthy state of "Yin and Yang harmony."

Commonly used TCM formulas include Zhibai Dihuang Wan and Dabuyin Wan. Zhibai Dihuang Wan is a patent medicine composed of various herbs like Chinese yam, Poria, Alisma, and Cornus, which help regulate kidney Yin-Yang balance and reduce internal heat, particularly effective in treating symptoms like hot flashes, night sweats, and dry mouth and throat. Dabuyin Wan, made from ingredients such as turtle shell, pig spinal cord, Anemarrhena, and Rehmannia, belongs to the Foot Shaoyin category and has the effects of nourishing Yin, reducing fire, and replenishing essence. Therefore, for children with kidney deficiency and hyperactivity of fire type CPP, Zhibai Dihuang Wan and Dabuyin Wan can effectively alleviate clinical symptoms.

Research by Zhou (2022) showed that treating 40 girls with CPP using Zhibai Dihuang Wan resulted in an 85% overall efficacy rate, improving clinical symptoms, inhibiting uterine, ovarian, and follicle development, and reducing LH, FSH, and estradiol (E2) levels with high safety. Liu and Jin (2020) found that treating 80 girls with Dabuyin Wan combined with Zhibai Dihuang Wan for three months significantly improved symptoms and signs, enhanced clinical efficacy, and reduced hormone levels.

4. Integrated Traditional Chinese and Western Medicine Treatment

Research by Liao (2024) demonstrated that treating 70 girls with CPP using Yangyin Jianghuo formula combined with triptorelin effectively improved clinical symptoms and regulated sex hormone levels, delaying secondary sexual characteristic development. Tong and Yang (2024) treated 102 girls with CPP using Dabuyin Wan combined with leuprorelin acetate microspheres and found that it improved clinical symptoms, regulated secondary sexual development, reduced sex hormone levels, and had high safety. Zhao et al. (2021) treated 80 girls with CPP using Dabuyin Wan combined with triptorelin and found it effective in improving symptoms, reducing hormone levels, and being safe and reliable.

5. Adjunctive Therapies

5.1 Psychological Support Therapy

Children with precocious puberty do not experience advanced intellectual and psychological development, often feeling confused, shy, or inferior about early sexual maturity, potentially leading to psychological disorders. Parents may also feel anxious. Therefore, psychological counseling and medical education for both children and parents are crucial during treatment. This helps them understand that these manifestations are just early normal physiological processes and do not affect future health and normal life. Additionally, personal health guidance and follow-up management, such as managing menstrual periods and ensuring timely medication intake during treatment, are essential. Liu et al. (2013) found through a one-year study on 44 CPP children that psychological intervention had a definite effect in treating idiopathic CPP and should be further promoted. Wang et al. (2009) observed 60 CPP children for one year and found that psychological care had significant therapeutic effects, highlighting its importance and the need for promotion.

5.2 Lifestyle Intervention Therapy

Research shows that childhood obesity increases the risk of precocious puberty (Chen et al., 2017), and diet is closely related to it (Yang et al., 2018). Appropriate aerobic exercise can mitigate the growth slowdown caused by GnRHa treatment and positively impact height promotion (Ying et al., 2010). Meat, sugary drinks, and supplements may be dietary risk factors for precocious puberty, while foods rich in dietary fiber may be protective factors (Gu et al., 2020). Ma and Du (2000) found that exercise therapy significantly increased IGF-1 levels and improved adult height in 9 idiopathic central precocious puberty girls through pure exercise therapy. Zhang et al. (2023) managed 90 CPP children with aerobic exercise in combination with GnRHa treatment for six months, finding significant treatment effects, effective hormone regulation, slowed bone age advancement, and reduced body mass index (BMI). Lian and Gao (2024) explored the correlation between dietary habits and precocious puberty in obese children, finding that miR-125b expression levels in the peripheral blood of obese children with precocious puberty were higher than in healthy obese children, and poor dietary habits were more prevalent. Elevated miR-125b expression levels in peripheral blood and poor dietary habits were influencing factors for precocious puberty in obese children. Therefore, a healthy lifestyle has a certain adjunctive effect on the treatment of precocious puberty.

6. Summary

In conclusion, precocious puberty in children can harm their physical and mental development and requires special attention and active treatment to lower hormone levels and delay the development of sexual characteristics. There are various treatment options for this condition, and the choice of medication should be tailored to the type of precocious puberty. Peripheral precocious puberty (PPP) is generally treated etiologically, while central precocious puberty (CPP) is often idiopathic and usually treated with medication. GnRHa is the standard clinical treatment for CPP, showing significant therapeutic effects with good compliance. For adolescents whose epiphyses are about to close, combined treatment with recombinant human growth hormone (rhGH) can be used without increasing the risk of adverse reactions.

In clinical practice, integrating traditional Chinese and Western medicine treatment for idiopathic CPP has greater advantages. By combining psychological support, exercise therapy, and dietary control, new treatment ideas and plans are provided for clinicians. This comprehensive treatment approach helps to more effectively manage the condition of children with precocious puberty, promoting their healthy growth.

References

Aguirre, R. S., Eugster, E. A. 2018. Central precocious puberty: From genetics to treatment. Best Practice & Research Clinical Endocrinology & Metabolism, 32(4), Pp. 343-354.

Cai, X., Liang, Li., Shen, Y. 2005. Bone Metabolism Changes and Intervention Strategies in Children with True Precocious Puberty. Foreign Medical Sciences (Pediatrics), (02), Pp. 106-108.

Chen, C., Zhang, Y., Sun, W., et al. 2017. Investigating the relationship between precocious puberty and obesity: a cross-sectional study in Shanghai, China. BMJ Open, 7(4).

Cui, P., Zheng, T., Qi, L. 2023. Effect of GnRH Agonist Combined with Vitamin D on Bone Age and Sex Hormone Levels in Children with Central Precocious Puberty. Zhejiang Practical Medicine, 28(03), Pp. 208-212.

De Sanctis, V., Soliman, A. T., Di Maio, S., et al. 2019. Long-term effects and significant adverse drug reactions (ADRs) associated with the use of gonadotropin-releasing hormone analogs (GnRHa) for central precocious puberty: a brief review of literature. Acta Bio Medica: Atenei Parmensis, 90(3), Pp. 345.

Gu, Q., Xie, L., Shen, X. 2020. Research progress on diet and precocious puberty in children. Chinese Journal of Children's Health Care, 28(06), Pp. 642-644+688.

Han, X., Sun, Y., Wang, Y., et al. 2023. Randomized Controlled Study of ZiYin XieHuo Prescription Combined with Megestrol Acetate in the Treatment of Rapidly Progressive Precocious Puberty in Girls. Journal of Traditional Chinese Medicine, 64(13), Pp. 1336-1342.

Hu, H. 2008. Experience of Shi Yumin in Treating Precocious Puberty. Journal of Traditional Chinese Medicine, (10), Pp. 875-876.

Huang, W. 2003. Precocious Puberty in Children and Its Clinical Diagnosis and Treatment. Medical Literature Review, (01), Pp. 96-98.

Johnson, A. L., Zinser, G. M., Waltz, S. E. 2014. Loss of vitamin D receptor signaling from the mammary epithelium or adipose tissue alters pubertal glandular development. American Journal of Physiology-Endocrinology and Metabolism, 307(8), Pp. E674-E685.

Li, Q., Xia, C., Fu, C. 2023. Clinical Efficacy Analysis of Leuprorelin Acetate Microspheres in the Treatment of Central Precocious Puberty. The Great Doctor, 8(13), Pp. 30-32.

Lian, X., Gao, L. 2024. Analysis of the correlation between dietary habits and precocious puberty in obese children. Clinical Research, 32(01), Pp. 190-192.

Liao, Z. 2024. Therapeutic efficacy of Nourishing Yin and Reducing Fire Formula combined with GnRH-a in the treatment of idiopathic central precocious puberty in girls. China Traditional Chinese Medicine Science and Technology, 31(02), Pp. 345-347.

Liu, C., Xiao, Y., Luo, S. 2013. The role of psychological intervention in the treatment of idiopathic precocious puberty in children. Hainan Medical Journal, 24(15), Pp. 2339-2340.

Liu, J., Jin, M. 2020. Clinical study on the treatment of precocious puberty in girls by Da Tonic Yin Pill combined with Zhi Bai Di Huang Wan. New Chinese medicine, 52(07), Pp. 47-50.

Lou, Y., Xu, Y., Zhang, P., et al. 2024. Analysis of the Correlation between Serum Vitamin D Levels and Central Precocious Puberty in Girls. China Modern Doctor, 62(03), Pp. 16-20.

Lu, J., Cao, D., Gao, X., et al. 2014. Meta-Analysis and Efficacy Comparison of Yin-Nourishing Chinese Medicines in the Treatment of Precocious Puberty in Girls. Chinese Patent Medicine, 36(03), Pp. 485-491.

Ma, H., Du, M. 2000. Effects of aerobic exercise on growth and growth-promoting hormone axis function in girls with idiopathic central precocious puberty. Chinese Journal of Practical Pediatrics, (11), Pp. 666-668.

Seminara, S., Stagi, S., Candura, L., et al. 2005. Thyroid function changes during long-term growth hormone treatment in children with growth hormone deficiency. Hormone and Metabolic Research, 37(12), Pp. 751-756.

Shao, H., Ye, J. 2020. Summary of Traditional Chinese Medicine Treatment for Precocious Puberty in Children. Jiangsu Journal of Traditional

Chinese Medicine, 52(05), Pp. 47-49.

Shen, Q., Yu, M., Gao, P. 2023. Efficacy and Safety of Triptorelin in the Treatment of Central Precocious Puberty in Girls. Chinese Modern Applied Pharmacy, 40(22), Pp. 3141-3145.

Sun, J. 2020. Correlation between Serum Vitamin D Levels and Idiopathic Central Precocious Puberty in Girls. Journal of Clinical and Pathological Research, 40(01), Pp. 86-89.

Tong, L., Yang, X. 2024. Clinical study on the treatment of girls' idiopathic central precocious puberty with yin deficiency and fire exuberance evidence by combining Dazhongyin Wan with leuprolide acetate microspheres. New Chinese Medicine, 56(05), Pp. 31-35.

Wang, C., Zhao, X., Zhang, Q., et al. 2009. The Role of Psychological Nursing in the Treatment of Children with Idiopathic Central Precocious Puberty. Journal of Modern Integrated Traditional Chinese and Western Medicine, 18(23), Pp. 2834-2835.

Wang, Z., Han, J., Li, G. 2022. Case Report and Literature Review: GnRHa Combined with rhGH for the Treatment of Infantile Granulomatous Tumor. Journal of Shandong University (Medical Edition), 60(02), Pp. 48-53.

Wu, J., Zhu, L., Wu, J., et al. 2018. Consensus on the Diagnosis and Treatment of Female Precocious Puberty. Chinese Journal of Maternal and Child Health Research, 29(02), Pp. 135-138.

Xiong, Y., Cheng, Meng., Xu, K. 2023. Interpretation of Expert Consensus on Diagnosis and Treatment of Central Precocious Puberty (2022). Practical Journal of Obstetrics and Gynecology, 39(06), Pp. 422-424.

Xu, L., Li, P., Yuan, D. 2023. Confirming the association between low serum 25OHD levels in girls with central precocious puberty and its severity. BMC Pediatrics, 23(1), Pp. 624.

Yang, B., Liu, Q., Liu, S., et al. 2018. Systematic evaluation of the factors influencing the advancement of the chronological phase of pubertal initiation. Chinese Journal of Evidence-Based Medicine, 18(12), Pp. 1337-1351.

Ying, K., Dong, Q., Chen, Q. 2010. Research progress on the treatment of adult height in children with precocious puberty. Journal of Clinical Rational Use of Drugs, 3(02), Pp. 122-124.

Yu, J., Sun, W., Sun, Y. 2024. Guidelines for Integrated Traditional Chinese and Western Medicine in the Diagnosis and Treatment of Precocious Puberty in Children (2023 Edition). Journal of Traditional Chinese Medicine, 65(05), Pp. 546-552.

Yuan, Y., Yu, L., Wu, X. 2023. Effect of Leuprorelin Acetate Combined with Recombinant Human Growth Hormone on the Growth and Development of Girls with Central Precocious Puberty and Large Bone Age. Chinese Journal of Clinical Pharmacology, 39(24), Pp. 3547-3551.

Zang, Y., Xu, L., Shen, Y. 2022. Observation on the Effect of Triptorelin Combined with Recombinant Human Growth Hormone in the Treatment of Central Precocious Puberty in Girls. Medical & Pharmaceutical Journal of Chinese People's Liberation Army, 34(01), Pp. 53-56.

Zhang, Y., Sun, Y., Wu, S., et al. 2023. Effect of aerobic exercise management assisting gonadotropin-releasing hormone analogs in the treatment of obese idiopathic central precocious puberty. Chinese Community Physician, 39(32), Pp. 28-30.

Zhao, Y., Gao, H., Wang, K., et al. 2021. Clinical study on the treatment of precocious puberty in girls by Da Tonic Yin Pill combined with Treprostinil. New Chinese Medicine, 53(16), Pp. 31-34.

Zhou, X. 2022. Retrospective Study of Modified Zhibai Dihuang Pill in the Treatment of Idiopathic Central Precocious Puberty in Girls with Yin Deficiency and Fire Excess Syndrome. Wuhan: Hubei University of Chinese Medicine.