

Zhibai Dihuang Ointment Prescription for the Treatment of Isolated Premature Thelarche: A Qualitative Study

Kaifeng Li, Xuan Li, Xuan Zhang, Xiaofeng Fang, Guiwen Li, Wing-Fai Yeung, Jing Qin, Guiju Zhang, Shucheng Chen

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Kaifeng Li^{1*}; Xuan Li^{1*}; Xuan Zhang²; Xiaofeng Fang¹; Guiwen Li¹; Wing-Fai Yeung³; Jing Qin³; Guiju Zhang¹; Shucheng Chen³

¹ Shandong University of Traditional Chinese Medicine Jinan CN

² Affiliated Hospital of Shandong University of Traditional Chinese Medicine Jinan CN

³ The Hong Kong Polytechnic University Hong Kong CN

*these authors contributed equally

Corresponding Author:

Shucheng Chen

The Hong Kong Polytechnic University
The Hong Kong Polytechnic University
Hong Kong
CN

Abstract

Background: Isolated premature thelarche (IPT) is characterized by early breast development in girls under 8 years old without other signs of puberty. Zhibai Dihuang Ointment Prescription, a traditional Chinese medicine (TCM) formulation, has been proposed as an alternative.

Objective: This study aims to explore parents' perceptions of using this intervention for treating IPT in their children.

Methods: Semi-structured individual interviews were conducted online with 14 parents of children diagnosed with IPT who had been treated with Zhibai Dihuang Ointment Prescription for over six months. Participants were recruited through purposive sampling. Interviews were audio-recorded, transcribed verbatim, and analyzed using template analysis. NVivo 12 software was used to facilitate data.

Results: Three main themes emerged: (1) facilitators of Zhibai Dihuang Ointment Prescription for IPT, (2) barriers of Zhibai Dihuang Ointment Prescription for IPT, and (3) parental demands on Zhibai Dihuang Ointment Prescription for IPT. Facilitators included: (a) positive impacts on children and parents and (b) good acceptance among children and parents. Barriers included (a) limitations of the use of Zhibai Dihuang Ointment Prescription and (b) limitations in medical resources. Parental demands focused on (a) improvements in medication experience and (b) improvements in hospitals' medical services.

Conclusions: Zhibai Dihuang Ointment Prescription positively impacts children's development and family well-being. However, challenges like bitter taste, long treatment periods, and occasional side effects affect adherence. Improved healthcare access and patient-centered approaches are needed. Future quantitative and qualitative research are needed to evaluate its effects and understand patient experiences.

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Name of authors: Kai-Feng Li, MA ^{1#}

Xuan Li, MA ^{1#}

Xuan Zhang, PhD ²

Xiao-Feng Fang, MA ¹

Gui-Wen Li, MA ¹

Wing-Fai Yeung, PhD ³

Jin Qin, PhD ³

Gui-Ju Zhang, PhD ^{1*}

Shu-Cheng Chen, PhD ^{3*}

Name of department: 1 Shandong University of Traditional Chinese Medicine, Jinan, China;
2 Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, China; 3 The Hong Kong Polytechnic University, Hong Kong, China

***Corresponding Author:** Prof. Gui-Ju Zhang, Shandong University of Traditional Chinese Medicine, 16369 Jing Shi Road, Jinan, China

E-mail: 13685316296@163.com

Telephone: +86 13685316296

Dr. Shu-Cheng Chen, The Hong Kong Polytechnic University, 11 Yuk Choi Road, Hung Hom, Kowloon, Hong Kong, China

E-mail: cara-sc.chen@polyu.edu.hk

Telephone: +852 2766 1371

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Abstract

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Methods: Semi-structured individual interviews were conducted online with 14 parents of children diagnosed with IPT who had been treated with *Zhibai Dihuang Ointment Prescription* for over six months. Participants were recruited through purposive sampling. Interviews were audio-recorded, transcribed verbatim, and analyzed using template analysis. NVivo 12 software was used to facilitate data.

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Conclusions: *Zhibai Dihuang Ointment Prescription* positively impacts children's development and family well-being. However, challenges like bitter taste, long treatment periods, and occasional side effects affect adherence. Improved healthcare access and patient-centered approaches are needed. Future quantitative and qualitative research are needed to evaluate its effects and understand patient experiences.

Keywords

Chinese herb prescription, isolated premature thelarche, precocious puberty, qualitative study, interview, traditional Chinese medicine

1. Introduction

1.1 *Isolated Premature Thelarche*

Isolated Premature Thelarche (IPT) is a condition characterized by the isolated development of breast tissue in girls before the age of 8 years, without other signs of precocious puberty [1]. It is a common type of incomplete precocious puberty, with most cases being idiopathic [2]. The primary characteristic of IPT is unilateral or bilateral breast enlargement, which may exhibit cyclical fluctuations in size [3; 4]. The enlarged breast tissue may be tender for a short period, while there is neither significant change in the nipple or areola, nor appearance of pubic or axillary hair [5]. The external genitalia, labia majora, labia minora, and vagina remain in a prepubertal state [5]. The growth, skeletal maturation, the onset of menarche, and the pattern of pubertal development remain normal [6]. While IPT is generally considered a benign condition with no disproportionate growth or impairment of growth potential, and typically requires no treatment, it is crucial to closely monitor these girls [2; 7]. Approximately 4%-18% of cases may progress to central precocious puberty (CPP), a condition with significant implications for physical and psychological development [8]. Besides, the condition may greatly affect the child's parents or caregivers. Parents of girls with IPT often experience significant psychological stress and anxiety, which can be a contributor to the recurrence or exacerbation of the condition [9; 10]. Therefore, in addition to medical management, it is important to address the psychological and emotional needs of both the children and their parents or caregivers [11]. Providing accurate information, psychological support, and counseling can contribute to alleviating their concerns and promote a more positive outlook on the condition [10; 11; 12]. Effective pharmacological treatments for IPT are lacking in conventional western medicine, as the widely used gonadotropin-releasing hormone (GnRH) analogs are only effective on CPP and not suitable for IPT management [13]. While IPT is generally considered a self-limiting condition, the potential progression to CPP and the associated psychosocial impacts have highlighted the need for a comprehensive and multidisciplinary approach to its management [14; 15]. Exploring the complementary or alternative interventions, such as Chinese herbal medicine, may provide additional treatment options and a more holistic approach to address the physical and psychological aspects of this condition [8].

1.2 *Zhibai Dihuang prescription*

Zhibai Dihuang prescription is a classic formulation originating from the "*Yizong Jinjian*" [16], a renowned traditional Chinese medicine (TCM) medical book. It is composed of six

ingredients from the *Liuwei Dihuang* prescription (*Shudihuang*, *Shanzhuyu*, *Shanyao*, *Zexie*, *Fuling*, *Mudanpi*), with the addition of *Zhimu* and *Huangbai*. *Zhibai Dihuang* Pills have been widely used for the clinical treatment of yin deficiency, and made into other dosage forms of preparations, such as tablets, capsules, and granules [17]. This formulation is traditionally used to treat liver and kidney yin deficiency with internal heat syndrome [18]. Current research suggests that the *Zhibai Dihuang* prescription has potential therapeutic benefits in the treatment of various conditions, such as precocious puberty [19], purpura nephritis [20], type 2 diabetes mellitus [21], diminished ovarian reserve [22], vaginitis [23], and male infertility [24]. Pharmacological studies have indicated that the therapeutic mechanisms of *Zhibai Dihuang* prescription in treating IPT involve inhibiting excessive osteoblast activity, antioxidant effects, enhancing mitochondrial respiratory chain complex activity, regulating immunity and metabolism, and modulating hormone levels [25]. A study has indicated that *Zhibai Dihuang* prescription can act on targets associated with the onset of precocious puberty, such as prostaglandin-endoperoxide synthase 1, androgen receptor, estrogen receptor 1, progesterone receptor, gamma-aminobutyric acid A receptor, and nuclear receptor subfamily 3 group C member 1. Moreover, it can also influence tryptophan metabolism and steroid hormone biosynthesis [26].

1.3 Research gap

Previous studies have investigated the therapeutic potential of *Zhibai Dihuang* prescription and related formulations in treating various conditions, including precocious puberty and IPT. For instance, a study conducted by *Yue et al.* involving 78 girls with idiopathic precocious puberty found, that after treatment with *Zhibai Dihuang Pill*, the levels of FSH, LH, PRL, E2, UV, ROV, and LOV were significantly reduced compared to pre-treatment levels ($P < 0.01$) [27]. Another study carried out by *Qiu et al.* showed that *Liuwei Dihuang Pill* (a component of *Zhibai Dihuang Pill*) helped regulate sex hormone levels and alleviate polycystic ovary syndrome in a rat model, suggesting its potential therapeutic advantage over other herbal formulations [28]. Additionally, a regional population study by *Lin et al.* revealed that among the 3,495 newly diagnosed subjects with sexual precocity, 98.25% received TCM treatment, with *Zhibai Dihuang Pill* being the most frequently prescribed TCM formulation (23.73%) [19]. While these studies have provided valuable insights into the effects and potential mechanisms of action of *Zhibai Dihuang* prescription, several limitations can be identified. Many studies have relatively small sample sizes, which may limit the generalizability of the findings and increase the risk of bias. In addition, some studies lack rigorous methodology

and statistical analyses, potentially compromising the validity and reliability of the results. Besides, the outcome measures employed in these studies are often restricted to objective parameters, such as hormone levels or ovarian morphology, without considering the subjective aspects of the patient's experiences, such as quality of life, psychological well-being, and treatment satisfaction. These subjective factors are crucial for the management of conditions like IPT, which can have significant psychosocial implications for both the affected children and their caregivers. Furthermore, while previous quantitative studies have contributed to our understanding of the potential therapeutic benefits and mechanisms of *Zhibai Dihuang Pill*, there remains a significant research gap in exploring the subjective experiences and perspectives of patients and caregivers regarding their use in the treatment of IPT. A qualitative study addressed this gap by providing valuable insights into the subjective experiences, perceptions, and concerns of patients and caregivers, potentially uncovering additional research questions that had not been previously explored and contributing to the development of more comprehensive and patient-centered treatments for IPT [29]. Therefore, we designed and conducted this individual interview study for a deeper understanding of factors that might influence treatment adherence, satisfaction, and overall well-being, which were often overlooked in quantitative studies.

2. Aim

This study aimed to gain insights into the facilitators, barriers, and pertinent factors associated with the utilization of *Zhibai Dihuang Ointment Prescription* for the treatment of IPT in children, as perceived by parents.

3. Methods

This study utilized a qualitative research approach, and employed semi-structured individualized interviews. Ethical approval was obtained from the Affiliated Hospital of Shandong University of Traditional Chinese Medicine (SDUTCM) (2023-124-KY). The reporting of this study conformed to the guidelines provided by the consolidated criteria for reporting qualitative research (COREQ) checklists [30]. This study reported parents' experiences of receiving *Zhibai Dihuang Ointment Prescription* in their children with IPT. The treatment used a modified version of *Zhibai Dihuang* prescription, incorporating additional herbs such as *Shengdihuang*, *Lizhihe*, *Juhe*, *Gouqi*, *Sharen*, and *Maiya*, and it was transformed from the original prescription by adding sugar as an excipient [31]. After receiving the medicine, the child should take one package of the ointment prescription twice

a day for 3 months as a course, and the amount of each package was about 50 g. The TCM practitioners also innovatively applied the prescription as an ointment formulation, which was an ancient dosage form that offered advantages such as palatability, ease of administration, and reliable therapeutic effects [32; 33]. This innovation also makes it an attractive option for long-term use in pediatric patients [31].

3.1 Setting and participants

Individual interviews were conducted online utilizing the WeChat video chat [34]. In terms of health-care seeking behavior, individual interviews prove to be more efficient when comparing the number of items generated per participant, as individuals consistently generated a greater number of unique items in one-on-one interviews than those in focus groups [35]. The decision to conduct online interviews was based on their convenience and effectiveness in collecting the experiences of participants residing in diverse geographic areas. The feasibility of online interviews has been demonstrated in previous studies [36; 37]. This study was conducted at SDUTCM, located in Jinan City, Shandong Province, China.

Participants were recruited from the Department of Pediatrics at SDUTCM by means of purposive sampling [38]. Subjects were recruited from December 2023 to February 2024, by utilizing posters in outpatient departments and social media platforms. The participant inclusion criteria were as follows: (a) parents of children who received an official diagnosis of IPT; (b) children undergoing treatment with *Zhibai Dihuang Ointment Prescription* for a duration exceeding 6 months; (c) parents of children aged between 4 and 8 years; and (d) those who were willing to participate in the study and provided signed informed consent. Parents were excluded if they met any of the following criteria: (a) inability to fluently speak Mandarin; (b) difficulties in using instant messaging software; (c) parents whose children were diagnosed with precocious breast development caused by central or peripheral precocious puberty, or had severe neurological, cardiovascular, respiratory, digestive, hematological, endocrine, or other systemic diseases; and (d) treatment for their children was interrupted or irregular during the specified treatment period. Prior to their participation in the study, written informed consent was obtained from every participant.

3.2 Data collection

The interview guide in Chinese was developed by the first author (KFL), and an English version is provided for reference in Table 1. The guide underwent revisions by two TCM

practitioners (XL and XZ) as well as a qualitative researcher (SCC). To ensure the comprehensibility, a pilot test was conducted with the first participant to demonstrate the clarity of all the questions. Semi-structured interviews were then conducted via online video calls by two TCM practitioners (XL and KFL). The interviewers established a rapport with the participants by demonstrating genuine interest in their individual concerns. The moderator (XL), possessing extensive clinical expertise in Chinese herbs, received training from an experienced qualitative researcher (SCC). All interviews were audio-recorded, and field notes were taken during the study. Participation was voluntary, and participants were assured that their names would not be recorded despite the sessions being audiotaped. As an incentive, each participant's child received a complimentary bone age test.

3.3 Data analysis

All interviews were audio-recorded and transcribed verbatim in simplified Chinese prior to data analysis. Quoted statements were translated and back-translated by two researchers. Each participant was assigned a random generated code to ensure confidentiality. Descriptive characteristics of the demographic data were employed to provide an overview of the sample profile. The transcripts underwent template analysis, a thematic analysis approach that emphasizes hierarchical coding [39]. The process of template analysis involved the following steps: (a) thorough reading and rereading to establish researcher familiarity; (b) implementation of initial coding; (c) organization of the relationships between themes; (d) generation of the initial template; (e) refinement of the initial template through further data analysis; and (f) finalization of the template and use across the entire dataset [39; 40]. Data transcription and coding were performed by the first author (KFL) and the second author (XL), while another researcher (XZ) reviewed the codes for accuracy and consistency. Any discrepancies were resolved through consultation with the corresponding author (SCC). NVivo 12 software was utilized for data analysis [41].

4. Results

Fourteen parents took part in the research study and underwent individual interviews between January and March 2024. Data saturation was employed as a guiding principle for data collection [42], whereby themes and subthemes were initially identified within the first nine interviews and further enriched following the fourteenth interview. The interviews had an average duration of 43 min, ranging from 37-49 min.

4.1 Participants' characteristics

Fourteen parents, consisting of twelve females (85.7%) and two males (14.3%), who had children with IPT, participated in the interviews. The average age of the parents was 36.6 years (SD = 4.2), while that of their children was 9.3 years (SD = 1.3). Among the participants, nine (64.3%) possessed tertiary education qualifications. The demographic details of the participants are displayed in Table 2.

4.2 Main themes

Three themes were identified regarding the participants' experiences of using *Zhibai Dihuang Ointment Prescription*: (1) facilitators of *Zhibai Dihuang Ointment Prescription* for IPT, (2) barriers of *Zhibai Dihuang Ointment Prescription* for IPT, and (3) parental demands on *Zhibai Dihuang Ointment Prescription* for IPT. The specific subthemes corresponding to each theme were described, and the code structure is presented in Table 3.

4.2.1 Theme 1: Facilitators of Zhibai Dihuang Ointment Prescription for IPT

This particular theme consisted two distinct subthemes: (a) positive impacts on children and parents, and (b) good acceptance among children and parents.

The positive impacts of receiving *Zhibai Dihuang Ointment Prescription* on children and parents were evident in various aspects on the children's sexual development, physique, mental health, as well as the parents' mental well-being and the parent-child relationships. Firstly, there was a notable improvement in the children's sexual development, as observed in the following testimonials: "After taking the medicine, I could clearly feel that the lump disappeared. It used to be as big as a grape and as hard as a date. After some time, when I touched it again, it was indeed soft" (003), and "She initially had a high bone age, and that has been controlled now. She hasn't developed any further in the past six months" (009). Additionally, the children's overall physique showed improvements, including diet, sleep, defecation, and height: "After taking the medicine, things changed. She no longer experiences physical weakness, night sweats, or poor digestion. She can eat normally and control her development...I am also pleased with the increase in height. She is now 1.36 meters tall. I'd be even happier if she grew a little more to over 1.4 meters in the next few months" (006). Furthermore, there was a positive impact on the children's mental health, as one parent explained: "When she was initially diagnosed, she was quite worried. However, after taking the medicine and seeing her symptoms disappear, she stopped worrying" (004). This

improvement in the children's well-being also extended to the parents' mental health: *"Before taking the medicine, I was very anxious like a headless chicken. It was hard. I couldn't sleep and eat, constantly doubting myself. I felt it was all my fault. After taking this medicine, my mood improved a lot. I wasn't anxious and I could sleep at night"* (009). Moreover, the treatment positively affected the parent-child relationships: *"At the beginning, some parental anxiety will definitely be passed on to the children. You feel like you have done a lot for her, but she doesn't understand...After taking this medicine, my mood improved significantly... When you are in a good mood, the child's mood will also improve. It's a positive cycle"* (007).

The acceptance of receiving *Zhibai Dihuang Ointment Prescription* among children and parents was highly positive, evident in various aspects. Firstly, children demonstrated high acceptance due to convenience of taking ointment. One mother shared, *"There was a period of time when she felt really upset, especially with the prospect of having to take growth hormone injection every day. This can be painful for both children and adults, causing a lot of anxiety and distress. After seeing the effects of the medicine, she gradually relaxed about avoiding injections"* (007). Moreover, parents exhibited high acceptance of the treatment for several reasons. They appreciated the ointment's minimal side effects, as mentioned by a father: *"Chinese herb is relatively safe and positive. As for the double hormone injection, it is difficult to accept because of its cost. We estimate that 20 months of treatment would cost around 400,000 yuan"* (013). The lower cost of the ointment than western medicine was a significant factor for its acceptance. Additionally, parents valued the avoidance of interference from western medicine, as they preferred the use of this intervention. This sentiment was reflected in their acceptance of *Zhibai Dihuang Ointment Prescription* as an alternative treatment option. A mother mentioned, *"I think there are high risks associated with affecting hormones using Western medicine, especially in children's overall growth."* (012). Furthermore, the convenience of taking the ointment contributed to its acceptance among children and parents. One parent expressed, *"My child can accept this Chinese medicine ointment prescription. We have tried other Chinese medicine formulations before, and the taste makes you not want to drink it."* (009).

4.2.2 Theme 2: Barriers of Zhibai Dihuang Ointment Prescription for IPT

The barriers encompassed the following two subthemes: (a) limitations in the use of *Zhibai Dihuang Ointment Prescription*, and (b) limitations in medical resources.

The use of *Zhibai Dihuang Ointment Prescription* was associated with certain limitations, as observed in the following aspects. First, there were limitations associated with the experience of receiving this prescription. One limitation was the bitter taste, which was found to be unpleasant in some children. As one parent mentioned, "*Chinese medicine is bitter. She dislikes the bitterness and always says, 'Mom, the medicine is too bitter'*" (003). Additionally, the medication period for receiving this prescription could be lengthy, requiring daily intake over a considerable duration. This was challenging for both children and parents, as expressed by a parent: "*Chinese medicine is not as simple as taking three or five doses and being done. You have to take it daily, so over three months that amounts to around 180 bags*" (010). Moreover, there was a cost associated with the processing fee of using this prescription. While the medicine itself might not be expensive, the processing fee could be relatively high, as stated by a parent: "*Although Chinese medicine itself is not expensive, the processing fee is costly. For a one-month supply, the processing fee seems to be around 300 yuan, which is relatively high*" (008). Second, there were limitations in terms of treatment effects and adverse reactions. For instance, one parent mentioned the rapid development of bone age without significant inhibition: "*Her bone age developed quite quickly, and there was basically not much inhibition*" (001). Some children might experience nausea and the urge to vomit, although it was uncertain whether this was directly related to taking the prescription: "*The Chinese medicine doesn't taste very good. It is normal. My child feels nauseous and wants to vomit in the morning now. Actually, I don't know if this is related to drinking this prescription*" (007).

Moreover, the limitations in medical resources were evident in the following aspects. First, there was an imbalance in medical resources, particularly for individuals living in remote areas. Accessing medical services was inconvenient for those who were not located near medical facilities. One parent expressed their desire for video consultations: "*Since we are not in Jinan, can we have video consultations? We can show the doctor the test results through video, and then get prescriptions. The medicines can be mailed to us. This could solve a large part of the inconvenience for people like us who live out of town*" (008). This highlights the need for improved access to medical resources for individuals residing in remote areas. Additionally, strained medical resources posed difficulties for patients receiving the treatment. There were also challenges associated with the registration process, finding parking, seeing a doctor, and obtaining the necessary medicine. One parent described the inconvenience of long waiting time for appointments and the additional hurdles involved in

blood draws: *"Every time we make an appointment with a doctor, we have to wait for a long time, which is very troublesome. As for the blood draw, the child is very hungry because it needs to be done on an empty stomach. I have to wait in line again before taking the child for the blood draw"* (001).

4.2.3 Theme 3: Parental Demands on Zhibai Dihuang Ointment Prescription for IPT

Parental demands on using this prescription included (a) improvements in medication experience, and (b) improvements in hospitals' medical services.

There was a need for the improvements in the medication experience concerning *Zhibai Dihuang Ointment Prescription*. These improvements were required in the following aspects: On the one hand, improvements were desired in the taste and administration process of the ointment. The bitter taste of the prescription was a challenge for some patients. It would be beneficial to explore ways to enhance the taste or administration route, such as developing a drink mix or small pill form, to make it more convenient and easier for children to take, as suggested by another parent: *"She can't consciously take it herself. Thus, adults always need to be there to supervise. It might be more convenient if there is something like a drink mix or a small pill"* (010). On the other hand, there was a need for customizing individual prescriptions to improve the treatment's overall effectiveness. Some parents expressed concerns about the consistency of the ointment's medicinal ingredients and whether there were different prescriptions tailored to specific symptoms. One parent inquired: *"We have been taking it for more than half a year, and the medicinal ingredients in the ointment have not changed. Are there different prescriptions for different people's symptoms?"* (012).

Improvements in medical services were proposed to enhance the overall patient experience. For the one thing, there was a need to improve the medical experience through various means. Online consultation platforms could be established to facilitate communication between healthcare providers and patients, as one parent expressed: *"Since you provide such a platform, could you create a WeChat group for us to communicate?"* (002). This would enable convenient and timely access to medical advice, particularly for individuals who might face challenges in physically visiting medical facilities. Additionally, setting up specialized clinics dedicated to specific illnesses could greatly benefit patients. It would address the concerns of cross-infection and reduce the excessive waiting time. As suggested by one parent: *"Is it possible to have a dedicated service window for specific illnesses?... It*

would be much more convenient if there was a special window where we could just go in and get a prescription for the ointment and then pick up the medicine" (006). For the other thing, there was a need to strengthen follow-up visits and establish effective means of communication with healthcare providers. Parents expressed the desire: "Is there any service like follow-up observation?... Is it possible to get timely and effective feedback from doctors through online means?" (002).

5. Discussion

5.1 Main findings

The study presented parents' view of using *Zhibai Dihuang Ointment Prescription* for IPT in their children. Three themes, including facilitators, barriers, and parental demands, emerged. The facilitators highlighted the positive effects of the prescription on children's sexual development, physique, mental health, as well as the parents' well-being and the parent-child relationships. **Acceptance of the prescription was high among children due to the convenience of taking ointment, while parents appreciated the minimal side effects, low cost, and the prominent therapeutic effects.** By contrast, barriers included the bitter taste, long medication period, processing costs associated with this intervention, occasional adverse reactions, and varying treatment effectiveness. Parental demands emphasized the need for improvements in the medication experience, such as alternative administration methods and customized prescriptions based on specific symptoms. Enhancing medical services, including online consultations, specialized clinics, streamlined medication processes, and strengthened follow-up visits, would further enhance the overall patient experience. Addressing these aspects would contribute to equitable access, convenience, and effectiveness of *Zhibai Dihuang Ointment Prescription* for IPT.

The findings of this study highlight several distinct advantages of *Zhibai Dihuang Ointment Prescription* for the management of IPT in children. The perceived positive impacts on children's sexual development, physical well-being, and mental health. The effects of the intervention on children's sexual improvements were consistent with previous research. Previous studies have shown that *Zhibai Dihuang Prescription* can act on targets associated with precocious puberty [43], regulate hormone levels [44; 45], and exert antioxidant effects [46]. The current study added to the evidence of this prescription on improving children's breast development, bone age progression, overall physique, and anxiety. Furthermore, this study also revealed the psychosocial benefits of the intervention, which have been relatively

unexplored in previous quantitative studies. Addressing these psychosocial aspects becomes crucial for the holistic management of IPT, given the potential psychological and emotional impacts on patients [47]. While previous studies have primarily focused on objective outcomes, such as hormone levels or ovarian morphology [45], this qualitative study provides additional insights by exploring the subjective experiences and perspectives of patients and caregivers. This intervention provides a complementary or alternative option that is perceived as safer, more cost-effective, and potentially less disruptive to the children's natural development.

The results identified several obstacles and constraints related to the utilization of *Zhibai Dihuang Ointment Prescription* for the management of IPT. Notably, the bitter taste of the formulation and the prolonged treatment period required for daily intake emerged as the significant challenges, which might negatively impact patient adherence and therapeutic effects. Similar palatability and adherence issues have been reported in previous studies investigating Chinese herb for various conditions, underscoring the importance of addressing these barriers [48]. Furthermore, the study revealed variations in treatment effects and occasional adverse events, such as nausea and vomiting, across different patients. This variability aligns with the nature of TCM interventions, involving individualized prescriptions tailored to the patient's specific condition and constitution [49]. While some patients experienced positive outcomes, others reported rapid bone age progression or lack of significant inhibition, highlighting the potential for differential responses to the same treatment. Previous studies have investigated various strategies, such as the use of granules or dissolvable dosage forms, to improve the acceptability of Chinese herb in the pediatric populations [50; 51]. The individualized nature of TCM interventions necessitates a thorough understanding of patient-specific factors [52], which may also lead to the difference in effects among patients.

The parental expectations focus on the need for a patient-centered approach in the administration of this intervention for children. These demands reflect the current landscape of healthcare delivery in mainland China [53] and align with the growing emphasis on enhancing patient experiences [54] and leveraging technology to improve accessibility and continuity of care [55]. The desire for customized individual prescriptions aligns with the fundamental principles of TCM, which emphasize personalized treatments based on the patient's specific condition, age, gender, body constitution, and disease patterns [52]. The

integration of online consultation platforms and communication channels resonates with the rapid adoption of telemedicine and digital health solutions in China [55; 56], particularly during the COVID-19 pandemic [57], and conforms to the government's efforts to promote the "Internet Plus Healthcare" initiative [58]. The implementation of such platforms would require regulatory oversight, data privacy measures, and robust infrastructure to ensure secure and reliable communication between healthcare providers and patients [58]. The establishment of specialized clinics dedicated to specific conditions like IPT could address concerns of cross-infection and streamline the delivery of medical services. However, this may require substantial resource allocation and coordination among healthcare facilities, as well as considerations for patient distribution.

5.2 Implications

For TCM practitioners, exploring alternative formulations including drink mixes or small pills can improve the palatability and adherence among pediatric patients. Customizing prescriptions on children is also recommended to optimize the treatment effects. Researchers are expected to conduct large clinical trials to quantitatively evaluate the effect and safety of this treatment, and incorporate qualitative measures to capture the feasibility and adherence from patients' experiences. Pediatricians should remain open to the collaboration with TCM practitioners for the integrative management of IPT, considering complementary TCM interventions alongside conventional therapies. Policymakers should promote to establish regulatory frameworks for telemedicine and online consultations and allocate resources for specialized clinics or dedicated services for conditions like IPT.

5.3 Strengths

Strengths of this study are as follows. At first, this study adopted an individualized interview approach to investigate the sensitive topic of IPT, which provided a conducive environment for participants. Second, the participants were carefully selected from the SDUTCM, an institution renowned for its expertise in ointment prescriptions, ensuring the study's representativeness and credibility. Third, in the modern medicine, IPT is often not considered a condition requiring specific intervention, as a result, research in this area is lacking, let alone studies exploring the broader outcomes, and this study addressed this gap to some extent.

5.4 Limitations

Limitations of this study should be acknowledged. First, although the participants were parents of children receiving the intervention for at least six months, the actual frequency and quantity of treatment varied among children due to differences in adherence and individual situations, which might potentially impact the comparability of participants' experiences. Second, while the online interviews without video cameras protected participants' privacy for this sensitive condition, they might have missed important nonverbal cues, such as gestures and facial expressions, which could have provided insights into participants' emotional states and reactions.

6. Conclusion

The findings in this study indicate that *Zhibai Dihuang Ointment Prescription* positively affects the sexual development, physical health, and mental well-being of children, and enhances their parents' mental health and family relationships. Both children and parents highly accept the treatment due to its minimal side effects, low cost, and ease of use. However, challenges such as the bitter taste, lengthy treatment period, and occasional adverse reactions may impact the treatment adherence and efficacy. Additionally, medical resource limitations, especially for remote families, underscore the need for improved healthcare access through telemedicine and specialized clinics. Parents express a desire for a more patient-centered approach in IPT management. Future research should prioritize large-scale clinical trials to evaluate the effect and safety of this treatment, incorporating qualitative insights to better understand patient experiences and adherence.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Shandong University of Traditional Chinese Medicine Affiliated Hospital's Ethics Committee for Human Research. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

KFL: Data curation, Investigation, Writing – original draft. XL: Formal analysis, Investigation, Methodology, Writing – original draft. XZ: Investigation, Data curation. XFF: Data curation. GWL: Data curation. WFY: Methodology, Writing – review & editing. JQ: Conceptualization, Writing – review & editing. GJZ: Conceptualization, Writing – review & editing. SCC: Conceptualization, Methodology, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table**Table 1. Questions for the semi-structured interview**

1.	Could you please briefly describe your child's situation, such as diagnosis time and basic status?
2.	What impact does your child's illness have on you and other guardians?
3.	What do you need to improve your child's symptoms of early breast development?
4.	What is your experience with our hospital's pure Chinese medicine treatment?
5.	What improvements did the child have during treatment?
6.	What is the reason why you can persist in coming to our hospital for treatment?
7.	What is the reason why the child may not insist on the treatment provided by our hospital?
8.	In addition to traditional Chinese medicine treatment, have you tried any other treatments for your child's early breast development? How do you evaluate these treatments?
9.	Do you have any suggestions for treatment in our hospital?

Table 2. Demographic Characteristics of Participants Interviewed (n=14)

Children	
Gender, no.(%)	
Male	0□0□
Female	14□100□
Age at onset of IPT, y , mean (SD)	7.2□0.8□
Height at onset of IPT, cm, mean (SD)	124.9□5.5□
Age at time of interview, y, mean (SD)	9.3□1.3□
Height at time of interview, cm, mean (SD)	141.0□8.4□
Treatment duration, month, mean (SD)	12.8□8.1□
Use western medicine, no.(%)	
Yes	1□7.1□
No	13□92.9□
Parents	
Age, y, mean (SD)	36.6□4.2□
Gender, no. (%)	
Male	2□14.3□
Female	12□85.7□
Education level,no.(%)	
Primary Education	1□7.1□
Secondary Education	4□28.6□
Tertiary Education	9□64.3□
Family annual income, no.(%)	
50k or below	0□0□
50k to 100k	2□14.3□
100k to 300k	8□57.1□
300k or above	4□28.6□

Abbreviation: IPT: isolated premature thelarche. y: years. cm: centimeter. SD: Standard deviation.

k: thousands.

Table 3. Code structures

Theme	Sub-theme	Coding Units
Facilitators of Zhibai Dihuang Ointment Prescription for IPT	➤ Positive impacts on children and parents	➤ Improvements in child’s sexual development (breast and bone age) ➤ Improvements in child’s physique (diet, sleep, defecation and height) ➤ Improvements in child’s mental health (anxiety, stress and self-discipline) ➤ Improvements in parent’s mental health ➤ Improvements in parent-child relationship
	➤ Good acceptance among children and parents	➤ High acceptance among children (convenience of taking ointment) ➤ High acceptance among parents (minimal side effects,low cost,and the prominent therapeutic effects)
Barriers of Zhibai Dihuang Ointment Prescription for IPT	➤ Limitations of the use of Zhibai Dihuang Ointment Prescription	➤ Limitations in experience of receiving this intervention (bitter taste, long medication period, and high processing fee) ➤ Limitations in treatment effects (occasional adverse reactions, and occasional poor effectiveness)
	➤ Limitations in medical resources	➤ Imbalance in medical resources (inconvenient for those living in remote areas) ➤ Strain of medical resources (difficulty in registering, parking, seeing a doctor, and getting medicine)
Parental demands on Zhibai Dihuang Ointment Prescription for IPT	➤ Improvements in medication experience	➤ Refinements in medication experience (taste and process) ➤ Customization of individual prescriptions to improve treatment effects
	➤ Improvements in hospitals’ medical services	➤ Improvements in medical experience (online consultation, setting up specialized clinics, and optimizing the process of getting medicines) ➤ Improvements in patients’ follow-up visit

Abbreviation: IPT: isolated premature thelarche.