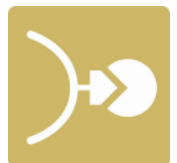


17-OH-Progesterone in Serum and Saliva



1. Introduction	3
1.1. 17-OH-Progesterone - Physiology	3
1.2. Indication for 17-OH-P determinations - Congenital Adrenal Hyperplasia	3
1.2.2. <i>Typical CAH symptoms</i>	4
1.2.2. <i>Monitoring of the therapy</i>	4
2. 17-OH-Progesterone ELISA in Serum; RE52071	6
2.1. Normal values for serum	6
2.2. Age dependence and diurnal rhythm	6
2.3. Clarification of positive samples	9
2.4. IBL International 17-OH-Progesterone ELISA – Test characteristics.....	10
2.5. Method comparisons with reference methods	11
2.5.1. <i>Method comparison with LC-MS</i>	11
2.5.2. <i>Method comparison with GC-MS</i>	12
3. 17-OH-Progesterone ELISA in Saliva; RE52271	13
3.1. Normal values in saliva	13
3.2. Age and gender dependency	13
3.3. Diurnal rhythm	14
3.4. Menstrual cycle	16
3.5. IBL International 17-OH-Progesterone Saliva ELISA – Test characteristics	17
3.6. Method comparison with the reference method LC-MS.....	18
4. Literature	19

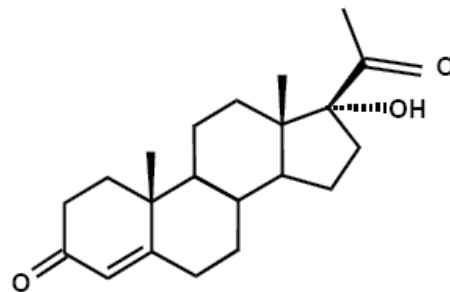
1. Introduction

1.1. 17-OH-Progesterone - Physiology

17-OH-Progesterone (17-OH-P) is a C21-Steroid mainly produced from Progesterone in the adrenal cortex. In healthy men, it is additionally synthesized as a precursor of Testosterone in the testes. In healthy women, 17-OH-P is produced in small quantities as a precursor of Estradiol in the ovary.

17-OH-P is also an intermediate product in the synthesis of other adrenal-cortical steroids as Cortisol and Aldosterone.

The synthesized hormones are released directly to the blood and circulate, in vast majority, bound to a carrier protein. In plasma, up to 55% of 17-OH-P is slightly bound to albumin, 41% is bound to Corticosteroid Binding Globulin (CBG) and in a small quantity to Sexual Hormone Binding Globulin (SHBG) (1). Bound steroidal hormones are biologically inactive.



1.2. Indication for 17-OH-P determinations - Congenital Adrenal Hyperplasia

The major clinical importance of 17-OH-P is related to the diagnosis and therapeutic monitoring of Congenital Adrenal Hyperplasia (CAH) (2). Different genetic enzymatic defects are summarized under CAH, related to the biosynthesis of Cortisol in the adrenal cortex. All these defects have in common that the necessary quantity of Cortisol can only be produced by an excessive production of ACTH and the subsequent hyperplasia in the adrenal cortex.

The most common form of CAH is a defect in the activity of 21-Hydroxylase. This leads to an interruption in the production of Cortisol and Aldosterone from 17-OH-P. Therefore, the concentration of 17-OH-P increases dramatically. The low Cortisol concentration leads to a low feedback in the regulatory system and to a chronic increase in the secretion of ACTH. The consequence is adrenal hyperplasia and high production of steroids, which can not be enzymatic hydrolyzed. The resulting high concentration of androgens (Androstenedione, Testosterone) yields to deficiencies in the gender differentiation and to clinical symptoms of virilization (3). In this case when deficiencies in the production of Cortisol are combined with deficiencies in the production of Aldosterone, the consequences in newborns will be a severe lack of control in the regulation of mineral and water balance. This is called CAH with salt lost syndrome. If this is not treated, it may lead to death.

Depending on the severity of the enzymatic defect, the CAH related symptoms externalize either during the puberty or later or in women, it can be detected only during infertility diagnosis (late-onset CAH).

1.2.2. Typical CAH symptoms

The following table summarizes the effects of CAH (2):

<p>Abnormal production of glucocorticoids:</p> <ul style="list-style-type: none"> - Tiredness, apathy, low stress tolerance - Hypoglycemia, higher predisposition to infections - Addison-like crisis - Hyperplasia of adrenal cortex
<p>Abnormal production of mineralocorticoids:</p> <ul style="list-style-type: none"> - Hyponatraemia - Salt lost syndrome - Metabolic acidosis - Hypotension
<p>Excessive production of androgens:</p> <p>Prenatal:</p> <ul style="list-style-type: none"> - Virilization, deformation of the outside female genitals <p>Postnatal:</p> <ul style="list-style-type: none"> - Praecox pseudo puberty in both genders - Accelerated bone aging - Higher growth rate

Due to the fact that CAH is one of the most common congenital diseases (worldwide ~1:12,000) (4), the diagnosis should take place as part as a neonatal screening. This consists in the quantification of 17-OH-P from a dried blood spot. Further quantifications of 17-OH-P in serum can be used as a confirmatory method. The quantification of 17-OH-P in serum can also be used for a later diagnosis. Not treated CAH patients present levels between 2 to 1000 times higher than healthy people.

1.2.2. Monitoring of the therapy

The treatment of CAH is based on the adequate replacement of the deficient hormones.

Hydrocortisone is used as glucocorticoide, Prednisone and Dexamethason can be also used but only once the growth is complete.

The dosage is around 15 to 20 mg/Hydrocortisone per m² body surface. Normally it is split in 3 doses a day, around 50% is administrated during the morning and the rest during noon and evening.

0.025 to 0.1 mg/day of Fludrocortison (Astonin H) is used as mineralocorticoid. During the first months of life, a supplement of NaCl is recommended to compensate the salt lost syndrome.

A problem in the treatment of CAH in children and young people with this chronic sickness is the lack of cooperation. It is difficult to convince parents and patients about the importance of a regular medication intake and monitoring controls. The fear of children of blood withdrawal produces stress situations, which lead to higher values of 17-OH-P. Due to the lack of direct pain, many patients are not aware of the consequences of a non-proper therapy but until a later critical point. Nevertheless, patients suffering from insufficiency and under acute stress situations may find themselves at high risk and may even die.

The quantification of 17-OH-P in saliva is an alternative for all, who may take part of a monitoring therapy and when the dosage must be adjusted according to individual needs.

The saliva from CAH patients presents also very high 17-OH-P values, which may be even 100 times higher than those of the normal population.

Based on the study of several patients with different growth rates, reference values in saliva during substitution therapy were determined for a clinical orientation. In the following table, 3 situations: strong, normal and inadequate suppression of the adrenal cortex (5), are detailed:

Table 1: Reference ranges of 17-OH-P in morning, noon and evening saliva (pg/mL) during treatment. Dependency with adrenal cortex suppression in children with CAH (1-17 years old) according to (5).

Suppression of adrenal cortex	17-OH-P in Saliva (pg/mL)		
	Morning	Noon	Evening
Too high	< 200	< 100	< 50
Right	200 – 1000	100 – 300	50 – 100
Too low	> 1000	> 300	> 100

The data provided by the menstruation-related 17-OH-P values, can be used as an additional criteria for an optimal setting of corticoids based therapy for CAH patients, who are willing to have children and undergo a fertility therapy.

The concentration of 17-OH-P in saliva from CAH patients showed values, which are not comparable to those corresponding to a normal cycle (6). There was no evidence of differences between the post-menstrual and pre-menstrual halves of cycle. Although they present high oscillations, all values in saliva from CAH patients are quite high and above those corresponding to the luteal phase in healthy women.

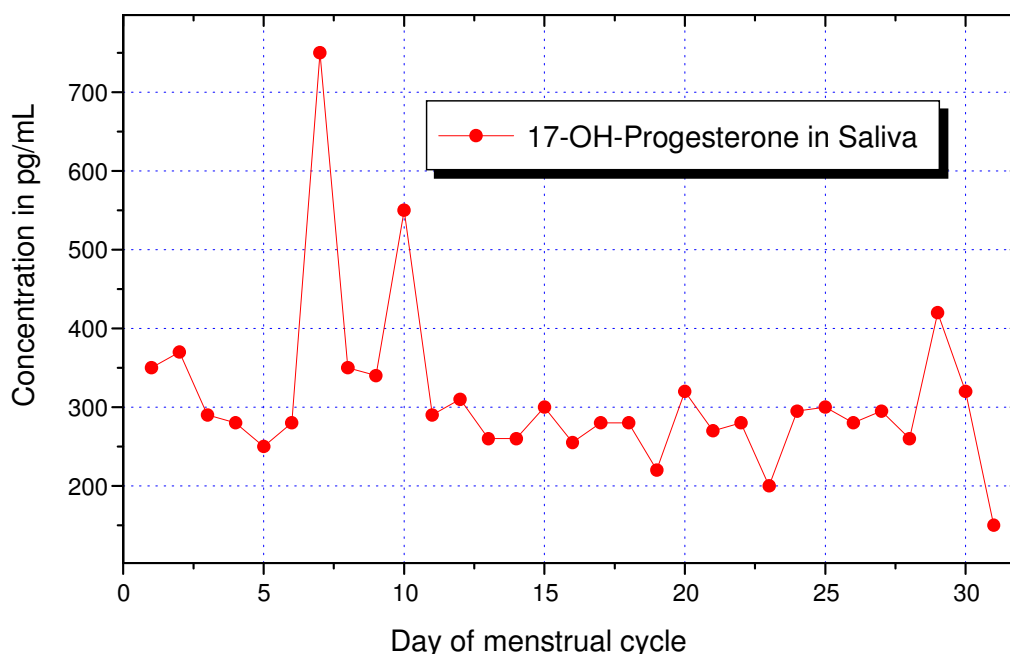


Fig. 1: Profile of 17-OH-P in morning saliva of young CAH patients (n=10) during the menstrual cycle (mean values), according to (6). The goal of the therapy, according to Höpffner (7), is to control the dosage in order to achieve levels of 17-OH-P in saliva lower than 600 pmol/L (=200 pg/mL) during the menstruation cycle.

2. 17-OH-Progesterone ELISA in Serum; RE52071

2.1. Normal values for serum

The concentration of 17-OH-P in serum depends on age, daytime, gender, phase of the menstrual cycle and pregnancy.

Normal values are also influenced by physical and psychological stress.

2.2. Age dependence and diurnal rhythm

The concentration of 17-OH-P increases during the first months of life (Fig. 2) and remains almost unchanged during the childhood (Fig. 3). There is no evidence of gender related differences (Table 2):

Table 2: Concentrations of 17-OH-P in serum of healthy female and male children (from 1 month up to 8 years old). The values were measured with IBL ELISA, Cat.-No. RE52071.

Gender	Male	Female
Number (n)	124	98
Mediane (ng/mL)	0.29	0.34
5%- Percentile (ng/mL)	0	0
95%- Percentile (ng/mL)	2.79	1.97

During puberty, young women show an increase in the concentration of 17-OH-P 1-2 years before young men do. The values in pubertal stage are around 1.5 times higher than those corresponding to younger children.

The following graphics show the concentration of 17-OH-P in young children and preadolescents. (Fig. 2 and Fig. 3)

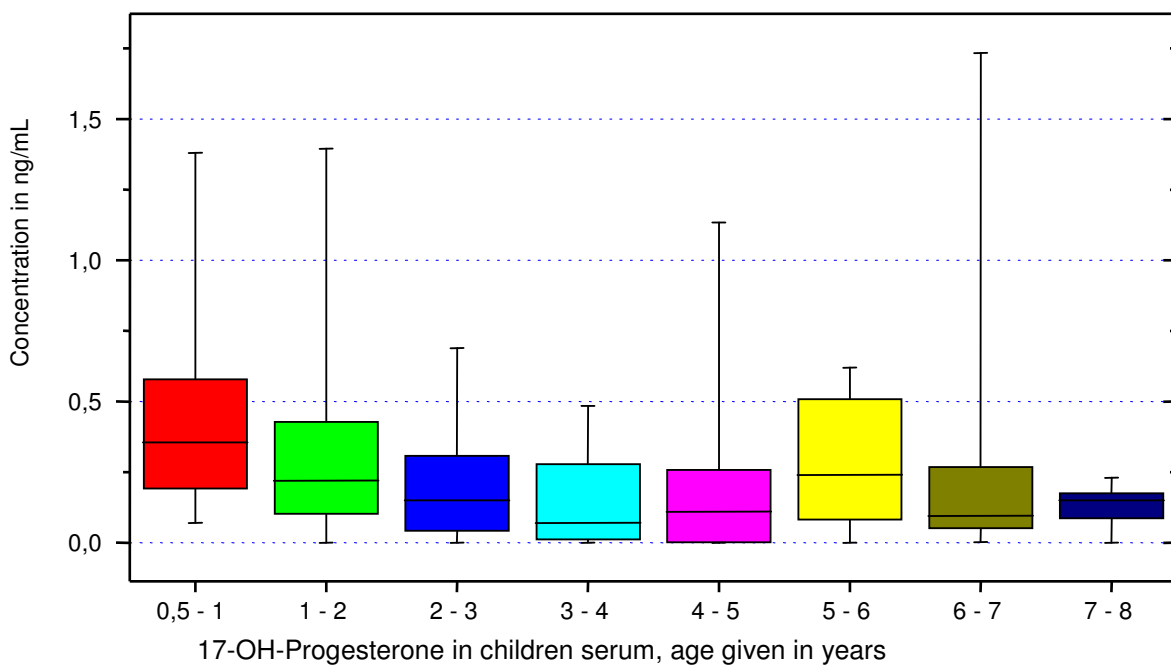
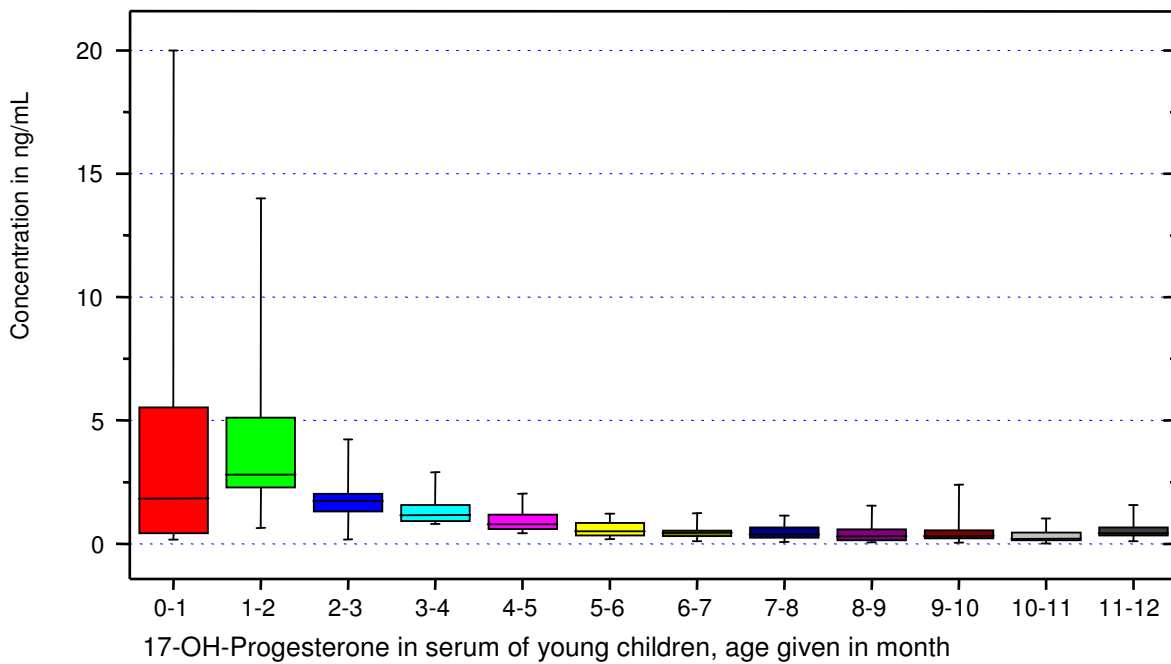


Fig. 2 and 3: Age dependency of 17-OH-P in serum of 195 healthy young children (up to 1 year old) and of 139 healthy children (1 to 8 years old). Illustration in Box-Whysker-Chart. Median, 25-75% Percentile (box), 10-90% Percentile (line). The values were measured with IBL ELISA, Cat. No. RE52071 (values in ng/mL).

The concentrations measured in young male adults are around 3 to 5 times higher than those of young boys, although they present high variability.

The concentration of 17-OH-P decreases with the age. Pirke et al. (8) studied 80 healthy males, between 19 to 93 years old, who were divided into two groups according to their age. Their comparison proved an age-related decrement of around 47.5%. While the young men (N=45, 19 to 54 years old) showed a mean concentration of 17-OH-P of 1.39 ng/mL, the hormone level in the older group (N=35, 68 to 93 years old) reached a mean value of only 0.73 ng/mL. Seeland (9) found a statistical correlation between the increment of age and decrement of 17-OH-P of about 0.03 ng/mL yearly.

As seen in males, the concentrations of 17-OH-P in serum of young healthy women are clearly higher than those of preadolescents. The concentration also depends on the phase of the menstruation cycle; the values measured during the luteal phase are 2-3 times higher than those corresponding to the follicular phase.

There is a marked increase of 17-OH-P during pregnancy.

The following table summarizes the normal ranges, measured with 17-OH-Progesterone ELISA from IBL:

Table 3: Normal ranges of 17-OH-P in serum, measured with IBL ELISA, Cat. No. RE52071

17-OH-Progesterone	Number (n)	Mediane (ng/mL)	5% - 95% Percentile (ng/mL)
Newborns (0 - 10 days)	11	1,28	0,29 - >20
Children	1 – 6 months	73	1,29
	6 – 12 months	110	0,36
	1 – 8 years	139	0,17
Adults, Males	48	0,7	0,2 – 1,4
Adults, females	Follicular phase	16	0,4
	Luteal phase	16	0,8
	Pregnant, 3. Trimester	51	9,7

The circadian rhythm of 17-OH-P presents its higher concentrations during the morning, decreasing during the course of the day. Therefore, the serum samples should be taken during the morning.

Except children up to 6 months old, all values of 17-OH-P were found lower than 3.2 ng/mL for all groups, independently from their age.

Very high values of 17-OH-P are measured directly after birth, although they quickly decrease, as shown in the literature (10):

Table 4: 17-OH-P Values in serum (CB = umbilical cord blood) after birth (10)

Time (ng/mL)	CB. venous	2 h	4 h	6 h	12 h	24 h	4 d	7 d	2w-2m
	32,9	6,6	5,9	4,0	2,0	0,9	0,8	0,9	0,8

2.3. Clarification of positive samples

A CAH suspicion can be expressed principally through follow-up control and rising 17-OH-P values. For this reason the 17-OH-P concentrations should always be measured in same laboratory and with same method.

Persistent high 17-OH-P values should be clarified with complementary analysis (17-OH-P after extraction, urine steroids, ACTH test or genetic analysis). Artificially elevated values can be due to the presence of hydrophilic conjugates of steroid hormones. The results themselves should not be the only reason for any therapeutical consequences. They have to be correlated to other clinical observations and diagnostic tests (11).

The following extraction protocol can be recommended:

- Pipette 150 µL sample (serum or plasma) to the bottom of the glass tube.
- Add 1.5 mL from a mix of ethyl acetate : hexane (3:2-volume ratio) (Quality of the solutions: spectrophotometric grade)
- Mix with a vortex for 60 seconds and let it rest until the phases separate.
- Remove 1 mL of the organic phase (upper phase) and let it dry under air or nitrogen flow.
- Add 100 µL of Zero-Standard and incubate at room temperature for at least 30 minutes, either on an orbital shaker (200 rpm) or shake it repeatedly during the incubation time.

The following normal ranges were determined by measuring 135 samples of young children with 17-OH-Progesterone-ELISA, Cat. No. RE52071.

	17-OH-Progesterone in Serum					
	without extraction			With extraction		
Age in months	0 - 1	1 - 6	6 - 12	0 - 1	1 - 6	6 - 12
Number	8	46	81	8	46	81
Mediane (ng/mL)	0,68	1,17	0,38	0,53	0,42	0,13
5%-Percentile (ng/mL)	0,19	0,40	0,06	0,11	0,11	0,05
95%-Percentile (ng/mL)	>20	3,08	1,11	18,83	0,91	0,55

Table 5: Normal range of 17-OH-P in serum for young children, with and without extraction, measured with IBL 17-OH-Progesterone-ELISA, Cat. No. RE52071

2.4. IBL International 17-OH-Progesterone ELISA – Test characteristics

The following table summarizes the main characteristics of the IBL 17-OH-Progesterone ELISA for serum and plasma samples.

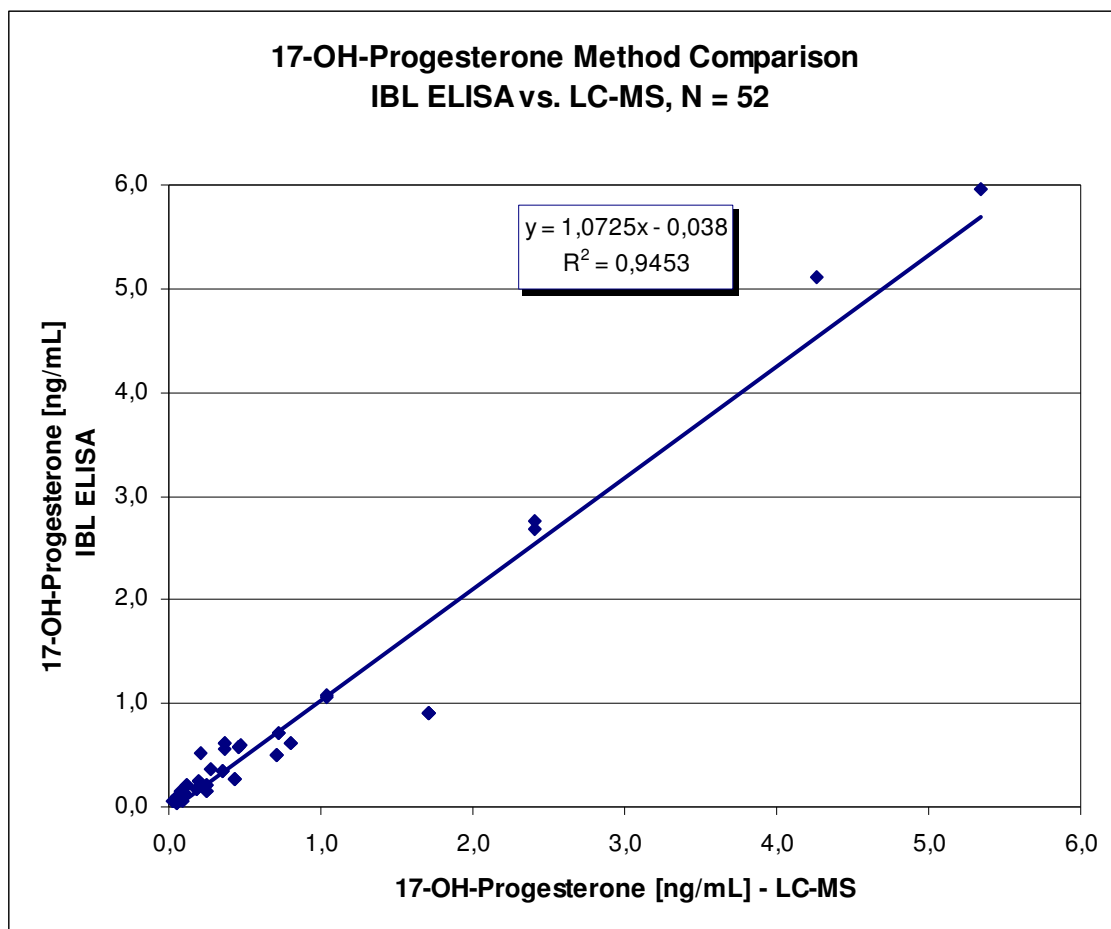
Working principle	Competitive immunoassay		
Intended use	Quantitative determination of total 17-OH-Progesterone in serum and in EDTA plasma		
Regulatory status	CE label, FDA 510(k) exempt		
Format	12 Microtiter-Strips, each with 8 break apart wells.		
Sample	25 µl Serum or EDTA-Plasma		
Standards	7 Standards, ready to use 0/0.15/0.5/1.5/3.0/7.5/20.0 ng/mL		
Incubation	60 min (room temperature) 10 min (room temperature)		
Substrate	Tetramethylbenzidine (TMB)		
Expected values		<u>5% - 95% Percentile</u>	
	Children	1 – 6 Months	0.34 – 4.7 ng/mL
		6 – 12 Months	0.08 – 1.3 ng/mL
		1 – 8 Years	0.0 – 0.8 ng/mL
	Males		0.2 – 1.4 ng/mL
	Women	Follicular phase	0.3 – 0.9 ng/mL
		Luteal phase	0.3 – 2.5 ng/mL
	Pregnant women	(3 rd trimester)	2.8 – 13.2 ng/mL
Sensitivity	0.03 ng/mL		
Precision	Intraassay:	2.8 – 4.9 %	for 2.44 – 11.4 ng/mL
	Interassay:	5.8 – 9.2 %	for 0.26 – 5.74 ng/mL
Specificity	Cross reactivity (Abraham-Method)		
	17-OH-Pregnenolone		1.7 %
	Progesterone		1.4 %
	11-Desoxycortisol		1.3 %
Controls	2 Kit-Controls		
Automation	possible on different open ELISA processors (DSX, Triturus,...)		
Cat. No.	RE 52071		

2.5. Method comparisons with reference methods

2.5.1. Method comparison with LC-MS

Children serum (52 normal samples and CAH samples) have been measured in parallel with the IBL 17-OH-Progesterone ELISA and the reference in house LC-MS.

The following results have been obtained:

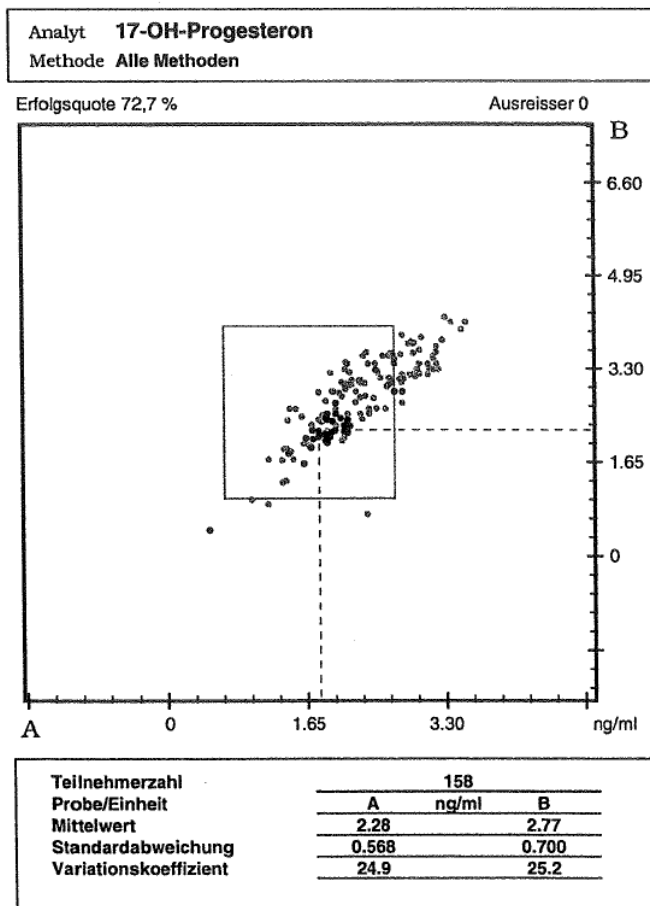


2.5.2. Method comparison with GC-MS

Furthermore we are regularly participating to the external Quality Assessment Scheme organized from the Deutsche Gesellschaft für Klinische Chemie (DGKL) with our 17-OH-P ELISA. The method reference for the trial samples is the GC-MS. Taking part to this proficiency testing enables us to regularly check the right calibration and reliability of our assay.

Our reagent code is the number 41 and the ELISA method is represented with (M) 2.

The stability and reproducibility of our assay can also be pointed out thanks to the mostly very low variation of results between participants.



Probe A (RMW = 1.69 ng/ml)

M	Kit	N	Min	16.P	50.P	84.P	Max	0	1.65	3.3
Alle	158	0.500	1.73	2.17	2.93	3.55				
1	36	3	1.20	1.47	1.84	2.28				
1	41	4	1.42	2.06	2.70	3.12				
1	44	17	1.60	2.05	2.70	3.37				
1	52	3	1.36	1.62	2.19	2.64				
1	53	13	2.05	1.94	2.13	2.53				
1	99	11	1.88	2.31	2.89	3.20				
1	111	41	1.90	1.47	1.69	2.49				
1	143	4	1.39	2.12	2.31	2.45				
2	35	8	2.10	1.72	1.92	2.15	2.80			
2	41	34	0.500	1.19	1.40	2.15				
2	111	3	1.60	1.53	2.15					
11	99	5	1.45							

Probe B (RMW = 2.53 ng/ml)

M	Kit	N	Min	16.P	50.P	84.P	Max	0	1.65	3.3	4.95	6.6
Alle	158	0.460	2.10	2.87	3.49	4.22						
1	36	3	1.70	1.85	2.09	3.09						
1	41	4	1.88	2.95	3.77							
1	44	17	2.40	2.76	3.54	3.77						
1	52	3	1.69	1.99	4.13							
1	53	13	0.740	2.87	3.10	3.53						
1	99	11	2.74	2.78	3.05	3.56						
1	111	41	2.20	2.68	3.20	4.13						
1	143	4	1.70	1.86	1.95							
2	35	8	2.10	2.21	2.50	2.59	2.60					
2	41	34	0.460	2.02	2.21	2.50	3.28					
2	111	3	0.920	1.60	1.92							
11	99	5	2.59	2.60	3.40							

Andere Kits (Anzahl):
1 13(1), 1 43(2), 1 49(1), 1 76(1), 2 42(2), 2 76(1), 2 99(1), 4 44(1), 4 111(1), 7 99(1).

Die Abweichung Ihrer Ergebnisse vom Median des zugehörigen Unterkollektives (Kit) beträgt: A -6.10 % B -0.23 %

Hormonbestimmung Gruppe 1, HM03/08

3. 17-OH-Progesterone ELISA in Saliva; RE52271

3.1. Normal values in saliva

The values of free 17-OH-P in saliva are found to be more than 10 times lower than those of total 17-OH-P measured in serum. Nevertheless, the values in saliva and serum present a correlation. This is especially good for pathological high values.

Krüger (12) studied 207 pairs of serum and saliva ranging from 0 to 15 ng/mL (normal and pathological range) and established the following correlation:

Serum = 28.8 x Saliva – 0.4; R=0.98; N=207

3.2. Age and gender dependency

In order to determine the normal range of 17-OH-P in saliva, two studies were performed using saliva samples from 129 apparently healthy children aged 6 – 12 years, 132 males aged 21 - 70 years, and 252 females of non-pregnant women with regular menstrual cycles, aged 21 - 50 years.

Saliva samples were collected in the morning, frozen at -20°C, and analyzed using the IBL 17-OH-Progesterone saliva ELISA kit (RE52271).

The following ranges were calculated from this study:

Table 6: Summary of normal range for 17-OH-P in morning saliva of healthy young children and adults (pg/mL), measured with our IBL 17-OH-Progesterone saliva ELISA (RE52271)

	Age group		Mean	S.D.	Range 5 - 95%
Children	6 – 12 yrs	N = 129	16.9 pg/mL	9.5 pg/mL	3.0 – 32.9 pg/mL
Women	21 – 50 yrs	Follicular phase: N = 124	22.0 pg/mL	11.1 pg/mL	8.2 – 41.1 pg/mL
		Luteal phase: N = 128	51.2 pg/mL	17.3 pg/mL	28.1 – 84.8 pg/mL
Men	21 – 70 yrs	N = 152	24.9 pg/mL	12.6 pg/mL	10.6 – 54.8 pg/mL

3.3. Diurnal rhythm

The following graphic (modified according to (12)) shows the circadian rhythm of 17-OH-P in saliva with a maximum during the morning and a minimum during the afternoon. Differences in the concentration up to 70%, within a day, were detected. The values corresponding to the males are located between those corresponding to the different phases of the menstrual cycle of the females.

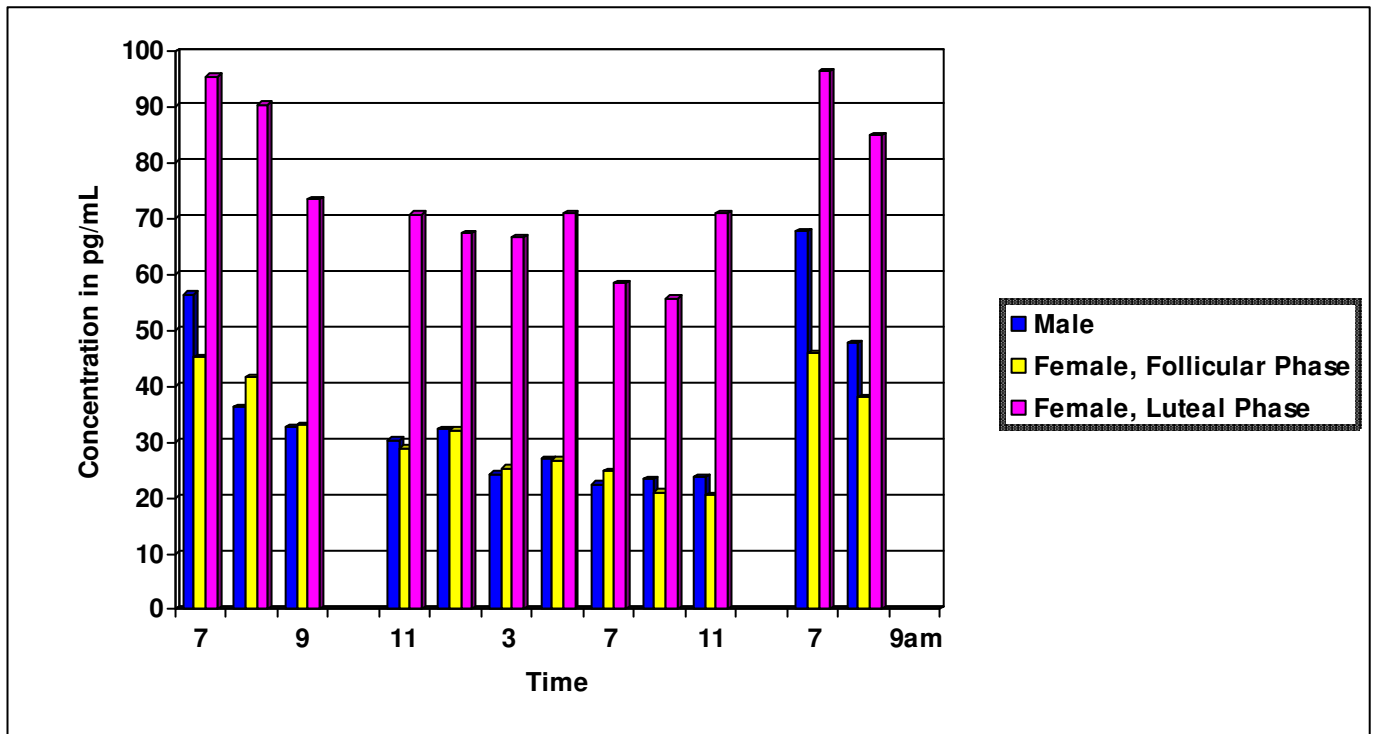


Fig. 4: Mean concentration of 17-OH-P in pg/mL: Daily profile in saliva for adults (8 males; 8 females (follicular stage); 6 females (luteal stage)), modified according to (12).

The highest concentration is measured between 7 – 8 a.m..

The following circadian rhythm was found in healthy children (5):

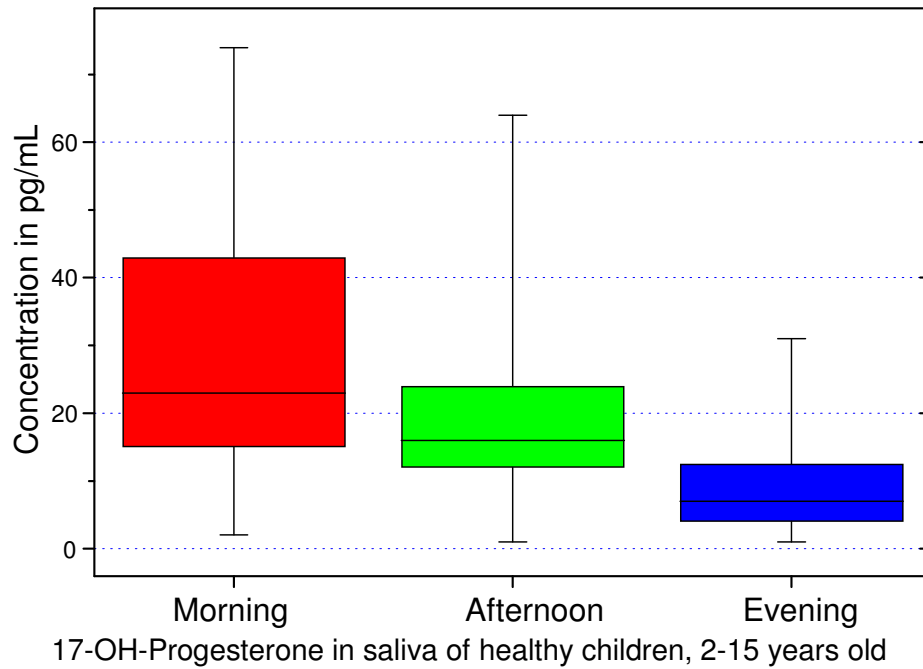


Fig. 5: 17-OH-P (pg/mL) in morning, noon and evening saliva of healthy children from 1 to 15 years old (N=72), according to (5).

3.4. Menstrual cycle

In healthy women and during their menstrual cycle, a marked difference in the concentration of 17-OH-P can be detected. The values during the follicular phase are much lower than those corresponding to the luteal phase. An increase in the concentration is detected between day 16-18, followed by a constant decrease until day 28, when the end of the follicular stage is reached (6):

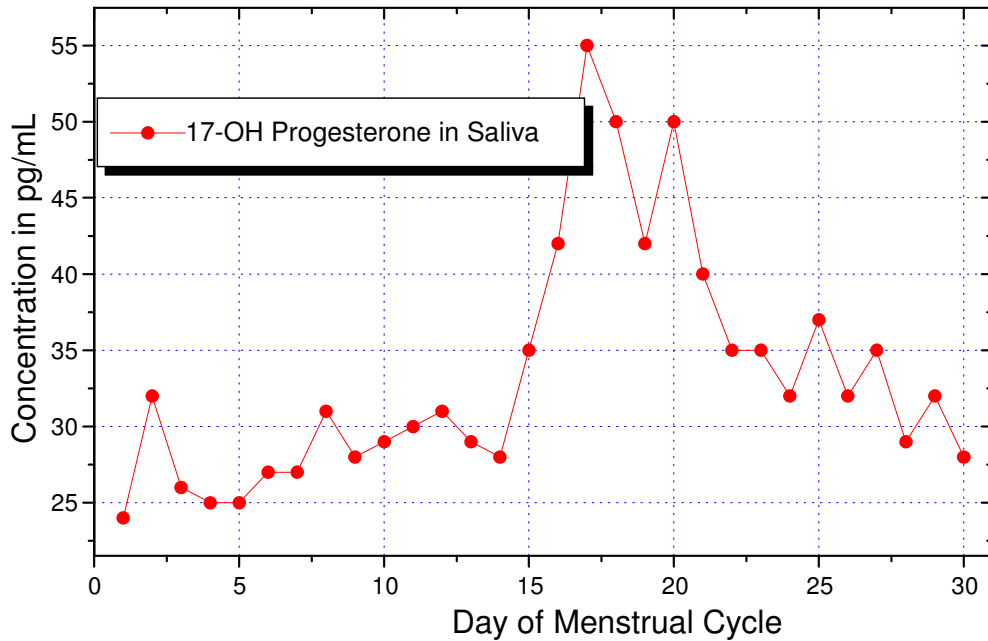


Fig. 6: Profile of 17-OH-P in morning saliva of healthy young women (N=30) during the menstrual cycle (mean value), modified according to (6).

3.5. IBL International 17-OH-Progesterone Saliva ELISA – Test characteristics

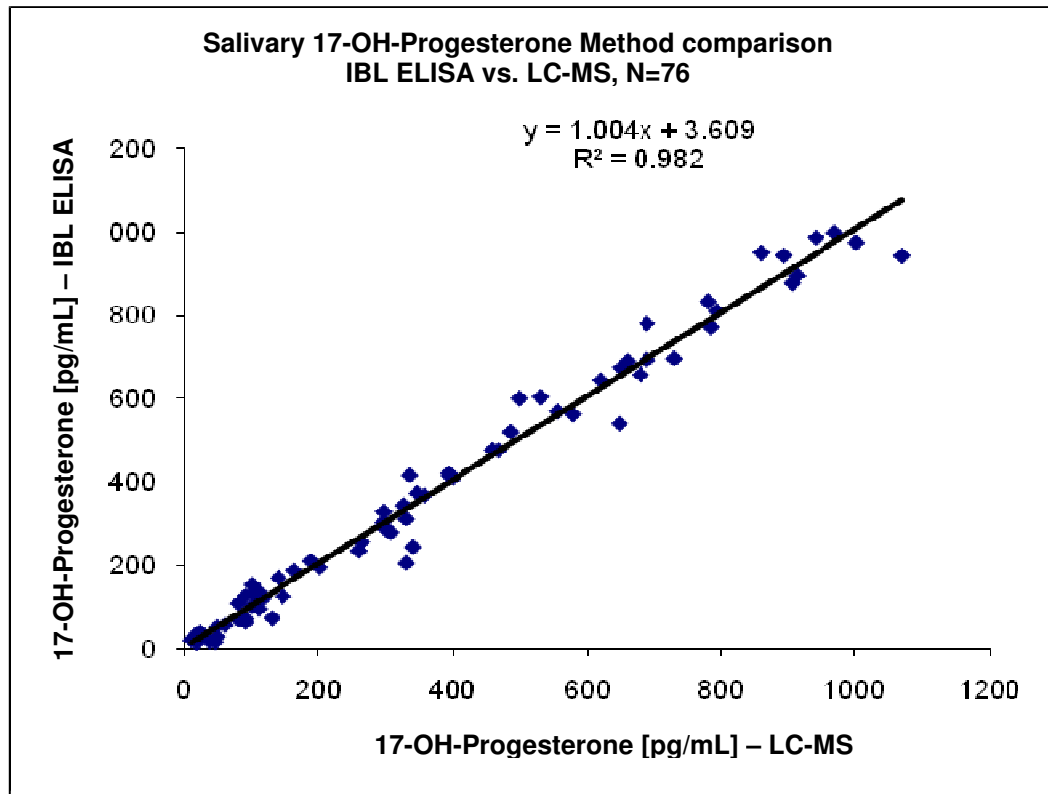
The following table summarized the main characteristics of the 17-OH-Progesterone ELISA for saliva samples of IBL.

Working principle	Competitive immunoassay		
Intended use	Quantitative determination of active free 17-OH-P in saliva		
Regulatory status	CE-labeled		
Format	12 Microtiter-Strips, each with 8 break apart wells		
Sample	25 µL Saliva		
Standards	8 Standards, ready to use 0/5/10/50/100/500/1.000/5.000 pg/mL		
Incubation	60 min (room temperature) 15 min (room temperature)		
Substrate	Tetramethylbenzidine (TMB)		
Expected values			<u>5% - 95% Percentile</u>
	Children	6 – 12 Years	3.0 – 32.9 pg/mL
	Males	21 – 70 years	10.6 – 54.8 pg/mL
	Women	Follicular phase	8.2 – 41.1 pg/mL
		Luteal phase	28.1 – 84.8 pg/mL
Sensitivity	3 pg/mL		
Specificity	Cross reactivity (Abraham-Method)		
	11-Desoxycortisol		1.4 %
	Progesterone		1.2 %
Controls	2 Kit controls		
Automation	possible on different open ELISA processors (DSX, Triturus,...)		
Cat.-No.	RE52271		

3.6. Method comparison with the reference method LC-MS

Non spiked Saliva from adult normal and CAH-patients were assayed in parallel with the IBL 17-OH-Progesterone Saliva ELISA and a reference LC-MS. Seventy-six patient saliva samples were tested on both the LC-MS and the IBL ELISA test.

The following results were obtained:



4. Literature

1. Dunn, J.F., Nisula, B.C., Rodbart, D: Transport of steroid hormones: Binding of 21 endogenous steroids to both testosterone-binding globuline and corticosteroid-binding globulin in human plasma. *J.Clin.Endocrin.Metabol* 53(1), 58-68, 1981
2. Dörr, H.G., Sippell, W.G., Adenogenitales Syndrom (AGS) mit 21-Hydroxylase-Defekt. *Monatsschr. Kinderheilk.* 141, 609-621, 1993
3. Bidlingmaier, F. Pathobiochemie und klinisch-chemische Diagnostik der Organ- und Systemerkrankungen. Lehrbuch der Klinischen Chemie und Pathobiochemie, Greiling H, Gressner A.M., Schattauer 1995
4. Pang, S., Wallace, M.A., Hofman, L., et al., Worldwide experiences in newborn screening for classic adrenal hyperplasia due to 21-hydroxylase deficiency. *Pediatrics*, 81, 866-870, 1988
5. Plattig, B., Speichel-17-Hydroxyprogesteron bei Kindern mit Adrenogenitalem Syndrom und 21-Hydroxylase-defekt: Bedeutung für die Therapieüberwachung, Dissertation Erlangen-Nürnberg, 2004
6. Gröschl, M., Zur Verwendung von Speichel für die nichtinvasive Steroidanalytik im Kindes- und Jugendalter unter besonderer Berücksichtigung der Therapiekontrolle des adrenogenitalen Syndroms mit 21-Hydroxylasedefekt., Dissertation Erlangen-Nürnberg 2001
7. Höpfner et al., Pregnancies in patients with congenital adrenal hyperplasia with complete or almost complete impairment of 21-hydroxylase activity. *Fertil. Steril.* 81, 1314-1321, 2004.
8. Pirke et al in (9)
9. Seeland, U., Pathogenetische und klinische Bedeutung von 17a-OH-Progesteron und seiner Metabolite bei gesunden Männern und Patienten mit erektiler Dysfunktion, Dissertation, Homburg/Saar, 2003
10. Sippell, W.G., Dörr, H.G., Bidlingmaier, F., Knorr, D., Plasma levels of aldosterone, corticosterone, 11-desoxycortisone, progesterone, 17-hydroxyprogesterone, Cortisol and cortisone during infancy and childhood. *Pediatr. Res.* 14, 39-46, 1980
11. Dörr, H.G., Nennstiel-Ratzel, U., AGS-Screening Neugeborenenenscreening auf das Adrenogenitale Syndrom mit 21-Hydroxylase-Defekt. *Kinderärztliche Praxis* 76, 284-291, 2005.
12. Krüger, C., Radioimmunologische Bestimmung von 17-Hydroxyprogesteron in nicht extrahierten Speichel und dessen Bedeutung für die Therapiekontrolle des Adrenogenitalen Syndroms (21-Hydroxylasedeffekt), Dissertation Göttingen, 1990

Version 5

MG/06.05.2010