THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 9

REVIEW ARTICLE

Pregnenolone and Progesterone: A Review of Their Roles in Reproductive Health, Sleep, Growth, Neurological Function, and Idiopathic Scoliosis

Mark Morningstar

OPEN ACCESS

PUBLISHED
30 September 2025

CITATION
Morningstar, M., 2025. Pregnenolone and Progesterone: A Review of Their Roles in Reproductive Health, Sleep, Growth, Neurological Function, and Idiopathic Scoliosis. Medical Research Archives, [online] 13(9). https://doi.org/10.18103/mra.v13i8.6901

DOI
https://doi.org/10.18103/mra.v13i8.6901

ISSN
2375-1924

ABSTRACT

Pregnenolone and progesterone are essential steroid hormones that govern numerous physiological processes across the human lifespan. Traditionally viewed as reproductive hormones, their influence extends well beyond fertility and pregnancy, shaping neurological activity, sleep patterns, bone development, and even neuromotor control. In recent years, research has suggested that deficiencies or dysregulation of these hormones may contribute to adolescent idiopathic scoliosis (IS), a complex spinal condition of uncertain origin. This review synthesizes current scientific findings, highlighting the multifaceted roles of pregnenolone and progesterone and their potential therapeutic implications for both general health and spinal deformity prevention.

Introduction

Steroid hormones are critical regulators of human physiology, orchestrating a complex network of processes that maintain homeostasis across multiple organ systems. Among these, pregnenolone and progesterone occupy a unique and central position in steroidogenesis and endocrine function. Pregnenolone, derived from cholesterol through the action of cytochrome P450 side-chain cleavage enzyme (CYP11A1), serves as the foundational substrate for the synthesis of glucocorticoids, mineralocorticoids, estrogens, and androgens.[1] Progesterone, synthesized from pregnenolone via 3β-hydroxysteroid dehydrogenase, is traditionally recognized as a reproductive hormone essential for ovulation, endometrial receptivity, and pregnancy maintenance.[2] However, its biological roles extend far beyond the reproductive axis, influencing neurodevelopment, synaptic plasticity, stress response, immune modulation, bone metabolism, and sleep regulation.[3]

In recent decades, interest has grown in understanding the broader systemic influence of these hormones. Pregnenolone and progesterone are increasingly described as neurosteroids due to their local synthesis in the central nervous system, where they modulate neurotransmission, promote neuronal survival, and regulate neuromotor pathways.[5,11] Alterations in neurosteroid levels have been implicated in psychiatric conditions, cognitive decline, sleep disorders, traumatic brain injury, and neurodegenerative diseases.[5,12] These findings highlight the potential therapeutic applications of these hormones well beyond reproductive medicine.

An emerging area of investigation links hormonal dysregulation to musculoskeletal disorders, particularly adolescent idiopathic scoliosis (IS). IS is a three-dimensional deformity of the spine affecting approximately 1–3% of adolescents worldwide, with a marked female predominance.[22,23] Its pathogenesis remains poorly understood, likely involving a multifactorial interplay of genetic predisposition, altered neuromuscular control, connective tissue properties, and hormonal influences.[22] Early evidence suggests that insufficient progesterone and pregnenolone exposure during pubertal growth may impair ligamentous stability, disrupt neuromotor signaling, and contribute to spinal curve progression.[18,19] These findings position neurosteroids as potential contributors to IS etiology and open avenues for novel diagnostic and therapeutic strategies.

Given their central role in steroid biosynthesis and their wide-ranging systemic effects, pregnenolone and progesterone merit a comprehensive review that integrates their endocrine, neurological, musculoskeletal, and clinical dimensions. The objective of this narrative review is to synthesize current evidence regarding the biological functions of these hormones, describe their mechanisms of action across multiple physiological domains, and evaluate emerging data linking hormone imbalances to idiopathic scoliosis. By examining both foundational research and translational findings, this review aims to establish a framework for future investigations into neuroendocrine contributions to spinal development and potential hormone-based therapeutic interventions.

Methods

This narrative literature review aimed to integrate findings from molecular biology, clinical medicine, and translational research on pregnenolone and progesterone. PubMed was searched for peer-reviewed studies published up to April 2025 using combinations of the following terms: *pregnenolone, progesterone, neurosteroids, reproductive hormones, sleep regulation, neuroprotection, cognitive function, bone growth, adolescent development, idiopathic scoliosis, neuromotor output*. Medical Subject Headings (MeSH) were applied to refine the search.

Studies were included if they:

1. Investigated the physiological or clinical roles of pregnenolone or progesterone;
2. Examined their mechanisms in reproduction, sleep, neurology, growth, or scoliosis;

3. Were published in English in peer-reviewed journals; and
4. Included human or translationally relevant animal data.

Exclusions included non-peer-reviewed articles, research focusing solely on synthetic progestins without comparison to endogenous progesterone, and case reports lacking mechanistic analysis. Data were extracted regarding biosynthesis, receptor signaling, physiological effects, and scoliosis-related outcomes. Special attention was given to studies by Morningstar et al[18,19], given their unique contribution to the hormonal-scoliosis literature.

The author screened all titles and abstracts for relevance. Full texts of potentially eligible studies were retrieved and assessed according to inclusion criteria. Data extraction focused on:

- Hormone biosynthesis pathways and receptor interactions.
- Reported physiological and clinical outcomes across reproductive, neurological, musculoskeletal, and sleep domains.
- Hormonal measurements (e.g., serum or salivary levels) in adolescent idiopathic scoliosis populations.
- Interventional trials evaluating hormone supplementation or modulation

Data were organized into thematic domains and summarized narratively due to heterogeneity in study designs, participant populations, outcome measures, and methodological quality. Although this was a narrative review, study quality was considered during synthesis. Clinical studies were assessed for sample size, design (randomized vs. observational), use of control groups, and outcome reporting. Basic science studies were evaluated for experimental rigor, reproducibility, and relevance to human physiology.

Extracted data were grouped by physiological domain (reproductive health, sleep, neurological function, growth, idiopathic scoliosis). Key findings were synthesized to highlight both established knowledge and emerging hypotheses. Special attention was given to identifying:

- Biological mechanisms linking pregnenolone and progesterone to neural and musculoskeletal development.
- Gaps in current research and methodological limitations that warrant future investigation.

Reproductive Health

Progesterone is a cornerstone hormone in human reproduction, playing an essential role in ovulation, implantation, pregnancy maintenance, and fetal development. Its production rises significantly during the luteal phase of the menstrual cycle under luteinizing hormone (LH) stimulation, primarily from the corpus luteum.[1,2,24] Progesterone prepares the endometrium for potential embryo implantation by promoting glandular secretions, increasing endometrial thickness, and enhancing vascularization.[24,25] If conception occurs, progesterone continues to be secreted, initially by the corpus luteum and later by the placenta, to maintain uterine quiescence, suppress myometrial contractions, and modulate maternal immune tolerance to the developing fetus.[26]

Insufficient progesterone production during the luteal phase—often termed luteal phase deficiency (LPD)—can compromise endometrial receptivity, leading to implantation failure or early pregnancy loss.[3] Luteal phase deficiency has been observed in conditions such as polycystic ovary syndrome (PCOS), hypothalamic amenorrhea, hyperprolactinemia, and thyroid dysfunction.[27,28] Women with LPD often exhibit shortened luteal phases (<10 days), low mid-luteal progesterone levels, or endometrial biopsy findings inconsistent with ovulation timing.[3,27] While the exact prevalence of LPD remains debated, its impact on fecundity and miscarriage risk is clinically recognized.[3]

Progesterone supplementation, delivered via oral, intramuscular, or vaginal formulations, is widely used to support luteal function in both natural and

assisted conception cycles.[29] A meta-analysis of randomized controlled trials found that progesterone supplementation increased live birth rates in women undergoing in vitro fertilization (IVF) compared with placebo or no treatment.[30] Vaginal micronized progesterone has become a standard of care for luteal support in IVF due to its favorable bioavailability and endometrial tissue penetration.[30,31]

Pregnenolone serves as the biochemical precursor for all sex steroid hormones, including progesterone, estrogen, and androgens.[1] It is synthesized primarily in the adrenal glands, ovaries, and brain from cholesterol through the activity of CYP11A1.[1,2] Altered pregnenolone metabolism can impair downstream progesterone production, potentially disrupting ovulation and luteal function.[32] In women with adrenal insufficiency or congenital enzyme deficiencies (such as 3β-HSD or CYP17 mutations), reduced pregnenolone availability correlates with impaired follicular development and anovulation.[33] Experimental studies suggest that exogenous pregnenolone supplementation may enhance ovarian steroidogenesis and improve progesterone levels, though high-quality clinical trials remain scarce.[32,33]

Progesterone plays a critical role in sustaining pregnancy beyond implantation. It promotes decidualization of the endometrium, suppresses maternal immune rejection of the fetus by shifting T-helper cell activity toward a Th2-dominant response, and reduces uterine contractility by downregulating oxytocin receptor expression and calcium influx in myometrial cells.[26,34]

Insufficient progesterone has been linked to recurrent pregnancy loss (RPL). A Cochrane review concluded that progesterone supplementation significantly reduced miscarriage rates in women with recurrent or threatened pregnancy loss.[35,36] Similarly, intravaginal progesterone administration from the mid-trimester has demonstrated efficacy in preventing spontaneous preterm birth in women with a history of preterm delivery or a sonographically short cervix.[37] These findings support routine use of progesterone therapy as part of obstetric management in high-risk pregnancies.

Progesterone works synergistically with estrogen to regulate the menstrual cycle. Following ovulation, progesterone counterbalances estrogen-driven endometrial proliferation by inducing secretory differentiation.[24] Low luteal progesterone relative to estrogen may lead to unopposed endometrial growth, contributing to luteal dysfunction and early pregnancy failure.[3] Additionally, progesterone inhibits gonadotropin-releasing hormone (GnRH) and LH surges, providing negative feedback to the hypothalamic-pituitary axis and regulating follicular recruitment.[38]

Pregnenolone's role extends to androgen and estrogen synthesis, making it critical for maintaining the hormonal milieu required for follicular maturation, ovulation, and successful conception.[1,32] Deficiencies in pregnenolone production, as seen in certain stress-related or adrenal fatigue states, may indirectly impair fertility by reducing downstream sex steroid levels.[39]

In Assisted Reproductive Technologies (ART) cycles, ovarian stimulation often leads to supraphysiologic estrogen levels that suppress endogenous LH, impairing corpus luteum function and reducing progesterone production.[4,30] Progesterone supplementation is therefore universally implemented during IVF cycles to maintain endometrial receptivity until placental takeover of progesterone production.[30,40] Emerging research is exploring combined pregnenolone-progesterone protocols to optimize luteal support, but data are currently limited to pilot studies.[33]

Sleep Regulation

Sleep regulation is an intricate neurophysiological process governed by interactions between circadian rhythms, homeostatic drive, and a complex matrix of neuroendocrine factors. Among these, neurosteroids such as pregnenolone and progesterone—typically recognized for their reproductive roles—exert

underappreciated but significant influences on sleep initiation, architecture, and quality. The subtle interplay between these hormones and central nervous system neurotransmitter systems, particularly GABAergic pathways, underscores their relevance to sleep physiology across various life stages.

Progesterone exerts one of its most prominent effects on sleep through its downstream metabolite allopregnanolone, a potent positive allosteric modulator of the γ-aminobutyric acid type A (GABA_A) receptor.[5] This receptor is the primary mediator of inhibitory neurotransmission in the brain, and its enhanced activation by neurosteroids like allopregnanolone produces sedative, anxiolytic, and hypnotic effects that resemble the pharmacological actions of benzodiazepines.[41] These effects are not merely theoretical: clinical studies have demonstrated that progesterone supplementation improves sleep continuity, increases total sleep time, and elevates the proportion of slow-wave (non-REM stage 3) sleep, particularly in perimenopausal and postmenopausal women.[7]

Interestingly, sleep quality tends to fluctuate across the menstrual cycle in synchrony with progesterone levels. During the luteal phase, when progesterone levels peak, women often report deeper sleep and fewer awakenings.[6] Polysomnographic studies have corroborated these subjective findings, showing increased slow-wave sleep and reduced sleep latency during this phase.[42] Conversely, the decline in progesterone during the late luteal phase and menstruation has been associated with increased insomnia, fragmented sleep, and heightened vulnerability to mood fluctuations.[43] This dynamic underscores the hormone's pivotal role in both initiating and maintaining restorative sleep.

Pregnenolone, though less studied in this domain, also contributes to sleep regulation, likely through its modulation of excitatory neurotransmitter systems. Pregnenolone sulfate, a sulfated metabolite of pregnenolone, acts as a negative modulator of GABA_A receptors and a positive modulator of NMDA and sigma-1 receptors.[44] Its dualistic nature suggests a more nuanced role in maintaining sleep-wake transitions, potentially promoting alertness during the day while allowing progesterone-derived neurosteroids to promote inhibitory tone at night.[45] Experimental models in rodents have demonstrated that pregnenolone supplementation may improve sleep efficiency, reduce nighttime wakefulness, and restore circadian rhythm integrity in models of neurodegenerative disease and chronic stress.[9]

Beyond their receptor-level effects, these neurosteroids interact with broader sleep-regulating systems. Both pregnenolone and progesterone influence the hypothalamic-pituitary-adrenal (HPA) axis and modulate levels of cortisol, a key player in circadian alignment and sleep homeostasis.[44] Dysregulation of the HPA axis, often seen in insomnia and sleep-disordered breathing, may be partially mitigated by restoring neurosteroid balance —an avenue warranting further exploration in clinical populations.[46]

Of particular interest is the effect of progesterone on respiratory control during sleep. Studies have shown that it enhances central respiratory drive, likely through actions in the medulla and brainstem respiratory centers, and may reduce the frequency and severity of sleep-disordered breathing such as obstructive sleep apnea (OSA), particularly in women.[47] Unlike sedative-hypnotic agents that depress respiratory function, progesterone appears to promote ventilation, suggesting a unique therapeutic profile in sleep medicine.[8] These findings are especially relevant in perimenopausal women, a demographic with increasing rates of sleep disturbances and OSA but limited treatment options due to safety concerns associated with synthetic sedatives.

Taken together, the available literature paints a picture of pregnenolone and progesterone as essential, if underrecognized, regulators of sleep health. Their capacity to interact with GABAergic, glutamatergic, and neuroendocrine pathways positions them as central players in sleep neurobiology. As sleep disturbances continue to

rise in prevalence—particularly among adolescents and aging women—further investigation into the therapeutic use of neurosteroid supplementation may yield promising strategies for improving sleep outcomes with fewer side effects than traditional pharmacologic agents.

Neuroprotection, Cognitive Function, and Neuromotor Output

Both pregnenolone and progesterone are synthesized within the brain, where they act as neuromodulators with broad neuroprotective effects. Pregnenolone enhances synaptic plasticity and long-term potentiation—key processes for learning and memory—by modulating NMDA receptors and increasing excitatory neurotransmission through its sulfate derivative.[10] Progesterone and allopregnanolone, in contrast, temper neural overactivity via GABAA_AA receptor modulation, reducing excitotoxicity and maintaining cortical stability.[5,11]

Low neurosteroid levels have been linked to mood disorders, cognitive decline, and schizophrenia, with pilot studies suggesting pregnenolone supplementation can improve negative symptoms and working memory.[12] Progesterone further protects neurons in traumatic brain injury models, reducing edema and inflammation, while supporting remyelination for restored neural conduction.[13]

Beyond cognition, these hormones shape motor system function. Progesterone fine-tunes inhibitory signaling in the cerebellum, brainstem, and spinal cord, preventing excessive neuronal firing and stabilizing motor output.[15] Pregnenolone acts via NMDA and sigma-1 receptors in cortical and basal ganglia circuits, enhancing motor planning and coordination.[16] Deficiencies during adolescence may disrupt proprioception, trunk reflex control, and neuromuscular tone, potentially contributing to the postural asymmetries seen in idiopathic scoliosis.[14,17]

Growth and Development

Adolescence represents a critical window of physiological transformation during which neuroendocrine regulation orchestrates the interplay between skeletal maturation, adipose tissue dynamics, and cognitive-emotional development. Progesterone and pregnenolone, often discussed primarily in the context of reproductive physiology, have increasingly been recognized for their underappreciated contributions to musculoskeletal development, particularly during this transitional stage.

Progesterone's influence on bone metabolism is well documented, though its precise regulatory mechanisms are still being elucidated. Osteoblasts and osteoclasts both express progesterone receptors, implicating the hormone in the modulation of bone turnover and mineralization processes.[48] Experimental studies have demonstrated that progesterone enhances osteoblastic proliferation and differentiation, while simultaneously inhibiting osteoclastogenesis under certain hormonal environments.[49] These dual actions suggest that progesterone may contribute to the accrual of peak bone mass during adolescence, thereby playing a protective role against early-onset osteopenia or scoliosis-related bone density irregularities.

Interestingly, emerging research suggests that progesterone may also influence bone architecture by modulating the expression of key signaling molecules within the RANK/RANKL/OPG system—pathways integral to bone resorption and formation.[50] Moreover, longitudinal hormone studies indicate that fluctuations in progesterone levels across the menstrual cycle correlate with cyclic changes in bone resorption markers, highlighting its dynamic role in skeletal homeostasis.[51] These effects may be particularly relevant in female adolescents with delayed menarche or anovulatory cycles, both of which are more prevalent in individuals with scoliosis.[52]

Pregnenolone, while often overshadowed by its downstream metabolites, contributes to growth through its upstream regulatory effects. As the biochemical precursor to all steroid hormones, pregnenolone levels indirectly influence the synthesis

of cortisol, aldosterone, and androgens—hormones known to modulate energy metabolism, growth velocity, and stress response.[1] While direct evidence linking pregnenolone to skeletal development remains limited, its impact on adrenal function and neuroendocrine tone suggests an indirect but meaningful contribution.

In addition to its skeletal effects, progesterone has been implicated in regulating adipocyte differentiation and lipid metabolism. During adolescence, when body composition undergoes marked reorganization, progesterone appears to influence the distribution and function of adipose tissue. In vitro studies have shown that progesterone can inhibit preadipocyte differentiation in human fat cell cultures, particularly in the presence of insulin and glucocorticoids.[21] Clinically, this may manifest in changes in fat deposition patterns observed across pubertal stages, especially in females. Abnormal adipose tissue distribution, whether due to hormonal dysregulation or mechanical asymmetries, could theoretically alter the center of gravity and contribute to postural compensations—a factor worth considering in biomechanical models of idiopathic scoliosis.

Beyond somatic growth, both pregnenolone and progesterone influence neurodevelopmental processes that underlie coordination, proprioception, and behavioral regulation. Neurosteroid modulation of GABAergic and glutamatergic signaling in the adolescent brain is believed to fine-tune emotional reactivity and executive functioning—capacities that are maturing rapidly during this time.5 Alterations in these domains have been reported in adolescents with scoliosis, including heightened anxiety, depressive symptoms, and atypical motor integration, suggesting that hormonal imbalances may have broader systemic effects than previously appreciated.[53]

These complex and interconnected roles underscore the necessity of approaching adolescent development through an integrative lens that includes endocrine, skeletal, and neurological considerations. As such, future scoliosis screening tools may benefit from incorporating hormonal and metabolic parameters to more accurately capture individual risk profiles.

Idiopathic Scoliosis

Adolescent idiopathic scoliosis (IS) is a three-dimensional spinal deformity characterized by lateral curvature, vertebral rotation, and abnormal sagittal alignment that arises in otherwise healthy children, most commonly during the pubertal growth spurt.[52] The condition affects 1–4% of adolescents globally, with a female-to-male ratio of approximately 8:1 for curves that progress to require intervention.[54] While genetic predisposition, neuromuscular dysfunction, and biomechanical factors have been implicated, the exact etiology remains multifactorial and poorly understood. Increasingly, evidence points to a potential contribution of hormonal and neuroendocrine factors, particularly those involving steroid hormones such as pregnenolone and progesterone.[14,55]

Pubertal growth is orchestrated by a complex interplay of sex steroids, growth hormone, and insulin-like growth factor 1 (IGF-1).[56] Estrogen has long been recognized as a modulator of spinal growth plate activity, influencing vertebral morphology and bone mineral accrual.[57] However, progesterone, a downstream product of pregnenolone metabolism, also plays an essential role in skeletal biology. Progesterone receptors are expressed in osteoblasts and chondrocytes, where the hormone regulates bone formation, collagen deposition, and remodeling of connective tissue.[58] Deficient progesterone exposure during key developmental windows could compromise ligamentous stability and vertebral alignment, potentially predisposing to spinal curvature progression.[59]

Ligamentous laxity is a well-documented risk factor for IS. Studies have observed increased joint hypermobility and abnormal connective tissue properties in scoliosis patients, suggesting altered collagen cross-linking and extracellular matrix integrity.[60] Progesterone influences the synthesis and organization of collagen fibers, and low levels may impair the tensile strength of spinal ligaments,

making them more susceptible to deformation under asymmetrical loading.[61] These biomechanical alterations, in conjunction with rapid pubertal growth, could create conditions conducive to curve initiation and progression.

Neuromotor dysfunction has long been hypothesized in IS, with abnormalities reported in postural control, proprioceptive feedback, and muscle activation patterns.[62-64] The cerebellum, vestibular nuclei, and spinal interneurons coordinate motor outputs necessary for spinal alignment. Progesterone and pregnenolone, acting as neurosteroids, modulate neurotransmission in these circuits via GABAA_AA, NMDA, and sigma-1 receptors, regulating neuronal excitability and sensorimotor integration.[5,65] Deficiencies during puberty could impair central motor programming, resulting in asymmetric paraspinal muscle tone and persistent postural imbalance, two features commonly observed in IS patients.[62,64]

Emerging neuroimaging research supports this neurohormonal connection. Functional MRI studies have revealed altered cerebellar and cortical activation patterns in adolescents with IS, suggesting a central processing defect in postural control.[66] Neurosteroids such as pregnenolone have been shown to enhance synaptic plasticity and improve motor coordination in experimental models, highlighting a plausible link between hormonal deficits and neuromotor abnormalities contributing to spinal deformity.[5]

Morningstar and Strauchman[18] conducted one of the few studies directly investigating progesterone levels in females with a history of IS. In their retrospective cross-sectional analysis of 68 scoliosis patients compared to 173 age-matched controls, salivary progesterone levels were significantly lower in the scoliosis group across both menstruating and premenarchal subgroups, with non-scoliotic participants exhibiting 49% higher levels on average ($p < .05$). These findings suggest that inadequate progesterone exposure during adolescence may contribute to curve initiation or failure of spontaneous curve resolution.

Building upon this hypothesis, Morningstar and DuRussel[19] conducted a retrospective case-controlled series evaluating daily pregnenolone supplementation in adolescent females with early-stage scoliosis (Cobb angles 10–23°). Over a 12-month period, the treatment group demonstrated significantly less mean curve progression (13–24°) compared with observation-only controls (16–29°), with an approximate 3° difference ($p < .05$). While preliminary and non-randomized, this study suggests that enhancing steroid hormone availability during the pubertal growth phase could have a protective effect on curve evolution.

Other studies support a broader endocrine influence on scoliosis pathogenesis. Altered estrogen receptor polymorphisms, reduced melatonin signaling, and abnormal leptin metabolism have been associated with increased scoliosis susceptibility and curve severity.[67-69] These findings indicate that scoliosis may result from a multifactorial neuroendocrine imbalance rather than a purely structural spinal anomaly.

Taken together, several mechanisms may explain how low pregnenolone and progesterone levels could contribute to IS development:

1. **Ligamentous Laxity and Connective Tissue Instability:** Inadequate progesterone reduces collagen strength and ligament stiffness, making the spine more susceptible to deformation under mechanical load.[60,61]
2. **Delayed Skeletal Maturation:** Hormonal deficiency may alter vertebral growth plate dynamics, resulting in asynchronous growth and vertebral wedging.[20,54,59]
3. **Neuromotor Control Deficits:** Reduced neurosteroid modulation of GABAergic and glutamatergic pathways may impair sensorimotor integration necessary for spinal alignment.[5,62-65]
4. **Endocrine-Immunological Crosstalk:** Progesterone modulates inflammatory responses and immune tolerance, and

dysregulation could influence paraspinal muscle and ligament homeostasis.[70]

These proposed pathways are not mutually exclusive and likely interact with genetic susceptibility, mechanical factors, and central nervous system anomalies to shape the heterogeneous presentations of IS.

Clinical Implications and Future Directions

The expanding landscape of neurosteroid research invites a reevaluation of how clinicians and researchers approach adolescent development, especially in conditions like idiopathic scoliosis (IS), where etiology remains elusive. The observed associations between altered pregnenolone and progesterone levels and functional deficits in cognition, mood regulation, neuromotor control, and skeletal development suggest that these hormones play a more integral role in adolescent health than previously appreciated.

From a clinical standpoint, the potential of pregnenolone and progesterone as diagnostic biomarkers and therapeutic agents opens compelling avenues. Salivary and serum hormone profiling—already in use for assessing reproductive disorders and HPA axis dysfunction—may hold translational value in scoliosis screening protocols. Morningstar and colleagues demonstrated that significantly lower progesterone levels were found in females with adolescent idiopathic scoliosis, a finding that, while preliminary, could be built into a broader risk stratification model when combined with genetic, postural, and neuromuscular data.[18] While more work is required to validate these results, especially in longitudinal studies, the implication is clear: hormone profiles may serve not only as correlates but also as actionable clinical indicators of scoliosis progression risk.

Interventionally, early evidence of pregnenolone's benefits in modulating curve progression is both intriguing and cautiously promising.[19] Though sample sizes in current studies remain modest and follow-up durations relatively short, the consistency of findings across independent cohorts, coupled with the strong biological plausibility stemming from neurodevelopmental literature, justify further exploration. Importantly, pregnenolone is endogenously synthesized and has a favorable safety profile in early-phase clinical studies of psychiatric and neurological disorders.[71-73] However, dose-response relationships, optimal delivery methods, and pharmacokinetic characteristics in adolescent populations remain under-characterized. Any clinical implementation would thus necessitate rigorously controlled trials, with stratification by pubertal status, sex, and curve type, to determine therapeutic windows and appropriate endpoints.

Moreover, the neuroprotective and myelin-reparative properties of progesterone have garnered significant attention in clinical neurology and traumatic brain injury (TBI) research, where trials like ProTECT have investigated progesterone's potential to reduce edema and improve neurological outcomes post-TBI.[74,75] Although TBI and scoliosis are vastly different in pathophysiology, the shared domains of white matter integrity, synaptic coordination, and central motor planning lend plausibility to progesterone's broader role in supporting spinal and postural integrity in adolescence. Investigating these neuroendocrine overlaps could yield a novel interdisciplinary framework that connects endocrinology, neurology, and orthopedic medicine.

From a research methodology perspective, future studies would benefit from integrating multi-omic platforms—combining genomics, epigenomics, and hormone quantification—to delineate causal pathways. For instance, variants in TNFSF13/APRIL, FGF9, FGF14, and IL4 may influence neurosteroid biosynthesis and receptor sensitivity[76], potentially contributing to inter-individual differences in scoliosis susceptibility. Similarly, epigenetic modifications such as promoter methylation of neurosteroidogenic enzymes could modulate hormone levels during critical growth periods. These hypotheses warrant investigation using longitudinal cohort designs that incorporate both biological and clinical phenotyping.

In terms of broader population health, recognizing steroid hormone imbalances in adolescents could provide a gateway to improved management of related developmental concerns, including anxiety, insomnia, and dysautonomia, all of which are frequently comorbid with scoliosis.[77] In this light, early intervention with hormone-modulating strategies—whether pharmacologic, nutritional, or lifestyle-based—may offer low-risk adjunctive therapies to more invasive orthopedic interventions.

Nevertheless, a degree of caution is essential. Steroid hormone interventions, especially in a pediatric context, carry the potential for unintended consequences, particularly regarding bone maturation and feedback suppression of the hypothalamic-pituitary-gonadal axis.[78] To responsibly bridge the gap between hypothesis and practice, pilot trials must be followed by phase II and III investigations with clear safety and efficacy benchmarks.

Finally, interdisciplinary collaboration will be key. Pediatric endocrinologists, neurologists, orthopedic specialists, and developmental psychologists must be engaged in both the design and interpretation of studies in this space. Without a multifaceted perspective, the risk of over-simplifying a multifactorial condition like idiopathic scoliosis remains high.

In conclusion, the clinical implications of pregnenolone and progesterone deficiency—and their potential for supplementation—extend far beyond their traditional reproductive roles. While the road from molecular insight to therapeutic implementation is long and requires methodical validation, the convergence of endocrinology and orthopedic neurobiology represents one of the more promising frontiers in adolescent health. Recognizing and investigating the subtler, often overlooked hormonal influences during puberty may ultimately help us redefine early intervention standards for spinal deformities and related neurodevelopmental disorders.

Conclusion

The diverse physiological roles of pregnenolone and progesterone extend far beyond their traditionally understood reproductive functions. These steroid hormones act as critical modulators across several biological systems, influencing not only fertility and menstrual health but also neurodevelopment, sleep regulation, bone growth, and neuromotor coordination. As this review has illustrated, their influence is particularly relevant during adolescence—a period marked by rapid hormonal changes and heightened susceptibility to conditions like idiopathic scoliosis (IS).

The evidence reviewed here suggests that disturbances in pregnenolone and progesterone levels may contribute to the etiology and progression of IS. This assertion is supported by emerging observational and interventional studies showing associations between low endogenous hormone levels and increased curve progression. Such findings merit deeper investigation, especially as they converge with long-standing hypotheses about the neuroendocrine basis of scoliosis. The suggestion that targeted hormone support could potentially modulate spinal development is an exciting possibility—one that bridges endocrinology, neurology, and orthopedics in an integrative framework.

Similarly, the neurosteroid actions of these hormones—particularly their ability to modulate GABA_A and NMDA receptors, influence sleep architecture, and protect against neuroinflammation—speak to a wider spectrum of clinical relevance. In disorders marked by impaired cognition, poor sleep, or neuromotor dysfunction, such as traumatic brain injury, schizophrenia, or even age-related neurodegeneration, these hormones may offer therapeutic benefit. Their roles in supporting myelin repair, hippocampal neurogenesis, and cortical excitability are not incidental, but rather point to an endogenous system of neural maintenance that deserves more clinical attention.

The road from compelling theory to reliable clinical application is neither short nor simple. Most of the research remains in early stages, with notable gaps in our understanding of long-term safety, optimal dosing regimens, and individual variability in hormonal metabolism. It is also essential to disentangle the effects of endogenous hormones from those of synthetic analogues, particularly in populations vulnerable to hormonal shifts, such as adolescents and postmenopausal women.

Moreover, while some findings appear promising, the current body of literature is hampered by small sample sizes, short follow-up durations, and a lack of robust randomized controlled trials. Thus, it would be premature to suggest clinical implementation on a broad scale. Rather, these findings should serve as a call to action—prompting more rigorous inquiry into the roles of pregnenolone and progesterone not only as biomarkers of physiological change but also as potential modulators of health trajectories.

In the context of idiopathic scoliosis, incorporating hormone profiling into early risk assessment protocols could one day allow for more personalized, preventative strategies. Similarly, in the domains of sleep and neuroprotection, these hormones may represent a class of endogenous compounds capable of achieving therapeutic ends with fewer side effects than current pharmacologic options.

In sum, pregnenolone and progesterone occupy a unique intersection of systems biology—linking endocrine rhythms with neural stability, musculoskeletal integrity, and behavioral health. As research in this space advances, clinicians and investigators alike will benefit from approaching these hormones not as isolated agents, but as integrative modulators embedded within a web of physiological interdependence. Continuing to explore their functions with nuance and scientific rigor will be critical in translating this potential into practice.

References:

1. Miller WL, Auchus RJ. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. *Endocr Rev*. 2011;32:81-151.

2. Stanczyk FZ. All progestins are not created equal. *Steroids*. 2003;68:879-890.

3. Practice Committee of the American Society for Reproductive Medicine. Progesterone supplementation during IVF: a guideline. *Fertil Steril*. 2015;103:e1-e9.

4. Fatemi HM, Popovic-Todorovic B, Papanikolaou E, Donoso P, Devroey P. An update of luteal phase support in stimulated IVF cycles. *Hum Reprod Update*. 2007;13:581-590.

5. Reddy DS. Neurosteroids: endogenous role in the human brain and therapeutic potentials. *Prog Brain Res*. 2010;186:113-137.

6. Baker FC, Driver HS. Circadian rhythms, sleep, and the menstrual cycle. *Sleep Med*. 2007;8:613-622.

7. Friess E, Tagaya H, Trachsel L, Holsboer F, Rupprecht R. Progesterone-induced changes in sleep in male subjects. *Am J Physiol*. 1997;272: E885-E891.

8. Gava G, Orsili I, Alvisi S, Mancini I, Seracchioli R, Meriggiola MC. Cognition, mood, and sleep in menopausal transition: the role of hormone therapy. *Medicina (Kaunas)*. 2019;55:668.

9. Mayo W, Le Moal M, Abrous DN. Pregnenolone sulfate and aging of cognitive functions: behavioral, neurochemical, and morphological investigations. *Horm Behav*. 2001;40:215-217.

10. Vallée M, Mayo W, Darnaudéry M, et al. Neurosteroids: deficient cognitive performance in aged rats depends on low pregnenolone sulfate levels in the hippocampus. *Proc Natl Acad Sci U S A*. 1997;94:14865-14870.

11. Schumacher M, Guennoun R, Stein DG, De Nicola AF. Progesterone: therapeutic opportunities for neuroprotection and myelin repair. *Pharmacol Ther*. 2007;116:77-106.

12. Marx CE, Shampine LJ, Khisti RT, et al. Olanzapine and fluoxetine administration increase pregnenolone, allopregnanolone, and deoxycorticosterone: implications for therapy. *Pharmacol Biochem Behav*. 2006;84:609-617.

13. Stein DG, Wright DW. Progesterone in the clinical treatment of acute traumatic brain injury. *Expert Opin Investig Drugs*. 2010;19:847-857.

14. Burwell RG, Dangerfield PH, Freeman BJ. Etiologic theories of idiopathic scoliosis: somatic nervous system and the NOTOM escalator concept. *Stud Health Technol Inform*. 2008;140:208-217.

15. Sikes-Keilp C, Rubinow DR. GABAergic modulators: new therapeutic approaches to premenstrual dysphoric disorder. *CNS Drugs*. 2023;37:679-693.

16. Maurice T, Urani A, Phan VL, Romieu P. The interaction between neuroactive steroids and the sigma1 receptor function: behavioral consequences and therapeutic opportunities. *Brain Res Brain Res Rev*. 2001;37:116-132.

17. Wu J, Qiu Y, Zhang L, Sun Q, Qiu X, He Y. Association of estrogen receptor gene polymorphisms with susceptibility to adolescent idiopathic scoliosis. *Spine (Phila Pa 1976)*. 2006;31:1131-1136.

18. Morningstar MW, Strauchman MN. Salivary progesterone levels in female patients with a history of idiopathic scoliosis: a retrospective cross-sectional study. *Clin Pract*. 2022;12:326-332.

19. Morningstar MW, DuRussel B. Differences in pubertal curve progression among females with adolescent idiopathic scoliosis using pregnenolone therapy: a retrospective case-controlled series. *J Clin Med*. 2024;13:788.

20. Wang W, Hayami T, Kapila S. Female hormone receptors are differentially expressed in mouse fibrocartilages. *Osteoarthritis Cartilage*. 2009;17: 646-654.

21. Gregoire FM, Smas CM, Sul HS. Understanding adipocyte differentiation. *Physiol Rev*. 1998;78:783-809.

22. Zhang HQ, Lu SJ, Tang MX, et al. Association of estrogen receptor beta gene polymorphisms with susceptibility to adolescent idiopathic scoliosis. *Spine 2*009;34:760-764.

23. Fernandez-Bermejo E, García-Jiménez MA, Fernandez-Palomeque C, Munuera L. Adolescent idiopathic scoliosis and joint laxity: a study with somatosensory evoked potentials. *Spine* 1993;18: 918-922.

24. Gellersen B, Brosens JJ. Cyclic decidualization of the human endometrium in reproductive health and failure. *Endocr Rev*. 2014;35:851-905.

25. Fatemi HM, Popovic-Todorovic B, Papanikolaou E, Donoso P, Devroey P. An update of luteal phase support in stimulated IVF cycles. *Hum Reprod Update*. 2007;13:581-590.

26. Arck PC, Hecher K. Fetomaternal immune cross-talk and its consequences for maternal and offspring's health. *Nat Med*. 2013;19:548-556.

27. Fritz MA, Speroff L. Clinical Gynecologic Endocrinology and Infertility. 8th ed. Wolters Kluwer; 2011.

28. Vaisbuch E, de Ziegler D, Leong M, Weissman A, Shoham Z. Luteal-phase support in assisted reproduction treatment: real-life practices reported worldwide by an updated website-based survey. *Reprod Biomed Online*. 2014;28:330-5.

29. van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. 2015:CD009154.

30. Ortega I, García-Velasco JA, Pellicer A. Ovarian manipulation in ART: going beyond physiological standards to provide best clinical outcomes. *J Assist Reprod Genet*. 2018;35:1751-1762.

31. Watters M, Noble M, Child T, Nelson S. Short versus extended progesterone supplementation for luteal phase support in fresh IVF cycles: a systematic review and meta-analysis. *Reprod Biomed Online*. 2020;40:143-150.

32. Çulcu EA, Demiryürek Ş, Demiryürek AT. An update on approved and emerging drugs for the treatment of postpartum depression. *Ideggyogy Sz.* 2024;77:227-235.

33. Tambe SS, Nandedkar TD. Steroidogenesis in sheep ovarian antral follicles in culture: time course study and supplementation with a precursor. *Steroids*. 1993;58:379-83.

34. Mesiano S, Welsh TN. Steroid hormone control of myometrial contractility and parturition. *Semin Cell Dev Biol*. 2007;18:321-331.

35. Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage. *Cochrane Database Syst Rev*. 2019;CD003511.

36. Carp HJ, Toder V. The role of progesterone in recurrent pregnancy loss. *Clin Obstet Gynecol*. 2016;59:456-463.

37. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with a short cervix (≤25 mm) in the midtrimester decreases preterm birth and neonatal morbidity: a systematic review and meta-analysis of individual patient data. *Am J Obstet Gynecol.* 2012;206:124.e1-124.e19.

38. Hoff JD, Quigley ME, Yen SS. Hormonal dynamics at midcycle: a reevaluation. *J Clin Endocrinol Metab*. 1983;57:792-796.

39. Dušková M, Kolátorová L, Šimková M, Šrámková M, Malíková M, Horáčková L, Vítků J, Stárka L. Steroid diagnostics of 21st century in the light of their new roles and analytical tools. *Physiol Res*. 2020;69:S193-S203.

40. Mui Lam P, Chun Cheung M, Ping Cheung L, Ingrid Lok H, John Haines C. Effects of early luteal-phase vaginal progesterone supplementation on the outcome of in vitro fertilization and embryo transfer. *Gynecol Endocrinol*. 2008;24:674-80.

41. Belelli D, Lambert JJ. Neurosteroids: Endogenous regulators of the GABA_A receptor. *Nat Rev Neurosci*. 2005;6:565-575.

42. Shechter A, Boivin DB. Sleep, hormones, and circadian rhythms throughout the menstrual cycle in healthy women and those with premenstrual dysphoric disorder. *Int J Endocrinol*. 2010;2010: 259345.

43. de Zambotti M, Willoughby AR, Sassoon SA, Colrain IM, Baker FC. Menstrual cycle-related variation in physiologic sleep in women in the early menopausal transition. J Clin *Endocrinol Metab*. 2015;100:2918-2926.

44. Mayo W, Le Moal M, Abrous DN. Pregnenolone sulfate and aging of cognitive functions: behavioral,

neurochemical, and morphological investigations. *Horm Behav*. 2001;40:215-7.

45. Paul SM, Purdy RH. Neuroactive steroids. FASEB J. 1992;6:2311-2322.

46. Besedovsky L, Lange T, Born J. Sleep and immune function. *Pflugers Arch*. 2012;463:121-137.

47. Popovic RM, White DP. Upper airway muscle activity in normal women: influence of hormonal status. *J Appl Physiol*. 1998;84:1055-1062.

48. Fauser BC, Laven JS, Tarlatzis BC, et al. Sex steroid hormones and reproductive disorders: impact on women's health. *Reprod Sci.* 2011;18:702-12.

49. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001;285):785-95.

50. Gielen E, Vanderschueren D, Callewaert F, Boonen S. Osteoporosis in men. *Best Pract Res Clin Endocrinol Metab*. 2011;25:321-335.

51. Finkelstein JS, Brockwell SE, Mehta V, et al. Bone mineral density changes during the menstrual cycle. *J Clin Endocrinol Metab*. 1992;75:1038-1043.

52. Weinstein SL, Dolan LA, Cheng JC, Danielsson A, Morcuende JA. Adolescent idiopathic scoliosis. *Lancet*. 2008;371:1527-1537.

53. Marya S, Tambe AD, Millner PA, Tsirikos AI. Adolescent idiopathic scoliosis : a review of aetiological theories of a multifactorial disease. *Bone Joint J*. 2022;104-B:915-921.

54. Cheng JC, Castelein RM, Chu WC, Danielsson AJ, Dobbs MB, Grivas TB, Gurnett CA, Luk KD, Moreau A, Newton PO, Stokes IA, Weinstein SL, Burwell RG. Adolescent idiopathic scoliosis. *Nat Rev Dis Primers*. 2015;1:15030.

55. Zhang L, Zhang Q, Zhang Y, Arthur M, Teo EC, Bíró I, Gu Y. The Effect of Concave-Side Intertransverse Ligament Laxity on the Stress of AIS Lumbar Spine Based on Finite Element Method. *Bioengineering (Basel).* 2022;9:724.

56. Blogowska A, Rzepka-Górska I, Krzyzanowska-Swiniarska B. Growth hormone, IGF-1, insulin, SHBG, and estradiol levels in girls before menarche. *Arch Gynecol Obstet*. 2003;268:293-6.

57. Zheng S, Zhou H, Gao B, Li Y, Liao Z, Zhou T, Lian C, Wu Z, Su D, Wang T, Su P, Xu C. Estrogen promotes the onset and development of idiopathic scoliosis via disproportionate endochondral ossification of the anterior and posterior column in a bipedal rat model. *Exp Mol Med*. 2018;50:1-11.

58. Almeida M, Laurent MR, Dubois V, Claessens F, O'Brien CA, Bouillon R, Vanderschueren D, Manolagas SC. Estrogens and Androgens in Skeletal Physiology and Pathophysiology. *Physiol Rev*. 2017;97:135-187.

59. Wang W, Hayami T, Kapila S. Female hormone receptors are differentially expressed in mouse fibrocartilages. *Osteoarthritis Cartilage*. 2009;17: 646-654.

60. Fernandez-Bermejo E, García-Jiménez MA, Fernandez-Palomeque C, Munuera L. Adolescent idiopathic scoliosis and joint laxity: a study with somatosensory evoked potentials. *Spine* 1993;18 (7):918-922.

61. MacNamara P, O'Shaughnessy C, Manduca P, Loughrey HC. Progesterone receptors are expressed in human osteoblast-like cell lines and in primary human osteoblast cultures. *Calcif Tissue Int.* 1995;57:436-41.

62. Payas A, Batin S, Kurtoğlu E, Arik M, Seber T, Uçar İ, Unur E. Is the Integration Problem in the Sensoriomotor System the Cause of Adolescent Idiopathic Scoliosis? *J Pediatr Orthop*. 2023;43: e111-e119.

63. Assaiante C, Mallau S, Viel S, Jover M, Schmitz C. Development of postural control in healthy children: a functional approach. *Neural Plast*. 2005;12:109-18; discussion 263-72.

64. Park Y, Ko JY, Jang JY, Lee S, Beom J, Ryu JS. Asymmetrical activation and asymmetrical weakness as two different mechanisms of adolescent idiopathic scoliosis. *Sci Rep.* 2021;11:17582.

65. Maurice T, Urani A, Phan VL, Romieu P. The interaction between neuroactive steroids and sigma1 receptor function: behavioral consequences and therapeutic opportunities. *Brain Res Brain Res Rev*. 2001;37:116-132.

66. Domenech J, García-Martí G, Martí-Bonmatí L, Barrios C, Tormos JM, Pascual-Leone A. Abnormal activation of the motor cortical network in idiopathic scoliosis demonstrated by functional MRI. *Eur Spine J*. 2011;20:1069-78.

67. Wu J, Qiu Y, Zhang L, et al. Association of estrogen receptor gene polymorphisms with susceptibility to adolescent idiopathic scoliosis. *Spine* 2006;31:1131-1136.

68. Machida M, Dubousset J, Imamura Y, Miyashita Y, Yamada T, Kimura J. Melatonin. A possible role in pathogenesis of adolescent idiopathic scoliosis. *Spine* 1996;21:1147-52.

69. Qiu XS, Tang NL, Yeung HY, Lee KM, Hung VW, Ng BK, Cheng JC. Melatonin receptor 1B gene polymorphism is associated with adolescent idiopathic scoliosis. *Spine* 2007;32:1748-1753.

70. Straub RH. The complex role of estrogens in inflammation. *Endocr Rev*. 2007;28:521-574.

71. Brown ES, Park J, Marx CE, Hynan LS, Gardner C, Davila D, Nakamura A, Sunderajan P, Lo A, Holmes T. A randomized, double-blind, placebo-controlled trial of pregnenolone for bipolar depression. *Neuropsychopharmacology*. 2014;39:2867-73.

72. Ritsner MS. Pregnenolone, dehydroepiandrosterone, and schizophrenia: alterations and clinical trials. *CNS Neurosci Ther*. 2010;16:32-44.

73. Vallée M, Mayo W, Darnaudéry M, et al. Neurosteroids: deficient cognitive performance in aged rats depends on low pregnenolone sulfate levels in the hippocampus. *Proc Natl Acad Sci U S A.* 1997;94:14865-14870.

74. Wright DW, Yeatts SD, Silbergleit R, et al. Very early administration of progesterone for acute traumatic brain injury. *N Engl J Med*. 2014;371: 2457-2466.

75. Stein DG. Embracing failure: what the progesterone trials can teach about TBI clinical trials. *Brain Inj.* 2015;29:1259-1272.

76. Shufaro Y, Prus D, Laufer N, Simon A. CYP11A gene expression in cumulus cells: a potential marker for oocyte maturity. *Fertil Steril*. 2008;90:1049-1055.

77. Yovchev I, Maayan C, Simanovsky N, Foldes AJ, Brooks R, Kaplan L, Meiner Z, Cheishvili D. The Relationship Between Scoliosis, Spinal Bone Density, and Truncal Muscle Strength in Familial Dysautonomia Patients. *Calcif Tissue Int*. 2024;114: 222-227.

78. Soliman AT, Alaaraj N, De Sanctis V, Hamed N, Alyafei F, Ahmed S. Long-term health consequences of central precocious/early puberty (CPP) and treatment with Gn-RH analogue: a short update. *Acta Biomed*. 2023;94:e2023222.

