



**THE 17-HYDROXYPROGESTERONE LEVEL,
ANDROSTENEDIONE LEVEL, AND SIDE EFFECT
POST HYDROCORTISONE THERAPY
OF CONGENITAL ADRENAL HYPERPLASIA PATIENTS**

A RESEARCH ARTICLE

**Submitted to fit-out requisite
in passing bachelor degree of Faculty of Medicine**

**R. RIZCKY ERIKA PRATAMI
G2A006145**

**UNDERGRADUATE EDUCATION PROGRAM
FACULTY OF MEDICINE
DIPONEGORO UNIVERSITY
SEMARANG
2010**

**KADAR 17-HYDROXYPROGESTERONE, ANDROSTENEDIONE, DAN
EFEK SAMPING PASCA TERAPI HIDROKORTISON PADA PASIEN
CONGENITAL ADRENAL HYPERPLASIA**

R. Rizcky Erika Pratami¹, Ahmad Zulfa Juniarto²

ABSTRAK

Latar Belakang: *Congenital Adrenal Hyperplasia* (CAH) merupakan DSD yang paling banyak ditemukan pada 46,XX dan muncul jika terjadi defisiensi pada salah satu dari enzim yang dibutuhkan untuk sintesis cortisol dan aldosteron di kelenjar adrenal, sehingga terjadi ketidakseimbangan hormon adrenal. Terapi sulih hormon dengan menggunakan hidrokortison adalah salah satu cara untuk mengontrol keseimbangan hormon adrenal. Untuk memonitor keefektivitasan terapi ini, diperlukan pengukuran prekursor hormon adrenal (17OHP dan androstenedione). Selain itu, setiap terapi dapat menyebabkan efek samping yang perlu dikontrol. Tujuan dari penelitian ini adalah untuk mencari perbedaan kadar hormone sebelum dan sesudah terapi dan mencatat efek samping.

Metode: Desain pre-eksperimental dengan satu kelompok pre tes dan post tes dilakukan untuk mengobservasi kadar 17OHP dan androstenedione. Penelitian terhadap efek samping terapi hidrokortison menggunakan analisis deskriptif. Sample pada penelitian ini adalah setiap pasien CEBIOR yang terdagnosis CAH secara klinis, sitogenetika, dan hormonal dan atau analisis mutasi pada gen CYP-21 kemudian menerima terapi hidrokortison dan pengontrolan terapi. Sampel plasma darah digunakan sebagai material pre-terapi dan saliva digunakan sebagai material post-terapi, kemudian dianalisis menggunakan ELISA Hormonal data dianalisis menggunakan uji *Wilcoxon*. Data efek samping dipresentasikan dengan narasi deskriptif.

Hasil: Analisa *Wilcoxon* dengan membandingkan data pre dan post terapi menghasilkan penurunan dengan $p=0.987$ untuk 17-OHP and peningkatan dengan $p=0.04$ untuk androstenedione. Terdapat 12 subjek dengan perawakan pendek setelah terapi hidrokortison dan beberapa dari mereka menyampaikan keluhan penyerta. Keluhan penyerta terbanyak adalah dehidrasi (44.44% dari keluhan total).

Simpulan: Perbandingan antara 17-OHP pre dan post terapi menunjukkan penurunan yang tidak signifikan, sedangkan pada androstenedione terdapat peningkatan yang signifikan. Penyebab efek samping terbanyak adalah dosis terapi yang tidak adekuat.

Kata kunci: congenital adrenal hyperplasia, CAH, hidrokortison, 17-OHP, androstenedione, efek samping

¹Mahasiswa Program Pendidikan S-1 Kedokteran Umum Fakultas Kedokteran Universitas Diponegoro

²Center of Biomedical Research (CEBIOR), Fakultas Kedokteran Universitas Diponegoro, Jl. Dr. Sutomo 18, Semarang

THE 17-HYDROXYPROGESTERONE LEVEL, ANDROSTENEDIONE LEVEL, AND SIDE EFFECT POST HYDROCORTISONE THERAPY OF CONGENITAL ADRENAL HYPERPLASIA PATIENTS.

R. Rizcky Erika Pratami¹, Ahmad Zulfa Juniarto²

ABSTRACT

Background: Congenital Adrenal Hyperplasia (CAH) is the most common 46,XX DSDs, which occurred when one of the enzymes required for cortisol and aldosterone synthesis in adrenal gland is deficit, therefore performed adrenal hormone imbalance. Hormone replacement therapy using hydrocortisone is an option that allows control of the adrenal hormones balance. To monitor the effectiveness of therapy, measuring the adrenal hormones precursors (17-OHP and androstenedione) is required. Nevertheless, every therapy has side effect that must be controlled. The aim of this research is to seek 17-OHP and androstenedione levels post- compared to pre-therapy and also side effect of hydrocortisone therapy.

Method: A pre-experimental study with one group pretest-posttest design was done to observe 17-OHP and androstenedione levels. The side effect post hydrocortisone therapy used a descriptive study. Samples of this research were all patients recorded in CEBIOR which are diagnosed as CAH after the clinical, cytogenetic and hormonal check-up and/or after the CYP21-gene mutation analysis then receive hydrocortisone therapy and follow-up. Blood plasma sample for hormonal pre-therapy and saliva sample for hormonal post therapy were analyzed using ELISA. This hormonal data was analyzed *Wilcoxon* test. Side effect data were presented in a descriptive narration.

Result: 38 cases (12.88%) of DSDs were registered in CEBIOR, and 23 were suitable to inclusion criteria. *Wilcoxon* analysis by comparing pre and post therapy hormonal data showed decline with $p=0.987$ for 17-OHP and elevation with $p=0.04$ for androsetedione. There were twelve subjects with short stature after hydrocortisone therapy and some of them complained intercurrent illness. The most common intercurrent illness was dehydration (44.44% of total complain).

Conclusion: Comparison between 17-OHP pre and post therapy is insignificantly decreased, whereas in androstenedione there is significant elevation. Side effects of hydrocortisone therapy are frequently caused by inadequate doses.

Keywords: congenital adrenal hyperplasia, CAH, hydrocortisone, 17-OHP, androstenedione, side effect

¹Undergraduate student, Faculty of Medicine, Diponegoro University

²Center of Biomedical Research (CEBIOR), Faculty of Medicine, Diponegoro University, Jl. Dr. Sutomo 18, Semarang

INTRODUCTION

Congenital Adrenal Hyperplasia (CAH), which is classified as Disorders of Sex Development (DSDs), is usually diagnosed due to ambiguous genitalia in the newborn.¹ Mostly, the patients are genetically female (46,XX) with virilization. This disorder is occurred when one of the enzymes required for cortisol and aldosterone synthesis in adrenal gland is deficit.^{2,3} The condition results to hyperplasia of adrenal and stimulation of hormone precursors, such as 17-hydroxyprogesterone (17-OHP) and androstnenedione, thus leads to elevation of testosterone level.^{3,4}

In Medical Faculty of Diponegoro University/Dr. Kariadi Hospital Semarang, CAH cases are managed by gender adjustment team, after the diagnostic and therapeutic processes. Treatment for CAH patients is to provide adequate adrenal hormones substitution to prevent adrenal crises and to suppress excess adrenocortical testosterone production.⁵ Hormone replacement therapy using hydrocortisone is an option that allows control of the adrenal hormones balance.

To monitor the effectiveness of therapy, measuring the adrenal hormones precursors is required. Nevertheless, every therapy, including hydrocortisone therapy, has side effect that must be controlled. However, research in hormone precursors features post hydrocortisone therapy and also side effect of this therapy in Semarang has never been done.

The aim of this research is to seek the 17-OHP and androstenedione levels, as well as side effect post hydrocortisone therapy of CAH patients to get better

understanding of hydrocortisone therapy and also can be useful in further researches about CAH. This research also can provide information for the patients about the effectiveness of their therapy.

METHODS

Subjects for this research were all patients confirmed as CAH after clinical, cytogenetic and hormonal examination and/or mutation analysis and received hydrocortisone therapy and follow-up. This research was using a secondary data from medical records of CAH patients during period 2004 – July 2010. Data was obtained from physical examination, cytogenetic, hormonal work-up and mutation analysis.

This research was a pre-experimental study with one group pretest-posttest design to observe the 17-OHP and androstenedione levels. The side effect post hydrocortisone therapy of CAH patients used the descriptive method. This research was conducted at Center of Biomedical Research (CEBIOR) of Medical Faculty Diponegoro University / Dr. Kariadi Hospital Semarang.

In this study, after clinically diagnosed as CAH, blood sample was taken for cytogenetic, hormonal data pre therapy and mutation analysis. CAH patients under 17 years old received hydrocortisone therapy at the dose 10-12mg/m²/day with readjustment of doses when needed. Follow-up data was required to monitor the therapy, thus saliva sampling using Salivette® was done every three months after hydrocortisone achieved for hormonal work-up. Both pre and post therapy hormonal

work-up were analyzed using ELISA. Side effect data was also noted every three months when the patients come for follow-up. All examinations were done at CEBIOR, except initial hormonal data and mutation analysis were done in The Netherland.

Data processing on 17-OHP and androstenedione were analyzed using *Wilcoxon* test. Side effect data was reported using descriptive method. Tables and charts were presented to show the result.

RESULTS

Of all 40 patients suspected as CAH, only 38 left diagnosed as CAH after further examination. Furthermore fifteen of patients are excluded from this research due to reject follow-up (n=3), lost contact (n=4), not medicated (n=5), treated by prednisone (n=1), and hormonal post therapy has not been analyzed (n=2). Thus, total subject used in this research was 23.

From 23 subjects, mean of initial age at presentation was 4.948. All of the subjects were female, except one male and one undecided. Eighteen subjects had done DNA analysis and showed the mutation of DNA. Characteristic of the data can be seen in table below.

Table 1. Characteristic of Data

Number of Subjects	23	
Initial Age	4.948±4.770	
Minimum	0.02	
Maximum	15.65	
Before 2009	6.026±4.535	
2009	1.896±4.379	
Gender		
Male	1	4.35%
Female	21	91.30%
Undecided	1	4.35%
Gender classified by Karyotype		
46,XX	21	91.30%
Female	20	86.96%
Undecided	1	4.35%
46,XY (all male)	1	4.35%
46,XX (99%)/46,XY (1%) (all female)	1	4.35%
Quigley Stage		
0 (normal male)	1	4.35%
1	0	0.00%
2	1	4.35%
3	12	52.17%
4	5	21.74%
5	2	8.70%
6/7 (normal female)	2	8.70%
Mutation		
CYP21	16	69.57%
CYP11B2	2	8.70%
not yet analyzed	5	21.74%

Subjects in this study received hydrocortisone therapy. They had done hormonal examination pre and post therapy. The aim of post therapy hormonal check-

up was monitor hydrocortisone therapy. The first four times of follow up are presented in the charts below.

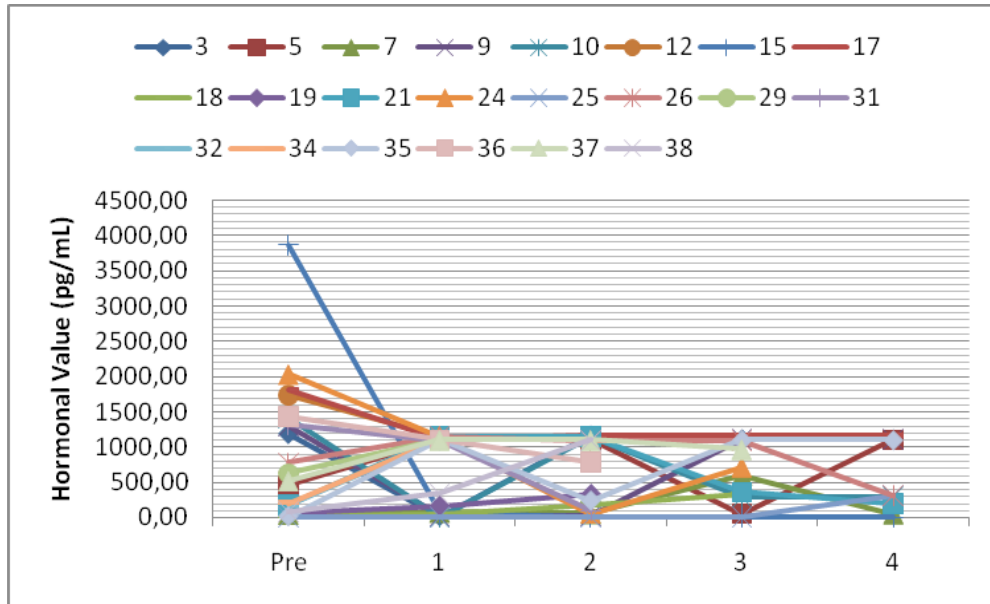


Figure 1. 17-Hydroxyprogesterone Follow-up

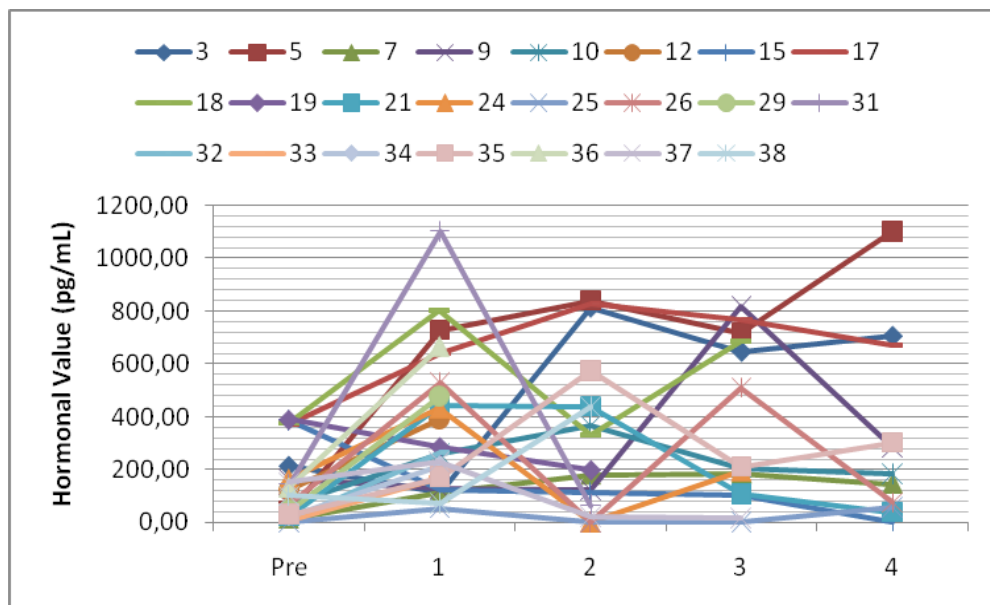


Figure 2. Androstenedione Follow-up

The most recent hormonal data is also performed in this study compared to initial data that was taken before therapy. The comparison between pre and post therapy were analyzed using *Wilcoxon* test. Table 2 shows the result of *Wilcoxon* test.

Table 2. *Wilcoxon* test for 17-OHP and androstenedione pre-post therapy

	Initial	Post Therapy	P
17-Hydroxyprogesterone	876.405±949.968	759.972±407.618	0.987
Androstenedione	132.248±131.279	325.577±286.592.	0.004

The side effect of hydrocortisone therapy was also noted. Data included the growth of the subjects pre and post therapy, and also intercurrent illness. Of 23 subjects, twelve were short stature. Table 3 shows the side effect of hydrocortisone therapy on the subjects.

Table 3. Side Effect Data

Subj. No.	Initial Age	Pre Therapy: Short Stature	Post Therapy: Short Stature	Intercurrent Illness	Remarks
3	10.53	no	Yes	Sp	ID*
5	9.78	no	Yes	D	ID*
7	6.56	no	No	-	NH
9	7.45	no	Yes	-	ID*
10	4.25	no	No	-	NH
12	19.23 m.o	yes	No	-	NH/U*#
15	2 m.o	yes	No	-	NH
17	10.22	yes	Yes	-	SS**
18	3.55	no (tall)	no (tall)	-	NH
19	9.98	no (tall)	No	Sp	NH
21	5.94	no	No	-	NH
24	7.77	no	No	-	NH
25	15.65	yes	Yes	-	SS/OD
26	11.67	no (nearly)	No	-	NH
29	4.01	no	No	-	NH*
31	4.87	no (tall)	No	-	NH*
32	0.57 m.o	no	Yes	-	U*#
33	2.83 m.o	yes	Yes	-	SS
34	1.07 m.o	yes	Yes	d†	SS*#
35	1.07 m.o	yes	Yes	o, sp	SS*
36	10.83	yes	Yes	-	SS*
37	1.40 m.o	no (nearly)	Yes	d†	SS*
38	0.27 m.o	no (nearly)	Yes	d,o	ID*

d : dehydration (vomiting, diarrhea); sp : skin problem (dermatitis, itch, vulnus excoriatum); o : other (cough, cold); † : died

ID : inadequate doses; OD : overdoses; SS short stature from the beginning; NH : normal height; U : unclassified, * : bad hormonal response; ** : very bad hormonal response; # : only once followed-up

DISCUSSION

From 2004 to July 2010, 295 patients are recorded as DSDs patients at Center of Biomedical Research (CEBIOR), and 38 cases (12.88% of DSDs) confirmed as CAH after clinical, cytogenetic and hormonal check-up and/or mutation analysis. In North Indian, CAH (36.2%) was the most common cause among DSDs (n=58).⁶ Great difference number between DSDs cases at CEBIOR and in that research in North Indian may result in different percentage of CAH and other DSDs cases.

CAH patients were varied in the ages at presentation. Before 2009 initial ages of CAH patients were varied in prepuberty, puberty and even adults, whereas the promptly diagnosis and treated of CAH is very important to prevent death in early infancy from Addisonian crisis. But in 2009, due to better information to medical and public communities, CAH cases in infants and even neonates became more reachable.

CAH were usually diagnosed due to virilization of external genitalia in genetically female (46,XX) patients. As we can see the most Quigley Stage present in the patients with CAH at CEBIOR is 3 (Quigley Stage for normal male is 0, while for normal female are 6 to 7). Two patients with initial Quigley Stage 6 had been operated before examined themselves.

Interestingly, there was a genetically male (46,XY) CAH patient. This male patient was diagnosed due to severe dehydration, which is typically salt-wasting CAH. On the other hand, of 21 cases of CAH in North Indian, fifteen were 46,XY. There was excess genetically males there, possibly due to frequent male gender.⁶

Five of all CAH patients at CEBIOR were not treated. Three of which chose to be male, thus they do not require maintenance therapy to reduce testosterone excess. The other two have normal hormonal levels from the beginning, but they both have ambiguous external genitalia and mutation on CYP21 gene, therefore diagnosed as CAH. In other research, two infants also confirmed as CAH with normal level of 17-OHP and both had CYP21 mutation. One patient carried the L30 nonclassic allele, the other had a classic CYP21 null genotype with ambiguous genitalia phenotype.⁷

Subjects of this research had done hormonal analysis pre and post therapy. The most recent 17-hydroxyprogesterone and androstenedione were compared to initial data. The decline on 17-OHP levels from initial data to post therapy were not significant statistically ($p=0.987$). From 22 subjects (one was missing), eleven were declined, and eleven were elevated. An odd significantly elevated ($p=0.004$) of androstenedione were performed in this study. Research in Turkey shows declined of 17-OHP and androstenedione levels in 100% subjects ($n=11$) after hydrocortisone therapy.⁸ The different result may be caused by several reason that would be explained below.

Pre therapy data in this study were measured using blood plasma as the material and analyzed using ELISA in The Netherlands with high sensitivity of ELISA-kit. The follow-up data were measured using saliva as the sample and also analyzed using ELISA at CEBIOR. The ELISA-kit for saliva has weaker sensitivity and can only detect up to 1 000 pg/mL, but saliva analyzing method is still able to reach the therapeutic goal range ($100-1\ 000\ \text{ng/dL}=10-100\ \text{pg/mL}$).³ Many

researches show strong correlation between 17-OHP and androstenedione in plasma and saliva.⁹⁻¹¹ Saliva is also an accepted non-invasive method, therefore saliva sample is good for follow-up the therapy, but could not shows the true decline or elevation with the real values that may influence the result.

Interestingly, in this result was that 17-OHP and androstenedione showed different condition statistically. Whereas, the majority of studied have shown good correlation between 17-OHP and androstenedione concentration in single sample, indicating that this hormones concentration are both under similar influence.¹⁰ In addition, pre therapy data were received in nmol/L (SI unit), and post therapy data were presented in pg/mL (conventional unit). Pre therapy data were converted to pg/mL (conversion factor from conventional units to SI: 17-OHP=0.3026; Androstenedione=0.349)¹² Therefore, error in converting may also influence the result.

The result may also occur due to non compliance of the subject. They used to consume the medication three times a day, but some of them admitted that sometimes they missed a therapy. In a new research using pharmacokinetic and pharmacodynamic study shows that modified-release hydrocortisone (MR-HC) represents a promising new treatment for CAH to substitute existing glucocorticoid treatment hydrocortisone (HC).¹³ In 14 subjects of that research, one week of thrice daily HC (10, 5 and 15 mg) was followed by one month of once daily MR-HC (30 mg at 22:00 hours). The outcomes were more fluctuated when using HC than MR-

HC. No serious adverse effect was noted using MR-HC and they merely have to consume the medication once a day.

We found polymorphism in the subjects at CEBIOR. The mutation that shows salt-wasting phenotype in subjects of previous researches occurred as only simple virilization in the subjects at CEBIOR. It may also influence the effectiveness of the therapy.

The result was unexpected, therefore the hormonal charts were presented to show the real condition. The charts showed fluctuated post therapy data in the first four times of follow-up. Subjects who showed elevation from pre to post therapy statistically, ever showed decline in some follow-up. The subjects in this therapy sometimes came after one week or more after the last medication. They may show the elevated result, when they came late.

Besides providing adequate substitution of glucocorticoid and mineralocorticoid and also suppression of adrenal androgen by controlling the 17-OHP and androstenedione levels, the other therapeutic goal is to maintain normal growth which can be defined by normal height at prepuberty, puberty and adults. Comparing the hormonal data to the growth was also helpful to show the condition in each patient. There were twelve subjects with short stature. Short stature is an unwanted effect of the therapy that can be caused by inadequate doses, overdoses and also premature closure of epiphyseal plate due to high testosterone level before receiving therapy. Patients with inadequate doses usually complained intercurrent illness due to electrolyte imbalance, such as dehydration that can be life-threatening

adrenal crisis¹⁴, while overdoses should have maintained the electrolyte balance. Overdoses usually show normal to low hormonal level after therapy. Therefore, to classify the samples into patient with inadequate doses, overdoses, and had high testosterone level before receiving therapy, we need to see initial stature, post therapy stature, intercurrent illness, and also hormonal data of the patients. Some patients with only one hormonal data in follow-up were hardly classified.

Five of the subjects with short stature were not short when they checked up for the first time and had high hormonal values in follow up. Most of them also complained intercurrent illness. They can be classified as patients with inadequate doses, except one with mere follow-up data (subject 32) cannot be classified. Of four patients with inadequate doses, one is a 46,XY salt-wasting type baby with severe intercurrent illness (subject no. 38). Normally, male do not receive any hydrocortisone treatment to suppress adrenal androgen, but in this case, this subject needs hydrocortisone to suppress the dose of fludrocortisone needed due to severe dehydration. But it still cannot reduce the severity of intercurrent illness, probably due to inadequate doses.

Seven subjects were short stature from the beginning. At diagnosis time, three of them were in the age of puberty. Two of which had high hormonal level (subj no. 36 & 17). Thus the short stature may be caused by uncontrolled testosterone level before therapy. One subject which was puberty at presentation had a good and even low hormonal value (subject no. 25). Before came to CEBIOR this subject had been treated. Therefore this subject may be classified to overtreatment. The other four were

still infants at presentation until the recent follow-up, therefore the normal height for them are probably below the percentile curve in the chart. Furthermore, the chart used was taken from Centers of Disease Control and Prevention (CDC), United States.¹⁵ Indonesian people may have different range of normal height.

Two subjects with normal height had bad hormonal value, but both of them cannot be classified because only one follow-up data performed. One other subject with normal data complained skin problem (acne), but the hormonal is still good control. Acne may also be caused by other than androgen excess.¹⁶

Insignificant Reduction of 17-hydroxyprogesterone level ($p=0.987$) and significant elevation of androstenedione ($p=0.004$) from initial data of androstenedione to post hydrocortisone therapy are performed in this study, which is not expected and may caused primary by inadequate doses due to non compliance, polymorphism of mutation and late coming for follow-up.

Side effects occurred were dehydration (44.44%), skin problem (33.33%) and others include cold and cough (22.22%). After analyzed, it mostly occurred due to inadequate doses that may lead to failure in therapy thus hormonal condition is not decline as in the hypothesis.

The difference between sample of pre and post therapy and the number of samples are suggested as factors which may affect the result. For further research, it will be good to use the same samples for pre and post hormonal therapy in either in blood or saliva with greater sample of research. Determining the optimal dosing regimen and long-term clinical outcome of MR-HC is also needed for further studies.

ACKNOWLEDGEMENTS

I am very grateful for the never ending assistance from dr. Ahmad Zulfa Juniarto, MSi.Med, Sp. And. I thank Prof. Dr. dr. Sultana M.H Faradz as the Director of Center of Biomedical Research (CEBIOR) for her permission to learn a lot in CEBIOR. We also want to thank sexual adjustment team of Dr. Kariadi Hospital/ Medical Faculty of UNDIP, the staff of CEBIOR laboratory and the laboratory in Netherland for providing cytogenetic, hormonal and mutation analysis data.

REFERENCES

1. Hutcheson, J. Ambiguous Genitalia and Intersexuality [serial online]. c 2009 [updated 2009 Jul 16; cited 2010 June 25]. Available from: <http://www.emedicine.com>
2. Speiser PW. Editorial: Improving Neonatal Screening for Congenital Adrenal Hyperplasia. *The Journal of Clinical Endocrinology and Metabolism*. 2004;89(8):3685-3686
3. Speiser PW, White PC. Medical Progress: Congenital Adrenal Hyperplasia. *The New England Journal of Medicine*. 2003 August 21;349:776-788.
4. Stikkelbroeck MML, Otten BJ. Congenital adrenal hyperplasia: clinical aspect and neonatal screening. *Ned Tijdschr Geneeskd*. 2002;146(6):246-249.
5. Charmandari E, Johnston A, Honour JW, Brook CG, Hindmarsh PC. Treatment with flutamide decrease cortisol clearance: implication for therapy in congenital adrenal hyperplasia. *J Pediatr Endocrinol Metab*. [serial online]. 2002 Apr [cited 2010 June 23] 15 (4): 435-9. Available from: <http://www.ncbi.nlm.nih.gov>
6. Kulkarni KP, Panigrahi I, Das R, Kaur S, Marwaha RK. Pediatric Disorder of Sex Development. *Indian J of Pediatr* 2009;79(9):956-958.
7. Fitness J, Dixit N, Webster D, Torresani T, Pergolizzi R, Speiser PW, et al. Genotyping of CYP21, Linked Chromosome 6p Markers, and a Sex-Specific

Gene in Neonatal Screening for Congenital Adrenal Hyperplasia. *J Clin Endocrinol Metab* 1999;84:960-966.

8. Poyrazođlu B, Günöz H, Darendeliler F. Serum leptin levels in patients with 21-hydroxylase deficiency before and after treatment. *Turk J Pediatr*. 2003;45:33-38.

9. Arisaka O, Shimura N, Nakayama Y, Arisaka N, Yabuta K. Salivary 17-hydroxyprogesterone concentration in monitoring of the treatment of congenital adrenal hyperplasia. *Dtsch Med Wochenschr*. [homepage on the internet] c1988 [cited 2010 August 5] 113(49):1913-5. Available from: <http://www.ncbi.nlm.nih.gov>

10. Hughes IA, Read GF. Simultaneous plasma and saliva steroid measurement as an index of control in congenital adrenal hyperplasia (CAH). *Horm Res*. [serial online] 1982 [cited 2010 August 5] 16(3):142-150. Available from: <http://www.online.karger.com/>

11. Otten BJ, Wellen JJ, Rijken JCW, Stoelinga BA, Benraad THJ. Salivary and plasma androstenedione and 17-hydroxyprogesterone levels in congenital adrenal hyperplasia. *The Journal of Clinical Endocrinology and Metabolism*. 1983;57(6):1150-54.

12. International System of Units (SI Units). [homepage on the internet] [cited 2010 July 15] Available from: http://www.questdiagnostics.com/hcp/intguide/SI_Units.pdf

13. Verma S, Vanryzin C, Sinaii N, Kim MS, Nieman LK, Ravindran S, et al. A pharmacokinetic and pharmacodynamic study of delayed- and extended-release hydrocortisone (Chronocort) vs. conventional hydrocortisone (Cortef) in the treatment of congenital adrenal hyperplasia. *Clin Endocrinol (Oxf)* 2010 Apr; 72(4):441-7.
14. Armstrong KL, Henderson C, Hoan NT, Warne GL. Living with Congenital Adrenal Hyperplasia in Vietnam: a survey of parents. *The Journal of Pediatric Endocrinology & Metabolism* 2006;19:1207-1223.
15. CDC Growth Chart [image on the internet] c2000 [cited 2010 July 14] Available from: <http://www.cdc.gov/growthcharts>
16. Acne [homepage on the internet]. c2006 [update 2006 January; cited 2010 Aug 17]. Available from: http://www.niams.nih.gov/Health_Info/Acne/default.asp