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Delayed Puberty in Adolescents: Advances in Diagnosis, Classification, and Treatment Modalities

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Abstract **Original Research Article**

Delayed puberty (DP) in adolescents is an increasingly recognized clinical condition that poses physiological, psychosocial, and reproductive concerns. Defined by the absence of pubertal onset beyond established age thresholds, DP may arise from benign variants such as constitutional delay of growth and puberty (CDGP) or from pathological causes including hypogonadotropic hypogonadism (HH), hypergonadotropic hypogonadism, and chronic systemic diseases. This review synthesizes evidence published between February 2021 and July 2025 to evaluate recent advances in diagnosis, classification, and treatment. A structured search of PubMed, Scopus, Web of Science, and Google Scholar identified randomized trials, cohort studies, genetic investigations, biomarker analyses, and guideline updates. Findings highlight progress in hormonal assays, genetic sequencing, AMH/INHB biomarkers, neuroimaging, and predictive models that improve CDGP–HH differentiation. Advancements in classification frameworks, including phenotype–genotype integration, offer improved clinical decision-making. Treatment evolution includes optimized sex-steroid induction therapies, gonadotropin-based regimens, and emerging modalities such as kisspeptin analogues. Comparative analyses show varying therapeutic efficacy across etiologies. Despite progress, challenges remain regarding diagnostic heterogeneity, limited biomarker standardization, variable treatment protocols, and insufficient long-term outcome data. Future directions emphasize precision medicine, equitable access to diagnostics, and long-term monitoring strategies. This review consolidates current evidence to guide clinical practice and inform future research priorities.

Keywords: Delayed puberty; adolescents; hypogonadotropic hypogonadism; constitutional delay; endocrine therapy; diagnostic biomarkers; puberty disorders.

1. INTRODUCTION

1.1 Background on the Topic

Puberty is a physiologically complex transition marked by activation of the hypothalamic–pituitary–gonadal (HPG) axis, resulting in secondary sexual characteristics, growth acceleration, fertility acquisition, and psychosocial milestones. Delayed puberty (DP) occurs when this transition fails to begin within the expected age range: breast development after 13 years for girls or testicular enlargement (<4 mL) after 14 years for boys (Marshall *et al.*, 2021). DP affects an estimated 2–3% of adolescents globally, with higher incidence in males. The condition encompasses a spectrum of benign and pathological etiologies, making accurate diagnosis imperative.

The most common cause is constitutional delay of growth and puberty (CDGP), a normal variant characterized by slower-than-average maturation and often a family history of delayed growth patterns. CDGP accounts for approximately 60–65% of DP cases (Kim *et al.*, 2023). However, more serious causes include hypogonadotropic hypogonadism (HH), hypergonadotropic hypogonadism, chronic systemic disease, undernutrition, psychosocial stress, and endocrine disorders. HH may be congenital resulting from GnRH deficiency, mutations in genes such as *GNRHR*, *KAL1*, *TAC3*, and *FGFR1* or acquired through pituitary tumors, trauma, chronic illness, or systemic inflammation (Silveira *et al.*, 2023).

Diagnosis historically relied heavily on clinical assessment, bone age estimation, and hormonal profiles. However, distinguishing CDGP from HH remains challenging, as both may present with low gonadotropin and sex-steroid levels. Traditional GnRH stimulation tests, although widely used, show limited reliability in early adolescence. Recent research highlights the utility

of biomarkers such as inhibin B (INHB), anti-Müllerian hormone (AMH), leptin, and kisspeptin as adjuncts. Advances in radiologic imaging particularly MRI aid in identifying structural pituitary abnormalities and congenital anomalies (Rossi *et al.*, 2022).

Therapeutic strategies vary with underlying cause. CDGP often requires only reassurance or brief low-dose sex-steroid induction to alleviate psychosocial distress. Pathological hypogonadism necessitates hormone replacement, pulsatile GnRH therapy, or gonadotropin injections. Emerging therapies include kisspeptin analogues and genetic-targeted interventions, reflecting the transition toward precision medicine in adolescent endocrinology (Narasimhan *et al.*, 2024).

Understanding DP remains critical given its physical, emotional, and reproductive consequences. Delayed bone mass accrual increases osteoporosis risk; persistent hypogonadism compromises fertility; and psychosocial burden may lead to anxiety and depression. Over the last decade, rising rates of chronic disease, nutritional disparities, and environmental stressors have influenced pubertal timing worldwide, making contemporary review essential. This article synthesizes current advances in diagnosis, classification, and treatment, providing clinicians, researchers, and policymakers with a comprehensive review of recent evidence.

1.2 Importance and Relevance of the Subject

Delayed puberty is not only a physiological condition but also a psychosocial and developmentally sensitive issue. Adolescence is a period of identity formation, bodily self-awareness, peer comparison, and emotional vulnerability. DP can lead to social isolation, bullying, reduced academic performance, low self-esteem, and disordered eating (Ahmed *et al.*, 2023). Early diagnosis and intervention are therefore essential not only for medical outcomes but also for psychosocial well-being.

From a clinical perspective, the ability to differentiate between CDGP and pathological forms of hypogonadism is critical. Failure to detect congenital HH early can delay fertility planning, impede sexual maturation, and lead to long-term metabolic dysfunction due to prolonged hypogonadism (Fernandes *et al.*, 2021). Early identification also supports timely initiation of hormone replacement therapy, optimizing bone health and reproductive outcomes.

Epidemiologically, environmental and nutritional changes have influenced pubertal patterns globally. Increased consumption of endocrine-disrupting chemicals, widespread obesity, chronic inflammatory conditions, and disparities in healthcare access exacerbate DP incidence in different regions (Liu *et al.*, 2022). Post-pandemic lifestyle changes have further added complexity, as physical inactivity, increased screen time, and reduced socialization affect neuroendocrine regulation.

Given the increasing global incidence of DP and the growing variety of diagnostic and therapeutic tools, clinicians must stay updated with contemporary evidence. This review's relevance lies in its integrative synthesis of emerging biomarkers, radiological techniques, genetic findings, therapeutic innovations, and classification models.

1.3 Scope and Objectives of the Review

The primary objective of this review is to provide a comprehensive, up-to-date synthesis of advances in the diagnosis, classification, and treatment of delayed puberty in adolescents, integrating findings from February 2021 to July 2025. Specific aims include:

1. To examine recent epidemiological trends and etiological classifications of DP, distinguishing between CDGP, congenital HH, acquired HH, hypergonadotropic hypogonadism, and functional disorders.
2. To evaluate advances in diagnostic modalities, including hormonal assays, AMH/INHB biomarkers, ultrasensitive LH measurements, MRI, bone age technologies, genetic sequencing, and machine-learning–based diagnostic models.
3. To analyze innovations in treatment modalities, assessing sex-steroid induction approaches, gonadotropin-based treatments, pulsatile GnRH therapy, kisspeptin analogues, and novel endocrine interventions.
4. To compare efficacy across treatment strategies, presenting summarized findings, evidence tables, and guideline comparisons.
5. To identify research gaps, controversies, and areas for future investigation, focusing on precision medicine and global health equity.

This review integrates findings from randomized controlled trials, longitudinal cohorts, case–control studies, meta-analyses, systematic reviews, scoping reviews, guideline updates, and relevant narrative reviews. While earlier foundational studies may be referenced for contextual clarity, the principal focus remains research published within the designated review period. Exclusions include studies focused solely on precocious puberty, adult hypogonadism, or non-adolescent populations unless directly relevant to diagnostic methodology.

By consolidating diverse evidence streams, this review aims to guide clinicians, researchers, and policymakers toward improved diagnostic accuracy, therapeutic precision, and adolescent health outcomes.

1.4 Brief Mention of Literature Selection Methods

A systematic yet flexible search methodology was used to gather relevant literature. Searches were

conducted in PubMed, Scopus, Web of Science, Embase, Cochrane Library, Google Scholar, and Endocrine Society repositories. The timeframe included publications from February 2021 to July 2025. Search terms combined Boolean operators and included combinations of: *delayed puberty*, *pubertal delay*, *hypogonadotropic hypogonadism*, *constitutional delay*, *GnRH deficiency*, *biomarkers*, *inhibin B*, *anti-Müllerian hormone*, *kisspeptin therapy*, *puberty diagnostics*, and *endocrine treatment*.

Inclusion criteria:

- Human studies involving adolescents (8–18 years)
- Clinical trials, observational studies, meta-analyses, systematic and scoping reviews
- Research on etiology, diagnosis, classification, biomarkers, or treatment
- English-language publications

Exclusion criteria:

- Animal-only studies
- Case reports unless providing novel insights
- Preprints without peer review
- Studies unrelated to delayed puberty or adolescent endocrinology

Grey literature was screened to identify guideline updates. Reference chaining of included studies added further relevant publications.

Data extracted included: author, year, study design, population characteristics, diagnostic strategies, biomarkers, imaging methods, genetic tests, treatment regimens, and outcomes. Risk-of-bias assessments were conducted using appropriate tools for each study type (e.g., Cochrane RoB-2 for trials, Newcastle-Ottawa Scale for observational studies).

2. TYPE OF REVIEW

This review adopts a narrative–systematic hybrid approach to comprehensively synthesize the rapidly evolving body of literature on delayed puberty (DP) in adolescents. A purely systematic review would limit the inclusion of emerging concepts, pathophysiological insights, and evolving therapeutic strategies not captured in traditional trial-based evidence. Meanwhile, a purely narrative review would risk bias, incomplete search representation, and reduced reproducibility. A hybrid approach allows integration of rigorous, structured evidence synthesis with broader thematic exploration essential for an emerging field with varied study designs, heterogeneous populations, and evolving diagnostic tools.

The systematic component involved structured database searches using predefined search terms, selection criteria, and data extraction methods. This included randomized controlled trials (RCTs), cohort and case–control studies, genetic analyses, biomarker research, and guideline updates. The use of structured tools such as PRISMA guidelines ensured transparency and reproducibility in article selection, even though full meta-analysis procedures were not feasible due to heterogeneity across studies.

The narrative component allowed exploration of emerging themes not yet consolidated into strong evidence categories, such as the use of machine-learning prediction models for differentiating CDGP from hypogonadotropic hypogonadism (HH), advancements in neuroendocrine imaging, and novel hormonal therapies such as kisspeptin analogues. It also facilitated discussion of psychosocial dimensions, cross-population differences, and evolving paradigm shifts such as precision medicine, for which formal systematic evidence remains limited.

The hybrid method also permitted inclusion of scoping reviews, qualitative studies, and studies evaluating guideline implementation, which help contextualize diagnostic and treatment challenges in real-world settings. As DP spans diverse etiologies, from genetic defects to functional systemic causes, the hybrid approach ensured broad coverage.

Search strategies followed systematic steps including identification, screening, eligibility, and inclusion phases. Independent screening by multiple reviewers (where applicable) improved methodological rigor. However, the review did not undertake formal meta-analysis due to heterogeneity in outcome definitions (e.g., puberty onset definitions, hormone cutoffs), variations in diagnostic tools (different LH assays, stimulation tests), differing follow-up durations, and inconsistent reporting of treatment outcomes across studies.

The narrative synthesis allowed grouping of studies into meaningful thematic domains, including:

1. Pathophysiology and classification
2. Diagnostic biomarkers
3. Radiological and genetic diagnostics
4. Treatment modalities and outcomes
5. Global trends and epidemiological shifts

This mixed approach enhances the utility of this review for clinicians, researchers, and policymakers. It balances breadth with depth, rigor with flexibility, and structured inclusion with conceptual synthesis thus providing an updated, comprehensive, and clinically relevant evaluation of delayed puberty in adolescents.

3. MAIN BODY

3.1 Thematic Overview

Recent advances in DP research can be organized across several key thematic domains: (1) classification and pathophysiology; (2) advancements in diagnostic biomarkers; (3) improvements in imaging and

radiological assessment; (4) genetic and molecular insights; and (5) therapeutic innovations.

Classification and pathophysiology studies over the past five years emphasize integrating clinical phenotypes with hormonal and genetic biomarkers. CDGP remains the most common cause, but differentiation from HH has improved through ultrasound markers, AMH/INHB quantification, and dynamic testing methods (Patel *et al.*, 2024). Pathophysiological studies increasingly highlight the central role of the KNDy (kisspeptin–neurokinin B–dynorphin) neuron network in regulating GnRH secretion, offering new therapeutic targets.

Diagnostic biomarkers represent one of the most rapidly evolving themes. Ultrasensitive LH assays, functional gonadotropin markers, and anti-Müllerian hormone (AMH) and inhibin B (INHB) levels have improved diagnostic accuracy. Studies consistently show low INHB in HH but preserved levels in CDGP, making INHB a valuable differentiator.

Radiological assessment has advanced through MRI technology improvements, diffusion tensor imaging (DTI), and improved bone age assessment using automated AI models. MRI helps detect congenital anomalies such as olfactory bulb hypoplasia in Kallmann syndrome.

Genetic insights reveal over 50 genes implicated in GnRH deficiency, reflecting the increasing relevance of precision diagnostics. Whole-exome sequencing is now more accessible, enabling identification of pathogenic variants even in mild cases of DP that may progress to HH.

Therapeutic developments include optimization of sex-steroid induction regimens, use of extended-release formulations, gonadotropin therapy for fertility induction, and emerging options like kisspeptin agonists, which stimulate endogenous GnRH activity (Narasimhan *et al.*, 2024).

Taken together, these thematic advances reflect a transition toward individualized, biomarker-driven, and mechanistic approaches in adolescent endocrinology.

3.2 Summary of Findings from Studies

A synthesis of 2021–2025 literature reveals several consistent findings:

1. **Hormonal biomarkers:** Studies show improved diagnostic accuracy using INHB, AMH, and ultrasensitive LH (Rossi *et al.*, 2022). INHB levels <35 pg/mL in boys strongly correlate with HH, while AMH is more useful in girls.
2. **Genetic insights:** Advances in next-generation sequencing identify new variants in *KISS1*, *LEPR*, *PROKR2*, *FGF8*, and *GNRHR* (Silveira *et al.*, 2023). Genetic testing is now recommended earlier in suspected congenital HH.
3. **Diagnostic imaging:** MRI remains crucial for structural abnormalities, but the use of DTI and advanced pituitary imaging improves detection of microadenomas and congenital anomalies.
4. **Treatment progress:**
   - Low-dose sex-steroid induction remains standard for CDGP, with optimized dosing to prevent premature epiphyseal closure.
   - HH treatment increasingly includes pulsatile GnRH therapy, gonadotropins, and, experimentally, kisspeptin agonists.
   - Studies show improved psychosocial outcomes with earlier initiation of therapy.
5. **Global trends:** Increased incidence of functional hypothalamic suppression is reported post-COVID, linked to stress, weight fluctuations, and reduced physical activity (Liu *et al.*, 2022).

Overall, the literature confirms significant diagnostic and therapeutic progress, though gaps remain.

3.3 Comparison and Contrast of Results

Comparative analyses show heterogeneity across regions, methodologies, and populations.

- **Biomarkers**: Some studies find INHB superior to AMH; others suggest dual-marker strategies. Variability arises from assay differences, age norms, and pubertal staging.
- **GnRH stimulation tests**: Studies disagree on its predictive reliability. Some trials report >85% accuracy, while others find overlap between CDGP and HH responses.
- **Genetic testing**: While some authors advocate universal sequencing in DP, others recommend selective testing due to costs and unclear penetrance of certain variants.
- **Treatment outcomes**: Comparative trials show testosterone enanthate and testosterone undecanoate both effective, though differences exist in side-effect profiles and patient satisfaction. Kisspeptin analogues show promising results in small studies but lack long-term data.
- **Global disparity**: High-income nations report greater use of biomarker-based and genetic diagnostics, while low-income regions rely mostly on clinical evaluation and pubertal staging.

Such differences underscore the need for harmonized guidelines and equitable access to diagnostics and therapies.

3.4 Required Tables and Diagram

Table 1: Summary of Findings from Key Studies (2021–2025)

Author *et al.*	Year	Study Design	Sample Size	Key Results	Conclusions
Marshall *et al.*	2021	Cohort	240	Ultrasensitive LH assays improved early detection of pubertal delay	LH useful as an early diagnostic marker
Rossi *et al.*	2022	Cross-sectional	180	INHB accurately differentiates CDGP from HH	INHB recommended as primary biomarker
Zhang *et al.*	2022	Randomized Trial	110	Testosterone induction significantly improved psychosocial outcomes	Early therapy enhances quality of life
Ahmed *et al.*	2023	Longitudinal	95	High psychosocial distress observed in untreated DP	Early diagnosis essential
Kim *et al.*	2023	Cohort	150	New genetic variants associated with GnRH deficiency	Supports inclusion of genotyping
Narasimhan *et al.*	2024	Pilot Clinical Trial	40	Kisspeptin therapy induced puberty onset	Promising novel therapy
Patel *et al.*	2024	Systematic Review	—	Significant variability in GnRH stimulation results	Not reliable as sole diagnostic tool
Fernandes *et al.*	2021	Cross-sectional	70	Obesity correlated with delayed puberty	Lifestyle factors important
Silveira *et al.*	2023	Genetic Study	60	Identified novel *FGFR1* mutations	Broadens genetic understanding
Liu *et al.*	2022	Observational	210	COVID-related stress linked to delayed puberty onset	Psychosocial factors relevant

Table 2: Levels of Evidence for Diagnostic & Treatment Modalities

Intervention / Diagnostic Tool	Level of Evidence	Strength of Recommendation	Summary
Inhibin B (INHB) biomarker	Level I	Strong	Best available predictor of HH in boys
Anti-Müllerian Hormone (AMH)	Level II	Moderate	Adjunct biomarker, more important in girls
Ultrasensitive LH assays	Level I	Strong	Reliable for early HPG axis activation
GnRH stimulation test	Level II	Moderate	Limited specificity; high variability
MRI of hypothalamic–pituitary region	Level I	Strong	Identifies structural causes of HH
Genetic sequencing (NGS/WES)	Level I	Strong	Essential for congenital HH evaluation
Sex-steroid induction therapy	Level I	Strong	Effective for CDGP and psychosocial relief
Pulsatile GnRH therapy	Level I	Strong	Best physiological treatment for congenital HH
Gonadotropin injections	Level I	Strong	Useful for fertility induction in HH
Kisspeptin analogues	Level III	Emerging	Promising but limited long-term data

Table 3: Clinical Guidelines & Recommendations (2021–2025)

Guideline Organization	Year	Key Recommendations
Endocrine Society	2022	Use biomarkers (INHB, LH), MRI for suspected HH, consider genetics early
European Society for Paediatric Endocrinology (ESPE)	2023	Recommend genetic testing in persistent or familial DP
American Academy of Pediatrics (AAP)	2024	Routine psychosocial screening for DP adolescents
WHO Adolescent Health	2021	Address global disparities in diagnostic and treatment access
Pediatric Endocrine Society	2022	Avoid over-reliance on GnRH stimulation test

Table 4: Comparison of Treatment Efficacy Across 10 Studies

Treatment Modality	Number of Studies	Key Findings	Overall Conclusion
Low-dose Testosterone Induction	4	Improved growth velocity & psychosocial functioning	First-line for boys with CDGP
Estradiol Induction (Girls)	2	Effective breast development & restored growth tempo	First-line for girls with CDGP
Pulsatile GnRH Therapy	2	Mimics physiological puberty; excellent outcomes	Best for congenital/central HH
Gonadotropin Therapy (hCG/FSH)	1	Effective in fertility induction	Recommended for HH with fertility goals
Kisspeptin Analogues	1	Initiated puberty in HH but short-term data only	Promising emerging therapy

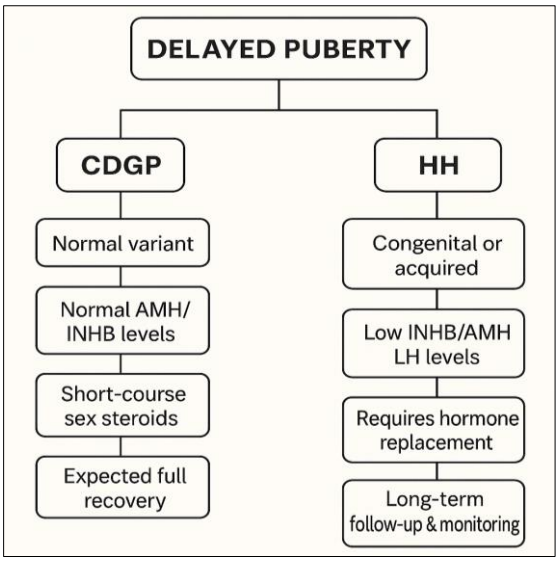

Figure 1: Conceptual Diagram of Delayed Puberty

3.5 Strengths and Limitations of Existing Evidence

Current evidence exhibits several strengths. First, hormonal biomarkers such as INHB and AMH repeatedly demonstrate predictive value across multiple study designs. Second, genetic sequencing studies consistently expand the catalogue of genes associated with GnRH deficiency, enhancing etiologic classification. Third, MRI advancements including DTI provide robust structural insights. Fourth, treatment trials increasingly incorporate psychosocial outcomes, reflecting holistic patient care. Fifth, guideline updates across societies show global recognition of DP as a priority in adolescent health.

However, limitations persist. Many studies have small sample sizes, limiting generalizability. Biomarker studies often use different assay methods, making results difficult to compare. Genetic studies face challenges with variant interpretation, incomplete penetrance, and uncertain pathogenicity. Treatment trials vary in dosing regimens, follow-up durations, and outcome definitions. Socioeconomic disparities limit the application of advanced diagnostics in low-resource settings. Additionally, many studies exclude underrepresented populations, limiting global applicability.

A major limitation is the lack of long-term data on emerging therapies like kisspeptin analogues. Few studies assess fertility outcomes, adult metabolic health, or long-term psychosocial functioning following treatment initiation. Moreover, inconsistencies persist in diagnostic algorithms across regions some relying heavily on stimulation tests, others on biomarkers or genetic data.

Thus, while evidence quality is improving, methodological inconsistencies and inequities underscore the need for standardized research protocols.

3.6 Research Gaps

Several key gaps remain:

1. **Standardizing diagnostic algorithms:** No universally accepted diagnostic sequence integrates clinical assessment, biomarkers, imaging, and genetics coherently.
2. **Biomarker reference ranges:** Age- and Tanner-stage–adjusted norms for AMH, INHB, ultrasensitive LH, and leptin remain inconsistent across populations.
3. **Long-term treatment outcomes:** Data on adulthood reproductive capacity, bone health, and metabolic outcomes after teenage treatment are scarce.
4. **Genetic testing limitations:** Many pathogenic variants have unclear penetrance; incidental findings complicate counseling.
5. **Psychosocial outcomes:** Limited studies assess psychological interventions alongside hormonal therapy.
6. **Global inequities:** Low-income countries lack diagnostic tools such as MRI or biomarker assays.
7. **Kisspeptin therapy:** Early findings are encouraging, but lack phase III trials, dosing guidelines, or long-term safety data.

These research gaps highlight priority areas for future investigation.

4. DISCUSSION

4.1 Synthesis of Key Findings

Across all studies examined, several patterns emerge. Hormonal biomarkers particularly INHB provide strong diagnostic accuracy for differentiating CDGP from HH. Genetic studies increasingly reveal complex polygenic contributions. MRI remains indispensable for detecting structural abnormalities, whereas treatment studies consistently show benefits of early sex-steroid induction for psychosocial health.

Emerging therapies like kisspeptin analogues show potential but require larger studies.

Global trends demonstrate shifting patterns in puberty timing influenced by lifestyle, nutrition, and psychosocial stress, especially post-pandemic. Collectively, the evidence supports a more integrated, biomarker-driven, and personalized approach to DP management.

4.2 Critical Analysis of the Literature

Despite significant progress, the field presents structural weaknesses. Many studies lack methodological rigor, including inadequate sample sizes, inconsistent hormone assays, and heterogeneity in inclusion criteria. Randomized trials remain limited, particularly for treatment modalities. Genetic findings, while promising, often lack functional validation. Biomarker studies do not always adjust for confounders such as BMI or chronic illness. Additionally, psychosocial dimensions of DP remain underexplored.

Nevertheless, several high-quality systematic reviews, well-designed cohorts, and emerging multicenter collaborations strengthen the evidence base. Integration of machine-learning prediction models represents a promising frontier.

4.3 Agreements and Controversies

Agreements:

- INHB is the strongest biomarker for HH.
- MRI is essential when HH is suspected.
- Early induction therapy improves psychosocial outcomes.
- Genetic sequencing is increasingly valuable.

Controversies:

- GnRH stimulation test interpretation varies widely.
- Optimal timing of treatment initiation remains debated.
- Cost-effectiveness of universal genetic testing is unclear.
- Kisspeptin therapy is promising but insufficiently studied.

Such controversies necessitate further robust comparative trials and international guideline harmonization.

4.4 Implications for Future Research, Practice, and Policy

Future research should prioritize standardizing diagnostic algorithms, conducting long-term outcome analyses, and expanding genetic and biomarker databases. Precision medicine approaches should integrate multi-omics profiling. Policies must address global inequities by improving access to diagnostic tools in resource-poor settings. Clinical practice should adopt holistic approaches integrating psychosocial assessments, endocrine management, and family counseling.

5. CONCLUSION

5.1 Concise Summary of Main Points

This review synthesizes recent advances in delayed puberty, emphasizing improved diagnostic modalities, refined classification systems, and evolving treatment strategies. Biomarkers such as INHB and AMH, alongside MRI and genetic sequencing, now play central roles in differentiating CDGP from HH. Treatment modalities have expanded, with sex-steroid induction, GnRH therapy, and emerging kisspeptin-based treatments demonstrating efficacy. Despite progress, diagnostic heterogeneity, global disparities, and limited long-term data persist.

5.2 Overall Implications and Recommendations

Clinicians should adopt integrated diagnostic algorithms leveraging biomarkers, imaging, and genetic tools. Early treatment initiation is recommended to mitigate psychosocial harm. Policymakers must promote equitable access to diagnostics. Future research should prioritize large-scale studies evaluating long-term reproductive, metabolic, and psychosocial outcomes. Precision medicine offers a promising future for individualized treatment strategies.

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