The Effects of Aromatase Inhibitors and Growth Hormone Therapy on Early Puberty and Height: A Randomized Control Trial (RCT) Study Proposal

Nazanin Roughani, Simon Fraser University

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Abstract

This study investigates the effectiveness of growth hormone (GH) therapy and aromatase inhibitors (AIs) in managing early puberty and promoting height growth in children aged 6-9 years. Participants are randomized into GH therapy, AIs, or placebo groups. The study's primary outcomes include assessing the delay in puberty onset and measuring height growth through standardized methodologies. The research aims to shed light on these treatments' potential benefits and comparative efficacy in addressing precocious puberty.

Keywords: early puberty, growth hormonal therapy (GH), aromatase inhibitors (AIs), puberty delay, height growth, clinical trail

The onset of early puberty poses significant challenges for children, including psychological issues and stunted growth (Geffner, 2009). These include but are not limited to the development of secondary sexual characteristics, changes in lean body mass and fat distribution, and accelerated growth of the musculoskeletal system (Hero et al., 2020). The review of the literature emphasizes the importance of hearing and the onset of adolescence and its potential consequences. Onset of adolescence in girls before the age of eight and in boys before the age of nine is associated with anxiety, depression, and body image issues (Merke & Cutler Jr, 1996). Furthermore, height growth may be slower in adolescence and cause children to feel inadequate. The potential role of aromatase inhibitors (AIs) and growth hormone (GH) therapy as interventions have also been examined (Hu et al., 2011). AIs that reduce and inhibit estrogen production have been reported to delay the precocious phase (Pre-KOH) onset in prepubertal children (Mauras et al., 2008). The literature review indicates that AI could be a promising alternative to GnRH analogs, which often cause complications from complete androgenic blockade and can lead to developmental disorders related to secondary sex characteristics. Conversely, GH has been shown to influence bone growth, enhancing height in affected children positively. (Hero et al., 2020). GH therapy can help delay early puberty and improve early puberty in children (Merke & Cutler Jr, 1996). The literature review reveals that the consequences of early adolescence can be significant, and early intervention may be needed to prevent further adverse effects on child growth and development.

Literature Review

The literature review explores existing research on the effectiveness of growth hormone (GH) therapy and aromatase inhibitors (AIs) in managing early puberty and promoting height

growth in children. Early puberty affects approximately 1 in 2,000 children, with a higher prevalence in girls than boys (Dunkel,2006).

Complications arising from early puberty include the development of secondary sexual characteristics, changes in lean body mass and fat distribution, and accelerated growth of the musculoskeletal system (Wit et al., 2021). The literature emphasizes the importance of understanding the onset of adolescence and its potential consequences. Puberty in girls before age eight and in boys before age nine is associated with anxiety, depression, and body image issues (Karaer et al.,2004).

The potential role of aromatase inhibitors (AIs) and growth hormone (GH) therapy as interventions has been examined in several studies (Hu et al., 2011). AIs that reduce and inhibit estrogen production have been reported to delay the onset of the precocious phase (Pre-KOH) in prepubertal children (Mauras et al., 2008).

The literature review indicates that AIs could be a promising alternative to GnRH analogs, which often cause complications from the complete androgenic blockade and can lead to developmental disorders related to secondary sex characteristics. Conversely, GH has been shown to positively influence bone growth, enhancing height in affected children (Hero et al., 2020). GH therapy can help delay early puberty, improving height outcomes in children (Karaer et al.,2004).

Research Statement, Question, and Proposal

The proposed research seeks to delve deeper into the effectiveness of growth hormone (GH) therapy and aromatase inhibitors (AIs) in delaying early puberty and improving height growth outcomes in children. The main research question is focused on understanding the extent to which the dual therapy of AIs and GH can delay puberty and lead to more significant

improvements in height growth compared to placebo. The hypothesis is that combining AIs and GH will result in a more significant delay in the pre-KOH stage and better height growth outcomes (Hu et al., 2011). The study's primary objective is to provide a comprehensive analysis of the effectiveness of AI and GH therapy in delaying early puberty and improving height growth outcomes in children experiencing precocious puberty (Hu et al., 2011).

To achieve this objective, a thorough literature review will be conducted to identify the existing research in this area. The study will then collect relevant data through clinical trials, which will involve administering the treatment to a sample group of children and monitoring their progress over time. The research will focus on assessing the impact of these treatments on the delay of early puberty and the improvement of height growth outcomes. The data collected will be analyzed using statistical methods to determine the effectiveness of the treatments, and any significant findings will be reported in the final research report. Overall, this research aims to contribute to a better understanding of the effectiveness of AI and GH therapy in delaying early puberty and improving height growth outcomes in children. The findings of this study could have important implications for the treatment of precocious puberty and could lead to improved outcomes for affected children.

Research Methods

Study Design

The study will employ a randomized controlled trial (RCT) design. The RCT will randomly assign participants into three groups: one receiving GH therapy, another receiving AIs, and the third, a control group receiving a placebo, where we can track participants over time and assess the cumulative impact of treatments. With this approach, we were able to examine the

associations between exposure to aromatase inhibitors and growth hormone therapy with the outcomes of early puberty onset and height growth in children.

Participant Requirements

The study population will include prepubertal children aged 6-9 who are at risk of early puberty due to various factors such as obesity, family history, and exposure to endocrine-disrupting chemicals (Akın Kağızmanlı et al., 2023). Participants will be recruited from pediatric endocrinology clinics. A stratified random sampling method will ensure diversity in the sample population. This method will involve dividing the population into subgroups based on specific characteristics, such as age, gender, and ethnicity, and then randomly selecting participants from each subgroup. By using this approach, the study will be able to collect data from a diverse group of participants (Dunkel, 2006).

Data Collection Method

To collect data, the study will use a combination of methods, including medical records, interviews, and anthropometric measurements. Medical records will be reviewed to obtain information on the children's medical history, including any previous diagnoses or treatments that may affect their growth and development. Interviews will be conducted with the children and their parents or guardians to gather information on their lifestyle, dietary habits, and physical activity levels (Soliman et al., 2014). Anthropometric measurements, such as height and weight, will be taken to assess height growth rates and body mass index (BMI).

To ensure accurate data collection, the study will involve regular medical assessments to monitor the progression of puberty and physical growth. These assessments will include Tanner staging, a widely used method for evaluating the development of secondary sexual characteristics, and height measurements (Soliman et al., 2014). The study aims to

comprehensively evaluate the effectiveness of the treatments by measuring the delay in the onset of puberty and height growth as primary outcome measures (Soliman et al., 2014). The delay in the onset of puberty will be assessed through a clinical evaluation of secondary sexual characteristics, including breast development, pubic hair growth, and testicular enlargement. Height growth will be measured using standard anthropometry, which involves measuring the participants' height using a stadiometer (Wit et al., 2021).

The study will employ advanced statistical techniques to analyze the data. These techniques will enable the researchers to compare the outcomes across the three groups and assess the differences and effectiveness of the treatments (Wit et al., 2021). This comprehensive approach ensures a thorough evaluation of the primary outcomes, such as delayed puberty and increased height, and secondary outcomes, which may include broader implications on bone health, cognitive development, fertility, and body composition.

Strengths and Limitations. One of the strengths of this research is its comprehensive outcome measures. The study uses clinical evaluations of puberty onset and standardized height growth measures, ensuring a holistic assessment of the effectiveness of the therapies. Another strength of the study is its diverse study population. By including children from a broad age range (6-9 years) and ensuring gender diversity, the study aims to produce findings more representative of the general population experiencing early puberty (Wit et al.,2021). There are a few limitations; one is the ethical and practical challenges of conducting research with children in a sensitive area like puberty. Obtaining informed consent, ensuring participants' understanding and comfort, and monitoring for adverse effects require careful consideration and may limit the study's scope (Mauras et al.,2023). Additionally, the study may need to be revised to track long-

term outcomes due to duration constraints. Finally, while the study focuses on physical outcomes, the psychological impact of early puberty and its treatment is not a primary measure.

Ethical Considerations. Ethical considerations are of utmost importance, especially regarding studies involving children (Mauras et al., 2008). Informed consent will be obtained from parents or guardians to ensure compliance with ethical standards. The study will be conducted to minimize risk to the participants, and continuous monitoring will be in place to detect any adverse effects of the treatments (Mauras et al., 2008). In any such occurrences, protocols will be followed to address them. The confidentiality of participants' data will be strictly maintained to protect their privacy.

GH Therapy Group. The GH Therapy Group study will administer GH therapy to participants at a dose of 0.3 mg/kg/week, following FDA-approved guidelines for GH deficiency (Karaer et al.,2004). In addition to the standard dose, this study will also test a high-dose GH therapy group at 0.7 mg/kg/week (Karaer et al.,2004). This high dose was inspired by pivotal trials that showed children receiving this dose experienced an additional growth of +4.6 cm after 36 months and +5.7 cm after four years compared to those on the conventional dose (Karaer, Oruç & Koyuncu, 2004).

AIs Therapy Group. Members of this group will be administered daily doses of either anastrozole (1 mg), letrozole (2.5 mg), or exemestane (25 mg). Studies have demonstrated that these AIs are highly effective in preventing tissue aromatization (96.7%, >99.1%, and 97.9%, respectively), indicating that increased dosages may result in more significant growth (Karaer et al.,2004). When used in combination with GH therapy, very short boys with GH deficiency receiving the GH/anastrozole treatment experienced a significant predicted adult height increase

of +4.5 cm after 24 months and +6.7 cm after 36 months compared to those receiving the GH/placebo treatment (Karaer et al.,2004).

Control group (Placebo). The purpose of including a placebo group in a clinical trial is to provide a baseline for comparison to evaluate the effectiveness of the tested interventions.

Bone Health. When utilizing AI technology, it is critical to consider its impact on bone mineralization. While estrogen blockade has been known to have adverse effects on bone health, as seen in estrogen-deficient men with osteopenia and osteoporosis, the situation is different when it comes to time-limited AI treatments during puberty (Hu et al., 2011). Boys with idiopathic short stature (ISS) who underwent letrozole treatment showed suppressed bone turnover, indicating a protective androgen-mediated effect on bone health (Hu et al., 2011). Long-term follow-up and detailed assessments, including dual-emission X-ray absorptiometry (DEXA) scans, revealed that lumbar spine bone mineral density remained within normal ranges for all treatment groups after 24 months, with the AI-alone group showing the lowest standard deviation scores (SDS) (Akın Kağızmanlı et al., 2023). These findings highlight the importance of conducting baseline and annual DEXA scans to monitor bone health throughout the study and ensure that the treatments have no detrimental impact.

Fertility and Sperm Health. Research suggests that the short-term use of AI does not negatively impact sperm production or viability, thus preserving fertility potential in treated individuals (Heroet al., 2020). Our study will closely monitor this aspect, given the notable increase in testosterone levels resulting from AI treatment and its possible impact on reproductive health.

Discussion

This study is significant in pediatric endocrinology, particularly in managing and understanding early puberty. This condition presents considerable challenges regarding physical growth and psychological well-being for affected children. By exploring the efficacy of growth hormone (GH) therapy and aromatase inhibitors (AIs) in moderating the onset of puberty and facilitating height growth, the existing research aims to illuminate a path toward refined, evidence-based interventions that are sorely needed in current practice.

Existing research suggests that the combined use of GH therapy and AIs can be an effective treatment strategy for delaying puberty and facilitating height growth in pediatric patients (Hero et al., 2020). These comprehensive studies examine the direct outcomes of delayed puberty and increased height and the broader implications on bone health, cognitive development, fertility, and body composition, providing a robust and reliable basis for future interventions. These findings position this area of research as a cornerstone with the potential to reshape how early puberty is approached and treated. Future research studies should explore the long-term ramifications of these interventions, assess their psychological impacts, and tailor treatments to specific patient demographics, such as different age groups and genders (Mauras et al., 2023).

The findings from these studies are anticipated to influence future research directions in pediatric endocrinology significantly. By highlighting the benefits and limitations of GH and AI treatments in a controlled, methodical manner, this research sets the stage for subsequent studies that could explore the long-term ramifications of these interventions, assess their psychological impacts, and tailor treatments to specific patient demographics (Mauras et al., 2008). Furthermore, this review could lead to a shift in standard care practices, advocating for a more

nuanced, individualized approach to treatment. This could dramatically improve the quality of care for children experiencing early puberty, offering them a better trajectory for growth and development, both physically and psychologically (Mauras et al., 2008).

Ultimately, this literature review's significance lies in its capacity to provide a rigorous, evidence-based foundation upon which future treatment strategies can be built. This ensures that interventions are effective in mitigating early puberty symptoms and supportive of the child's overall well-being. Through its comprehensive scope and potential to guide clinical practice, this review represents a significant leap forward in optimizing care for children facing the challenges of early puberty.

Conclusion

In conclusion, examining growth hormone (GH) therapy and aromatase inhibitors (AIs) as potential treatments for early puberty management represents a significant shift in pediatric endocrinological approaches. The study proposes that these treatments have the potential to delay the onset of puberty and improve height growth outcomes, offering a promising alternative to conventional methods. However, it is essential to consider the broader implications for bone health, fertility, and psychological well-being when evaluating treatment options. The existing literature provides compelling evidence supporting the efficacy of GH and AI therapies, indicating that combining these treatments could enhance outcomes for children with precocious puberty. Nonetheless, ongoing research is necessary to fully understand the long-term effects, potential side effects, and optimal treatment protocols. In addition, a more individualized treatment strategy is crucial, considering each patient's unique needs. The literature review and study can advance our current knowledge of treatment options and create opportunities for future investigations. They challenge researchers and clinicians to continue exploring innovative

solutions that are effective and aligned with the child's holistic well-being. Ultimately, the progress in managing early puberty, as highlighted in this review and study proposal, promise to improve the quality of life for affected children and guide them toward healthier growth and development trajectories.

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