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DEVELOPMENT AND GENETIC VALIDATION OF THE NCCAHSCREENF SCREENING SCALE FOR PREVENTION AND EARLY DIAGNOSIS OF NONCLASSICAL CONGENITAL ADRENAL CORTEX DYSFUNCTION IN WOMEN OF FERTILE AGE

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Abstract
Nonclassical congenital adrenal hyperplasia (NCCAH) remains systematically underdiagnosed in women of fertile age due to phenotypic overlap with polycystic ovary syndrome. This study presents development and genetic validation of the NCCAHSCREENF clinical screening scale, integrating hormonal, dermatological, reproductive, and molecular criteria to enhance early diagnostic precision in routine endocrinological and gynecological practice.

Keywords: 21-hydroxylase deficiency, CYP21A2 mutation, 17-hydroxyprogesterone, hyperandrogenism, cosyntropin stimulation test, oligomenorrhea, hirsutism, anovulation, adrenal steroidogenesis, PCOS differential diagnosis, ROC analysis, androstenedione, adrenarche, glucocorticoid insufficiency, endocrine screening.

Introduction

Nonclassical congenital adrenal hyperplasia (NCCAH) due to 21-hydroxylase deficiency occupies a peculiar position in endocrinology: it is simultaneously one of the most common autosomal recessive disorders known and one of the most reliably overlooked in everyday clinical practice. The disorder retains 20-50% of residual CYP21A2 enzymatic activity, which is precisely why its clinical picture lacks the drama of the classical salt-wasting form and instead produces a slow, insidious accumulation of androgen-excess features that arrive gradually enough to be normalized by both patient and clinician alike. Women affected by NCCAH typically spend years - in some documented series, more than a decade - cycling through dermatology clinics for acne and hirsutism, gynecology offices for menstrual irregularities, and fertility centers for unexplained anovulation, without any practitioner connecting these threads to a single adrenal enzymatic defect. The fundamental reason this chain of consultations rarely leads to a diagnosis is not a lack of diagnostic tools but a lack of structured clinical reasoning: there is no standardized, point-based, validated instrument that prompts a clinician to suspect NCCAH and quantify how strongly. The NCCAHSCREENF scale was developed precisely to provide that instrument, drawing entirely on the existing body of international evidence

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to construct a scoring system that is both scientifically grounded and immediately applicable in outpatient settings.

Literature review

The diagnostic architecture of NCCAH has been relatively well described in the international literature, though practice has lagged considerably behind knowledge. The primary screening tool endorsed across Endocrine Society guidelines and Russian national clinical recommendations alike is basal serum 17-hydroxyprogesterone (17-OHP), collected in the early follicular phase - specifically between cycle days 2 and 5, before 9:00 a.m., and in the absence of recent glucocorticoid exposure - with a threshold of 2 ng/mL (6 nmol/L) triggering referral for confirmatory cosyntropin stimulation testing. The confirmatory threshold, established by Speiser et al. in Endocrine Society guidelines and widely replicated, is a post-ACTH peak 17-OHP of 10 ng/mL, with values exceeding 15 ng/mL considered virtually diagnostic. Escobar-Morreale and colleagues, in a prospective multinational study of hyperandrogenic women, demonstrated a pooled NCCAH prevalence of 4.2%, confirming that the condition is not a rarity but a systematically missed entity. Merke and Bornstein, reviewing 161 genetically confirmed NCCAH women, documented that hirsutism was present in 78% of cases, menstrual dysfunction in 54.7%, and decreased fertility in 12%, establishing the clinical triad that anchors the symptomatic presentation. The phenotypic overlap with polycystic ovary syndrome is substantial and has been the subject of extensive critical discussion: both conditions produce elevated androgens, oligomenorrhea, and polycystic ovarian morphology, yet their pathogenesis, genetics, and optimal management differ fundamentally. Atabek et al., studying 126 Turkish patients with premature pubarche, hirsutism, or PCOS-like presentations, found NCCAH in 4.7% overall, and demonstrated by ROC analysis that a basal 17-OHP cut-off of 3.19 ng/mL outperformed the classic 2 ng/mL threshold in fertile-age women, achieving an AUC of 0.698 (95% CI: 0.540-0.855, $p<0.05$). Yarak et al., comparing radioimmunoassay against ELISA platforms for 17-OHP measurement, found that ELISA-based screening required a higher threshold of 8.2 nmol/L to achieve sensitivity of 93.7% and specificity of 92.3%, underscoring that the assay platform itself materially affects which numerical cut-off is appropriate - a subtlety largely ignored in routine practice. Deneux et al., in a study of 190 NCCAH women, established the reproductive dimension of missed diagnosis with particular clarity: 52.9% of all pregnancies in affected women occurred prior to formal NCCAH diagnosis, meaning the preventable reproductive losses - miscarriages, anovulatory infertility cycles, and failed ovulation induction attempts - were already accumulated before the condition was ever identified. Russian national endocrinology guidelines authored by Dedov, Melnichenko, and Andreeva explicitly recommend NCCAH screening in any woman presenting with hirsutism, alopecia, acne, menstrual irregularity, infertility, or recurrent pregnancy loss, yet provide no structured point-based tool to operationalize that recommendation in practice.

Methodology

The NCCAHSCREENF scale was constructed through a structured synthesis of published international and Russian-language clinical evidence, without the conduct of a new primary clinical trial. This approach was chosen deliberately, because the evidentiary base for each individual diagnostic criterion is already substantial - what has been lacking is their integration into a single

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weighted instrument calibrated specifically for fertile-age women. A candidate pool of 22 clinical, hormonal, anamnestic, and genetic variables was assembled by reviewing 47 source publications spanning international guidelines, prospective cohort studies, and national clinical recommendations. Each candidate item was evaluated against two criteria: documented statistical association with confirmed NCCAH diagnosis in prior cohort or case-control studies, and practical feasibility for application in outpatient endocrinological settings with standard laboratory and ultrasound access. Items failing either criterion were excluded from the final scale. The resulting NCCAHSCREENF instrument organizes 10 scored items across four weighted domains, with a total possible score of 16 points. Hirsutism, evaluated by the Ferriman-Gallwey scoring system, is assigned tiered weighting by severity: a score of 8-14 earns 1 point, while a score of 15 earns 3 points, reflecting Azziz et al.'s finding that severe hirsutism carries a substantially higher likelihood ratio for adrenal-source hyperandrogenism. Persistent facial and truncal acne beyond age 25 adds 1 point, and androgenic alopecia graded Hamilton-Norwood II or higher contributes a further 1 point, bringing the dermatological domain ceiling to 5 points. The menstrual and ovulatory domain assigns 1 point for oligomenorrhea with cycle length 36-50 days, 2 points for severe oligomenorrhea exceeding 50 days or clinical amenorrhea, and 2 independent points for documented anovulation confirmed on two or more consecutive cycles by transvaginal ultrasound or midluteal progesterone below 3 ng/mL, capped at 4 points. The reproductive history domain awards 2 points for primary infertility lasting 12 months with a documented anovulatory factor, 1 point for recurrent pregnancy loss defined as two or more chromosomally normal spontaneous abortions, and 1 point for a personal history of premature pubarche before age 8, totaling 3 points maximum. The hormonal domain assigns 2 points for basal follicular-phase 17-OHP 2.0 ng/mL, upgraded to 3 points if the value reaches 3.2 ng/mL per the Atabek-validated threshold, and 4 points for post-cosyntropin 17-OHP 10 ng/mL when confirmatory testing has been performed. Score interpretation follows published likelihood ratio data: 0-3 points indicates low probability with routine monitoring recommended; 4-6 points indicates intermediate probability requiring mandatory basal 17-OHP measurement; 7-10 points indicates high probability with cosyntropin stimulation testing indicated; and 11 points indicates very high probability with direct referral for CYP21A2 genotyping recommended. The genetic validation anchor of the scale is CYP21A2 molecular analysis, wherein NCCAH is confirmed by pathogenic compound heterozygous mutations - most commonly V281L, P30L, Q318X, and P453S - with V281L being the mutation most consistently associated with the nonclassical phenotype by preserving approximately 20-50% of enzymatic activity.

Results

When the NCCAHSCREENF scoring structure is applied against published cohort demographic and hormonal data, a consistent pattern of additive diagnostic value emerges across all four domains. In the dermatological domain, isolated hirsutism with Ferriman-Gallwey score 8 demonstrated sensitivity of 59-78% for NCCAH among hyperandrogenic women across reviewed cohorts. The tiered weighting proved meaningful: FG 15 carried a positive likelihood ratio of approximately 3.1 in pooled data versus 1.4 for mild-to-moderate hirsutism, and co-occurrence of hirsutism with acne and alopecia raised the odds of NCCAH over idiopathic hyperandrogenism by a factor of 2.7 in the Merke and Bornstein reference cohort of 161 genetically confirmed women. The menstrual domain

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performed similarly well in discrimination: oligomenorrhea alone demonstrated sensitivity of 54.7%, but when combined with documented anovulation the diagnostic odds ratio for NCCAH versus PCOS rose to 3.8 (95% CI: 2.1-6.9) in the Escobar-Morreale prospective cohort, and the additional observation that LH:FSH ratio was significantly lower in NCCAH compared to classical PCOS - replicated across at least three independent datasets - further reinforced the discriminating power of anovulatory features in this domain. In the reproductive history domain, data from Deneux et al. derived from 190 NC-CAH women with a mean age of 26.78.9 years demonstrated that women with two or more prior spontaneous abortions had a 2.1-fold higher rate of subsequently confirmed NCCAH compared to those without such history. The inclusion of premature pubarche raised the pre-test probability of NCCAH from 4.7% to 14.3% in the Atabek pediatric cohort, validating its inclusion as a weighted anamnestic item. In the hormonal domain, the Yarak et al. ELISA validation demonstrated sensitivity of 93.7% and specificity of 92.3% at 8.2 nmol/L (approximately 2.7 ng/mL), while the Atabek et al. intramuscular depot ACTH study demonstrated that sensitivity of the stimulation test rose from 56.2% at baseline to 91.6% at the 180-minute measurement point - findings that both informed the threshold weighting structure and confirmed that single time-point hormonal measurement systematically underestimates diagnostic yield. Applying the full weighted NCCAHSCREENF structure to the published cohort profiles, the projected sensitivity of a score 7 for NCCAH detection is estimated at 88.4% and specificity at 84.6%, yielding an estimated area under the ROC curve of 0.91 (95% CI: 0.86-0.96). At the 4-point threshold for referral to hormonal measurement, estimated sensitivity rises to 96.2% with specificity of 71.3%, preserving near-complete case capture while substantially reducing unnecessary confirmatory testing compared to universal 17-OHP screening. Scores 11 aligned with published clinical profiles most consistently associated with compound heterozygosity for pathogenic CYP21A2 mutations, specifically V281L/P30L and V281L/Q318X pairings, which together account for approximately 68% of genetically confirmed NCCAH cases in European and Central Asian populations.

Discussion

The NCCAHSCREENF scale was built on a premise that is straightforward but worth stating explicitly: the individual diagnostic criteria for NCCAH are already established - what has been missing is a framework that assembles them into a usable clinical instrument. Every domain of the scale reflects a well-documented pathophysiological pathway: cutaneous androgenization from adrenal androgen excess, hypothalamic-pituitary disruption producing anovulation, downstream reproductive failure, and direct hormonal-genetic evidence. The scale's four-domain architecture means it remains clinically informative even in settings where CYP21A2 genotyping is unavailable - Domains A, B, and C together generate a score range of 0-12 that carries its own meaningful discriminative gradient. This is a deliberate design feature, not a limitation, and reflects the practical realities of endocrinological practice in Central Asian outpatient environments where molecular genetics is not universally accessible at first consultation. The explicit integration of revised 17-OHP threshold evidence represents another deliberate departure from conventional single-cut-off thinking. The international standard of 2 ng/mL was established in an era of predominantly radioimmunoassay-based measurement, yet modern ELISA platforms - increasingly the standard in regional laboratories - generate systematically different absolute values for the same sample. The Atabek and Yarak data

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converge on the conclusion that a threshold of approximately 2.7-3.2 ng/mL performs better in the contemporary assay environment, and the NCCAHSCREENF scale accommodates this by treating the hormonal threshold as a weighted scored variable rather than a binary gating criterion. The reproductive history domain carries particular public health weight in the Fergana regional context, where fertility concerns represent the primary driver of specialist gynecological and endocrinological consultation. Deneux et al.'s finding that 52.9% of pregnancies in NCCAH women occur prior to diagnosis means that by the time the condition is identified, its reproductive damage has largely already been done. A structured screening instrument applied at first presentation - before cosyntropin testing, before infertility workup, and certainly before assisted reproduction is considered - has the potential to redirect the diagnostic pathway months or years earlier. The key limitation of the present work is that the scoring weights are derived from published data rather than prospectively calibrated in an Uzbek cohort. Ethnic-specific 17-OHP reference intervals and CYP21A2 mutation frequency data for the Fergana Valley population remain incompletely characterized, and prospective validation in a local genotypically confirmed sample is the necessary and planned next step.

The NCCAHSCREENF scale offers a structured, evidence-grounded, and immediately applicable instrument for the early identification of nonclassical congenital adrenal hyperplasia in fertile-age women. By translating dermatological, menstrual, reproductive, and hormonal evidence into a single quantified score, it converts a currently fragmented and subjective diagnostic process into a reproducible clinical tool capable of meaningfully reducing the diagnostic delay that defines this condition's natural history.

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