17-Hydroxyprogesterone

1 Name and description of analyte

1.1 Name of analyte
17-Hydroxyprogesterone (17-OHP).

1.2 Alternative names
17α-hydroxyprogesterone, 17-OH progesterone, 17-hydroxypregn-4-ene-3,20-dione.

1.3 NLMC code (to follow)

1.4 Description of analyte
17-Hydroxyprogesterone ($C_{21}H_{30}O_3$; MW = 330.46 Da) is an endogenous progestogen produced from 17-hydroxypregnenolone and progesterone through the actions of 3β-hydroxysteroid dehydrogenase and 17-hydroxylase, respectively. 17-OHP synthesis is stimulated by pituitary adrenocorticotrophic hormone (ACTH) as part of the hypothalamic–pituitary–adrenal (HPA) axis.

1.5 Function(s) of analyte
17-Hydroxyprogesterone is primarily produced within the *zona fasciculata* of the adrenal cortex; however, it can also be produced by the corpus luteum, gonads, and placenta. 17-OHP is an intermediate in the production of cortisol in the *zona fasciculata*, and an intermediate in the production of adrenal androgens in the *zona reticularis* (via 17,20 lyase) and 17α-hydroxyallopregnanolone (via 5α-reductase). In addition, 17-OHP is a relatively weak agonist of the progesterone receptor, a partial agonist of the glucocorticoid receptor, and an antagonist of the mineralocorticoid receptor.

2 Sample requirements and precautions

2.1 Medium in which measured
17-hydroxyprogesterone is predominantly measured in serum or EDTA or heparinised plasma; however, saliva, hair, and dried blood spot measurements can also be performed.

2.2 Precautions re: sampling, handling etc.

- Concomitant corticosteroid treatment can suppress 17-OHP.
- Serum and plasma samples should be separated upon receipt.
- Saliva samples should be frozen to precipitate salivary glycoproteins.
- Neonatal samples for the diagnosis of suspected congenital adrenal hyperplasia (CAH) should be taken prior to the administration of exogenous corticosteroids (where possible).
- Adult/adolescent female patient samples should be taken at early or mid-follicular menstrual phases, as 17-OHP concentrations are higher post-ovulation
- Samples for the identification of non-classical CAH (NC-CAH) in a female patient should be taken between 08:00 and 10:00 in the first five days following the beginning of the menstrual period.
- 17-hydroxyprogesterone measurement, 30–60 minutes following ACTH stimulation may be required to detect cases of NC-CAH as basal concentrations may be within the reference range. With low-dose ACTH stimulation tests, samples must be taken earlier, as 17-OHP concentrations peak at 10 min and return to baseline at 30 min.

3 Summary of clinical uses and limitations of measurements

3.1 Uses

The measurement of 17-OHP is most commonly used for the investigation of CAH, as its accumulation is associated with deficiencies of several enzymes involved in steroid biosynthesis – the most common of these being 21-hydroxylase (CYP21A2) deficiency.

3.2 Limitations

The analysis of circulating 17-OHP is hindered by the diurnal variation in its production (concentrations being highest in the morning). As a consequence, dynamic function testing of the adrenal response to synthetic ACTH – and subsequent simultaneous measurement of 17-OHP and cortisol – aids result interpretation and the differentiation between subtypes of CAH. As with cortisol measurement, however, 17-OHP concentrations are also affected in neonates by birth weight, gestational age, and assay interference by fetal steroids.

4 Analytical considerations

4.1 Analytical methods

4.1.1 Chromatographic

Both GC-MS and LC-MS/MS methods have been described. These methods have increased sensitivity and the ability to distinguish 17-OHP from other similar metabolites. GC-MS methods are typically labour-intensive and time-consuming and are less frequently performed although less prone to interferences. Both methods involve sample extraction prior to analysis.

4.1.2 Immunoassay

Radioimmunoassay has been a historically popular method for the measurement of 17-OHP. Displacement from binding proteins, through the use of danazol, must occur prior to the measurement of 17-OHP using specific targeted antibodies. Cross-reactivity occurs frequently with this method, particularly with steroids from the fetal adrenal zone.

4.2 Reference method

No reference method has been defined.

4.3 Reference materials

No reference material is available.

4.4 Interfering substances

11-deoxycorticosterone is a known isobaric interfering compound in LC-MS/MS assays. Fetal adrenal steroids and other steroid metabolites can interfere with immunoassay measurements.

4.5 Sources of error

17-hydroxyprogesterone concentrations are elevated in the morning due to diurnal variation of the analyte. Concentrations can also vary throughout the month in females, with the highest concentrations present after ovulation. Concomitant treatment with corticosteroids can suppress 17-OHP concentrations in CAH patients to within the reference range.

5 Reference intervals and variance

5.1 Reference interval (adults)

Population	*Basal (nmol.L^{-1})*	*30 min post-ACTH stimulation (nmol.L^{-1})*	*Assay*
Male (> 16 years)	1.2–5.0	3.0–10.0	GC-MS
Female (follicular phase)	1.0–4.5	2.0–8.0	GC-MS
Female (luteal phase)	1.0–6.0	2.0–10.0	GC-MS

5.2 Reference intervals (others)

Population	*Basal (nmol.L^{-1})*	*30 min post-ACTH stimulation (nmol.L^{-1})*	*Assay*
Male/female infant (≤ 5 days)	< 3.0	< 8.0	GC-MS
Male/female adolescent (≤ 16 years)	< 5.0	-	GC-MS

5.3 Extent of variation

5.3.1 Interindividual CV (RIA)
50.4 % (Male)
54.5% (Female)

5.3.2 Intraindividual CV (RIA)
19.6 %

5.3.3 Index of individuality (RIA)
0.39 (Male)
0.36 (Female)

5.3.4 CV of method
GC-MS: 6.3 %
RIA: 6 %
LC-MS/MS: 5.5 %

5.3.5 Critical difference
56.8 % (RIA)

5.3.6 Sources of variation
Diurnal variation, menstrual cycle phase, gestational age and birth weight (see sections 2.2, 3.2, and 5.1.1)

6 Clinical uses of measurement and interpretation of results

6.3 Indications and interpretation
17-hydroxyprogesterone measurement can aid in the investigation of patients with disorders of sexual differentiation, ambiguous genitalia, clitoromegaly, salt-wasting dehydration, symptoms of androgen excess, and premature adrenarche/precocious puberty. 17-hydroxyprogesterone measurements, along with measurements of renin, can also be used for the monitoring of hydrocortisone replacement in these patients. A normal basal 17-OHP concentration does not exclude non-classical CAH.

6.4 Confounding factors
Care should be taken if measurement of 17-OHP is used for monitoring purposes as assays perform differently and may yield different results for the same patient. Initiation of hydrocortisone treatment prior to sampling can lead to complete suppression of 17-OHP in a child with 21-hydroxylase deficiency and therefore a false negative result.

7 Causes of abnormal results

7.1 High values

7.1.1 Causes

Plasma 17-OHP concentrations are elevated in congenital adrenal hyperplasia due to CYP21A2, CYP11B1, and HSD3B2 deficiency – the latter the result of HSD3B1 isoenzyme activity. Defects in cytochrome P450-oxidoreductase and cytochrome b5, which form part of the electron transport chain for CYP21A2 and CYP17, can also cause a functional deficiency of these enzymes, and can lead to increased concentrations of 17-OHP. Non-classic CAH is typically a result of a partial enzyme deficiency such that cortisol production is maintained at the expense of excess androgen production. Enzyme activity can be reduced to approximately 50% of normal, resulting in increased plasma concentrations of 17-OHP. Heterozygotes for 21-hydroxylase deficiency can have an increased response to tetracosactrin ('Synacthen') stimulation, but usually <30 $nmol.L^{-1}$. Transiently raised 17-OHP is often seen in premature neonates. Plasma17-OHP concentrations may be raised in adrenal tumours and, less commonly, ovarian tumours.

7.1.2 Investigation

Urine steroid profiling (USP) can provide confirmation for a wide range of steroid metabolic enzymatic deficiencies and is a useful tool for the investigation of suspected CAH. With 21-hydroxylase deficiency, there is typically elevated urinary preganetriol and 11-oxo-pregnanetriol excretion, and with 11β-hydroxylase deficiency, typically raised urinary tetrahydro-11-deoxycortisol excretion. If 11β-hydroxylase deficiency is suspected, measurement of serum 11-deoxycortisol may also aid in diagnosis. If a tumour is suspected, 17-OHP concentrations may not respond or may partially respond to administration of dexamethasone, therefore indicating an ectopic source of its production. USP and imaging studies will aid in the confirmation of this diagnosis.

7.2 Low values

7.2.1 Causes

17-hydroxyprogesterone is present in the plasma at very low concentrations in health. As a result, there is no pathological cause of a low value; however, steroid treatment can suppress 17-OHP concentrations, as can a lack of pituitary function.

7.2.2 Investigation

Not applicable.

8 Performance

8.1 Classical CAH (> 80 $nmol.L^{-1}$)

Sensitivity: 100%
Specificity: 99.6%
Positive predictive value (PPV): 2.2%
Negative predictive value (NPV): 100%

8.2 NC-CAH (> 10.6 $nmol.L^{-1}$)

Sensitivity: 91%
Specificity: 91%
Positive predictive value (PPV): 59%
Negative predictive value (NPV): 99%

9 Systematic reviews and guidelines

9.1 Systematic reviews

Honour JW. 17-Hydroxyprogesterone in children, adolescents and adults. Ann Clin Biochem 2014;51(4):1–17.

9.2 Guidelines

Endocrine Society. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95(9):4133–4160.

9.3 Recommendations

- Barra CB, Silva IN, Pezzuti K, Januário JN. Neonatal screening for congenital adrenal hyperplasia. Rev Assoc Med Bras 2012;58(4):459–464.
- Taboada GF, Texeira RJ, Correa FHS *et al.* Sensitivity, specificity, and predictive value of baseline 17-hydroxyprogesterone levels in the diagnosis of nonclassic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Arq Bras Endocrinol Metab 2003,47(5):552–557.
- Rico C, Arbos MA. Quality goals for hormone testing. Ann Clin Biochem 1990;27:353–358.
- Rumsby G, Avey CJ, Conway GS, Honour JW. Genotype-phenotype analysis in late onset 21-hydroxylase deficiency in comparison to the classical forms. Clin Endocrinol 1998, 48:707–711.

10 Links

10.1 Related analytes

None

10.2 Related tests

1. Serum sodium (low), potassium (high), and glucose (low) measurement provide evidence supportive of a diagnosis of adrenal hypofunction.
2. Serum ACTH and cortisol measurement can be used to differentiate between primary and secondary adrenal insufficiency.
3. Renin measurement (alongside serum electrolyte measurements) is useful for the assessment of patients' ability to retain sodium and excrete potassium and to monitor fludrocortisone replacement.
4. Androstenedione can be used to aid the differential diagnosis of different enzyme deficiencies (suppressed with CYP17A2 deficiencies and elevated with HSD3B2, CYP11B1, and CYP21A2 deficiencies).
5. 21-Deoxycortisol and its metabolite, 11-oxo-pregnanetriol, can also be assayed as a specific marker of CYP21A2 deficiency.
6. Urinary steroid profiling can detect a larger number of steroid metabolites.

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