

## Artículo de investigación

# 17-hydroxyprogesterone levels in blood from the heels of healthy full-term newborns

*Niveles de 17 – hidroxiprogesterona en sangre de talón de neonatos a término sanos*

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**Abstract**

**Background and aim:** Congenital adrenal hyperplasia is caused by enzymatic abnormalities in the synthesis of adrenal steroids. A pilot study was carried out to measure the values of 17- hydroxyprogesterone (17-OHP) in a sample of healthy full-term newborns; the present study aims to determine if birth weight or gender have differences on 17-OHP. **Design:** Transversal, descriptive, and prolective study. **Methods:** We included 81 healthy full-term newborns with normal prenatal controls born between July 18th, 2014, and August 1st, 2015. We took whole blood using the heel prick test when the babies were three to five days old. Socioeconomic and clinical data were collected. Non-extracted 17-OHP ELISA was used. Its cut-off point was 20 ng/mL. If results were above cut-off point, babies were recalled for a new measure since transient high 17-hydroxyprogesterone levels are possible until babies are three months of age. **Results:** Gestational age varied between 37.0 to 41.5 weeks. Non-extracted 17-OHP levels ranged between 2.6 to 29.5 ng/mL (median: 11.5, IQR 7.2 to 15.1). 17-OHP levels variation per birth weight or gender were not found. **Conclusions:** In full term newborns is expected a lesser variation that may explain these results. Quality issues should be solved before starting a screening program in our population because socioeconomic issues cause most problems in recalling positive screening babies.

**Keywords:** 17-hydroxyprogesterone; Congenital adrenal hyperplasia; Screening; Newborn infant; Gestational age.

**Resumen**

**Justificación:** la hiperplasia adrenal congénita es una enfermedad autosómica recesiva ocasionada por anomalías enzimáticas en la síntesis de los esteroides adrenales. Se realizó un estudio para medir los valores de 17- hidroxiprogesterona en una muestra de neonatos a término sanos. El objetivo fue conocer si existían diferencias en el valor de 17-OHP según edad gestacional y sexo. **Diseño:** estudio transversal, descriptivo y prolectivo. **Métodos:** se incluyeron 81 neonatos con controles prenatales normales y nacidos entre julio 18 de 2014 y agosto 1 de 2015. Se obtuvieron muestras de sangre del talón cuando los bebés tenían entre tres a cinco días de vida. Se recolectaron datos socioeconómicos y clínicos. Se utilizó

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This disease affects the production of cortisol and aldosterone (in 75% of cases) (7), causing severe hyponatremia episodes associated with hypotension, hyperkalemia and hypoglycemia with high morbidity and mortality.

un ELISA de 17-OHP no extraída. El punto de corte de la prueba de ELISA de 17-OHP fue 20 ng/mL. Si los resultados estaban por encima del valor de corte, se citaron los bebés para una nueva medición, dado que es posible hallar una hiper 17-hidroxi-progesteronemia hasta los tres meses de edad. **Resultados:** la edad gestacional varió entre 37 a 41,2 semanas. Los valores de 17-OHP no extraída variaron entre 2,6 a 29,5 ng/mL (mediana 11,5 y RIQ 7,2 – 15,1). Los niveles de 17-OHP no variaron según peso al nacer o sexo. **Conclusión:** estos resultados se podrían explicar por una menor variación esperada en neonatos a término. Se deben resolver algunos problemas de calidad antes de poder empezar un programa de tamizaje en nuestra población, debido a que causas socioeconómicas generaron dificultad al reevaluar los niños con resultados positivos de tamizaje.

**Palabras clave:** 17-hidroxiprogesterona; hiperplasia adrenal congénita; tamizaje; neonato; edad gestacional.

## Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disease caused by enzymatic abnormalities in the synthesis of adrenal steroids. Defects in 21-hydroxylase enzyme (classical form, OMIM: #201910) originate 90-95% of cases, and its world incidence is 1:15000 live births (1). Genes involved are *CYP21A* and *CYP21P*, both located in short arm of chromosome 6 (6p21.3).

Near 75% of genetic abnormalities are point mutations that requires PCR diagnostic tests or exome sequencing (1-3). In Colombia, no precise data exists because such genetic testing is not widely available and clinical - hormonal diagnoses are made (4,5); and there is only one case report with genetic testing made through collaborative academic network between Universidad del Valle and Garrahan Pediatric Hospital (Argentina).

This disease affects the production of cortisol and aldosterone (in 75% of cases) (7), causing severe hyponatremia episodes associated with hypotension, hyperkalemia and hypoglycemia with high morbidity and mortality if left untreated/undiagnosed (8-10). Additionally, only 50% of affected patients present recognizable symptoms during their first two weeks of age and 25% after the first month (11,12).

CAH screening has been done since 1977 (13-16). 17-hydroxyprogesterone hormone (17-OHP), a marker in its classical form, is measured in a sample of dried blood on sample carrier paper taken from a heel prick between the third and fifth day of age (14,16). The cut-off point corresponds to the 99<sup>th</sup> percentile of the values according to the method used: radioimmunoassay (RIA), fluoroimmunoassay (ELFIA, DELFIA) or enzymatic immunoassay (ELISA), and it must be adjusted to a reference test in each studied population (17,18). Variability is associated with weight, gestational age, gender, and stress status (19).

In Colombia, the guide for the screening of inborn errors of metabolism includes recommendations about congenital adrenal hyperplasia. However, its neonatal screening is pilot testing, testing offered by request, or only offered in the private sector (20). For this reason, we conducted a study to describe 17-OHP levels in full-term newborns according to relevant known factors and did a first look approach to create a local newborn screening.

## Methods

A transversal, descriptive, and prolective study was carried out to measure the 17-OHP values in full-term newborns to be able to analyze variation according to gestational age, birth weight, gender, and birth method.

We included full-term healthy newborns between their third and fifth day of age, without major malformations, need for surgery, metabolic stress, need for intensive care, hypoxia, perinatal infection, small for gestational age (SGA) or obstetric trauma. For sample definition, the potential population was divided into six groups according to gender and birth weight (2500-2999 g, 3000-3499 g, 3500-3999 g). At least 30 subjects were expected inside each group for comparisons. A sample of 81 successive patients was collected.

A written informed consent was obtained from their parents which had been previously approved by the Ethics Committee for Scientific Research of the Universidad Industrial de Santander on August 13<sup>th</sup>, 2014. For each child, we obtained a registry of their family and associated social factors, clinical characteristics and initial exams by means of their systematized clinical histories. Afterwards, a sample of whole blood from the heel was taken (one to four hematic halos) on Sample Carrier Paper FT-2-460, using the Ascensia Microlet<sup>®</sup> adjustable pricking device (Bayer HealthCare, USA). The samples were dried at room temperature for 24 hours, put in individual bags and stored at 2-8 °C until their processing.

A transversal, descriptive, and prolective study was carried out to measure the 17-OHP values in full-term newborns.

Samples were processed using the Stat Fax<sup>®</sup> 2200 microplate incubator/shaker and the micro-ELISA Chromate<sup>®</sup> 4300 microplate reader (Awareness Technology Inc., USA) by means of the Neonatal 17-OHP kit Test System (AccuBind<sup>®</sup> ELISA Microwells, Monobind Inc., USA). This test is a microplate non-extracted ELISA (This test does not eliminate polar steroids that cause small interference in measures) with a 0.556 ng/mL sensitivity, 55 % hematocrit established for controls in calculations, and 33 % maximum expected variation (Monobind Inc., Online Insert).

We used 20 ng/mL (64.5 nmol/l) as a cut-off point of 17-OHP measure ([17](#)). Samples with values higher than 20 ng/mL were processed for a second time. In these cases, data was reported as the average of the measurements that did not exceed the expected variation. If final results were above cut-off point, babies were recalled and a second sample was obtained before the babies were three months old.

Two databases were created (Google Sheets<sup>®</sup> and Microsoft Excel 2013<sup>®</sup>) and compared, without differences. Anthropometric variables were classified according to the Fenton & Kim's tables ([21](#)). 17-OHP variation was estimated according to weight, gender, and birth method, adjusting it to other potential variables of confusion (e.g., gestational age, TSH level, age at the time of the sample) using a multiple linear regression model including gender, birth weight and C-section requirement, transforming the distributions that did not have a Gaussian form. The Stata 12.1 software (Stata Corp, 2014, USA) was used.

## Results

We included 81 full-term newborns with normal prenatal controls that were born between July 18<sup>th</sup>, 2014, and August 1<sup>st</sup>, 2015 ([Table 1](#)). Gestational age ranged between 37.0 and 41.5 weeks (median: 39.2, IQR 38.4 to 40.0). The median of the mothers' ages was 22 years (IQR 18 to 26 years).

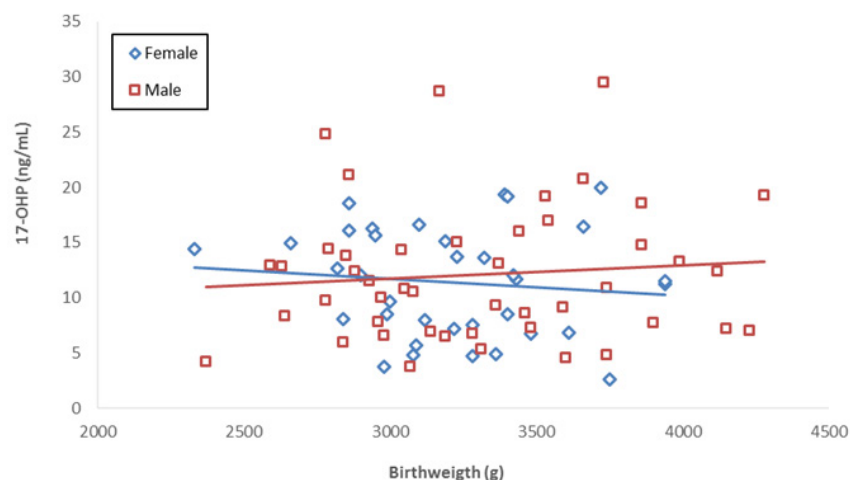
In the sample, 46 newborns (56.8%) were male and 69.1 % had C-section births. The median for birth weight was 3230 g (IQR 3171 to 3362 g), for height it was 52.3 cm (IQR 50 to 54 cm). There were 24 children between 2500 - 2999 g, 33 children between 3000 - 3499 g, 18 children between 3500 - 3999 g, four children >4000 g (4.9 %) and two <2500 g (2.5%). All newborns were euthyroid (TSH median: 2.9, IQR 1.7 to 4.2  $\mu\text{UI}/\text{mL}$ ). A few cases of low or high weighted births, without other comorbidities were expected (7.5% combined rate Vs. 10% expected rate).

**Table 1.** Sociodemographic characteristics (n = 81)

Characteristics	Values	Statistics
Gestational age (GA)	37.0 - 41.5 weeks	Median 39.2, IQR 38.4 - 40.0
Maternal age	16 - 45 years	Median 22, IQR 18 - 26
Sex	46 males	56.8%
	35 females	43.2%
Mode of birth	25 vaginal births	30.9%
	56 C-section births	69.1%
Birth weight	2330 - 4280 g	Median 3230, IQR 3171 - 3362
Birth weight by GA	-1.75 - 1.98 Z	Median -0.28, IQR -0.78 - 0.31
Birth height	46 - 59 cm	Median 52.3, IQR 50 - 54
Neonatal TSH	0.8 - 10.6 $\mu\text{UI}/\text{mL}$	Median 2.9, IQR 1.7 - 4.2

Non-extracted 17-OHP ranged between 2.6 and 29.5 ng/mL without differences by gender or weight ranges (median: 11.5, IQR 7.2 to 15.1).

There were no complications about heel punctions. Non-extracted 17-OHP ranged between 2.6 and 29.5 ng/mL without differences by gender or weight ranges (median: 11.5, IQR 7.2 to 15.1; [figure 1](#)). Seven children (8.6 %) from the sample showed 17-OHP values above 20 ng/mL; two of them were classified as false positive measures of this study by physical exam (performed by a pediatric endocrinologist) and a new 17-OHP measure before three months of age. There were two males and their initial 17-OHP values were 20.1 and 28.7 ng/mL and second 17-OHP levels were 10.1 and 15.4 ng/mL, with normal physical exams. The other five newborns could not be recalled because phone numbers did not work, their home addresses changed, or their parents did not bring them to control visits. 17-OHP values and gender of this babies were 21.8 (male), 31.2 (female), 29.5 (male), 24.8 (female) and 20.76 ng/mL (male). Rate of false positive tests was  $7/81 = 9\%$ .



**Figure 1.** 17-hydroxyprogesterone (17-OHP) variation in full-term newborns according to birth weight, and gender

During the linear regression analysis, we did not find any changes in 17-OHP values according to gender ( $\beta = 0.051$ ; 95 % CI: - 0.335 to 0.438), birth weight ( $\beta = - 0.000036$ ; 95 % CI: - 0.000410 to 0.000481) or C-section as birth method ( $\beta = 0.190$ ; 95 % CI: - 0.228 to 0.607). The correlation coefficient ( $p^2=0.015$ ) showed that there was no association between 17-OHP levels and the variables included in the model.

## Discussion

Individual screening for congenital adrenal hyperplasia has shown to be very useful, especially in its classical form. However, there are still some doubts regarding the best type of test, cut-off values and methodology (22). Despite its usefulness, a negative screening test does not eliminate clinical suspicion, given the fact that the 30 ng/mL cut-off point may have a false negative ratio of up to 30% for collections in three to five-day old babies (23). In these cases, it is not useful to take a second sample and clinical criterion should be used (24). In this study, we used the 20 ng/mL cut-off point as stated by Chennuri, *et al.* (17), as a means of decreasing the percentage of false negatives.

On the other hand, this test is known to show false positives according to the considered cut-off point. Thus, some adjustments consistent with various factors are suggested, including polar steroids that may affect the value for 17-OHP, making it necessary to report if they were extracted (25). In this study, we performed a non-extracted 17-OHP test (Monobind Inc).

The values for the test according to the factors studied showed that known variables affecting 17-OHP values in premature newborns, do not seem to have a relevant influence in full-term newborns. Reports from Votava *et al.*, Van der Kamp *et al.*, and Chennuri *et al.*, show lesser 17-OHP variation by birth weight near to 2500 g or higher (17, 23, 26). Also, we excluded small for gestational age babies, a recognized condition linked to 17-OHP variability, because of its association with other neonatal morbidities that cause confusion bias. For these reasons, the cut-off point may be the same in any healthy full-term newborn regard its sex o birth weight. Our two babies with birth weight lesser than 2500 g, were healthy and normal for gestational age according to the Fenton & Kim's tables (21).

This study reports a high number of 17-OHP false positives, identified by a second sample that was obtained before babies were three months of age. We assumed all 7 positive cases as false positives, given the low incidence of CAH globally. We follow a methodology like that used by Gidlöf *et al.*, with a similar cut-off point (20 ng/mL = 64.5 nmol/L, vs. 60 nmol/L) (27). Thus, a 30 ng/mL literature proposed cut-off point (22) could be a better one than the 20 ng/mL for neonatal 17-OHP kit (N-17OHP) test system from AccuBind® ELISA Microwells (Monobind Inc., USA), with a 0% recall rate inside our database with this adjusted cut-off point.

Newborns with 17-OHP elevated values should also be reevaluated for transitory hyper-17-hydroxyprogesteronemia, which appears close to the third month of age without being false positives of congenital adrenal hyperplasia cases (28). Furthermore, we suggest cautious interpretation of abnormal results, reviewing during a control if there are changes in weight, blood pressure or reactivity and, if necessary, ordering hormone measures, radiographs and pediatric endocrinologist assessment (29, 30).

It was not completely possible to exclude the presence of males with the simple virilizing and non-classical forms among cases with false-positive results, because of low recalling rates (50 %). However, two recalled babies showed normal physical exams and a 17-OHP decrease enough to consider low probability of CAH. Thus, quality issues in recalling should be solved before beginning a screening program in our population because socioeconomic issues became a most relevant problem.

In this year, a Colombian law project about newborn screening (in revision since 2015) was rejected by government because legal issues relative to cost-benefit control about tests that will be included and doubts about the reliability of diagnostic centers (31-33). If the universities develop the methods for conducting this tests at the local setting, a neonatal screening policy might perhaps be institutionalized.

Additionally, local datasets always be required to standardized tests and our data are first local Colombian dataset about CAH. In advantage, 17-OHP in full-term newborns are independent from birth weight and sex. Future research will have to complete 17-OHP dataset in preterm newborns and compare with term babies, and it would be desirable using extracted 17-OHP test to improve accuracy. Cost-benefit studies about CAH complications against the low cost of screening for metabolic diseases should be encouraged.

In summary, 17-OHP screening levels variation in healthy newborns per birth weight or gender is not expected, 30 ng/mL could be better cut-off than 20 ng/mL, and neonatal screening would be feasible in Colombia with low cost tests as ELISA.

17-OHP levels variation in healthy newborns per birth weight or gender is not expected, 30 ng/ml could be better cut-off than 20 ng/mL.

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