Vietnam National Children's Hospital

PRENATAL TREATMENT AND FERTILITY OF FEMALE PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA

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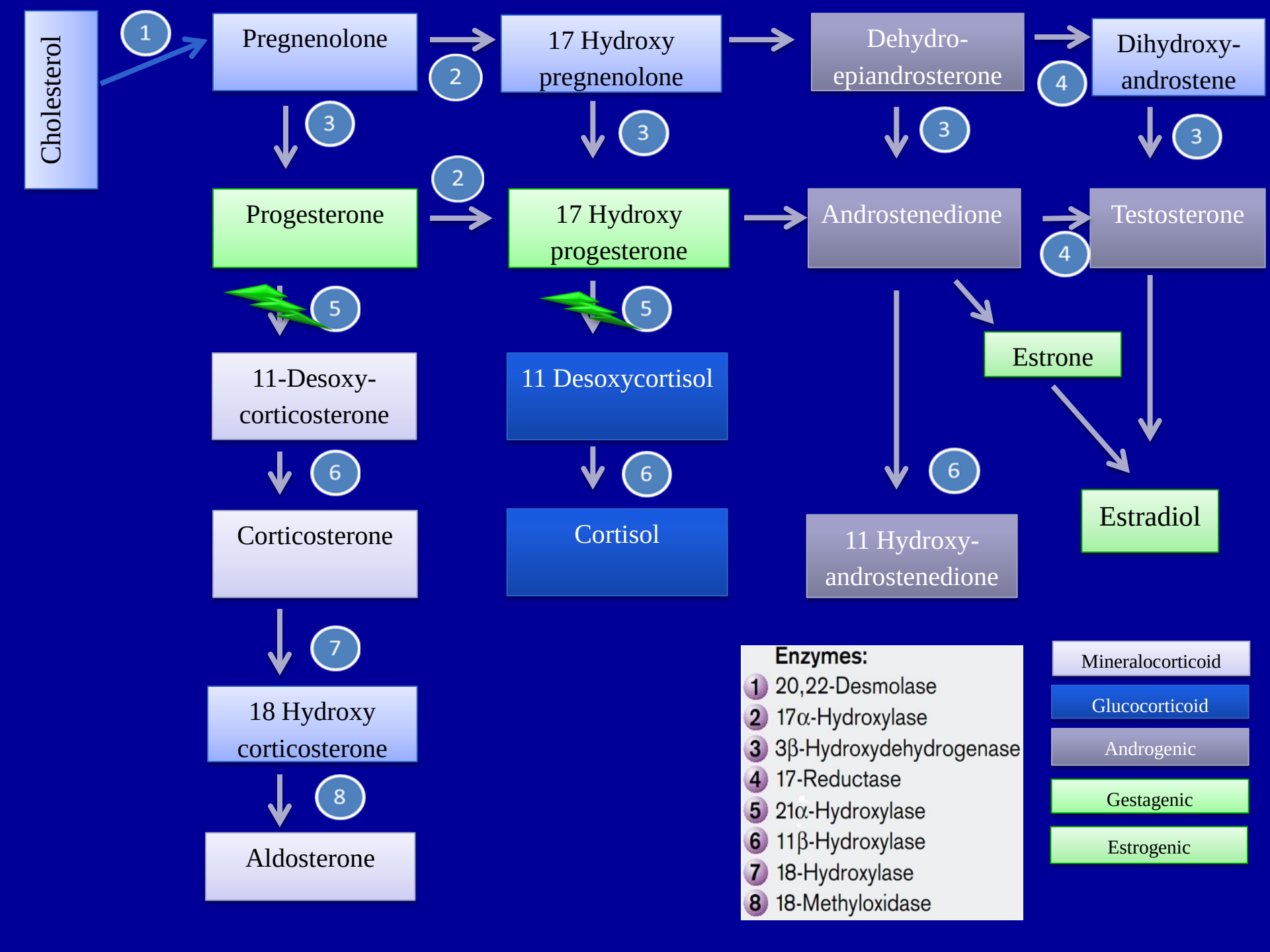
Outline

- Intruduction
- Prenatal diagnosis & treatment: case report
- Reproduction of women with CAH: case report
- Discussion
- Conclusions

Introduction

- Congenital adrenal hyperplasia – CAH comprises a group of autosomal recessive disorders
- Defects in one of several steroidogenic enzymes involved in the synthesis of cortisol from cholesterol in the adrenal glands.
- More than 95% of all cases of CAH are caused by 21-hydroxylase deficiency (21-OHD), which in addition to cortisol impairs synthesis of aldosterone.
- Most cause of ambiguous genitalia
- Incresing infertility


Cholesterol
1
Pregnenolone
2
17 Hydroxy pregnenolone
Dehydro-epiandrosterone
4
Dihydroxy-androstene
3
3
3
3
Progesterone
2
17 Hydroxy progesterone
Androstenedione
4
Testosterone
5
5
11-Desoxy-corticosterone
11 Desoxycortisol
Estrone
6
6
6
Corticosterone
Cortisol
11 Hydroxy-androstenedione
Estradiol
7
18 Hydroxy corticosterone
8
Aldosterone
Enzymes:
1 20,22-Desmolase
2 17α-Hydroxylase
3 3β-Hydroxydehydrogenase
4 17-Reductase
5 21α-Hydroxylase
6 11β-Hydroxylase
7 18-Hydroxylase
8 18-Methyloxidase
Mineralocorticoid
Glucocorticoid
Androgenic
Gestagenic
Estrogenic

TSTTBS thể cổ điển nam hóa đơn thuần

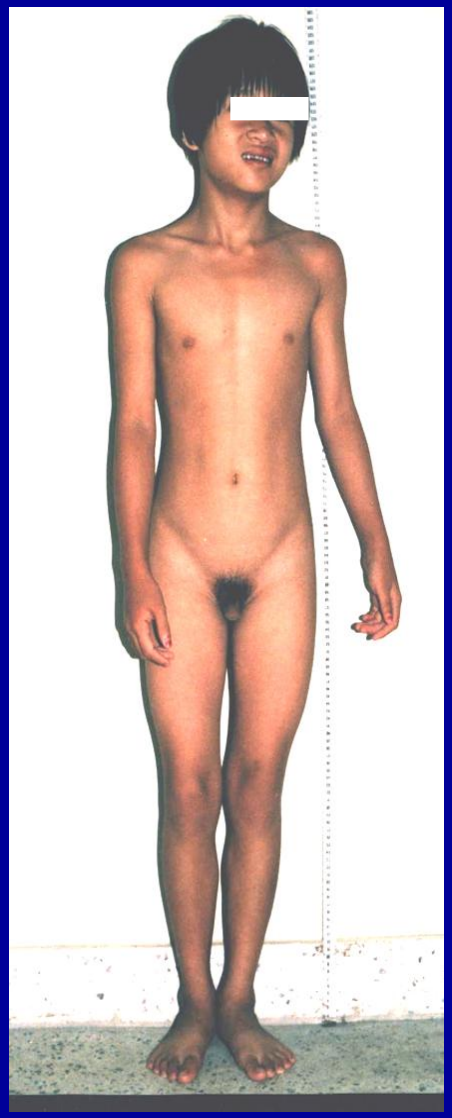
N.M.T 30 tuổi, 46XX

T.X. N 17 tuổi; 46,XX

B.N.B 15 tuổi 46,XX

N.T.H 7 tuổi 46,XX

Thể cổ điển nam hóa đơn thuần ở trẻ gái



Trẻ gái 7 tuổi

Prader typ IV

NST 46, XX

TSTTBS . Prader IV

22 giờ 557ST Trẻ gái, nam hóa bộ phận sinh dục ngoài sau đẻ

Q319X/IV2-13A/C >G

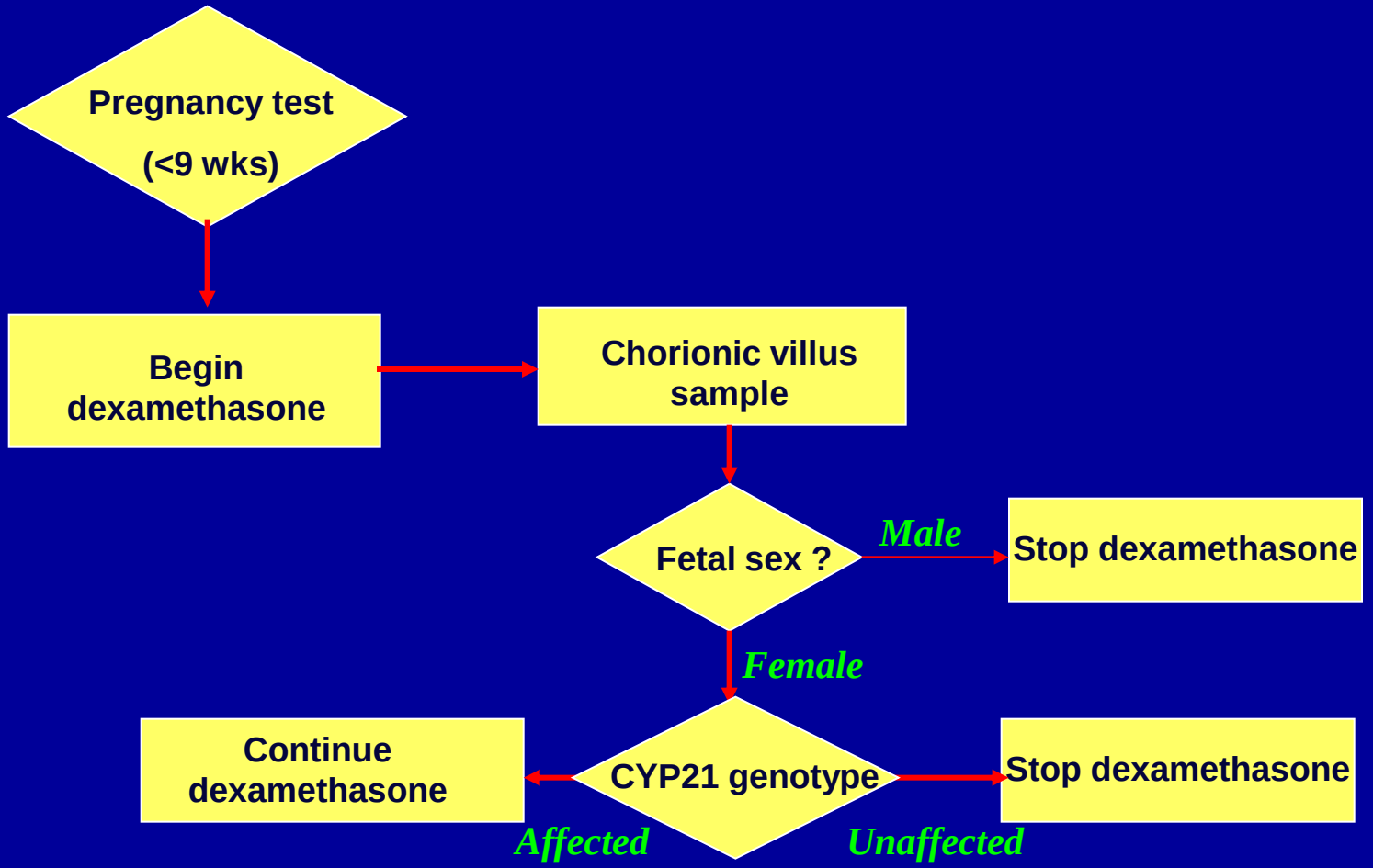
Incidence of CAH in Vietnam???

- Not available
- Number of new case/year at VCH: 40-70
- Data from 32 years: 805

Prenatal Diagnosis & Treatment

- To prevent virilization in pregnancies at risk for classical CAH
- Suppress of ACTH using dexamethasone
- Good outcome if start before 9 weeks.
- Efficacy in 80-85% (*New MI et al. 2001*)

Prenatal Diagnosis and Treatment



1/8 pregnancies

7/8 pregnancies

Reproductive Outcome in CAH Women

- Decreasing of fertility rates
- ➢ Recognized cause of low fertilities rates: suboptimal disease control, ovarian hyperandrogenism, polycystic ovarian syndrome.

Lo JC et al. Endocrinol Metab Clin North Am. 2001;30(1):207-29.

Reproductive Outcome in CAH Women

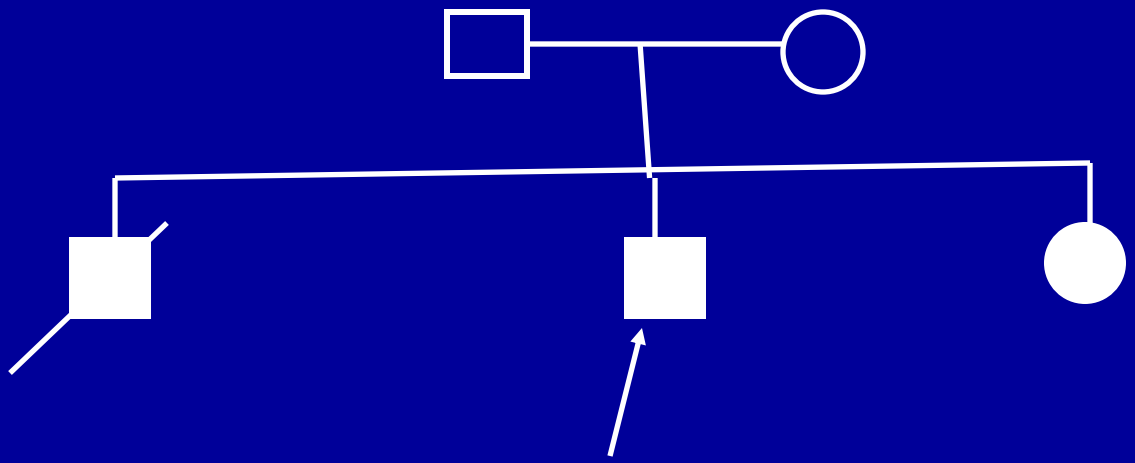
- Decreasing of fertility rates
- ➢ Recognized cause of low fertilities rates: complication related to genital surgery, psychological factors.

Lo JC et al. Endocrinol Metab Clin North Am. 2001;30(1):207-29.

Prenatal Diagnosis & Treatment

Case 1

Pedigree



- Severe hyperpigmentation
- No weight gain
- Vomiting
- Died at 3 months of age

- Hyperpigmentation
- No weight gain
- Dehydration
-Na 116; K 5.3 mmol/l
- *CYP21A2*: Homozygous of large deletion Exon 1-3

- Pranatal treatment
- Normal external genitalia

Prenatal Diagnosis & Treatment

- Proband: 2nd child of family

✓ DOB 26/2/2010

✓ Admission 27/4/2010

✓ WOB = 4 kg; weight at 2 months = 4 kg

✓ Hyperpigmentation, dehydration

✓ Plasma electrolyte: Na 116; K 5.3; Cl 116 mmol/l

✓ Plasma 17-OHP = 2300 ng/dl

✓ *CYP21A2*: homozygous large deletion: exon 1-3

Prenatal Diagnosis & Treatment

- Carrier confirmation of deletion of exon 1-3 for parents
- 3rd pregnancy: confirmation by ultrasound + hCG

✓ Mother age: 30

✓ Pre-pregnancy weight: 45 kg

✓ BP = 110/65 mmHg

✓ Genetic counseling & consent

Prenatal Diagnosis & Treatment

- Dexamethasone at 8 week of gestation

  20 μg/kg pre-pregnancy weight/day (divided in three doses) (Feb 5th 2014)
- Fetus gender using mother plasma: SRY (-) at 9 & 10 weeks of gestation
- Continuing of dexamethasone
- Amniocentesis

✓ Fetus karyotype: 46,XX

✓ *CYP21A2*: homozygous of large deletion exon 1-3.

Prenatal Diagnosis & Treatment

- Continuing of dexamethasone
- Observation: weight, BP, plasma glucose, HbA1C, edema, Cushing, growth of fetus by ultrasound.

Prenatal Diagnosis & Treatment

- At 39 weeks of gestation:

✓ Gaining of 10 kg

✓ BP = 120/80 mmHg; plasma glucose 5.3 mmol/l

✓ Cesarean

✓ Normal external genitalia

- ✓ Normal external genitalia
- ✓ Genotype confirmation: homozygous large deletion of exon 1-3 of *CYP21A2*
- ✓ Treatment: Hydrocortisone & Florinef

Reproduction of women with CAH: Cases report

Case 2

- Name: P.N.A; 6 yrs 7 months
- DOB: Dec 15th 1995
- Admission: July 3rd 2002
- History: hyperpigmentation & ambiguous genitalia from birth

Case 2 – Clinical

- P = 17 kg; H = 107 cm; S = 0.7 m^2
- BP = 80/50 mmHg
- Hyperpigmentation, no acne
- External genitalia:

✓ Without labia fusion

✓ Clitoromegaly (3 cm)

✓ No palpable testis

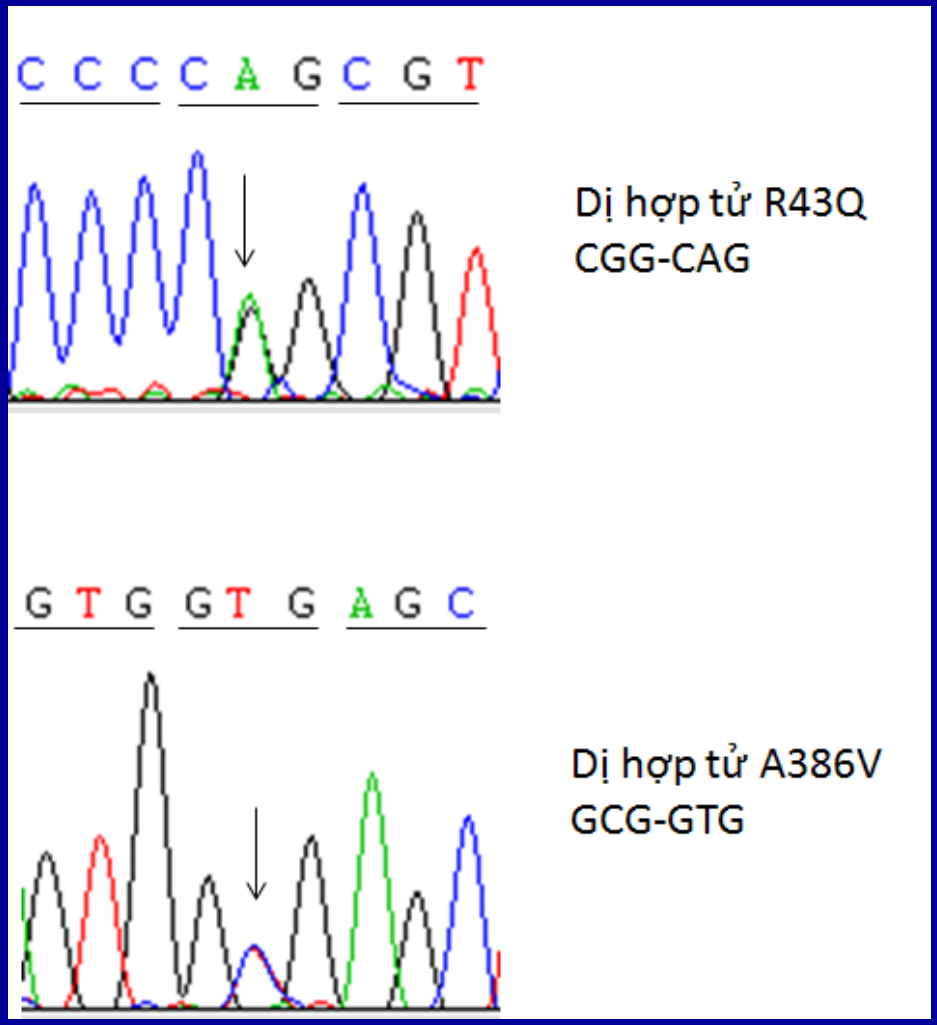
Case 2 – Investagations

- Karyotype: 46,XX
- Pelvic ultrasound:
  - ✓ Uterus 24 x 14 x 33 mm
  - ✓ R ovary: 15 x 13 mm
  - ✓ L ovary: 20 x 15 mm
- Bone age: 10 years
- Electrolyte: Na 145; K 4.6; Cl 107 (mmol/l)
- Plasma Testosterone = 10.05 nmol/l
- Plasma 17-OHP = 410 ng/dl

Mutation analysis of CYP21A2 and *CYP11B1*

- *CYP21A2*
  No mutation

- *CYP11B1*
  p.A386V/p.R43Q



25 weeks of gestation

- Diagnosis: CAH due to 11-OHD
- Treatment:

✓ Hydrocortisone 14 mg/m^2/day

✓ Clitoroplasty

- Menarch by 11 year 10 months
- 1st pregnancy at 20 yrs

Normal pregnancy

Cesarean

Normal daughter

Case 3

- Name: N.T.N; 13 yrs 1 month
- DOB: July 15th 1987
- Admission: August 18th 2000
- History: Ambiguous genitalia at birth, deep voice & muscle development from 6 years.

Case 3 – Clinical

- P = 42 kg; H = 139 cm; S = 1.35 m^2
- BP = 100/60 mmHg
- Deep voice, acne, muscle develpment
- Pubic hair: P4; Breast: B1
- External genitalia: Prader III

Case 3 – Investigations

- Karyotype: 46,XX
- Pelvic ultrasound:

✓ Uterus: 4 x 1.8 cm

✓ Normal ovaries

✓ Without adrenal mass

- Bone age: 17 years
- Electrolyte: Na 135; K 3.8; Cl 105 mmol/l
- Testosterone 13.2 nmol/l; Progesterone 67.4 nmol/l
- 17-OHP = 2860 ng/dl

Case 3 – Treatment & Follow up

- Treatment:

✓ Hydrocortisone 15 mg/m^2/day

✓ Clitoroplasty & vaginoplasty

- Follow up:

✓ Final height: 142 cm

✓ Menarche: 15 years, regular

✓ 1st pregnacy at 27 yrs (2014) & spontaneous miscarriage at 2 weeks

2nd pregnancy in 2015: normal pregnancy, full team, cesarean in April 5. 2016, normal daughter, WOB = 2.9 kg

Case 4

- Name: N.T.T.T; 11 years 7 months
- DOB: Dec 23rd 1989
- Admission: July 9th 2001
- History: ambiguous genitalia at birth, severe vomiting before 12 months, pubic hair by 6 years, muscle development from 10 years, hyperpigmentation

Case 4 – Clinical

- P = 40 kg; H = 142 cm; S = 1.33 m^2
- BP = 105/60 mmHg
- Deep voice, acne, muscle development, hyperpigmentation
- Pubic hair P4; Breast B1
- Clitoris 5 cm; Prader III; no palpable testis

Case 4 – Investigations

- Karyotype: 46,XX
- Pelvic ultrasound:

✓ Uterus 3.8 x 1.8 x 0.8 cm

✓ Ovaries: R 3.2 x 1.6 cm; L 3.0 x 1.4 cm

✓ No adrenal mass

- Bone age: 14 years
- Electrolyte: Na 135; K 4.1 ; Cl 106
- Testosterone = 21.9 nmol/l; progesterone = 7.5 nmol/l; 17-OHP = 5220 ng/dl

Case 4 – Treatment & Follow up

- Treatment:
- ✓ Hydrocortisone 15 mg/m^2/day
- ✓ Clitoroplasty & vaginoplasty
- Follow up:
- ✓ Final height 145 cm
- ✓ Menarche by 14 years, irregular

Case 4 – Follow up

- 1st pregnancy at 26 yrs
- Normal pregnacy
- Full team, boy
- WOB = 3.2 kg

Discussion
Prenatal diagnosis & treatment

- Prenatal dexamethasone for 325 pregnants:

✓ Eliminating genital virilization by Prader (-2.33, 95% CI -3.38. -1.27)

✓ No side effect of miscarrige, neonatal mortality, congenital malformation, mental development.

✓ Increasing edema

Mercè Fernández-Balsells M et al. Clin Endocrinol (Oxf). ***2010*** *Oct;73(4):436-44*

Discussion

Reproductive Outcome in CAH Women

- 1956-2000: 73 female patients with SV: 105 times of pregnancy. 10% spontaneous miscarriage.

Lo JC et al. Endocrinol Metab Clin North Am. 2001;30(1):207-29.

- 106 women with CAH from UK: 21 of 23 trying to conceive achieved 34 pregnancies (pregnancy rate of 91.3%), similar to normal population (95%).

Casteràs et al. Clin Endocrinol (Oxf). 2009;70(6):833-7.
Dumic M et al. J Pediatr Endocrinol Metab. 2005 Sep;18(9):887-95.

Discussion

Reproductive Outcome in CAH Women

- Infertility depends on severity: salt wasting 10%; simple virilization 33-50%; non classical 63-90%
- Only 30% female patients with CAH ever try to get pregnancy (normal control 66%)

Endocrinol Metab Clin North Am. ***2015*** *Jun;44(2):275-96.*

J Clin Endocrinol Metab. ***2010*** *Sep;95(9):4133-60*

Discussion

Reproductive Outcome in CAH Women

- Pregnants with CAH should be followed up by endocrinologists and obstetricians
- Continuing of taking hydrocortisone/prednisolone & fludrocortisone
- Dose incresing if adrenal crisis
- Stress dose when delivery

J Clin Endocrinol Metab. ***2010*** *Sep;95(9):4133-60*

Conclusions

- 1st case was successful prenatal treatment in VN: normal external genitalia
- 3 female patients with CAH gave normal babies.
- It is important to have good control in female patients with CAH
- Teamworks: pediatric endocrinologists, aldult endocrinologists, obstetricians.

Rare Disease Day 2016

Thank you very much!