Anogenital Distance as a Biomarker of Androgen Exposure and Female Sexual Function: Clinical Evidence and Mechanistic Links

Ahmed Ismail Mohamed [1], Amal Mohamed El-anwar [2], Nourhan Essam Mohamed Mohamed Mounir [3], Abdallah Fekry Abdelmaksoud[4]

1 Assistant Professor of Obstetrics & Gynecology, Faculty of Medicine, Zagazig University,

2 Professor of Obstetrics & Gynecology, Faculty of Medicine, Zagazig University,

3 Resident Physician of Obstetrics & Gynecology, El-Galaa Educational Hospital,

4 Lecturer of Obstetrics & Gynecology, Faculty of Medicine, Zagazig University,

Corresponding Author: Nourhan Essam Mohamed Mohamed Mounir

Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Anogenital distance (AGD) has emerged as a sexually dimorphic anthropometric measure reflecting prenatal androgen exposure. In females, AGD is increasingly investigated as a noninvasive biomarker of in utero androgenic programming, with potential implications extending into reproductive endocrinology and sexual medicine. Concurrently, testosterone—though present at substantially lower concentrations than in males—plays a critical role in female sexual desire, arousal, genital vasocongestion, and overall sexual well-being. However, the relationship between circulating testosterone levels and female sexual function remains complex and inconsistent across studies, partly due to assay limitations, variations in free versus total testosterone assessment, and multifactorial influences on sexual health. The integration of AGD, as a stable developmental marker, with adult androgen profiles may provide new insights into the biological underpinnings of female sexual function. This review aims to critically evaluate current clinical and mechanistic evidence linking anogenital distance and circulating testosterone levels to female sexual function and quality of life. We explore whether AGD can serve as a reliable biomarker of androgen exposure relevant to adult sexual outcomes and assess how prenatal and postnatal androgen influences interact across the lifespan. Emerging data suggest that longer AGD in women correlates with hyperandrogenic phenotypes, particularly polycystic ovary syndrome (PCOS), supporting its validity as a proxy of prenatal androgen exposure. Testosterone has demonstrated central and peripheral effects on sexual desire and arousal, especially in hypoactive sexual desire disorder (HSDD), with interventional trials showing benefit of transdermal testosterone in selected populations. However, correlations between endogenous testosterone levels and sexual function domains remain modest and inconsistent. Preliminary studies investigating AGD and sexual function suggest potential associations with desire and arousal domains, but evidence remains limited and methodologically heterogeneous.

Conclusion: Anogenital distance represents a promising developmental biomarker of androgen exposure with potential relevance to female sexual function. While circulating testosterone contributes to sexual physiology, its predictive value for sexual quality of life is limited when considered in isolation. Integrating AGD with hormonal, neuroendocrine, and psychosocial factors may offer a more comprehensive framework for understanding female sexual health. Further standardized, longitudinal, and mechanistically informed studies are required before AGD can be translated into routine clinical practice.

Keywords: *Anogenital Distance, Androgen Exposure, Female Sexual Function*

Introduction

Female sexual health is a fundamental determinant of overall well-being, interpersonal relationships, and quality of life. Epidemiological data indicate that female sexual dysfunction (FSD), encompassing disorders of desire, arousal, orgasm, and genitopelvic pain, affects a substantial proportion of women

across the lifespan. In a large U.S. population-based survey, approximately 43% of women reported sexual concerns, with a significant subset experiencing associated distress [1]. Contemporary diagnostic frameworks emphasize that sexual dysfunction requires both symptoms and personal distress, underscoring the complex biopsychosocial model that governs female sexual function [2]. While psychosocial determinants are essential, endocrine and neurobiological mechanisms remain central components of sexual motivation and response.

Androgens, particularly testosterone, play a pivotal role in female sexual physiology despite their lower circulating concentrations compared with men. In women, testosterone is derived from ovarian and adrenal secretion as well as peripheral conversion of androstenedione and dehydroepiandrosterone (DHEA) [3]. Androgen receptors are widely distributed in central nervous system regions involved in sexual motivation, including the hypothalamus and limbic system, as well as in peripheral genital tissues such as the clitoris and vagina [4]. Clinical and translational evidence supports a role for testosterone in modulating sexual desire, arousal, and genital vasocongestion [5]. Randomized controlled trials have demonstrated that transdermal testosterone therapy improves sexual desire and satisfying sexual events in postmenopausal women diagnosed with hypoactive sexual desire disorder (HSDD) [6]. Nevertheless, correlations between endogenous testosterone levels and sexual function scores remain inconsistent, partly due to assay limitations and the difficulty of accurately measuring low circulating concentrations in women [7].

Anogenital distance (AGD), defined as the distance between the anus and the genitalia, is a sexually dimorphic anatomical trait established during fetal development under androgen influence. Experimental and human data demonstrate that AGD reflects the degree of prenatal androgen exposure during a critical masculinization programming window [8]. In males, AGD is approximately twice that of females, and shorter AGD in men has been associated with impaired reproductive parameters, supporting its validity as a biomarker of androgen action [9]. In women, AGD has gained increasing attention as a noninvasive and stable anthropometric marker of prenatal androgen programming.

Emerging evidence suggests that longer AGD in females is associated with hyperandrogenic phenotypes, particularly polycystic ovary syndrome (PCOS), a condition characterized by androgen excess and reproductive dysfunction [10]. Studies have reported significantly longer AGD measurements in women with PCOS compared with controls, reinforcing the hypothesis that prenatal androgen exposure may contribute to its pathophysiology [11]. Unlike circulating testosterone levels—which fluctuate across the menstrual cycle, with aging, and in response to metabolic changes—AGD remains relatively constant after early life, potentially serving as a lifelong imprint of early endocrine environment [8,10].

Despite expanding research on both female androgen biology and AGD, the intersection between prenatal androgen exposure and adult female sexual function remains insufficiently explored. Most investigations into testosterone and sexual health rely on cross-sectional hormone measurements without consideration of developmental programming [5,7]. Conversely, AGD research in women has primarily focused on reproductive, metabolic, and gynecologic outcomes rather than sexual quality of life [10,11]. This separation of developmental endocrinology from sexual medicine represents a critical knowledge gap.

Research Gap and Aim

To date, no comprehensive synthesis has integrated anogenital distance, circulating testosterone levels, and female sexual function within a unified developmental and mechanistic framework. It remains unclear whether AGD independently predicts adult sexual desire and arousal domains, whether it modifies associations between circulating testosterone and sexual outcomes, or whether it has potential clinical utility in sexual medicine assessment.

The aim of this review is to critically evaluate current evidence linking AGD and testosterone to female sexual function and quality of life. Specifically, we seek to: (1) examine AGD as a biomarker of prenatal androgen exposure; (2) analyze the role of circulating testosterone in female sexual physiology and dysfunction; (3) synthesize clinical data exploring associations between AGD and sexual outcomes; and

(4) propose an integrative developmental–endocrine model to guide future research and clinical application.

Conceptual and Biological Framework: Prenatal Androgen Programming and Lifelong Sexual Function

Sexual differentiation of the human reproductive tract and external genitalia occurs during a critical window of fetal development, often referred to as the masculinization programming window. During this period, androgen exposure—principally testosterone and its more potent derivative dihydrotestosterone (DHT)—plays a decisive role in determining genital morphology and sexually dimorphic traits [12]. Experimental animal models have consistently demonstrated that disruption or augmentation of androgen signaling during this window permanently alters anogenital distance (AGD), supporting its validity as a developmental biomarker of androgen action [13]. In humans, converging clinical and epidemiological data suggest that AGD reflects cumulative prenatal androgen exposure and remains relatively stable throughout life, providing a retrospective anatomical index of early endocrine programming [8].

The concept of developmental programming proposes that hormonal exposure during sensitive windows exerts lasting effects on organ structure, neuroendocrine pathways, and adult disease susceptibility. In females, prenatal androgen excess has been implicated in long-term alterations of ovarian function, metabolic regulation, and hypothalamic–pituitary–gonadal (HPG) axis dynamics [14]. Observations from congenital adrenal hyperplasia (CAH), a condition characterized by excess prenatal androgen exposure, demonstrate both genital virilization and later-life reproductive and behavioral differences, reinforcing the enduring impact of early androgen milieu [15]. These data provide a biologically plausible foundation for considering AGD as not merely an anatomical measurement, but as a surrogate marker of developmental endocrine trajectory.

Beyond peripheral genital development, androgens influence central nervous system organization. Prenatal androgen exposure has been shown to modulate sexually dimorphic brain structures, neurotransmitter systems, and behavioral phenotypes [16]. Neuroimaging and neuroendocrine studies suggest that androgen signaling contributes to the structural and functional differentiation of limbic and hypothalamic regions involved in sexual motivation and reward processing [17]. These central organizational effects may theoretically shape adult sexual desire and responsiveness independently of circulating hormone levels later in life.

In adulthood, female sexual function reflects the interaction between organizational (prenatal) and activational (postpubertal and adult) hormonal influences. The organizational–activational hypothesis posits that prenatal hormones establish structural frameworks that are later modulated by circulating sex steroids [18]. In this context, AGD may represent an index of organizational androgen exposure, whereas serum testosterone levels represent activational influences. Discrepancies between circulating testosterone and sexual function outcomes in adult women may therefore be partially explained by differences in early-life androgen programming that are not captured by serum measurements alone [5].

Hyperandrogenic disorders, particularly polycystic ovary syndrome (PCOS), further illustrate the interplay between developmental and adult androgen effects. PCOS is characterized by elevated androgen levels, ovulatory dysfunction, and metabolic disturbances, and growing evidence suggests a potential fetal origin linked to prenatal androgen excess [14,19]. Women with PCOS have been reported to exhibit longer AGD compared with controls, supporting a developmental androgen exposure hypothesis [11]. Importantly, sexual function outcomes in PCOS populations are heterogeneous, ranging from increased sexual desire in some cohorts to higher rates of sexual dissatisfaction and distress in others, underscoring the complexity of androgen–sexuality relationships [20].

Collectively, these findings support a multidimensional model in which prenatal androgen exposure shapes genital anatomy and neural circuitry, while adult testosterone levels modulate ongoing sexual physiology and behavior. Integrating AGD as a stable developmental biomarker with circulating

testosterone as a dynamic endocrine measure may therefore offer a more comprehensive understanding of female sexual health trajectories. However, empirical evidence directly linking AGD to validated sexual function outcomes remains limited and methodologically heterogeneous, necessitating careful evaluation in subsequent sections of this review.

Anogenital Distance in Females: Measurement, Determinants, and Clinical Validity

Anogenital distance (AGD) in females is typically defined using two standardized measurements: the distance from the center of the anus to the anterior clitoral surface (AGD-AC) and the distance from the anus to the posterior fourchette (AGD-AF). These measurements are obtained with digital calipers while the patient is in the lithotomy position, ensuring minimal soft tissue compression and consistent anatomical landmarks [8]. Studies have demonstrated acceptable intra- and interobserver reliability when standardized protocols are followed, supporting its feasibility in both research and clinical environments [21]. However, subtle variations in technique—including leg positioning, degree of hip abduction, and perineal pressure—can introduce measurement variability, highlighting the need for rigorous methodological consistency.

AGD is strongly sexually dimorphic, with male neonates exhibiting approximately twice the AGD of females, reflecting androgen exposure during the masculinization programming window [8,12]. In females, AGD is largely established in utero and shows relative stability from infancy through adulthood, although minor changes related to growth and adiposity may occur [22]. Longitudinal pediatric studies suggest that AGD tracks across early life, reinforcing its utility as a marker of prenatal endocrine influences rather than postnatal hormonal fluctuations [23]. Unlike circulating testosterone, which varies across the menstrual cycle and declines with age, AGD is considered a fixed anatomical endpoint of early androgen signaling.

Several biological and environmental determinants may influence AGD in females. Maternal endocrine conditions, particularly hyperandrogenic states such as polycystic ovary syndrome (PCOS), have been associated with longer AGD in female offspring, suggesting transplacental androgen effects [11]. Additionally, exposure to endocrine-disrupting chemicals (EDCs) with anti-androgenic or androgenic properties has been linked to alterations in AGD, further supporting its sensitivity to prenatal hormonal milieu [24]. These findings underscore AGD as an integrative marker of intrauterine androgen balance rather than a reflection of adult endocrine status.

Body mass index (BMI), parity, and ethnicity have also been evaluated as potential confounders in adult AGD measurement. Some studies report modest associations between BMI and AGD, potentially due to perineal adiposity affecting measurement precision rather than true anatomical variation [21]. Parity and obstetric trauma may theoretically alter perineal anatomy; however, available evidence suggests that AGD measurements remain relatively preserved postpartum when standardized landmarks are used [25]. Ethnic variability in AGD has been observed, necessitating population-specific normative ranges to enhance interpretability [22].

Clinical validity of AGD in women has been primarily explored in relation to reproductive and endocrine phenotypes. Cross-sectional studies have demonstrated that longer AGD correlates with higher ovarian follicle counts and features of hyperandrogenism, including elevated free androgen index [10]. Women diagnosed with PCOS consistently exhibit longer AGD compared with matched controls, reinforcing its association with androgen excess conditions [11,26]. Conversely, shorter AGD has been hypothesized to reflect lower prenatal androgen exposure, although clinical correlates in adult women remain less well characterized.

Despite its promise, several limitations temper the clinical application of AGD. First, there is no universally established reference range for adult women across diverse populations. Second, AGD does not directly measure circulating androgen levels or receptor sensitivity; rather, it reflects cumulative developmental exposure. Third, current evidence is predominantly cross-sectional, limiting causal inference. Therefore, while AGD represents a biologically plausible and noninvasive biomarker of prenatal androgen programming, its translation into sexual medicine requires careful integration with endocrine, psychological, and relational factors.

In summary, AGD in females is a reproducible, developmentally determined anatomical measure influenced by prenatal androgen exposure and modulated by environmental and maternal factors. Its demonstrated association with hyperandrogenic phenotypes supports its validity as a biomarker of early androgen action. However, whether AGD independently predicts adult sexual function or modifies the relationship between testosterone and sexual outcomes remains to be clarified through rigorously designed studies.

Testosterone Physiology in Women: Production, Measurement Challenges, and Tissue-Level Actions

Testosterone is an essential sex steroid in women, although circulating concentrations are approximately one-tenth to one-twentieth of those observed in men. In premenopausal women, testosterone derives from three principal sources: direct ovarian secretion, adrenal production, and peripheral conversion of androstenedione and dehydroepiandrosterone (DHEA) in adipose and other tissues [3]. The relative contribution of each source varies across the lifespan. During reproductive years, both ovaries and adrenal glands contribute substantially, whereas after menopause ovarian testosterone production declines but does not cease entirely, and adrenal and peripheral sources become relatively more important [27]. This complex biosynthesis underscores the difficulty of attributing sexual function outcomes to a single endocrine source.

Circulating testosterone exists in three fractions: bound to sex hormone–binding globulin (SHBG), loosely bound to albumin, and unbound (free). Only free and albumin-bound fractions are considered bioavailable and capable of diffusing into target tissues [7]. SHBG levels are influenced by multiple physiological and pathological factors, including obesity, insulin resistance, thyroid function, estrogen exposure, and use of combined oral contraceptives [28]. Consequently, total testosterone may not accurately reflect androgenic activity at the tissue level. The free androgen index (FAI), calculated from total testosterone and SHBG, has been proposed as a surrogate marker of bioavailable testosterone, particularly in hyperandrogenic states such as polycystic ovary syndrome (PCOS) [19].

Accurate measurement of testosterone in women presents substantial analytical challenges. Conventional immunoassays often lack sensitivity and specificity at the low concentrations typical of female physiology, leading to potential misclassification [7]. Liquid chromatography–tandem mass spectrometry (LC–MS/MS) is currently considered the gold standard for measuring low testosterone levels due to superior analytical precision [29]. Variability in assay methodology has contributed to inconsistent findings across studies examining associations between endogenous testosterone levels and female sexual function. Additionally, testosterone levels demonstrate diurnal variation and fluctuate across the menstrual cycle, further complicating interpretation [5].

At the tissue level, testosterone exerts its effects through binding to intracellular androgen receptors, which function as ligand-activated transcription factors. Androgen receptors are widely expressed in the female genital tract, including the clitoris, vestibular glands, and vaginal epithelium, supporting a role in genital vasocongestion, lubrication, and sensory responsiveness [4]. Androgens also influence nitric oxide synthesis and vascular smooth muscle relaxation, mechanisms central to sexual arousal physiology [30]. In the central nervous system, testosterone modulates dopaminergic and serotonergic pathways involved in reward, motivation, and sexual desire [5,16]. These central and peripheral actions collectively provide a biological rationale for the role of testosterone in female sexual function.

Clinical interventional evidence further supports testosterone's activational role. Randomized controlled trials have demonstrated that transdermal testosterone therapy improves sexual desire and frequency of satisfying sexual events in postmenopausal women with hypoactive sexual desire disorder (HSDD) [6,31]. Meta-analyses confirm modest but statistically significant benefits in carefully selected populations, while emphasizing the importance of appropriate dosing and monitoring to minimize androgenic adverse effects [32]. However, not all women with low sexual desire exhibit low serum testosterone, and symptom improvement does not consistently correlate with baseline hormone concentrations, suggesting that tissue sensitivity and central processing may be equally important determinants.

Importantly, endogenous testosterone levels in healthy premenopausal women show weak and inconsistent correlations with validated sexual function scores such as the Female Sexual Function Index (FSFI) [5]. These findings suggest that circulating hormone levels alone may not adequately predict sexual quality of life. Factors such as mood disorders, relationship satisfaction, body image, chronic disease, and medication use frequently exert stronger influences on sexual outcomes than isolated endocrine parameters [2]. Therefore, testosterone should be conceptualized as one component within a multidimensional biopsychosocial framework rather than as a singular determinant of female sexual health.

In summary, testosterone in women originates from multiple endocrine sources and acts via complex central and peripheral mechanisms. Measurement challenges and interindividual variability in receptor sensitivity limit the predictive value of serum testosterone alone. Integrating dynamic hormonal measures with developmental biomarkers such as anogenital distance may provide deeper insight into individual differences in female sexual function, a hypothesis that warrants systematic evaluation in subsequent sections.

Mechanistic Links Between Androgens and Female Sexual Function: Central and Peripheral Pathways

Female sexual function is a multidimensional process involving coordinated central neural activation, peripheral genital responses, vascular dynamics, endocrine signaling, and psychological integration. Sexual desire—the motivational component of sexual response—is primarily regulated at the level of the central nervous system, particularly within limbic and hypothalamic structures [5]. Functional neuroimaging studies have demonstrated activation of the amygdala, anterior cingulate cortex, insula, and hypothalamus in response to erotic stimuli, regions known to be modulated by sex steroids including testosterone [33]. Androgens enhance dopaminergic signaling within mesolimbic reward pathways, thereby facilitating sexual motivation and responsiveness [16]. These central mechanisms provide biological plausibility for the association between androgen availability and sexual desire.

Testosterone's central effects are further supported by experimental endocrine manipulation studies. In women undergoing surgical menopause, abrupt reductions in circulating androgens are associated with declines in sexual desire and arousal, effects that may improve with testosterone supplementation [6]. The central modulation of sexual interest appears to be mediated not only by androgen receptor activation but also by local aromatization of testosterone to estradiol within the brain, suggesting a complex interplay between androgenic and estrogenic pathways [5]. These mechanisms help explain why circulating testosterone levels alone do not fully account for sexual motivation, as intracrine metabolism and receptor sensitivity may differ substantially among individuals.

Peripheral mechanisms are equally important in female sexual response. Sexual arousal involves genital vasocongestion, clitoral tumescence, vaginal lubrication, and increased genital sensitivity. Androgen receptors have been identified in the clitoral corpora cavernosa, vestibular glands, and vaginal epithelium, supporting a role in maintaining genital tissue integrity and responsiveness [4]. Androgens enhance nitric oxide synthase activity and promote smooth muscle relaxation within genital vasculature, facilitating increased blood flow during sexual stimulation [30]. Animal and human studies suggest that androgen deprivation may reduce genital blood flow and tissue trophicity, effects that are partially reversible with androgen replacement [34].

In addition to vascular mechanisms, androgens influence peripheral sensory thresholds. Evidence suggests that testosterone may modulate nociceptive and sensory processing within genital tissues, potentially affecting sexual pleasure and orgasmic capacity [35]. Reduced androgen levels have been associated with vulvovaginal atrophy and dyspareunia, particularly in postmenopausal women, although estrogen deficiency remains the dominant driver of these symptoms [5]. Thus, testosterone likely acts synergistically with estrogen to maintain optimal genital function rather than serving as an isolated determinant.

Psychological and relational factors significantly modulate the translation of biological arousal into subjective sexual satisfaction. Contemporary models, including the circular model of female sexual

response, emphasize that desire may be responsive rather than spontaneous and highly context dependent [36]. Androgen-mediated biological readiness does not guarantee sexual satisfaction if relational conflict, depressive symptoms, or body image concerns are present. Indeed, studies demonstrate that mood disorders and interpersonal dissatisfaction are stronger predictors of female sexual dysfunction than isolated hormonal abnormalities [2]. Therefore, androgenic mechanisms must be interpreted within a biopsychosocial framework.

Importantly, discordance between physiological arousal and subjective desire is common in women. Laboratory studies measuring genital blood flow using vaginal photoplethysmography often reveal physiological arousal without corresponding subjective desire, indicating complex central integration [37]. Testosterone may enhance motivational components of sexual response more than purely physiological arousal, aligning with clinical trial findings where improvements are most prominent in desire domains rather than lubrication or orgasm scores [31,32]. This distinction is critical when evaluating associations between androgen biomarkers and validated sexual function instruments such as the Female Sexual Function Index (FSFI).

Taken together, androgen effects on female sexual function involve intricate central and peripheral pathways. Testosterone enhances dopaminergic reward signaling, modulates hypothalamic activation, supports genital vascular and tissue health, and interacts with psychological context to shape sexual experience. These activational mechanisms likely interact with earlier organizational influences established during fetal development. Therefore, integrating circulating testosterone levels with developmental biomarkers such as anogenital distance may provide a more nuanced understanding of interindividual variability in female sexual desire and quality of life.

Clinical Evidence: Anogenital Distance and Female Sexual Function Outcomes

Direct investigation of the relationship between anogenital distance (AGD) and female sexual function remains limited, but emerging clinical data suggest biologically plausible associations. Given that AGD reflects prenatal androgen exposure, and androgens are implicated in adult sexual motivation, researchers have hypothesized that women with longer AGD may exhibit differences in sexual desire, arousal, or overall sexual satisfaction. However, available studies are predominantly cross-sectional, involve modest sample sizes, and vary in measurement techniques, limiting definitive conclusions [8,21].

Initial explorations into AGD and sexual parameters have often been conducted within populations characterized by altered androgen environments, particularly polycystic ovary syndrome (PCOS). Women with PCOS consistently demonstrate longer AGD compared with controls, supporting a developmental androgen exposure hypothesis [11,26]. Sexual function in PCOS, however, is heterogeneous. While hyperandrogenism might theoretically enhance sexual desire, systematic reviews demonstrate that women with PCOS more frequently report sexual dissatisfaction, impaired arousal, and reduced quality of life, likely mediated by body image concerns, obesity, infertility, and psychological comorbidities rather than androgen excess per se [20]. These findings highlight that longer AGD does not necessarily translate into improved sexual well-being.

Beyond PCOS, limited observational studies in general female populations have examined correlations between AGD and validated sexual function indices such as the Female Sexual Function Index (FSFI). Preliminary findings suggest that longer AGD may be modestly associated with higher sexual desire scores, but these associations are inconsistent and often attenuate after adjustment for body mass index (BMI), age, and relationship status [8]. Importantly, most studies have not differentiated between spontaneous and responsive desire, nor have they consistently accounted for sexual distress, a key determinant of clinically meaningful dysfunction [2].

The distinction between sexual function and sexual distress is particularly relevant when interpreting AGD associations. Modern definitions of female sexual dysfunction require the presence of both symptoms and distress to warrant clinical diagnosis [2]. Even if AGD were associated with specific FSFI domains such as desire or arousal, the clinical significance of such findings would depend on whether differences translate into meaningful improvements or impairments in quality of life. Current

evidence does not demonstrate robust or clinically actionable predictive value of AGD for sexual distress outcomes.

Another important consideration is the potential confounding effect of current androgen status. Women with longer AGD may also exhibit higher free androgen index or other biochemical markers of hyperandrogenism, particularly in PCOS cohorts [10,26]. In such cases, it becomes difficult to disentangle whether sexual function differences reflect prenatal organizational influences (indexed by AGD), current activational hormonal effects, or psychosocial mediators. Few studies have employed multivariable models integrating both AGD and circulating testosterone simultaneously to assess independent contributions.

Ethnic and cultural variability further complicates interpretation. Normative AGD ranges differ across populations [22], and sexual attitudes, relationship dynamics, and reporting patterns vary substantially by sociocultural context. Studies conducted in homogeneous cohorts may therefore lack generalizability. Additionally, measurement heterogeneity—specifically differences between AGD-AC and AGD-AF—may influence observed associations, as these measurements may reflect slightly distinct anatomical dimensions [21].

Importantly, no large-scale longitudinal studies have yet examined whether AGD measured in infancy or childhood predicts adult sexual function outcomes. Such prospective designs would provide stronger causal inference by linking developmental androgen exposure directly to later sexual health trajectories. Current reliance on adult cross-sectional measurements limits the ability to determine whether AGD exerts independent predictive value beyond adult endocrine and psychosocial factors.

Clinical Evidence: Circulating Testosterone Levels and Female Sexual Function

Observational research assessing endogenous testosterone and female sexual function has produced mixed results, largely because female sexual response is multifactorial and serum testosterone is an imperfect proxy for tissue androgen activity. Population studies commonly show weak or non-significant correlations between total testosterone and global sexual function scores, with stronger associations sometimes seen for **free testosterone**, **free androgen index (FAI)**, or low SHBG states (often linked to adiposity and insulin resistance). These associations frequently attenuate after adjusting for depression, relationship satisfaction, medications (eg, SSRIs), and metabolic factors, suggesting that testosterone is one contributor among many rather than a dominant determinant of sexual quality of life [5,7]. Clinical interpretation is further limited by assay problems in the female range and by variability in study endpoints (desire vs arousal vs distress) [7]. [38]

Evidence is strongest for testosterone therapy in carefully selected women with **hypoactive sexual desire disorder (HSDD)**, particularly in postmenopausal populations. Multiple randomized controlled trials of transdermal testosterone (patch or gel formulations) in surgically and naturally postmenopausal women have demonstrated improvements in sexual desire and frequency of satisfying sexual events, typically with modest effect sizes but clinically meaningful changes for some patients [6,31]. These trials also highlight that baseline total testosterone does not reliably predict response, supporting the concept that central processing, receptor sensitivity, and psychosocial context modify treatment outcomes. [39]

Systematic reviews and meta-analyses have synthesized randomized evidence and provide the clearest signal: in postmenopausal women with diminished sexual well-being, non-oral testosterone improves several domains including desire, arousal, orgasm, pleasure, and reduces sexually related distress, while increasing the frequency of satisfying sexual events. At the same time, these analyses emphasize careful risk–benefit counseling and avoidance of supraphysiologic dosing, because androgenic adverse effects (eg, acne, hirsutism) increase with higher exposure and long-term safety data remain limited for some outcomes [40]. [40]

Major professional guidance has converged on a narrow evidence-based indication. The **Global Consensus Position Statement** concluded that the **only evidence-based indication** for systemic testosterone therapy in women is treatment of HSDD, with recommended use of doses that achieve physiologic premenopausal testosterone concentrations and with monitoring for side effects and

testosterone levels to avoid excess [41]. The **International Society for the Study of Women's Sexual Health (ISSWSH)** guideline provides a practical framework for patient selection, baseline assessment (including evaluation of psychosocial drivers and medication contributors), dosing using non-oral preparations, and follow-up monitoring, while also stressing that compounded formulations are generally discouraged due to variable dosing and limited quality assurance [42]. [41,42]

In reproductive-age women, evidence is less consistent and the therapeutic role is less established. Some data suggest potential benefit in select premenopausal women with HSDD, but effects appear smaller and the evidence base is less robust than in postmenopause, contributing to more conservative guideline positions [40,41]. In hyperandrogenic conditions such as PCOS, higher endogenous androgens do not uniformly translate into better sexual function, likely because body image distress, depression/anxiety, infertility stressors, obesity, and relationship factors may outweigh any androgen-driven enhancement of desire [20]. Therefore, in routine Ob/Gyn practice, testosterone should be interpreted as one biological dimension within a broader biopsychosocial assessment rather than a standalone explanation for sexual symptoms. [20,41]

Integrating AGD and Testosterone: Convergence, Divergence, and an Ob/Gyn-Oriented Clinical Model

A clinically useful way to integrate **anogenital distance (AGD)** and **testosterone** is to treat them as markers of two different "androgen stories." AGD is best interpreted as an **organizational** marker—an anatomical imprint of **prenatal androgen signaling**—whereas circulating testosterone (and especially bioavailable fractions) reflects **activational** androgen status that can change with age, adiposity, medications, ovarian function, and SHBG dynamics. This distinction helps explain why some women may have sexual symptoms despite "normal" serum testosterone, and why others may have elevated testosterone without improved sexual quality of life: organizational programming, tissue sensitivity, and psychosocial context may amplify or blunt activational effects. [5,8,18]

Clinical data directly combining AGD, testosterone, and validated sexual outcomes are still sparse, but newer studies suggest AGD may correlate with sexual function and sexual quality-of-life instruments. For example, a 2023 study evaluating women using FSFI and SQOL-F reported significant correlations between both AGD-AC/AGD-AF and sexual function/quality-of-life scores, while serum testosterone did not correlate with AGD in that sample—illustrating how a developmental marker and a circulating hormone can diverge in their associations. These findings are intriguing but must be interpreted cautiously because cross-sectional designs cannot establish causality, and unmeasured confounders (relationship quality, depression, medications, pelvic pain) may strongly influence outcomes. [43,47,44]

In Ob/Gyn practice, the most immediate clinical integration point is to use AGD as a **contextual biomarker** rather than a diagnostic test: it may help stratify hypotheses about whether an individual's sexual phenotype is more consistent with developmental androgen influences (organizational) versus current endocrine or iatrogenic factors (activational). However, any attempt to infer sexual health from anatomy alone risks oversimplification. Sexual function instruments (e.g., FSFI) quantify domains such as desire, arousal, lubrication, orgasm, satisfaction, and pain, while distress measures (e.g., FSDS/FSDS-R) capture the element that defines clinically significant dysfunction in modern nosology. Therefore, the clinically relevant endpoint is not "function score" alone, but **function + distress + patient goals**, which can be discordant. [43,46,2]

Menopause and the genitourinary syndrome of menopause provide another lens for integration, because both tissue trophicity and sexual function can change with endocrine transitions. Some observational work in postmenopausal women has reported associations between AGD-related measures and vulvovaginal atrophy and sexual impairment, suggesting that perineal anatomy and menopausal tissue change may co-vary in ways that matter for symptoms. Still, menopause is dominated by estrogen deficiency, and any androgen-related contribution must be interpreted within the broader context of GSM, pelvic floor health, comorbid pain, and relational factors. [45,5]

Putting these strands together, an Ob/Gyn-oriented clinical model can be summarized as follows: **(1)**

prenatal androgen signaling (indexed imperfectly by AGD) may shape genital anatomy and neurobehavioral substrates for sexual responsiveness; **(2)** adult testosterone availability (best assessed with accurate assays and SHBG-aware interpretation) may modulate desire and arousal in selected contexts, but often does not predict sexual outcomes on its own; and **(3)** psychosocial, relational, and iatrogenic determinants frequently dominate symptom expression and distress. This integrated model supports future research designs that simultaneously measure AGD, high-quality androgen assays, validated sexual function instruments, and distress scales—ideally longitudinally—to determine whether AGD adds independent predictive value beyond known drivers. [8,41,42,43,46]

Conclusion

Anogenital distance (AGD) represents a biologically grounded, developmentally determined anatomical marker that reflects prenatal androgen exposure. Its sexually dimorphic nature and demonstrated associations with hyperandrogenic phenotypes—particularly polycystic ovary syndrome—support its validity as an index of early endocrine programming. Unlike circulating testosterone levels, which fluctuate across the lifespan and are influenced by metabolic, pharmacologic, and reproductive factors, AGD remains relatively stable, potentially serving as a lifelong imprint of organizational androgen effects.

Testosterone, in contrast, functions primarily as an activational hormone in adult women, modulating central sexual motivation and peripheral genital responsiveness. Evidence from randomized trials confirms that physiologic testosterone therapy can improve sexual desire and reduce sexual distress in carefully selected postmenopausal women with hypoactive sexual desire disorder. However, endogenous serum testosterone concentrations correlate inconsistently with sexual function scores, reflecting the complexity of female sexual health and the limitations of serum-based assessment. Measurement challenges, interindividual variability in receptor sensitivity, and intracrine metabolism further complicate interpretation.

Integrating AGD and testosterone within an organizational–activational framework offers a more nuanced understanding of female sexual function. Prenatal androgen programming may influence genital anatomy, neural circuitry, and behavioral predispositions, while adult testosterone availability modulates ongoing sexual responsiveness. Nevertheless, sexual quality of life is ultimately shaped by a dynamic interplay between biological substrates and psychosocial determinants, including relationship context, mental health, cultural norms, and comorbid medical conditions.

At present, AGD should be considered an emerging research biomarker rather than a clinical diagnostic tool for sexual dysfunction. While preliminary data suggest possible associations between AGD and sexual function domains, the evidence remains limited, heterogeneous, and predominantly cross-sectional. There is insufficient justification for routine AGD measurement in sexual medicine practice. Future longitudinal and mechanistically informed studies are needed to determine whether AGD independently predicts sexual health outcomes beyond adult hormonal and psychosocial factors.

From an Obstetrics and Gynecology perspective, the most clinically responsible approach is comprehensive and patient-centered: evaluating sexual concerns through validated instruments, assessing distress, reviewing endocrine status with accurate assays when appropriate, and addressing relational and psychological contributors. Testosterone therapy should remain reserved for evidence-based indications, while AGD continues to be explored as a developmental biomarker within research settings.

Ultimately, understanding female sexual health requires moving beyond reductionist hormone-only models toward an integrated developmental, endocrine, and biopsychosocial framework. AGD and testosterone each provide partial insight; together, they contribute to a broader and more sophisticated model of female sexual function and quality of life.

References

1. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA.* 1999;281(6):537-544.
2. Parish SJ, Goldstein AT, Goldstein SW, et al. Toward a more evidence-based nosology and nomenclature for female sexual dysfunctions—Part II. *J Sex Med.* 2016;13(12):1888-1906.
3. Burger HG. Androgen production in women. *Fertil Steril.* 2002;77(Suppl 4):S3-S5.
4. Sherwin BB. The role of androgens in female sexual function. *Menopause.* 2002;9(3):153-160.
5. Davis SR, Wahlin-Jacobsen S. Testosterone in women—the clinical significance. *Lancet Diabetes Endocrinol.* 2015;3(12):980-992.
6. Braunstein GD, Sundwall DA, Katz M, et al. Safety and efficacy of a testosterone patch for the treatment of hypoactive sexual desire disorder in surgically menopausal women. *Arch Intern Med.* 2005;165(14):1582-1589.
7. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. *J Clin Endocrinol Metab.* 2007;92(2):405-413.
8. Thankamony A, Pasterski V, Ong KK, Acerini CL, Hughes IA. Anogenital distance as a marker of androgen exposure in humans. *Andrology.* 2016;4(4):616-625.
9. Eisenberg ML, Hsieh TC, Walters RC, Krasnow R, Lipshultz LI. The relationship between anogenital distance and reproductive hormone levels in adult men. *J Urol.* 2011;185(2):594-601.
10. Mendiola J, Roca M, Mínguez-Alarcón L, et al. Anogenital distance is related to ovarian follicular number in young Spanish women: a cross-sectional study. *Environ Health.* 2012;11:90.
11. Barrett ES, Sathyanarayana S, Janssen S, et al. Anogenital distance in newborn daughters of women with polycystic ovary syndrome indicates fetal testosterone exposure. *J Clin Endocrinol Metab.* 2018;103(8):2734-2742.
12. Welsh M, Suzuki H, Yamada G. The masculinization programming window. *Endocr Dev.* 2014;27:17-27.
13. van den Driesche S, Scott HM, MacLeod DJ, et al. Relative importance of androgen and estrogen exposure on anogenital distance in the rat. *Endocrinology.* 2011;152(4):1622-1632.
14. Abbott DH, Dumesic DA, Franks S. Developmental origin of polycystic ovary syndrome—a hypothesis. *J Endocrinol.* 2002;174(1):1-5.
15. Meyer-Bahlburg HFL. Gender identity outcome in female-raised 46,XX individuals with congenital adrenal hyperplasia. *Arch Sex Behav.* 2005;34(4):415-428.
16. Hines M. Prenatal testosterone and gender-related behaviour. *Eur J Endocrinol.* 2006;155(Suppl 1):S115-S121.
17. Sacher J, Okon-Singer H, Villringer A. Evidence from neuroimaging for the role of sex hormones in human brain structure. *Trends Cogn Sci.* 2013;17(7):309-317.
18. Phoenix CH, Goy RW, Gerall AA, Young WC. Organizing action of prenatally administered testosterone on the tissues mediating mating behavior. *Endocrinology.* 1959;65(3):369-382.
19. Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JSE, Legro RS. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of PCOS. *Endocr Rev.* 2015;36(5):487-525.
20. Pastoor H, Timman R, de Klerk C, et al. Sexual function in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update.* 2018;24(3):307-319.
21. Mendiola J, Stahlhut RW, Jørgensen N, et al. Shorter anogenital distance predicts poorer semen quality in young men. *Environ Health Perspect.* 2011;119(7):958-963.
22. Sathyanarayana S, Barrett ES, Janssen S, et al. Anogenital distance and penile width measurements in newborns: reliability and normative data. *Environ Health Perspect.* 2010;118(9):1337-1342.
23. Thankamony A, Ong KK, Dunger DB, Acerini CL, Hughes IA. Anogenital distance from birth to 2 years: a population study. *Environ Health Perspect.* 2009;117(11):1786-1790.
24. Swan SH, Main KM, Liu F, et al. Decrease in anogenital distance among male infants with prenatal phthalate exposure. *Environ Health Perspect.* 2005;113(8):1056-1061.
25. Barrett ES, Parlett LE, Windham GC, et al. Prenatal exposure to diethylstilbestrol and anogenital distance in adult women. *Hum Reprod.* 2016;31(9):2147-2154.
26. Cesta CE, Öberg AS, Ibrahimson A, et al. Anogenital distance in women with polycystic ovary syndrome: a Swedish population-based study. *J Clin Endocrinol Metab.* 2019;104(7):2797-2805.
27. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females. *J Clin Endocrinol Metab.* 2005;90(7):3847-3853.
28. Hammond GL. Diverse roles for sex hormone–binding globulin in reproduction. *Biol Reprod.* 2011;85(3):431-441.
29. Handelsman DJ, Wartofsky L. Requirement for mass spectrometry sex steroid assays. *J Clin Endocrinol Metab.* 2013;98(10):3971-3973.
30. Traish AM, Goldstein I, Kim NN. Testosterone and erectile function. *Eur Urol.* 2007;52(1):54-70.
31. Davis SR, Moreau M, Kroll R, et al. Testosterone for low libido in postmenopausal women not taking estrogen. *N Engl J Med.* 2008;359(19):2005-2017.

32. Achilli C, Pundir J, Ramanathan P, Sabatini L, Hamoda H, Panay N. Efficacy and safety of transdermal testosterone in postmenopausal women with hypoactive sexual desire disorder. *Fertil Steril.* 2017;107(2):475-482.e15.
33. Georgiadis JR, Kringelbach ML. The human sexual response cycle. *Prog Neurobiol.* 2012;98(1):49-81.
34. Traish AM, Park K, Dhir V, Kim NN, Moreland RB, Goldstein I. Effects of castration and androgen replacement on erectile function. *Endocrinology.* 1999;140(4):1861-1868.
35. Leiblum SR, Hayes RD, Wanser RA, Nelson JS. Vaginal atrophy in the postmenopausal woman. *Menopause.* 2009;16(4):711-716.
36. Basson R. The female sexual response: a different model. *J Sex Marital Ther.* 2000;26(1):51-65.
37. Chivers ML, Seto MC, Lalumière ML, Laan E, Grimbos T. Agreement of self-reported and genital measures of sexual arousal. *Arch Sex Behav.* 2010;39(1):5-56.
38. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Utility, limitations, and pitfalls in measuring testosterone. *J Clin Endocrinol Metab.* 2007;92(2):405-413.
39. Davis SR, Moreau M, Kroll R, et al. Testosterone for low libido in postmenopausal women. *N Engl J Med.* 2008;359(19):2005-2017.
40. Islam RM, Bell RJ, Green S, Page MJ, Davis SR. Safety and efficacy of testosterone for women: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol.* 2019;7(10):754-766.
41. Davis SR, Baber R, Panay N, et al. Global Consensus Position Statement on the Use of Testosterone Therapy for Women. *J Clin Endocrinol Metab.* 2019;104(10):4660-4666.
42. Parish SJ, Simon JA, Davis SR, et al. ISSWSH clinical practice guideline for systemic testosterone for HSDD. *J Sex Med.* 2021;18(5):849-867.
43. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI). *J Sex Marital Ther.* 2000;26(2):191-208.
44. Kulaksiz D, Akbayir O, Goksu M, et al. The relationship between anogenital distance and female sexual life quality. *Eur Rev Med Pharmacol Sci.* 2022;26(3):1062-1068.
45. Domenici L, Di Donato V, Giannini A, et al. Comparison of anogenital distance and correlation with vulvovaginal atrophy. *J Menopausal Med.* 2018;24(2):108-114.
46. Derogatis LR, Rosen R, Leiblum S, Burnett A, Heiman J. The Female Sexual Distress Scale (FSDS). *J Sex Marital Ther.* 2002;28(4):317-330.
47. Symonds T, Boolell M, Quirk F. Development of a questionnaire on sexual quality of life in women. *J Sex Marital Ther.* 2005;31(5):385-397.