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Precocious Puberty in Girls: Pathogenesis, Genetic Architecture and Emerging Molecular Therapies

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Abstract: Precocious puberty, defined as the onset of secondary sexual characteristics before age 8 in girls and 9 in boys, occurs more frequently in females and carries significant medical, psychosocial, and long-term health consequences. This review synthesizes current knowledge on the molecular, genetic, epigenetic, and environmental determinants of early pubertal onset, with a particular focus on female precocious puberty. Central precocious puberty (CPP) arises from premature activation of the hypothalamic–pituitary–gonadal (HPG) axis, driven by dysregulation of kisspeptin–GPR54 signaling, neurokinin B pathways, and inhibitory factors such as MKRN3 and DLK1. Peripheral precocious puberty (PPP), by contrast, results from gonadotropin-independent estrogen production due to somatic mutations (e.g., GNAS1 in McCune-Albright syndrome) or hormone-secreting ovarian tumors. Environmental exposures, particularly endocrine-disrupting chemicals (EDCs), and metabolic factors such as obesity and leptin excess, further contribute by altering neuroendocrine signaling and inducing epigenetic modifications of key puberty-related genes. Current therapeutic standards rely on gonadotropin-releasing hormone (GnRH) agonists to suppress HPG activation, but emerging approaches—including kisspeptin and neurokinin B antagonists, epigenetic modulators, and gene-based strategies—offer promise for precision medicine. By integrating neuroendocrine biology, genetic architecture, and environmental risk factors, this review underscores the complexity of pubertal regulation and highlights future directions for early diagnosis and targeted therapy in precocious puberty.

Keywords: *Precocious Puberty, Central Precocious Puberty (CPP), Peripheral Precocious Puberty (PPP), Hypothalamic–Pituitary–Gonadal (HPG) Axis, Kisspeptin–GPR54 Signaling, MKRN3, DLK1, Neurokinin B (TAC3/TACR3), Epigenetics, Obesity and Leptin, Pubertal Timing.*

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I. INTRODUCTION

Precocious puberty, which is more common in females (the female-to-male ratio is roughly 10:1), is characterized by the start of secondary sexual characteristics before the ages of 8 for girls and 9 for boys [1]. Girls who experience this early stimulation of the hypothalamic-pituitary-gonadal (HPG) axis may acquire physical characteristics including breasts, pubic hair, and menstruation earlier than expected. A child's overall development may be impacted by this disorder, which frequently has significant medical and emotional repercussions even though it can occasionally be idiopathic and benign.

Clinically speaking, early exposure to estrogen may accelerate bone maturation, resulting in growth plate closure too soon and eventually lowering a child's potential adult height [2]. Girls who undergo precocious puberty may also face emotional and psychological difficulties, including anxiety, depression, and early sexualization, as a result of the discrepancy between their physical appearance and emotional or cognitive development [3, 4]. Furthermore, there is evidence linking early menstruation to a higher chance of obesity, metabolic syndrome, cardiovascular disease, and breast cancer in later life [5, 6].

According to epidemiological research, premature puberty is becoming more commonplace globally, particularly in urban and industrialized regions [7, 8]. Improved diet, increased childhood obesity rates, exposure to endocrine-disrupting chemicals (EDCs), and inherited genetic features are some of the reasons that seem to be responsible for this trend [9, 10]. For example, obesity has been linked to increased levels of insulin and leptin, which can affect gonadotropin-releasing hormone (GnRH) release and cause puberty to begin sooner [11].

Puberty is regulated by a complex network of neuroendocrine signals at the molecular level. GnRH neurons play a key role in this process; they are controlled by chemicals like kisspeptin and neurokinin B and are influenced by feedback from sex hormones that the gonads generate [12].

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Important genetic and epigenetic factors that affect the onset of puberty have been identified by researchers in recent years. For instance, both familial and sporadic occurrences of central precocious puberty have been associated with mutations in the MKRN3 gene, a maternally imprinted gene found on chromosome 15q11.2 [13]. The timing of GnRH release is also influenced by epigenetic modifications, including DNA methylation and histone acetylation of important genes in the hypothalamus [14].

The purpose of this review is to examine what we now know about the molecular processes underlying female precocious puberty. We provide a thorough examination of the neuroendocrine systems, genetic alterations, epigenetic changes, and environmental factors that lead to early pubertal onset. We intend to direct future studies and aid in the creation of more potent treatment plans by illuminating these fundamental processes.

II. NORMAL PUBERTAL ONSET: MOLECULAR BASIS

A tightly controlled biological process, the start of normal puberty is mainly caused by the hypothalamic-pituitary-gonadal (HPG) axis being activated. Everything starts when gonadotropin-releasing hormone (GnRH) is pulsatilely secreted by specific neurons in the hypothalamus again [15]. This hormone is a crucial signal that causes the anterior pituitary gland to generate follicle-stimulating hormone (FSH) and luteinizing hormone (LH). After reaching the ovaries, these two hormones promote the formation of ovarian follicles, increase the synthesis of estrogen, and cause secondary sexual traits like pubic hair and breast development to emerge [16]. A network of genetic and neuropeptidergic cues that control the activity of neurons that produce GnRH fine-tune this process at the molecular level.

Through their modulation of the hypothalamic-pituitary-gonadal (HPG) axis, a number of important molecular signals play crucial roles in controlling the start of puberty. The KISS1 gene produces the protein kisspeptin, which is one of the most significant participants. By attaching to the GPR54 receptor, sometimes referred to as KISS1R, kisspeptin functions as a potent GnRH neuron stimulator, causing the release of GnRH [17]. The arcuate nucleus and the anteroventral periventricular nucleus of the hypothalamus contain the majority of the neurons that generate kisspeptin. These neurons help control the timing of puberty by combining inputs from metabolic and hormonal pathways. Both central precocious puberty and delayed puberty have been associated with mutations in the KISS1 gene, highlighting the crucial regulatory function of kisspeptin.

The G protein-coupled receptor known as GPR54 (KISS1R) is in charge of mediating kisspeptin's stimulatory effects on GnRH neurons. Changes in the onset of puberty can result from disruptions in the signaling pathway caused by mutations in this receptor. Central precocious puberty has been connected to activating mutations in GPR54, whereas hypogonadotropic hypogonadism, a disease in which puberty is markedly delayed or absent, has been linked to inactivating mutations [18].

Neurokinin B, which is encoded by the TAC3 gene, and its receptor, TACR3, are also crucial parts of this regulatory network. KNDy neurons, so termed because they co-express kisspeptin, neurokinin B, and dynorphin, are a subset of neurons that also express these chemicals. These neurons, which are found in the arcuate nucleus, aid in controlling the GnRH pulses' frequency and strength. Mutations in TAC3 or TACR3 are examples of disruptions in this system that have been linked to both early and delayed puberty and can affect GnRH pulsatility [19].

Last but not least, a key factor in delaying the onset of puberty is the MKRN3 (Makorin Ring Finger Protein 3) gene, which is found in the Prader-Willi syndrome critical region on chromosome 15q11-q13. Maternally imprinted and paternally expressed, MKRN3 is a gene that is quite active in early childhood but starts to wane shortly before puberty. This decrease seems to serve as a biological cue for the resumption of GnRH release. Numerous familial examples of central precocious puberty, particularly in girls, have been linked to loss-of-function mutations in MKRN3, indicating that MKRN3 plays a crucial role as a gatekeeper in puberty timing [20].

These chemical cues cooperate to regulate the HPG axis's activity and guarantee that puberty starts at the right moment. Any disturbance in this network can result in conditions like premature or delayed puberty, which can have serious effects on development, growth, and long-term reproductive health.

III. PATHOGENESIS OF CENTRAL PRECOCIOUS PUBERTY (CPP)

When the hypothalamic-pituitary-gonadal (HPG) axis becomes activated earlier than usual, secondary sexual features emerge prematurely, a condition known as central precocious puberty (CPP). The kisspeptin-GPR54 signaling axis is one of the most crucial mechanisms that initiates this early activation. When this pathway is hyperactive, it causes the pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by increasing the pulsatile release of gonadotropin-releasing hormone (GnRH). The physical changes linked to puberty are then triggered by these hormones, which in turn stimulate the creation of estrogen [21]. This process is supported by evidence from animal studies, which highlight the crucial role kisspeptin and its receptor, GPR54 (also known as KISS1R), play in the development of CPP [22]. Experiments have demonstrated that overexpression of either kisspeptin or its receptor is sufficient to induce early puberty.

- *Loss of Inhibitory Signals*

In addition to activating signals, inhibitory mechanisms that block the hypothalamic-pituitary-gonadal (HPG) axis during childhood also regulate the development of puberty. It has been determined that two important

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inhibitory regulators are essential for postponing the beginning of puberty:

One of the most significant genes that suppress puberty is MKRN3 (Makorin Ring Finger Protein 3). Only the copy inherited from the father is active since it is both paternally expressed and maternally imprinted. As an E3 ubiquitin ligase, MKRN3 targets puberty-activating proteins for degradation, which contributes to its inhibitory action. This inhibitory mechanism is compromised by loss-of-function mutations in MKRN3, which causes GnRH-secreting neurons to activate too soon and puberty to begin earlier. Indeed, the most common genetic cause of familial central precocious puberty (CPP), especially in girls, is MKRN3 mutations [23].

Another maternally imprinted, paternally expressed gene that inhibits, this time via the Notch signaling system, is DLK1 (Delta-like 1 Homolog). DLK1 plays a role in regulating hypothalamic neuron growth and neurogenesis. Increased HPG axis activity is made possible by the loss of DLK1 function brought on by mutations, which helps explain the early development observed in CPP [24].

- *Glial-Neuronal Interactions*

Glial cells in the hypothalamus are crucial in controlling the maturation and activity of GnRH neurons in addition to the direct influence of neurons. For instance, by encouraging glial cell-neuron adhesion and activating erbB receptors on GnRH neurons, glial-derived substances like Transforming Growth Factor-Alpha (TGF-α) and Epidermal Growth Factor (EGF) aid in stimulating the release of GnRH. The onset of puberty is directly associated with their increased presence [25]. Furthermore, sustaining hypothalamic neural progenitor cells and directing their development into GnRH neurons depend on the Notch signaling system. By interfering with neurogenesis and the hypothalamic plasticity, disturbances or anomalies in Notch signaling can impact the timing of puberty [26].

In general, the GnRH pulse generator is regulated by a complicated balance between stimulatory and inhibitory signals, which leads to central precocious puberty (CPP). In addition to providing insight into the biology of puberty, a better knowledge of these complex processes may pave the way for the creation of genetic screening tools and targeted therapies for CPP patients.

IV. PERIPHERAL PRECOCIOUS PUBERTY (PPP): MOLECULAR CAUSES

Gonadotropin-independent precocious puberty, or peripheral precocious puberty (PPP), is a condition in which secondary sexual traits emerge early as a result of excessive sex steroid production that is not brought on by early hypothalamic-pituitary-gonadal (HPG) axis activation. PPP is caused by autonomous sources of androgen or estrogen, as opposed to Central Precocious Puberty (CPP), which begins when the brain's GnRH pulse generator is activated. These may include somatic gene mutations, diseases of the adrenal glands, or tumors that secrete hormones.

- *Mccune-Albright Syndrome (Mas)*

McCune-Albright Syndrome (MAS), which results from postzygotic somatic activating mutations in the GNAS1 gene, is one of the most well-known causes of PPP. The alpha subunit of the stimulatory G protein (Gsα) is encoded by this gene [28]. Because of these mutations, adenylate cyclase is constantly activated, which results in abnormally high amounts of cyclic AMP (cAMP) within the afflicted cells.

This hyperactive cAMP pathway causes the ovaries to release estrogen on their own in girls with MAS, independent of follicle-stimulating hormone (FSH) or luteinizing hormone (LH). This leads to early puberty symptoms include rapid bone maturation, recurrent vaginal bleeding (menarche), and breast development (thelarche). The intensity and particular organs affected might vary greatly because the mutation occurs after conception and only affects a small percentage of cells (mosaicism). From isolated hormonal imbalances to the complete traditional trifecta of fibrous bone dysplasia, café-au-lait skin patches, and PPP, this causes a wide range of symptoms [29].

The intermittent nature of estrogen secretion in MAS can lead to variable pubertal symptoms and make diagnosis more difficult. In order to differentiate MAS from CPP, testing with GnRH stimulation usually reveals low or prepubertal levels of LH and FSH. In order to lessen the consequences of high estrogen, treating MAS can be challenging and frequently involves the use of anti-estrogen pharmaceuticals such fulvestrant or tamoxifen, as well as aromatase inhibitors [30].

- *Granulosa Cell Tumors (Gcts)*

Granulosa cells, which typically generate estrogen during the menstrual cycle, are the source of rare ovarian cancers known as Granulosa Cell cancers (GCTs). GCTs are one of the most prevalent ovarian tumors associated with peripheral precocious puberty (PPP) in prepubertal girls [31]. Secondary sexual features including breast growth, vaginal discharge, and menstrual-like bleeding appear quickly since these tumors manufacture estradiol on their own. This sets these cases apart from puberty caused by central hormonal activation, even when gonadotropin levels are still low or suppressed.

A meticulous and comprehensive approach is necessary to diagnose GCTs, which includes blood testing for tumor indicators such as inhibin B and estradiol and pelvic ultrasonography to detect ovarian tumors [32]. Surgical excision of the tumor is the cornerstone of treatment and is frequently curative, particularly for benign tumors. In order to prevent extended exposure to excessive estrogen levels, which can cause early closure of growth plates in bones and result in shorter adult height, early diagnosis and care are crucial. Furthermore, prompt action lowers the chance of malignancy, which can happen in some tumor subtypes [33].

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V. ENVIRONMENTALAND EPIGENETIC INFLUENCES

Although strictly regulated neuroendocrine signals are the main driver of pubertal development, there is mounting evidence that environmental influences and epigenetic modifications also significantly influence this process. Variations in the timing of puberty can result from these outside factors interfering with the hypothalamic-pituitary-gonadal (HPG) axis's regular function. Specifically, they have been connected to the increased prevalence of early puberty, particularly in girls.

➢ *Endocrine Disrupting Chemicals (EDCs)*

Synthetic and natural substances that can disrupt the body's hormonal systems are known as endocrine-disrupting chemicals (EDCs). By imitating natural hormones, preventing their effects, or changing the way hormones are made, transported, digested, or excreted, they do this. The effects of a number of EDCs on the timing of puberty have been extensively researched. These include parabens, preservatives found in many personal care products; phthalates, which are used as plasticizers in products like cosmetics, toys, and food packaging; industrial pollutants like dioxins and polychlorinated biphenyls (PCBs); and bisphenol A (BPA), which is frequently found in plastic containers, the linings of canned foods, and thermal paper receipts.

- *Mechanisms by Which EDCs Promote Precocious Puberty*

Through a number of important processes, endocrine-disrupting drugs (EDCs) can encourage premature puberty. First, via binding to the estrogen receptors ERα and ERβ, many EDCs, particularly parabens and bisphenol A (BPA), exhibit estrogen-like action. Even in cases when natural estrogen levels are low or nonexistent, this interaction can prematurely activate estrogen-responsive pathways, resulting in early breast development, endometrial expansion, and feedback effects on the hypothalamic-pituitary-gonadal (HPG) axis [34]. Furthermore, the kisspeptin system, which is essential for the onset of puberty, may be stimulated by EDCs. EDCs can speed up the GnRH–LH/FSH–estrogen cascade and accurately simulate central puberty by upregulating the expression of the KISS1 gene, especially in the arcuate nucleus of the hypothalamus, which prematurely activates GnRH neurons [35]. In addition to these direct effects, early exposure to EDCs can alter the epigenetics of genes that control puberty, such as Kiss1, GnRH, and MKRN3, by causing DNA hypomethylation or histone acetylation. For instance, it has been demonstrated that prenatal BPA exposure demethylates the Kiss1 promoter, causing overexpression of the protein and early GnRH neuron activation [36]. Lastly, research on animals indicates that exposure to EDCs during crucial developmental windows, such pregnancy or early childhood, may permanently alter the circuits of neurons in the hypothalamus. Long-term changes in reproductive function and an advanced pubertal onset are possible outcomes of this reprogramming [37].

- *Epidemiological Evidence*

Higher urine levels of Bisphenol A (BPA) and phthalate metabolites in prepubertal girls have been associated with an earlier onset of menstruation (menarche) and breast development (thelarche), according to a number of long-term cohort studies. However, it is still difficult to make direct cause-and-effect findings because of variations in study designs, demographics, and other environmental conditions [38].

➢ *Nutrition, Obesity, and Leptin*

Particularly for girls, nutritional and metabolic factors are important in determining when puberty occurs. In many nations, there has been a discernible decrease in the age at which puberty starts in tandem with the rise in childhood obesity worldwide. The hormone leptin, which is mostly produced by fat cells, is a major participant in this process. By indicating the body's energy level, leptin serves as a metabolic gatekeeper during puberty. Increased leptin levels in obese children suggest adequate energy storage, which activates kisspeptin neurons in the hypothalamus, which have a large number of leptin receptors. This triggers the production of gonadotropin-releasing hormone (GnRH) and initiates puberty [38]. Additionally, leptin accelerates sexual maturity by enhancing gonadotropin secretion and ovarian steroid synthesis in conjunction with other hormones such as insulin and insulin-like growth factor 1 (IGF1) [39].

- *Nutrient-Sensitive Pathways and Epigenetic Mechanisms*

A key player in determining the body's energy level and controlling puberty is the leptin–insulin–IGF1 axis. Chronic hyperinsulinemia, which is frequently brought on by overnutrition, causes ovarian theca cells to produce more androgen. In adipose tissue, aromatization transforms these androgens into estrogens. Even in the absence of the typical gonadotropin signals, the estrogens found in fat can work locally and across the body to promote uterine growth and breast development, thus simulating peripheral puberty. Obesity is associated with epigenetic modifications in the hypothalamus, including DNA methylation changes that impact the expression of important puberty genes including GnRH and Kiss1, in addition to these hormonal impacts. Dietary lipids, elevated blood sugar, and inflammation are some of the variables linked to excess fat that may be responsible for these alterations [40]. Furthermore, in response to nutritional cues, puberty-related gene expression is modulated by microRNAs (miRNAs) that control appetite and energy balance, such as let-7 and the miR-200 family.

VI. GENETIC ARCHITECTURE OF PRECOCIOUS PUBERTY

A complex network of genes that either stimulate or inhibit the hypothalamic-pituitary-gonadal (HPG) axis determines the onset and regulation of puberty. The delicate balance governing pubertal timing may be upset by mutations in these genes, leading to either peripheral premature puberty (PPP) or central precocious puberty (CPP). In the discussion that follows, several of the important genes that play a part in this process are examined, along with their functions and the ways that genetic variants affect early puberty.

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Table 1 Primary Role of Genes Involved in Precocious Puberty

Gene	Primary Role	Mutation Effect	Pathway/Mechanism
MKRN3	Inhibitor of puberty onset	Loss-of-function → early GnRH release → CPP	Ubiquitin-proteasome system [41, 46]
KISS1/GPR54	Stimulates GnRH secretion	Activating mutations → increased GnRH pulsatility → CPP	Kisspeptin-GPR54 signaling [42, 47]
DLK1	Notch pathway inhibitor	Loss-of-function → disinhibition of hypothalamic neurons → CPP	Notch signaling [43, 48]
TAC3/TACR3	Regulates GnRH pulsatility	Gain-of-function mutations → enhanced GnRH secretion → CPP	Neurokinin B/NK3R pathway [44, 49]
GNAS1	Stimulates estrogen production	Activating mutations → constitutive cAMP signaling → PPP	cAMP/PKA pathway [45, 50]

➢ *MKRN3 (Makorin Ring Finger Protein 3)*

Chromosome 15q11–q13 contains the maternally imprinted and paternally expressed gene MKRN3. Through the breakdown of proteins that stimulate GnRH neurons, it generates an E3 ubiquitin ligase enzyme, which is essential for postponing puberty. This inhibitory impact is diminished in MKRN3 loss-of-function mutations, which permits premature release of GnRH and initiates early activation of the hypothalamic-pituitary-gonadal (HPG) axis, ultimately resulting in precocious puberty [41, 46].

➢ *KISS1 and GPR54 (KISS1R)*

Kisspeptin, a neuropeptide that interacts to the GPR54 receptor (sometimes called KISS1R) on GnRH neurons, is encoded by the KISS1 gene. The initiation of puberty depends on this interaction. Central precocious puberty (CPP) results from activating mutations in either KISS1 or GPR54, which increase the kisspeptin signaling pathway and cause earlier and stronger GnRH secretion [42, 47].

➢ *DLK1 (Delta-Like Homolog 1)*

The Notch signaling pathway is inhibited by the paternally expressed gene DLK1, which is essential for the development of hypothalamic neurons. These inhibitory controls are eliminated by loss-of-function mutations in DLK1, which raises hypothalamic activity and causes early puberty. Remarkably, metabolic disorders have also been connected to mutations in DLK1 [43, 48].

➢ *TAC3 and TACR3 (Neurokinin B System)*

Neurokinin B and its receptor, NK3R, are encoded by the genes TAC3 and TACR3, respectively, and are essential for sustaining the pulsatile release of GnRH. Certain gain-of-function mutations or epigenetic modifications can increase GnRH secretion, which can lead to the development of CPP, whereas loss-of-function mutations typically cause delayed puberty [44, 49].

➢ *GNAS1(Guanine Nucleotide-Binding Protein, Alpha Stimulating)*

McCune-Albright Syndrome (MAS), which is typified by autonomous endocrine activity, is brought on by activating somatic mutations in GNAS1. These mutations cause peripheral precocious puberty in ovarian tissue by causing the cAMP/PKA signaling pathway to continuously produce estrogen, regardless of the hypothalamic-pituitary-gonadal axis control [45, 50].

VII. THERAPEUTIC IMPLICATIONS AND MOLECULAR TARGETING

If left untreated, central precocious puberty (CPP) can have detrimental repercussions on both physical and mental development. Treatment's main objectives are to minimize emotional and social difficulties, aid maximize adult height, and prevent or limit early pubertal development. New therapeutic approaches that go beyond conventional hormone-based medications are starting to appear as research deepens our understanding of the molecular mechanisms underlying CPP, giving rise to fresh optimism for more focused and efficient interventions.

➢ *Current Standard Therapy: Gnrh Agonists*

The use of gonadotropin-releasing hormone (GnRH) agonists is the main treatment for Central Precocious Puberty (CPP). These medications function by first activating and subsequently desensitizing anterior pituitary GnRH receptors. Long-term exposure to GnRH agonists causes these receptors to be downregulated, which suppresses the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). This, in turn, prevents the generation of gonadal estrogen and stops the pubertal development [51]. Histrelin, which is provided via a subdermal implant that offers 12 months of suppression and enhances compliance; triptorelin, which is given as a long-acting depot injection; and leuprolide acetate, which is given as an intramuscular injection either monthly or every three months [52]. GnRH agonists have the ability to prevent or even reverse pubertal growth, maintain the potential for height in adulthood, and lessen psychological anguish brought on by disparities in emotional and physical maturity. However, these treatments have drawbacks, such as the inability to treat peripheral precocious puberty (PPP), which happens without the stimulation of GnRH, the potential for a brief flare-up that exacerbates symptoms, and the need for long-term administration with frequent monitoring to guarantee sufficient suppression.

➢ *Emerging Molecular and Targeted Therapies*

A number of innovative and focused treatments are being researched to treat Central Precocious Puberty (CPP) as a result of increased understanding of the molecular processes that control pubertal timing. Kisspeptin antagonists, which try to interfere with the crucial kisspeptin–GPR54 (KISS1R) signaling pathway that activates GnRH neurons, are among the most promising treatment options. These antagonists

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lower GnRH production by inhibiting GPR54 receptors. Such antagonists offer a more upstream intervention that might have fewer systemic effects than current GnRH agonist therapy, as preclinical studies in animal models have demonstrated that they delay the beginning of puberty and lower LH and FSH levels [54]. The neurokinin B system, and more especially the TAC3 and TACR3 genes, is another target of interest. GnRH pulse frequency is influenced by this pathway, and although mutations in this pathway usually cause delayed puberty, GnRH release in CPP may be suppressed by modulating it with neurokinin B receptor antagonists, such as Fezolinetant, which is presently being studied for menopausal vasomotor symptoms [55].

At the same time, epigenetic dysregulation in CPP is becoming more widely acknowledged. For instance, aberrant promoter methylation can silence MKRN3, whereas histone modification may cause KISS1 to be overexpressed. The early activation of GnRH secretion is a result of these epigenetic abnormalities. To restore appropriate gene expression within these pathways, experimental medicines including histone deacetylase inhibitors and DNA methyltransferase inhibitors (e.g., 5-azacytidine) are being investigated. These therapies have the potential to be used in a more customized, precision medicine approach to CPP, even though they are currently in the early or preclinical stages [56].

Lastly, improvements in medication delivery technologies are making current treatments more useful and efficient. Because of its ease of use and better adherence, the histrelin acetate implant has become more and more popular. It offers stable hormone suppression for up to 12 months [53]. In order to improve patient outcomes and lessen the stress of frequent physician visits, extended-release formulations, such as 6-month and 1-year depot injections, are also being developed.

- *Future Directions and Personalized Medicine*

Advances in molecular genetics and biotechnology are driving the shift toward more customized and accurate approaches to controlling premature puberty. Comprehending certain gene alterations, like those in MKRN3, DLK1, and KISS1R, paves the way for genotype-guided treatment approaches, in which medications are customized according to each patient's own genetic profile. Furthermore, biomarker-driven monitoring based on circulating levels of MKRN3, kisspeptin, and leptin may assist track response to treatment, forecast the course of the disease, and facilitate early identification. In the future, gain- or loss-of-function mutations linked to early puberty may be directly corrected by gene-editing technologies such as CRISPR and RNA interference (RNAi). Even though these methods are still in the experimental stage, they provide promising prospects for long-term, focused treatments for premature puberty.

VIII. CONCLUSION

Early activation of molecular, neuroendocrine, and environmental processes that control sexual maturation is a complicated aspect of premature puberty. Premature activation of the hypothalamic-pituitary-gonadal (HPG) axis causes central precocious puberty (CPP), which is frequently caused by genetic abnormalities in important regulators such KISS1, GPR54, MKRN3, DLK1, and TAC3/TACR3. On the other hand, gonadotropin-independent hormone production brought on by somatic mutations such as GNAS1 or hormone-secreting tumors causes peripheral precocious puberty (PPP).

By modifying gene expression through epigenetic mechanisms and hormonal feedback loops, metabolic factors like obesity and environmental exposures—especially to endocrine-disrupting chemicals (EDCs)—also play important roles. Through both cerebral and peripheral mechanisms, overweight children's elevated levels of leptin, insulin, and IGF-1 can postpone the beginning of puberty.

GnRH agonists, which inhibit the release of LH and FSH to postpone future sexual development, continue to be the accepted treatment for CPP. On the other hand, novel treatments like epigenetic modulators and kisspeptin and neurokinin B antagonists present encouraging targeted substitutes. Gene-based treatments, biomarker-driven monitoring, and molecularly profiled customized treatment plans are some of the future prospects.

In the end, a better knowledge of the genetic, environmental, and epigenetic factors that contribute to premature puberty will result in earlier detection, more successful treatments, and better long-term results for kids who are impacted.

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