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Review Article

Late-Onset Congenital Adrenal Hyperplasia Presenting with Secondary Amenorrhoea: A Review of Published Cases

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Abstract

Background: Late-onset congenital adrenal hyperplasia due to 21-hydroxylase deficiency presents in adolescence or adult life with androgen excess and is described as a mimic of polycystic ovary syndrome.

Objective: To determine how often the condition presents with secondary amenorrhoea and whether menstrual disturbance justifies testing.

Methods: Narrative review of published cohorts, prevalence studies, genotyping series and individual case reports.

Findings: Oligomenorrhoea was the second commonest presenting complaint in a series of 220 patients, at 54%. Yet among 1,564 women tested, oligomenorrhoea was present in 20.3% of the 74 with confirmed disease against 40.1% of those without. No cohort reports secondary amenorrhoea as a presenting complaint with its own denominator.

Conclusions: The published record supports hirsutism rather than cycle disturbance as the reason to test, and genotyping to confirm; it does not support any frequency for secondary amenorrhoea.

Keywords: Congenital adrenal hyperplasia; 21-hydroxylase deficiency; Secondary amenorrhoea; Hirsutism; Polycystic ovary syndrome

Introduction

Late-onset, or non-classic, congenital adrenal hyperplasia due to 21-hydroxylase deficiency is a partial enzyme defect that spares the neonate and declares itself, if at all, in adolescence or adult life as androgen excess [1,2]. Its clinical vocabulary was fixed early: the hormonal reference data that separated the non-classic form from the classic and from the heterozygous state were published four decades ago [3], and the first phenotypic series followed shortly after [4]. Since then the condition has been described, repeatedly, as a mimic of polycystic ovary syndrome [5], and menstrual disturbance has become one of the standard reasons to test for it.

This review examines whether that reasoning survives inspection. It is a review of published records only; no patient of the authors is described anywhere in it, and every clinical particular below is drawn from a named publication. The specific question posed by the title — how often late-onset congenital adrenal hyperplasia presents with secondary amenorrhoea — cannot in fact be answered from the published literature, and saying so is one of the two useful things this paper can do.

The other is to set out a contradiction that the review literature has smoothed over. Menstrual disturbance is the second commonest presenting complaint in reported cohorts of non-classic disease. Yet in the only large series to test the question directly, oligomenorrhoea was significantly less common among the women who proved to have the disorder than among those who did not. Both statements are true, they are not reconcilable as a disease association, and the resolution — referral bias — changes whom a clinician should test.

Prevalence, and the Numbers That Cannot Be Traced

The prevalence figures in general circulation do not withstand comparison with their stated source. The original family-based study, using HLA-B genotype

segregation with hormonal testing and with families rather than a screened population as its denominator, reported non-classic 21-hydroxylase deficiency in 3.7% of Ashkenazi Jews, 1.9% of Hispanics, 1.6% of Yugoslavs, 0.3% of Italians and 0.1% of diverse non-Jewish Caucasians, alongside a classic-disease figure of 1 in 8,000 births [6]. The widely repeated reciprocals of 1 in 40 for Hispanics and 1 in 50 for Slavs do not correspond to 1.9% and 1.6%, and the ubiquitous figure of 1 in 100 in the general population has no denominator anywhere in that paper; nor does the assertion, common in review introductions, that the condition affects between 1 in 500 and 1 in 100 births worldwide [7]. These should be treated as untraceable rather than repeated.

Molecular estimation gives firmer ground. Direct CYP21A2 genotyping of 200 unrelated healthy Ashkenazi Jews and 200 random United States Caucasians found non-classic carrier rates of 15% (95% CI 10.4-20.7) and 9.5% (95% CI 5.8-14.4) respectively, a difference that was not significant ($P = 0.13$; $N = 400$) [8]. Among women presenting with androgen excess the pooled worldwide prevalence is 4.2% (95% CI 3.2-5.4) [9]; a prospective Spanish series of 270 consecutive unselected hyperandrogenic women found 6 (2.2%; 95% confidence limits 0.5-3.9) [10], consistent with earlier prospective screening in hyperandrogenic women [11]. Among 2,409 women referred for cosyntropin testing the yield was 4.7% by radioimmunoassay ($n = 1,564$) and 7.5% by ELISA ($n = 845$) [12]. In an unselected Chinese population with suspected polycystic ovary syndrome, long-read sequencing found a prevalence of 0.73 per 1,000 (1 of 1,372; 95% CI 0.02-4.05 per 1,000) with any CAH-variant carriage in 4.45% (61 of 1,371) [13]. Prevalence therefore tracks the referral filter almost exactly, and a figure quoted without its sampling frame conveys very little. The gap between a 4.2% pooled prevalence in hyperandrogenic women and 0.73 per 1,000 in an unselected population with suspected polycystic ovary syndrome is not a disagreement between studies but a description of two different populations.

Menstrual Disturbance as a Presenting Complaint

The presenting-feature data come from a small number of cohorts. In an international multicentre series of 220 patients with non-classic disease diagnosed on basal or stimulated 17-hydroxyprogesterone above 30.3 nmol/l, the features at presentation among those aged 10 years and over were hirsutism 59%, oligomenorrhoea 54%, acne 33%, infertility 13%, clitoromegaly 10%, alopecia 8%, primary amenorrhoea 4% and premature pubarche 4%; below 10 years, 92% presented with premature pubarche [14]. The French cohort of 161 unrelated women is quoted by two independent reviews as showing hirsutism in 78%, menstrual dysfunction in 54.7% and decreased fertility in 12% [15,7]; these figures were not verifiable in the primary report [16] and are given here at second hand. Among 280 molecularly confirmed individuals, 63.2% of females older than 8 years had a polycystic-ovary-like phenotype [17].

Two cautions attach to these numbers. First, the primary-amenorrhoea proportion is unstable: the multicentre series gives 4% for all patients aged 10 years and over, while a review restates a higher age-banded figure attributed to the same cohort, and the two cannot be reconciled from the published abstracts. Second, and more importantly for the present title, none of these series reports secondary amenorrhoea as a distinct presenting complaint with its own denominator. The categories used are oligomenorrhoea, primary amenorrhoea, and undifferentiated menstrual dysfunction. The absence of a secondary-amenorrhoea denominator anywhere in the cohort literature is itself a finding, and it means that the frequency implied by the title of this review is not currently a knowable quantity.

The Contradiction: Presenting Complaint Against Diagnostic Yield

The largest series to compare symptoms between women who tested positive and negative reverses the expected direction. Among 1,564 women assessed by radioimmunoassay, oligomenorrhoea was present in 614

(40.1%) of those in whom non-classic disease was not confirmed but in only 15 (20.3%) of the 74 in whom it was ($P < 0.001$); amenorrhoea was present in 376 (25.2%) against 17 (23.0%), which did not differ ($P = 0.79$). In the ELISA cohort of 845 women the corresponding figures were 314 (40.2%) against 21 (33.3%) for oligomenorrhoea ($P = 0.35$) and 201 (25.6%) against 10 (15.9%) for amenorrhoea ($P = 0.11$) [12]. Genotyping in a suspected polycystic ovary syndrome population points the same way: the non-classic carrier rate was 1.88% in women with irregular menstruation and 2.04% in those with regular cycles ($P = 0.751$; $N = 946$), whereas it was 3.90% in those with hirsutism against 0.37% in those without ($P < 0.001$) [13].

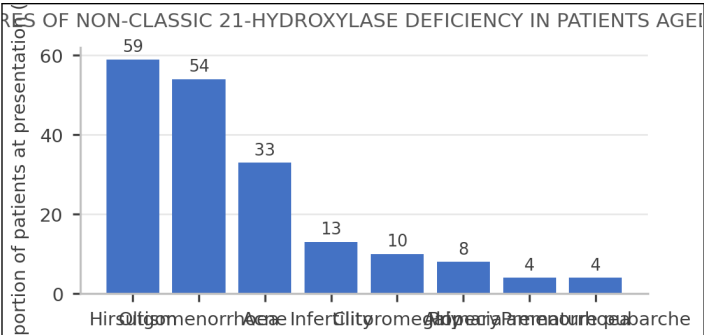


Figure 1: Presenting features in an international multicentre series of patients with non-classic 21-hydroxylase deficiency aged 10 years and over, in whom oligomenorrhoea was the second commonest complaint, N = 220 [14].

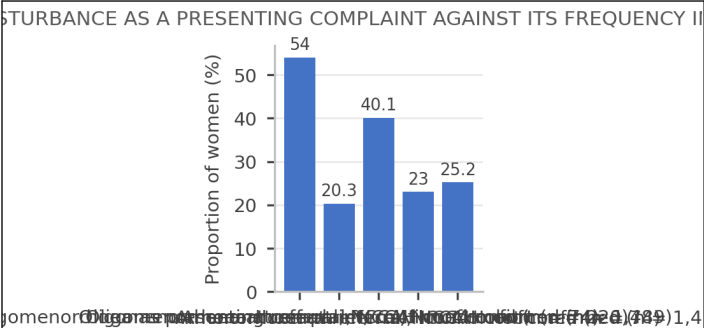


Figure 2: Oligomenorrhoea as a presenting complaint in confirmed cases (N = 220) set against menstrual symptom frequency in women confirmed and not confirmed on cosyntropin testing, where oligomenorrhoea was significantly less common in the confirmed group, N = 1,564 tested [14,12].

The contradiction is therefore genuine and should not be dissolved. Menstrual disturbance is the second

commonest presenting complaint in cohorts of confirmed cases, at 54% and 54.7%, and simultaneously it is not more common in confirmed cases than in the women tested alongside them. The resolution is that the cohort figures describe who is referred and diagnosed, not what the disease does. Women reaching an endocrine or hirsutism clinic with cycle disturbance are enriched for it by the referral pathway; once a consecutively tested population is examined, the signal disappears. The same referral effect explains why a review synthesis places menstrual irregularity at a far lower band in non-classic disease than the cohort series do, a discrepancy whose primary source could not be traced. The practical consequence is that hirsutism, not cycle disturbance, is the symptom that should raise the pre-test probability [13]. A clinician deciding whom to test should read the cohort figures as a description of a referred population and not as a likelihood ratio, because used as the latter they will generate mostly false positives.

Diagnostic Thresholds and Their Failure Modes

The recommended screening test is an early-morning follicular-phase basal 17-hydroxyprogesterone with a threshold of 2 ng/ml (6 nmol/l), and a value of 10 ng/ml (30 nmol/l) basally or after cosyntropin is treated as diagnostic [9,18]. Both ends of that scheme fail in defined ways. The basal threshold produces false negatives in a minority of genotype-confirmed women, a proportion reported only at review level and therefore not quantified here [7]. Assay dependence is measurable: the optimal basal cut-off was 6.1 nmol/l for radioimmunoassay (sensitivity 93.2%, specificity 91.7%, negative predictive value 99.6%, positive predictive value 35.8%; n = 1,564) and 8.2 nmol/l for ELISA (93.7%, 92.3%, 99.5% and 49.6%; n = 845), and applying the radioimmunoassay cut-off to ELISA left sensitivity unchanged but dropped specificity to 84.5% (P < 0.001) [12]. A locally derived receiver-operating-characteristic threshold of 1.7 ng/ml achieved 100% sensitivity and 88.6% specificity with an

area under the curve of 0.97 (95% CI 0.934-1.008) in 270 women [10].

Table 1: Diagnostic thresholds for 17-hydroxyprogesterone and CYP21A2 testing, with reported performance and the pitfall stated by the source study.			
Test and threshold	Reported performance	N	Stated pitfall
Basal 17-OHP 2 ng/ml (6 nmol/l)	Conventional screening cut-off	Review level	A minority of genotype-confirmed women fall below it
Basal 17-OHP by RIA, 6.1 nmol/l	Sens 93.2%, spec 91.7%, NPV 99.6%, PPV 35.8%	1,564	PPV about one in three; most positives are not NCCAH
Basal 17-OHP by ELISA, 8.2 nmol/l	Sens 93.7%, spec 92.3%, NPV 99.5%, PPV 49.6%	845	RIA cut-off applied to ELISA drops specificity to 84.5%
Basal 17-OHP, local ROC cut-off 1.7 ng/ml	Sens 100%, spec 88.6%, AUC 0.97	270	Cut-off must be re-derived in each laboratory
Post-cosyntropin 17-OHP 30 nmol/l	Confirmatory in guidelines	40	Only 5 of 21 meeting it (24%) were confirmed
Post-cosyntropin 17-OHP 45 nmol/l	Biallelic variants generally identifiable	Review level	Grey zone of 30-45 nmol/l still holds true cases
CYP21A2 genotyping	21 of 45 genotypes (46.7%) correlated	1,507 families	Concordance is cohort-dependent and disputed
Post-ACTH 21-deoxycortisol 0.55 ng/ml	Higher in heterozygotes but overlapping	330 relatives	12 heterozygotes fell below it; cannot replace genotyping

The confirmatory threshold fails in the opposite direction. Of 40 consecutive hyperandrogenic women, 21 had basal or post-ACTH 17-hydroxyprogesterone of 30 nmol/l or above, yet urinary steroid profiling with genetics confirmed non-classic disease in only 5 of those 21 (24%); four were heterozygotes and twelve carried no CYP21A2 mutation at all [19]. Biallelic variants are generally identifiable above 15 ng/ml (45 nmol/l), leaving a grey zone between 10 and 15 ng/ml in which genotype-confirmed cases nonetheless sit [9]. Genotyping itself is not a clean arbiter: only 21 of 45 genotypes (46.7%) in 1,507 affected families yielded a phenotypic correlation, with good concordance for salt-wasting and non-classic

disease and poor concordance for simple virilising forms [20,21], and other cohorts report far higher overall concordance, so no single figure should be quoted. Among 124 genotyped probands, one severe mutation was present in 63.7%, with higher hormonal values but no clinical difference from those carrying two mild alleles [16].

What the Published Cases Show

Eight published records with a menstrual or hyperandrogenic presentation were identified. Two are full peer-reviewed reports: a 27-year-old with two years of secondary amenorrhoea, hirsutism and clitoromegaly whose stimulated 17-hydroxyprogesterone rose from 2.16 to 30.6 ng/ml and who improved on dexamethasone with an antiandrogenic contraceptive, though her menstrual outcome was not stated [22]; and a woman presenting with polymenorrhagia since menarche and markedly elevated 17-hydroxyprogesterone, whose hirsutism and clitoromegaly were unchanged at six months on dexamethasone [23]. Three further records are conference abstracts and one is available only as a title; they are listed for the presentation and label they document and no clinical detail beyond that should be attributed to them.

Two cases carry the most instruction. A 21-year-old presented with isolated hirsutism, no virilisation and entirely regular cycles, with 17-hydroxyprogesterone of 579.56 ng/dL rising above 1,000 ng/dL after cosyntropin, and treatment was deliberately deferred [24] — the presentation that the menstrual framing would have missed entirely. The second is a 36-year-old with infertility labelled as non-classic disease on a post-cosyntropin 17-hydroxyprogesterone of 31.8 ng/ml, in whom CYP21A2 testing was negative, dexamethasone failed to suppress, and computed tomography revealed an adrenal tumour cured by adrenalectomy. A fully diagnostic stimulated value was a false positive, and only genotyping and a failed suppression test exposed it.

Treatment and Reproductive Outcome

Table 2: Published records of late-onset congenital adrenal hyperplasia with a menstrual or hyperandrogenic presentation, including two instructive counter-cases; not stated indicates the record is silent.				
Report	Age and presenting complaint	Prior label	17-OHP and genotype	Treatment and outcome
Ali 2024	27; secondary amenorrhoea 2 years, hirsutism	Not stated	2.16 to 30.6 ng/ml post-ACTH; not genotyped	Dexamethasone plus antiandrogenic COC; hirsutism resolved, menses not stated
Rizwan 2015	Adult, age not stated; polymenorrhagia since menarche	Not stated	Markedly high, values not stated; not genotyped	Dexamethasone; hirsutism and clitoromegaly unchanged at 6 months
Ramos Moreno 2025 (abstract)	32; oligomenorrhoea and infertility	PCOS	Basal 698, stimulated 1,051 ng/dL; not reported	Hydrocortisone 15 mg daily; spontaneous conception
SAT-478 2025 (abstract)	31; irregular menses, hirsutism	Not stated	Stimulated 3,341.85; basal normalised on repeat; not reported	Declined steroid; spironolactone; outcome not stated
Endocrine Abstracts WD4.4 (abstract)	36; irregular periods, hirsutism, weight gain	Investigated for years, PCOS overlap	17-OHP 13 nmol/l; CYP21A2 variants confirmed	Dexamethasone 0.25 mg nocte, later stopped; metabolic cost
Kondo 2026 (title only)	Not stated	PCOS for about a decade	Not stated	Not stated
Navabi 2025 (counter-case)	21; isolated hirsutism, regular cycles	None	579.56 ng/dL, stimulated over 1,000; not genotyped	Treatment deferred; symptom-driven follow-up
Adrenal tumour case (counter-case)	36; infertility 4 years	NCCAH	Post-cosyntropin 31.8 ng/ml; CYP21A2 negative	Adrenalectomy; 17-OHP and cosyntropin response normalised

Glucocorticoid does restore cycles in those with established disturbance. Of 38 patients with oligo-amenorrhoea before treatment, 27 (71%) achieved regular cycles on hydrocortisone at a mean dose of 17.5 (SD 7.5) mg daily, and of 11 with amenorrhoea only 3 remained amenorrhoeic [9,25]. Fertility is nevertheless largely preserved without it: among 190 women, 187

pregnancies occurred in 85 and 141 births in 82, with 99 of 187 pregnancies (52.9%) conceived before the diagnosis was made and 83% of pregnancies obtained within one year [25]. Miscarriage rates fell from 26.3% without glucocorticoid to 6.5% with it in that cohort [25], and from 35 of 138 (25.4%) before maternal diagnosis to 4 of 65 (6.2%) after it in an international cohort of 203 pregnancies in 101 women ($P < 0.002$) [26]. A third cohort did not reproduce the effect: among 75 women with 187 pregnancies, first-trimester miscarriage occurred in 38 (20.3%) at a similar rate whether or not glucocorticoid was given, and time to conception was 4.0 (SD 7) months untreated against 3.3 (SD 3) treated ($P = 0.43$) [27].

Offspring risk, not cycle control, is the strongest argument for making the diagnosis: 4 of 162 live births (2.5%; 95% CI 0.7-6.2) had classic disease and 24 of 162 (14.8%; 95% CI 9.0-20.6) had non-classic disease [26], which with the carrier frequencies above [8] supports genotyping the partner of a woman carrying a severe allele [16]. Current guidance does not recommend daily glucocorticoid merely to regulate the cycle, favouring antiandrogenic contraception for menstrual irregularity [18,7]; a head-to-head comparison of cyproterone acetate with hydrocortisone exists [28], but no trial with a menstrual endpoint settles the choice.

Conclusion

Menstrual disturbance is common among women given this diagnosis and is not, in consecutively tested populations, a discriminating reason to suspect it. Secondary amenorrhoea in particular has never been reported as a presenting complaint with its own denominator, so the frequency implied by this review's title remains unmeasured. Hirsutism should drive testing; the basal threshold should be derived locally and interpreted by assay; a diagnostic stimulated value should not close the differential without genotyping; and the diagnosis, once made, matters more for offspring risk and miscarriage than for the cycle itself.

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