Congenital Adrenal Hyperplasia Due to Steroid 21-hydroxylase Deficiency

Naomi Weintrob
The Pediatric Unit for Endocrinology and Diabetes
Dana-Dwek Children's Hospital
Tel Aviv Sourasky Medical Center

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Outline

- **Background**
- Prenatal therapy
- Complications and mortality
- Newborn Screening

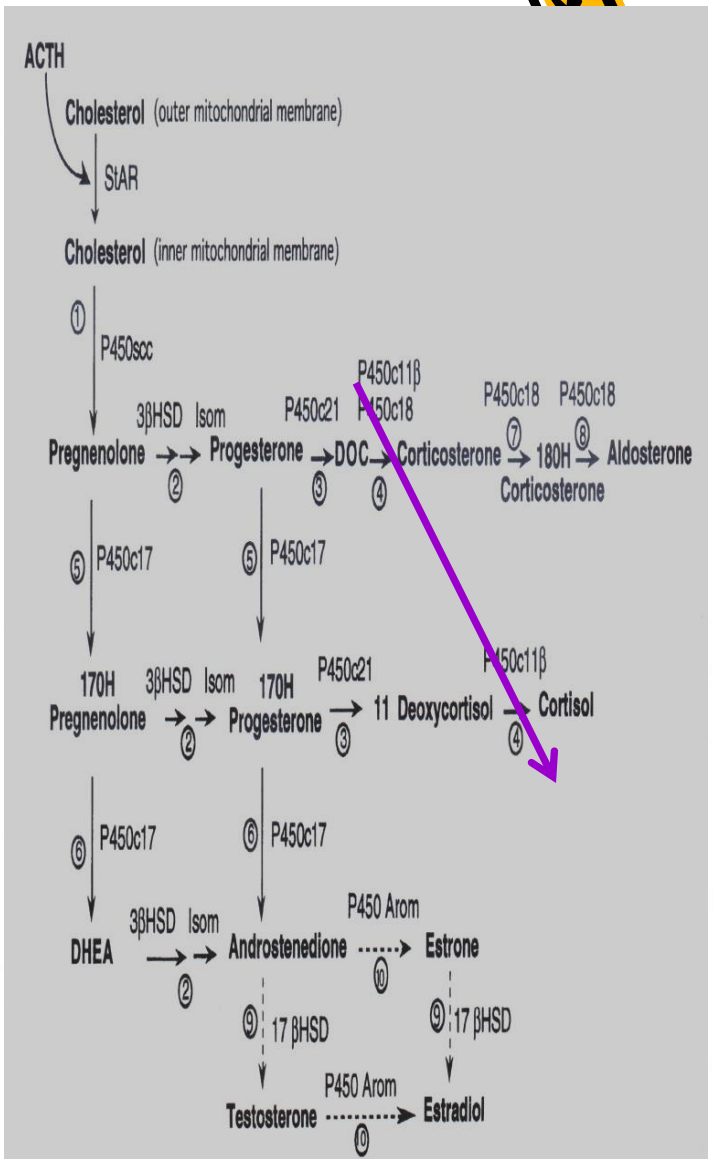
Congenital Adrenal Hyperplasia (CAH)

- CAH is a group of autosomal recessive disorders characterized by impaired cortisol synthesis
- The most common form of CAH (1:10,000-1:28,000) is caused by mutations in *CYP21A2* encoding the enzyme 21 hydroxylase
- One of the most common genetic inborn errors of metabolism
- Deficient adrenal cortisol production → overproduction of ACTH, cortisol precursors that are diverted to adrenal androgens

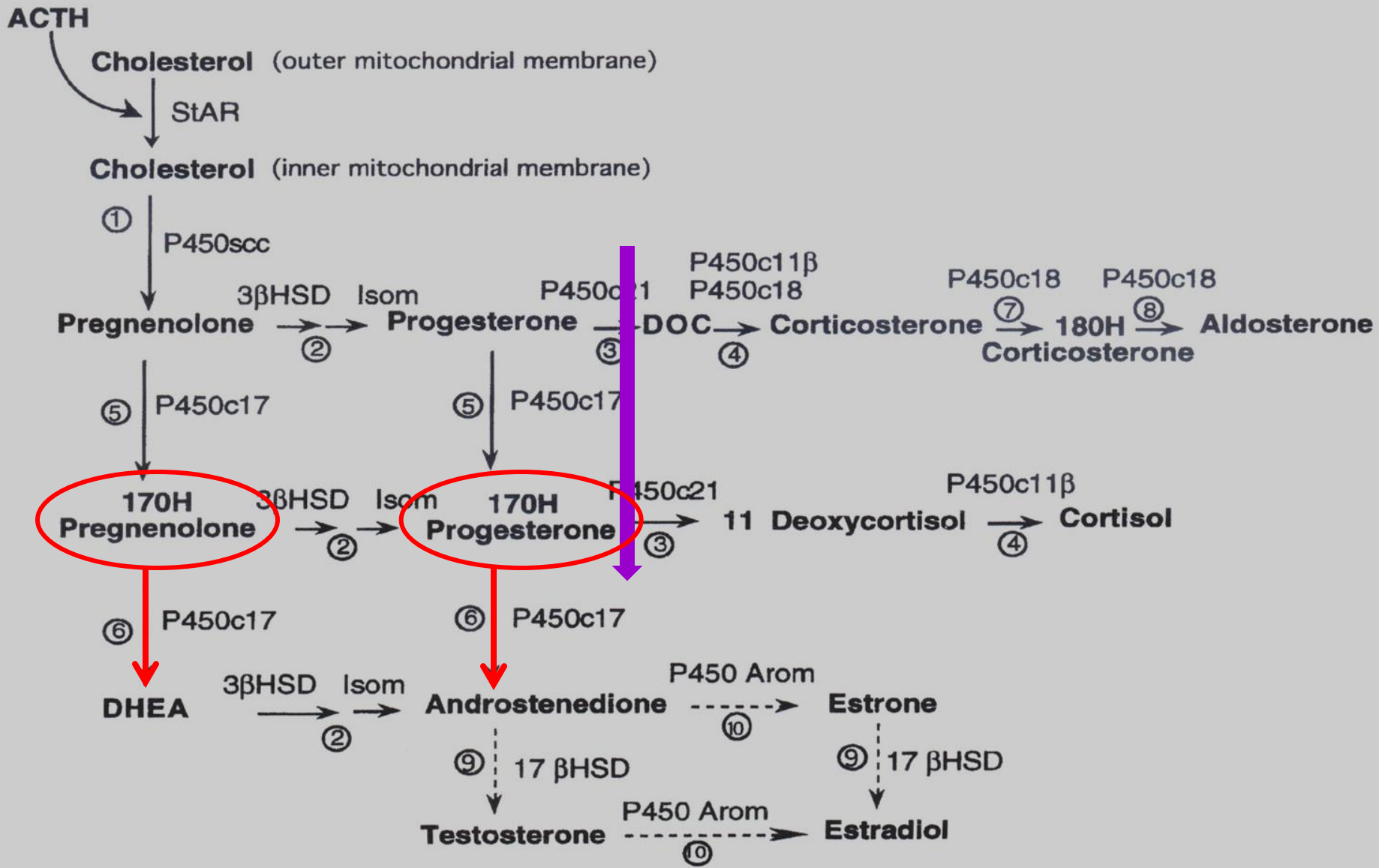
Congenital Adrenal Hyperplasia

11β-hydroxylase deficiency

- 5-8% of cases of CAH
- 1:100,000, 1:7000 in Moroccan Jews
- Mutations in the gene for 11β-hydroxylase (8q24.3)
- Female pseudohermaphroditism, postnatal virilization in males and females,hypertension
- Elevated ACTH and suppressed plasma renin activity, hypokalemia, increased basal and ACTH-stimulated 11 deoxycortisol (compound S), deoxy corticosterone (DOC) and serum androgens



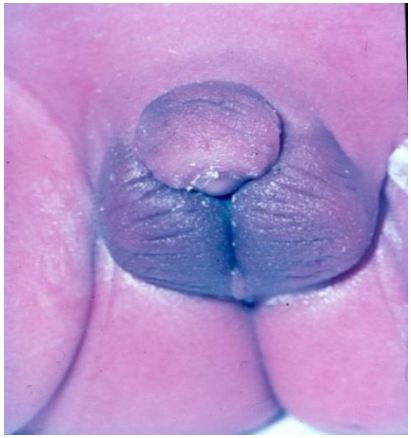
PATHWAYS OF STEROID BIOSYNTHESIS



Congenital Adrenal Hyperplasia (CAH) Due To Steroid 21-Hydroxylase Deficiency

Three types according to severity of expression

Classic



- **1. Salt wasting**
  - neonatal electrolyte disturbances
  - ambiguous genitalia in females
  - rapid somatic growth
  - accelerated bone maturation
  - precocious pseudo-puberty or true precocious puberty
  - premature epiphyseal fusion
  - shortened adult height
- **2. Simple virilizing** - as in salt wasting without electrolyte disturbances
- **3. Non-classic 21-OHD** - different degrees of postnatal virilization or asymptomatic

Diagnosis of CAH- Biochemical!!

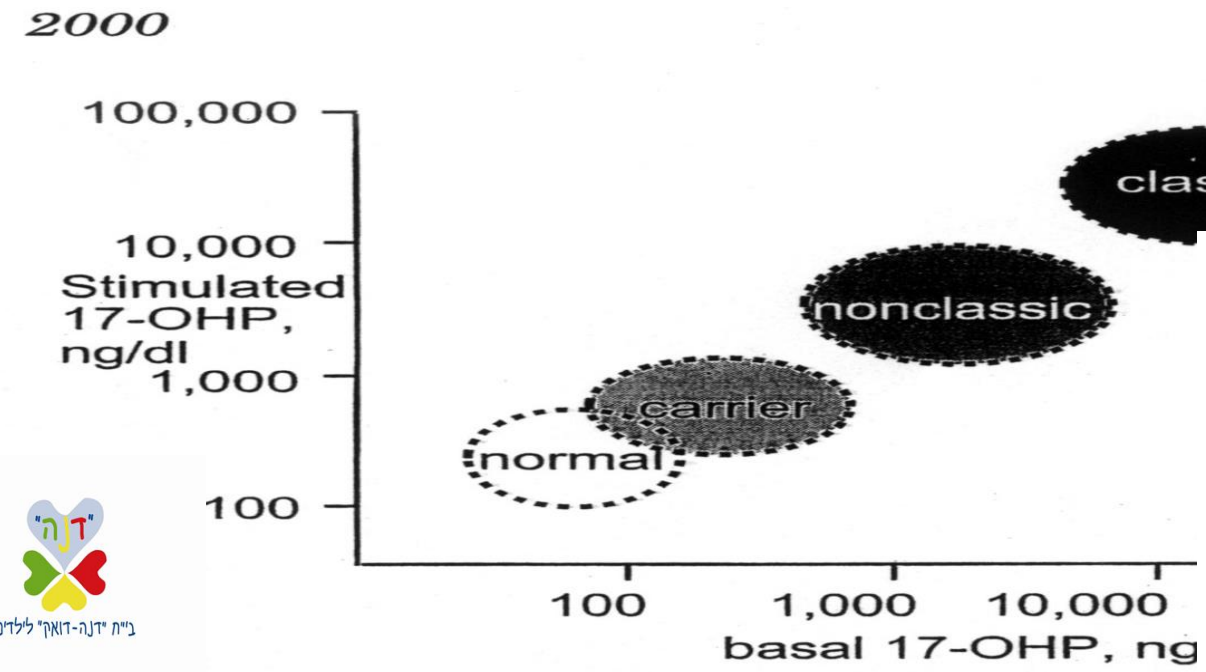
Basal 17 OHP levels (nmol/L)*

>300	6-300	<6
Likely Classic	Likely NCCAH	Likely Unaffected

17 OHP Levels Post ACTH Stimulation

>300	45-300	<45 (<30)
Classic CAH	NCCAH	Unaffected or heterozygote

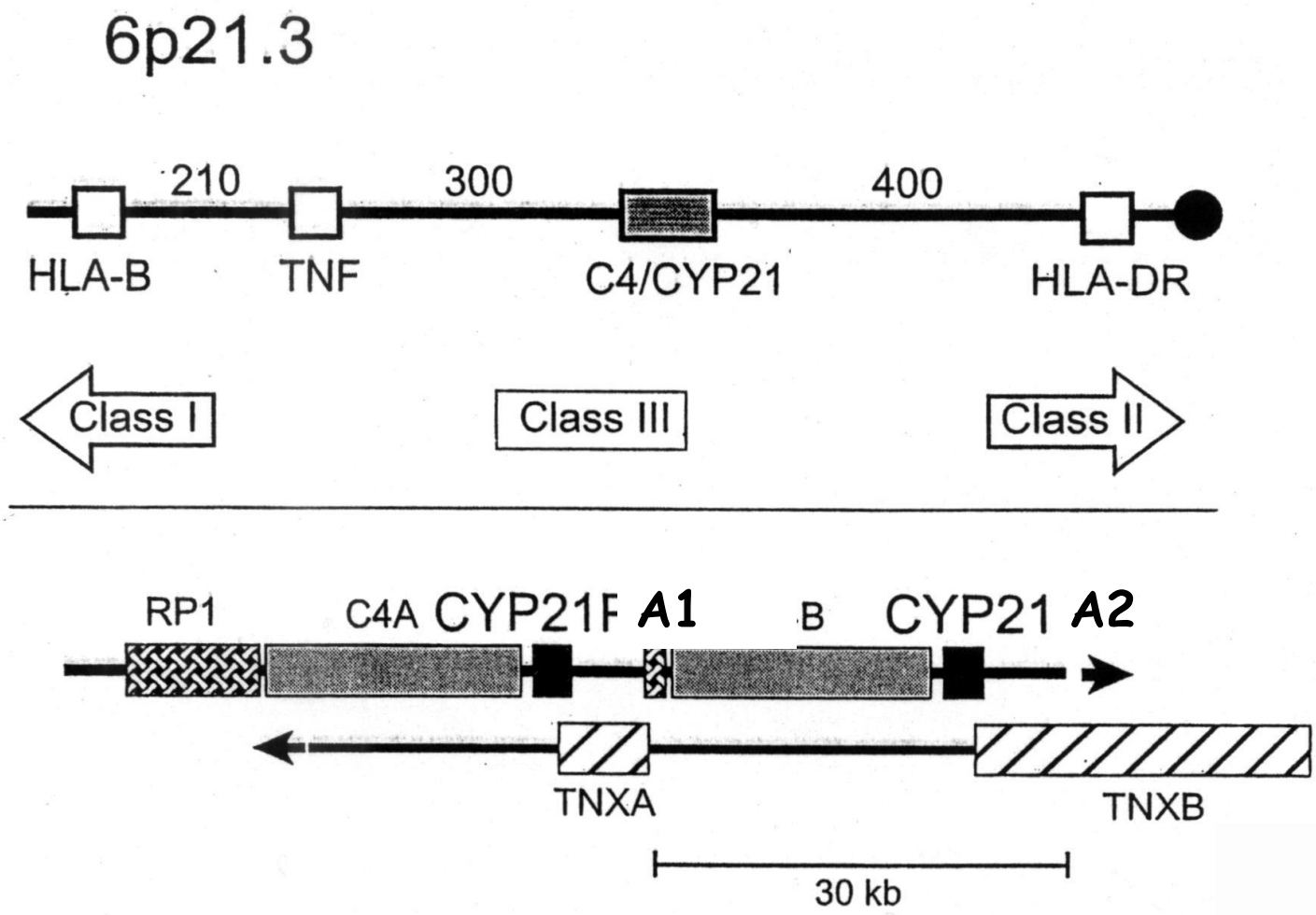
* For ng/ml divide by 3, for ng/dl divide by 0.03



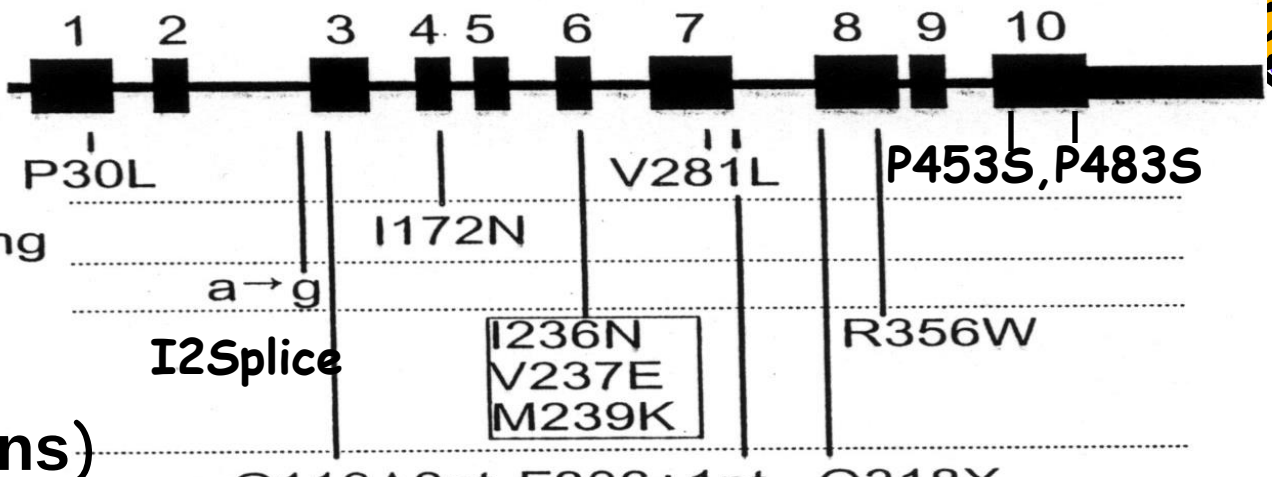
New MI et al, 1983
JCEM, 57:320-326

Speiser WS et al., 2010
JCEM 95:4133-4160

CYP21A2 And CYP21A1P Genes



Congenital Adrenal Hyperplasia: Genotype Phenotype Correlations



(Null Mutations)

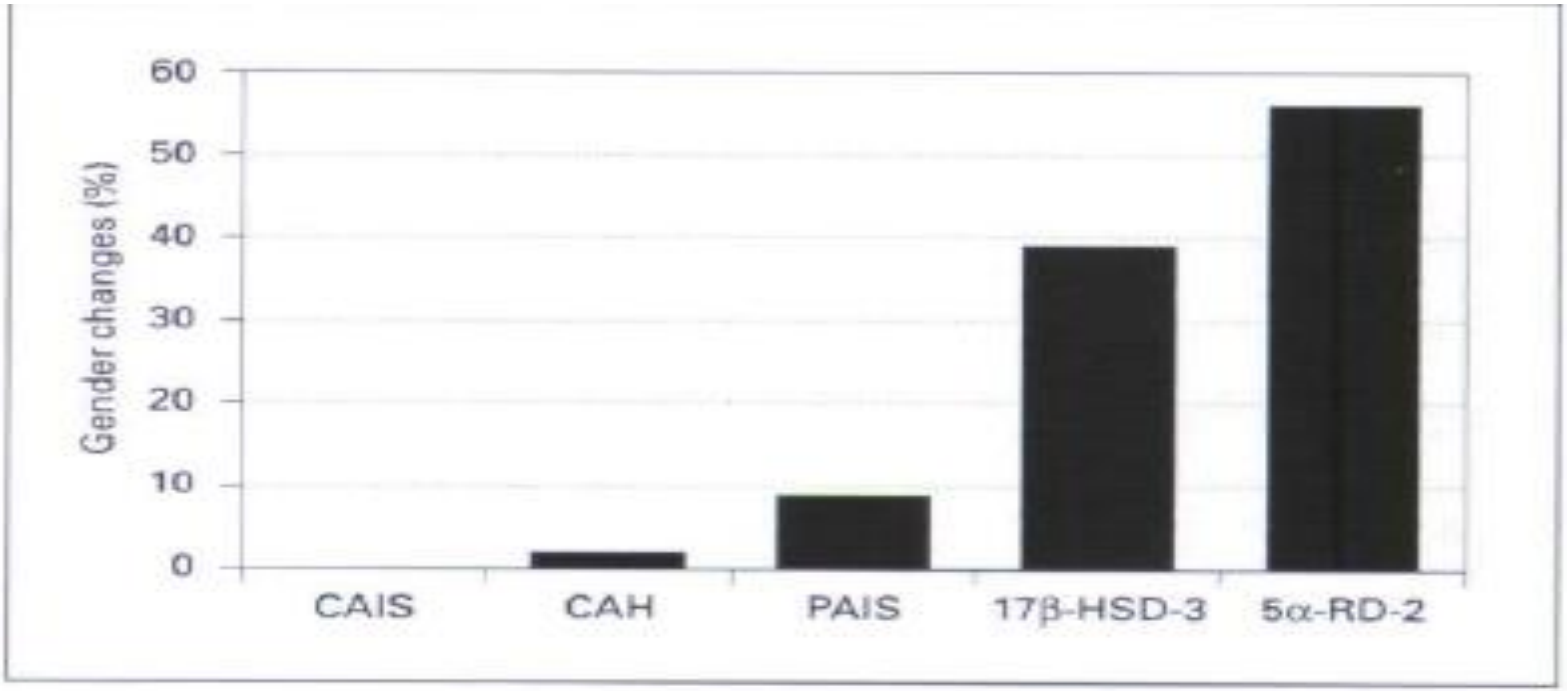
Different ethnic distribution

Wilson RC, 2007, Molecular genetics and Metabolism 90:414-421

Percentage of Patients with DSD Opting to Change Sex

The gender identity was female in 92% of 46,XX patients with CAH raised as girls (n=250)

Dessens et al. 2005 Arch Sex Behav.34:389-397



Subjects No: 156 250 99 49 110

Cohen-Kettenis P, 2005 Hor Res, 64,Supp 2:27-30

Gender Role and Sexual Orientation

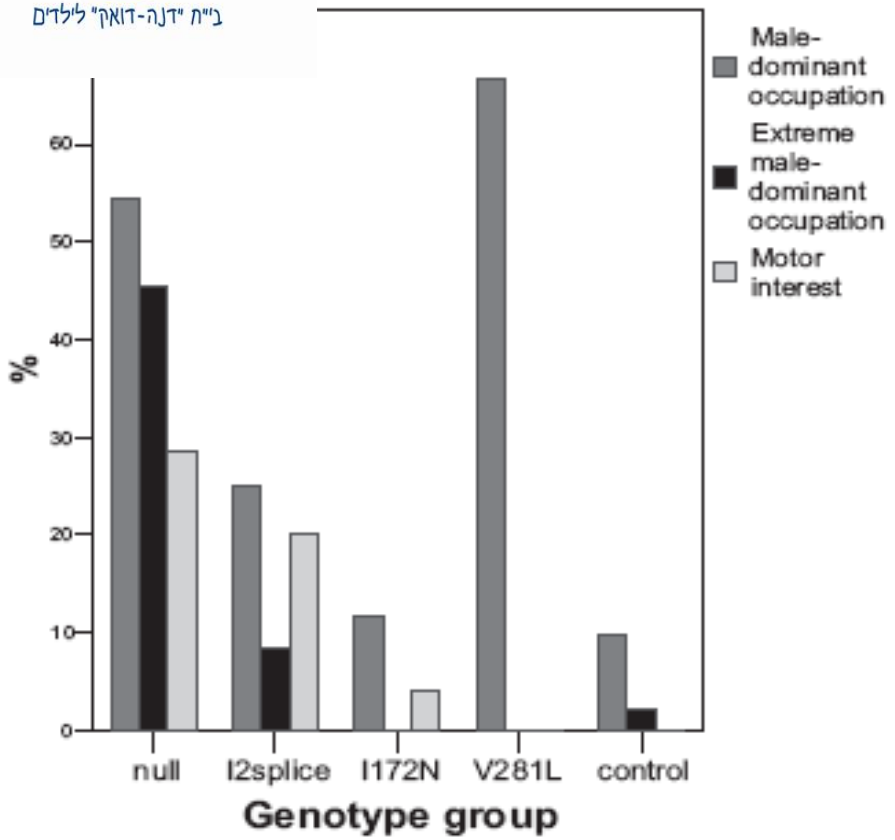


FIG. 1. Male-dominant occupations (≤25% females in occupation), extreme male-dominant occupations (≤11% females in occupation) and motor vehicles as main interest, given as the percentage for the different *CYP21A2* genotype groups and the controls.

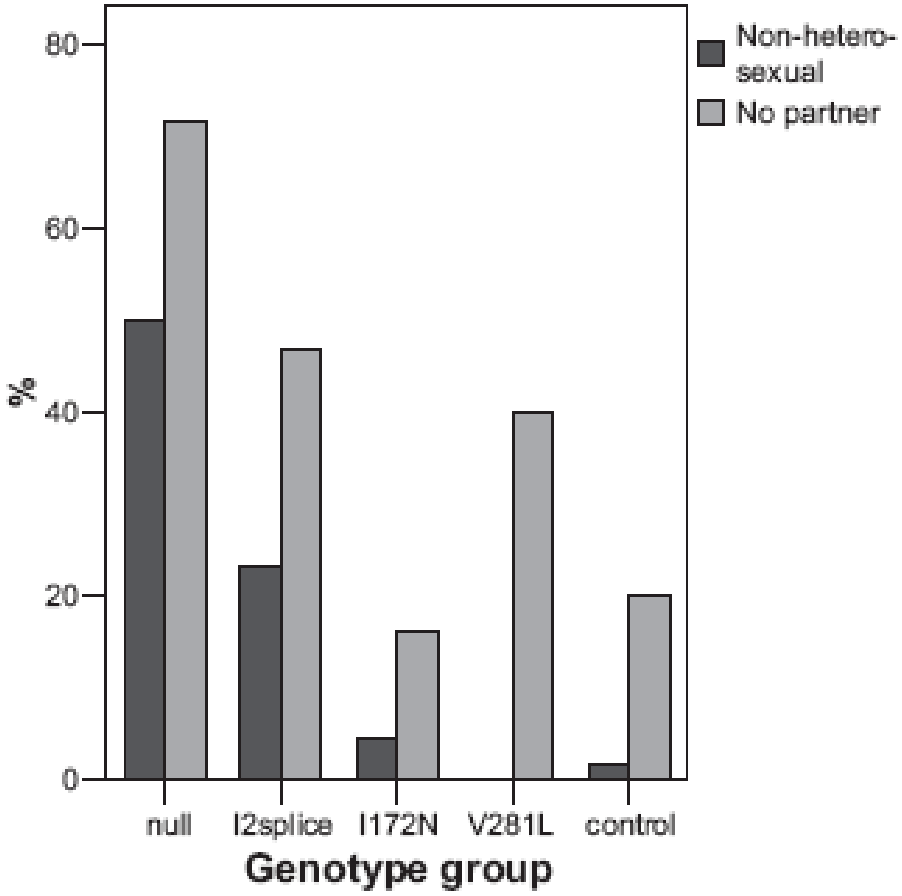


FIG. 2. Women with bi- or homosexual orientation and women with no partner given as percentage for the *CYP21A2* genotype groups and the controls.

Frisen L et al., 2009 JCEM 94:3432-39
Meyer-Bahlburg HF, 2008 Arch Sex Behav 37:85-99

Lessons we Learn from Nature

Congenital Adrenal Hyperplasia:

- Increased fetal exposure to androgens in XX females might cause changes in gender role and sexual orientation, but usually not in gender identity or measures of quality of life
- Multidisciplinary teams involving mental health staff with expertise in managing psychosocial problems specific to CAH and different sexual development (DSD)

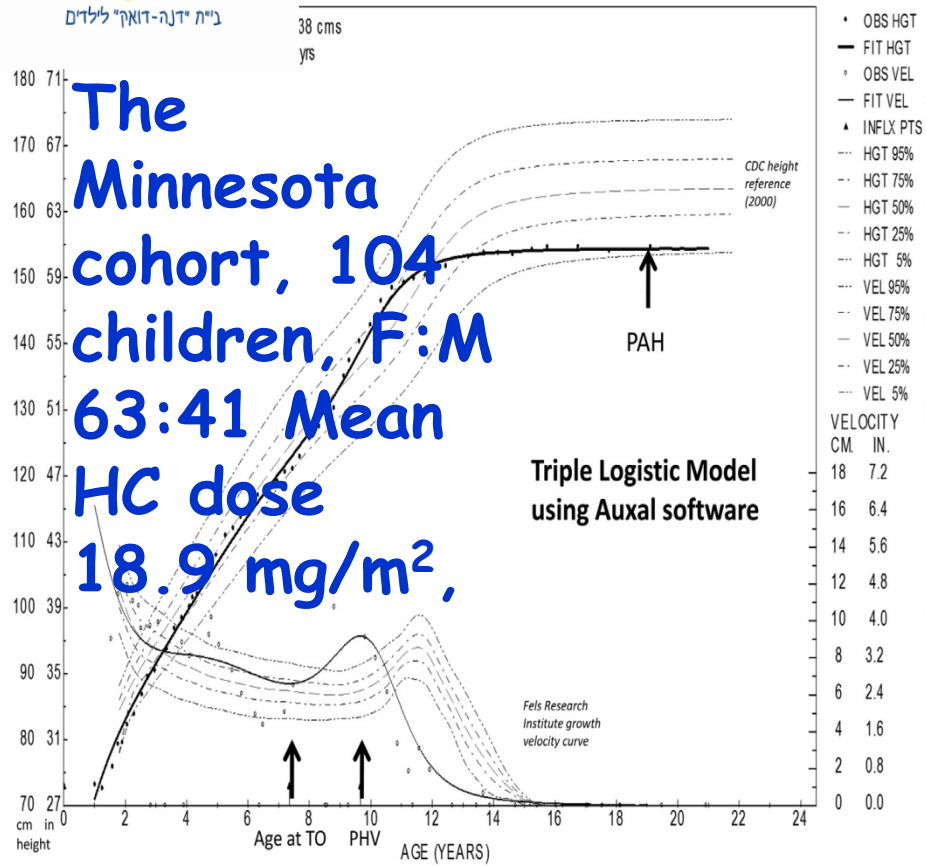
Feminizing Surgery

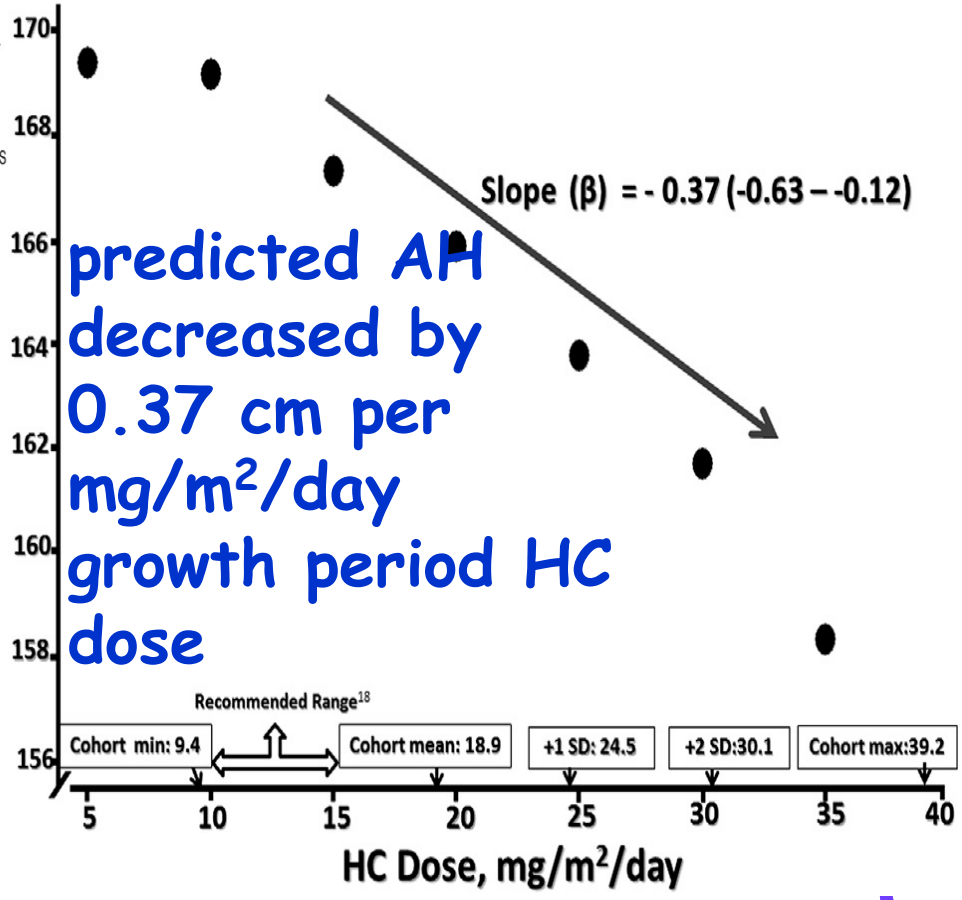
- There are no randomized controlled studies of either the best age or the best methods for feminizing surgery
- There is no evidence at this time that either early or late surgery better preserves sexual function
- Early surgery reduces parental anxiety, allows acceptance of the child congenital anomaly, avoids stigmatization of a girl with masculinized genitals, and the psychological trauma of genital surgery during adolescence
- Late reconstruction allows patient autonomy regarding surgery that may damage sexual function, and diminishes the risk for vaginal stenosis and the need for subsequent dilation
- **Neurovascular sparing clitoroplasty and vaginoplasty using total or partial urogenital mobilization**
- **The majority of women with CAH surveyed favored genital surgery before adolescence**

Farkas A et al., J Urology 2001 165: 2341-6
Wisniewski AB et al., 2004 J Urology 171:2497-501
Nordenskjold A et al., 2008 JCEM 93:380-6
Strum RM et al., J Urology March 2015 E Pub ahead

Growth in Classic CAH

The Minnesota cohort, 104 children, F:M 63:41 Mean HC dose 18.9 mg/m², predicted AH decreased by 0.37 cm per mg/m²/day growth period HC dose





As the HC dose increased from 15 to 39.2 mg/m²/day PAH progressively decreased from 167.5 to 158 cm

AH was better in SV (173, 161cm) than in SW (169,158)

Difference between PAH to AH only 0.5 cm

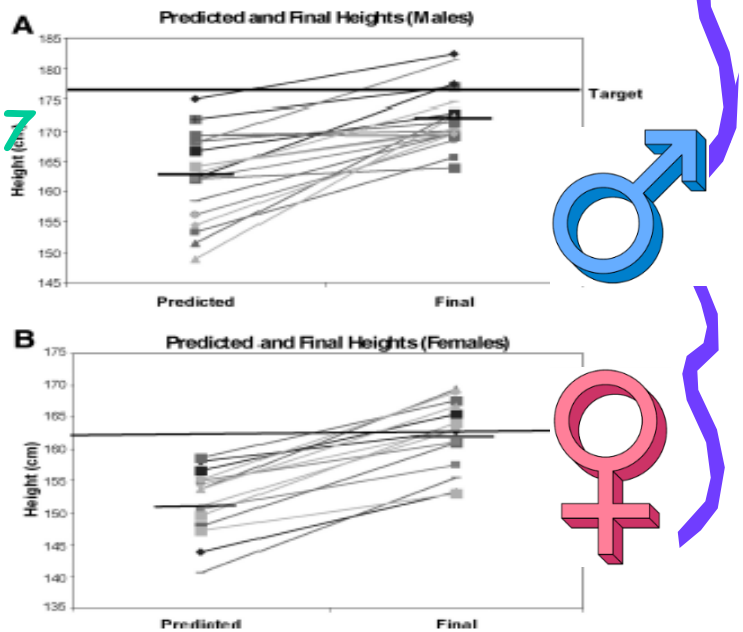
Bomberg EM et al., 2015 J Pediatr 166:743-750

GH-treated subjects with and without LHRHa

	LHRHa (n 27)	No LHRHa (n 7)	P
Male:female	16:11	3:4	
SW:SV:NC	11:7:9	3:1:3	
BA at start of GH	11.8 (1.6)	9.9 (2.3)	<0.05
Age at start of GH	8.9 (2.2)	7.4 (2.0)	0.05
Gain in height (cm)	**9.2 (5.8)**	**11.8 (4.0)**	NS
Adult height SDS	**-0.37 (0.8)**	**-0.07 (0.8)**	NS
GH tr. duration	5.1 (1.9)	5.2 (1.5)	NS

Lin-Su K et al., 2011 JCEM 96:1710-1717

Predicted VS Adult Height



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Experimental Therapies

Growth enhancement

- Children with CAH and predicted FH of ≤2.25 SD might be considered for experimental treatment in appropriately controlled trials
- Prospective, large, randomized studies to determine whether the use of growth promoting drugs increase AH in subjects with CAH are needed

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Outline

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- **Prenatal therapy**
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Prenatal Treatment of CAH

Rational for therapy:

- Suppression of fetal adrenal androgens in classic CAH is feasible by administrating high dose of dexamethasone to the mother (20 mcg/kg/day devided to 3 doses
- Treatment aims to:
  1. reduce female genital virilization
  2. the need for reconstructive surgery
  3. The emotional distress associated with the birth of a child with ambiguous genitalia

Forest MG et al.,1998, Trends Endocrinol Metab 9:284-289
New MI et al., 2001, JCEM 86:5651-5657

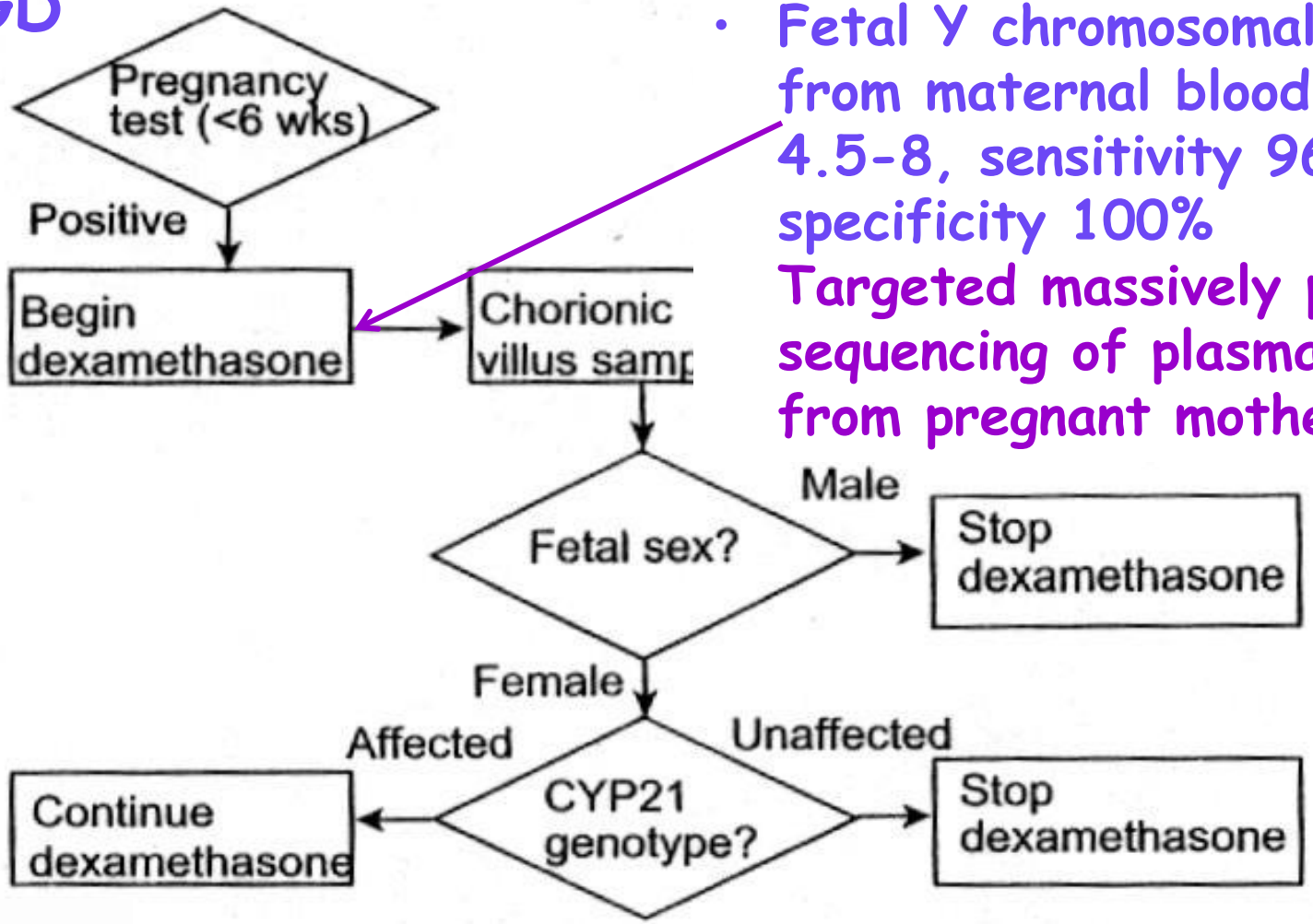
Prenatal Treatment

- The female fetus may become virilized begining six-seven weeks after conception
- Treatment must be instituted as soon as the woman knows she is pregnant and not later then the 8th week of gestation
- Dexamethasone (DM) is the only option for fetal treatment - because it is not inactivated by placental 11beta-hydroxysteroid dehydrogenase type 2
- To prevent virilization in one CAH girl, seven out of eight fetuses will be exposed to DEXA treatment unnecessarily from 6-12 weeks' gestations.

White PC et al., Endocr Rev 2000, 18:135-156
New MI et al., Seminars in Reproductive Medicine 2012 30:396

Flowchart For Prenatal Diagnosis And Therapy In 21-OHD

PGD



- Fetal Y chromosomal DNA from maternal blood at week 4.5-8, sensitivity 96% specificity 100%
  Targeted massively parallel sequencing of plasma DNA from pregnant mothers

Rijnders RJ et al., 2001 Obstet Gynecol 98:374-378
Tardy-Guidollet V et al., 2014 JCEM,99:1180 -1188
New MI et al., 2014 JCEM99:E1022-E1030

Prenatal Diagnosis Referrals 1978 - March 2011

719

DEX- 392

No DEX- 327

CL	NC	Unaff	CL	NC	Unaff
16% 97	25% 10	73% 285	31	8	288
F 63 / M 34	F 4 / M 6	F 152 / M 133	F 11 / M 20	F 4 / M 4	F 156 / M 132

Prader

NI. F -15

I-II - 26

III-IV - 17

Avg. 1.70

Prader

III - 3

IV - 8

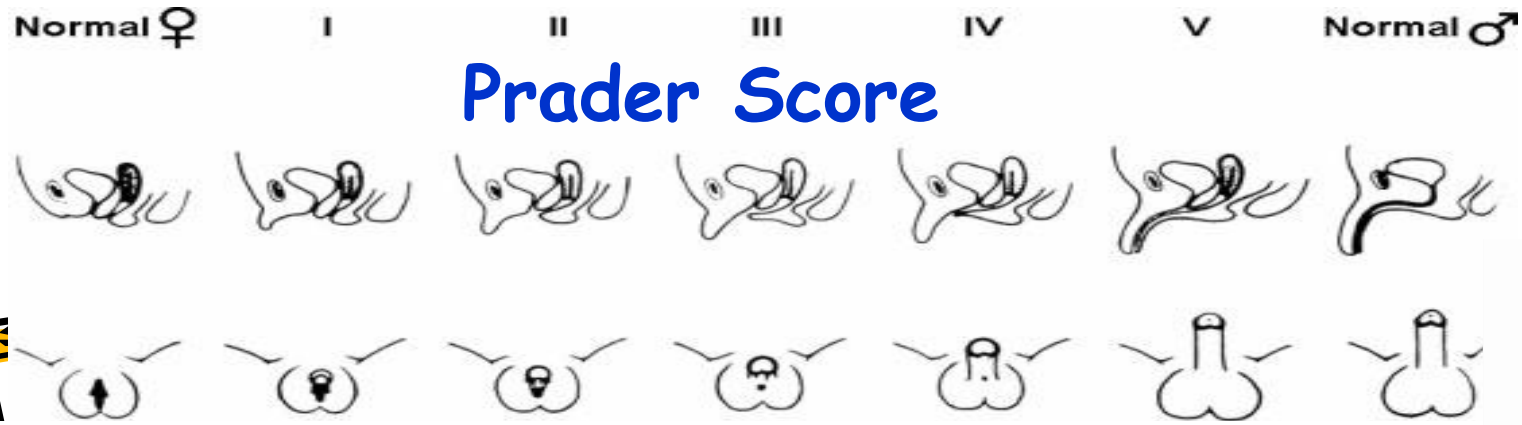
Avg. 3.73

CL – classical for of CAH

NC – non-classical form of CAH

DEX – Dexamethasone

Prader – Prader Score



Prader Score

New MI et al., 2012 Seminars in Reproductive Medicine 30:396

Prenatal Treatment-fetal risk

Animal studies :

- Prenatal DM altered post natal renal structure and function and produced hypertension in rodents

  Celsi G et al., 1998 Pediatr res 44:317-322

- High dose maternally administered DM disrupted development of hippocampal neurones in fetal rhesus monkeys

  Uno H et al., 1990 Dev Brain Res 53:157-167

Human studies

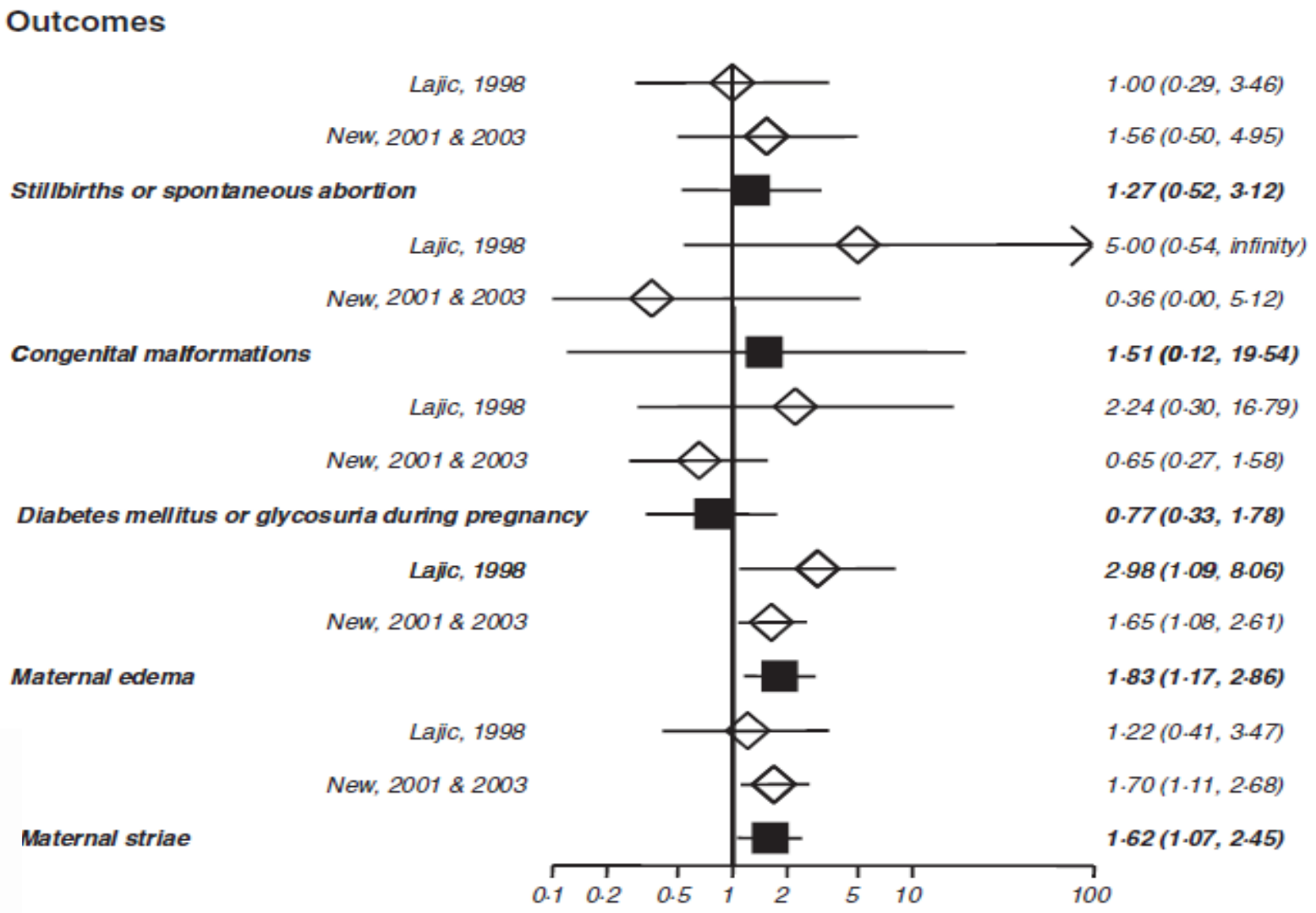
- the constant DM dose currently used may result in GC levels that exceed physiological midgestation fetal levels by 60 fold

  White PC, 2006 J clin Invest 116:872-874

- Early maternal exposure to glucocorticoid between 1-8 weeks gestation was more frequent in a group of newborns with cleft lip or cleft palate compared to control (odds ratio 1.7)

  Carmichael SL et al., 2007, Am J Obstet Gynecol 197:585

Prenatal DM use for the prevention of virilization in pregnancies at risk for classical : a systematic review and meta-analyses, Maternal Safety



Ferna´ndez-Balsells MM et al., 2010 Clin Endocrinol 73:436-444

Prenatal Treatment-fetal risk

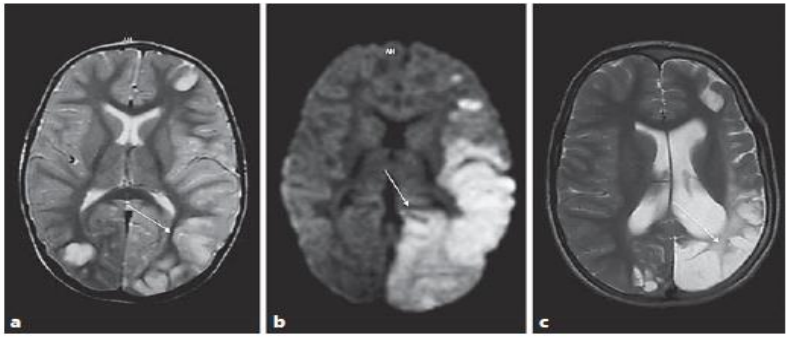
- Follow-up reports of prenatally treated children have reported birth weights (BW) in the normal range, but mean BW was reduced by about 0.4-0.6 kg with normal post natal growth

  Lajic S et al., 1998 JCEM 83:3872-3880
  New MI et al., 2001 JCEM 86:5651-5657
  Forest MG, 2004 Hum Reprod update 10:469-485

- There are no data on long term follow-up of physical and metabolic outcomes in children exposed to dexamethasone

  Ferna´ndez-Balsells MM et al., Clin Endocrinol 2010, 73:436-444

- Case reports of two prenatally DM treated children with CAH who suffered acute ischemic stroke and focal neurologic deficits.



Grunt S et al,2013 Hormone res Ped. 80:57-63

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Prenatal Treatment-Late Effects

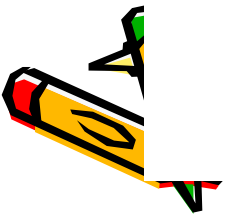
- Results of neuropsychological tests are conflicting: one study reported more shyness and inhibition in prenatally DM treated subjects; a second study found no differences between treated and untreated groups with respect to nine social/developmental scales; a third study found no differences in intelligence, handedness or long term memory. However, CAH-unaffected children prenatally treated short term had poorer verbal working memory, rated lower on self perception of scholastic competence and had increased self-rated social anxiety.
- There was no differences in psychopathology, behavioral problems or adaptive functioning

Trautman PD et al.,1995 psychoneuroendocrinology 20:439
Meyer-Bahlburg HF et al., 2004 JCEM 89:610
Hirvikoski T et al., 2007 JCEM 92:542, JCEM 2012 97: 1881-83

Prenatal Treatment

- The long-term effects of this treatment on physical and neuropsychological health of the offspring remain unclear:
  whether the potential neuropsychological and physical consequences of treatment outweigh the physical and psychological impact of ambiguous genitalia remains to be determined
- The decision about initiating treatment should be based on patients' values and preferences and requires fully informed and consenting parents

Ferna´ndez-Balsells MM et al., Clin Endocrinol 2010, 73:436-444



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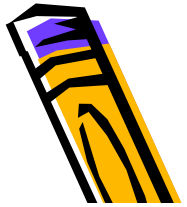
Prenatal Treatment



- All published practice guidelines from numerous medical societies caution that prenatal treatment of CAH with dexamethasone is at best experimental, and at worst contraindicated
- The concern is treating seven unaffected and/or male fetuses to treat one affected female in the context of inadequate data regarding the long term risks of this therapy

Speiser PW et al.,JCEM 2010, 95:4133-4160

Miller WL, Best Practice & Research Clinical Endocrinology & Metabolism, E-pub ahead, 01.2015

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Prenatal Treatment-fetal risk

- FDA and UMA classified DM administration during pregnancy as a category B drug (its safety in pregnancy is not known), therefore the administration of DM for prenatal CAH is an off label use

Prenatal Treatment

Our experience

- Five mothers choose DM, one twice, in three pregnancies stopped at week nine due to positive SRY in cell free DNA in maternal plasma. Two continued to end of pregnancy, one CAH female with completely normal genitalia, one refused any test, healthy baby
- Three choose PGD: one three preg., one 2 preg., one In process
- One spontaneous pregnancy, female carrier.

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Complications of CAH

Metabolic syndrome

- Compared to controls, children and adults with CAH have higher BMI due to increased fat mass, higher prevalence of overweight and obesity (16-33%), and higher dyslipidamia,serum leptin and insulin levels.
- BMI is higher for DEXA treated (28) vs HC treated (26) patients.

Volkl TM et al., 2009 Eur J Endocrinol 160:239
Finkielstain GP et al, 2012 JCEM 97: 4429–4438
Bouvattier C et al ,March 2015 JCEM E-pub ahead

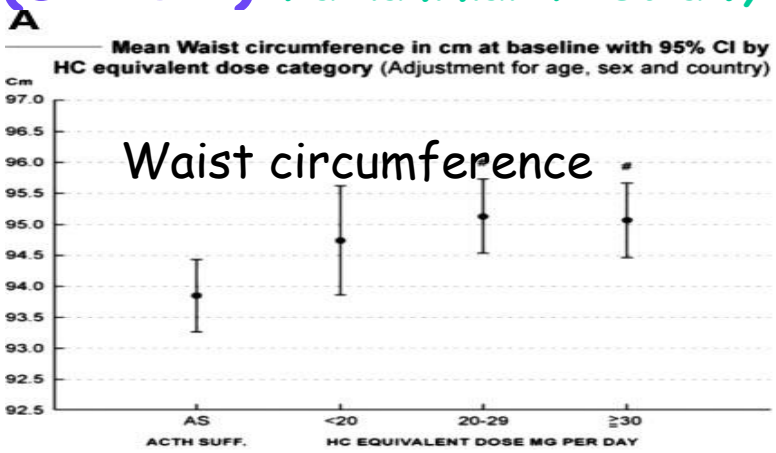
Hypertension is more prevalent in children with classic CAH than in the general population and is related to BMI and MC therapy independent of GC therapy.

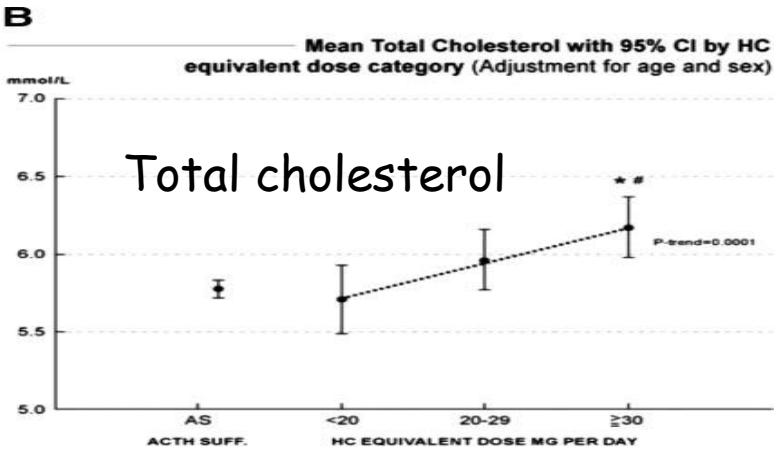
Roche EF et al., 2003 Clin Endocrinol 58:589
Volkl TM et al., 2006 JCEM 91:4888
Finkielstain GP et al, 2012 JCEM 97: 4429–4438

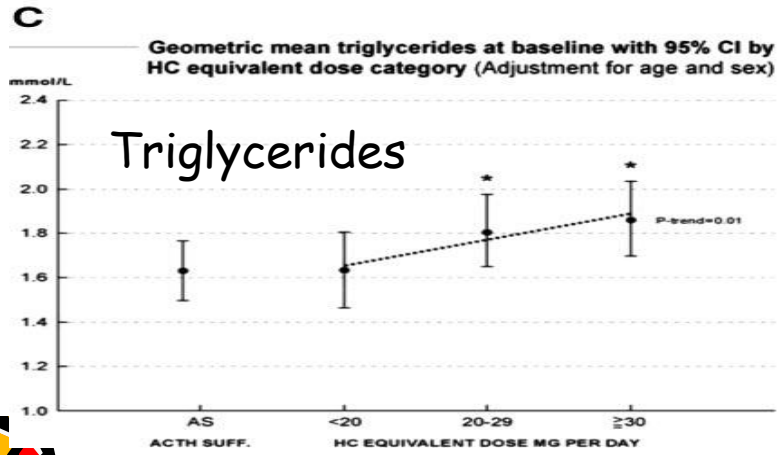
Complications of CAH

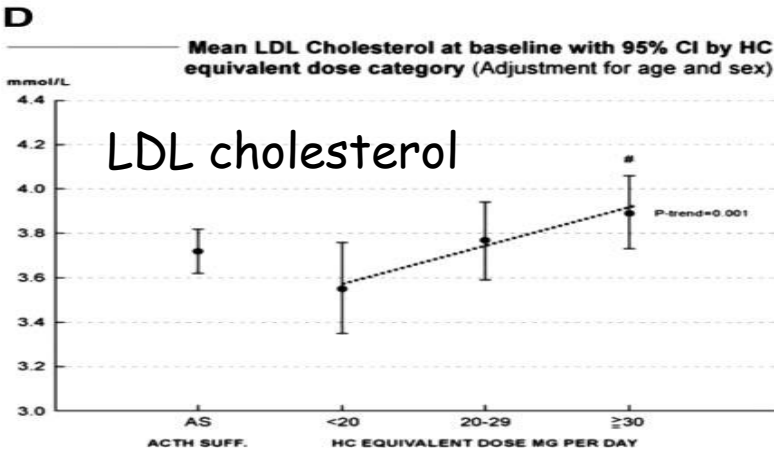
Iatrogenic Cushing's syndrome

- Gestational diabetes was increased (20%) among classic CAH women compared to healthy controls (5-10%) *Falhammar H et al., 2007 JCEM 92:110-116*









Filipsson H et al., 2006 JCEM 91:3954

Complications of CAH

- IGT and diabetes are uncommon in CAH and reports on lipid levels are conflicting
- High prevalence of over and under treatments in adults with CAH

Arlt W et al 2010 JCEM 95:5110-5121

Finkielstain GP et al,2012 JCEM 97: 4429-4438

- **Long term lifestyle counseling and Exelence Centers for CAH patients**

Complications of CAH

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Bone Mass Density

- In CAH children and adolescents on standard GC therapy (10-20 mg/m2/day) there is no evidence of decreased BMD

  Girgis R et al., 1997 JCEM 82:3926
  Gussinye M et al., 1997 Pediatrics 100:671
  Mora S et al., 1996 Bone 18:337

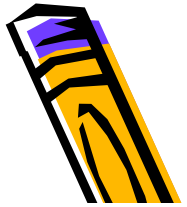
- Age-appropriate vitamin D and calcium intake along with weight bearing exercise
- Adults: 40% osteopenia 7% osteoporosis.

Adrenal Mass

- A high prevalence of benign adrenal mass (82%) have been observed in adults with CAH
- Adrenal CA have rarely been reported

  Jaresch S et al., 1992 JCEM 74:685
  Barzon L et al., 2007 J Endocrinol Invest 30:615

Complications of CAH



Menstrual irregularity and secondary PCOS

No difference in the prevalence of irregular menses between treated CAH and control woman

- The prevalence of polycystic ovaries on US in adolescent girls with well controlled CAH correspond to that of the general population

Hagenfeldt K et al., 2008, Hum Reprod23:1607
Fleischman A et al., 2007 J Pediatr Adolesc Gynecol 20:67

- Menstrual irregularity is typically one of the presenting signs in NC21OHD

Complications of CAH

Fertility

- Fertility is reduced in salt wasting CAH females and in some untreated NC21OHD patients. Only 25-30 % of classic CAH women wished pregnancy compared with 66% of controls. Success rate was 54%

  Hagenfeldt K et al., 2008 Hum Reprod 23:1607-1613
  Frisen L et al, 2009., JCEM, 94:3432-39
  Casteras A et al., 2009 Clinical Endocrinology, 70:833-837
  Arlt W et al., 2010 JCEM, 95:5110-5121

- Spontaneous abortions occurred more frequently in untreated compared to treated females with NC21OHD(?)

  Moran C, Azziz R, Weintrob N et al., JCEM 2006 91:3451-3456
  Bidet M et al 2010 JCEM 95:1182-1190

- Treatment may benefit infertile NC21OHD women or those with history of miscarriage

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Mental Health

Quality of life (QoL)

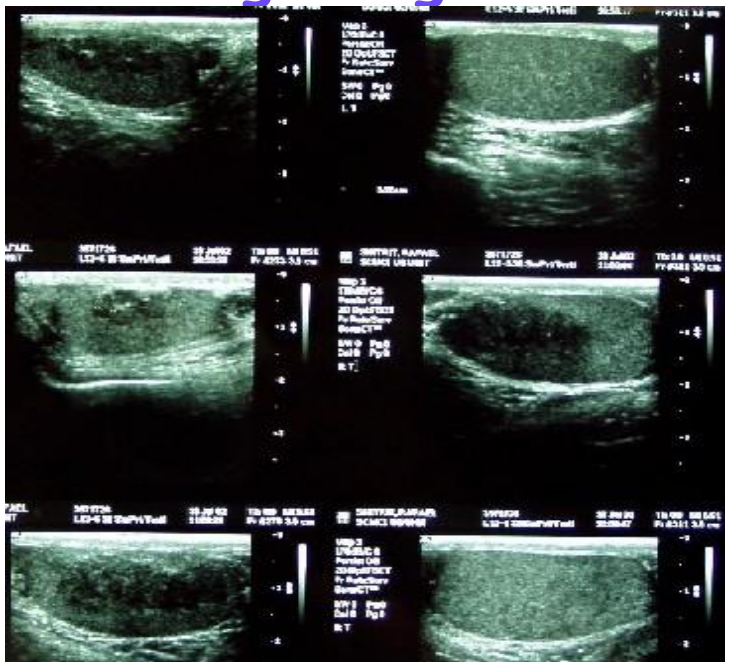
- CAH patients, both children and adults, men and women, usually did not differ from controls in measures of QoL and psychological adjustment
- Significant impairment were found concerning body image and attitude toward sexuality
- CAH women were more often single and fewer of them had children
- Impaired bodily self-image associated with short stature, overwieght and hirsutism

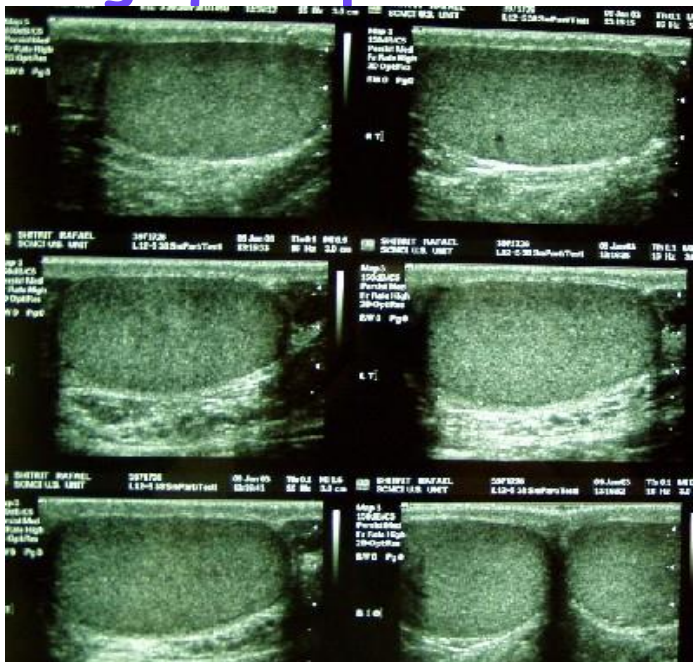
Berenbaum SA et al., 2004 J pediatr 144:741-746
Jaaskelainen J et al., 2000 Acta Paediatr 89:183-187
Kuhnle U et al., 1997 Pediatr Surg Int 12:511-515

Complications of CAH

Testicular Adrenal Rest Tumors (TART)

- Prevalence in classic CAH 21-42%
- Usually bilateral, related to suboptimal therapy and decrease in size under increased dose of GC
- Cause high degree of severe oligoqazospermia.





Claahasen-van der Grinten HL et al., 2007 Eur J Endocrinol 157:339

Martinez-Aguayo A et al., 2007 JCEM 92:4583

Bouvattier C et al ,March 2015 JCEM E-pub ahead

Mortality in CAH

- Reports on mortality in patients with CAH are scarce
- Recent study from Sweden compared mortality rate and causes of death in patients with classic 21-hydroxylase deficiency (n=588),born 1952-2009,to that of healthy control (n=58,800)
- The mean age of death was 41.2 years in CAH patients and 47.7 years in controls (P<0.001)
- Among CAH patients 23 (3.9%) had deceased compared to 942 (1.6%) of controls
- The hazard ratio of death was 2.3 (1.2– 4.3) in CAH males and 3.5 (2.0–6.0) in CAH females
- Causes of death in CAH patients were adrenal crisis (42%), cardiovascular (32%), cancer (16%), and suicide (10%).

Falhammar H et at al, 2014 JCEM, 99:E2715-E2721

Mortality in CAH

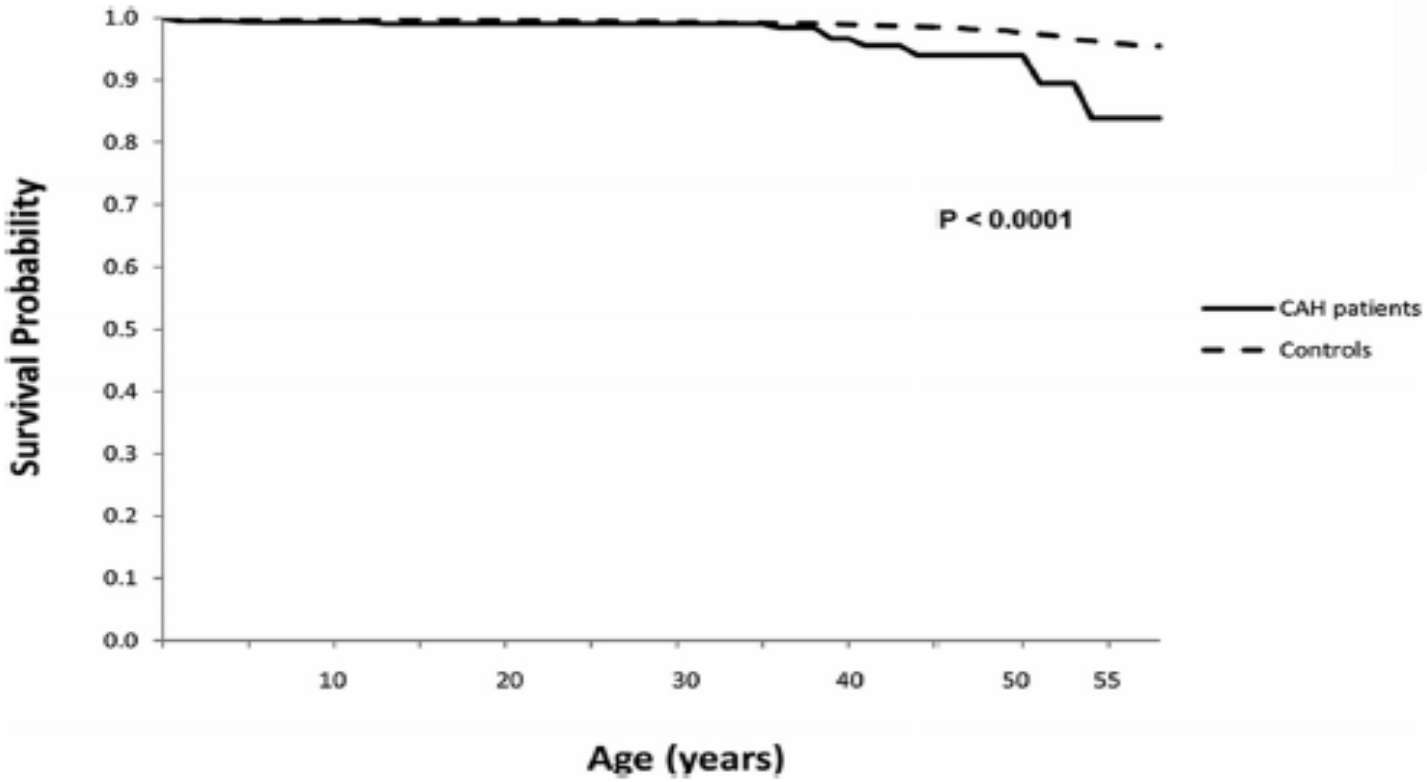


FIG. 1. Survival probability of 550 CAH individuals with 21-hydroxylase deficiency compared with 55 000 age- and sex-matched controls, year of birth 1952–2009, ie, from the commencement of the Swedish Cause of Death Registry in 1952.

Falhammar H et at al, 2014 JCEM , 99:E2715-E2721

Genetic Counseling

- The genotype and phenotype of CAH+ correlate well.25% probability that siblings of the index case will have CAH and 50% probability that they will be asymptomatic carriers
- Carrier rate of severe and mild CYP21 gene mutations in the general population is ~ 1:60 (1.6%) and 1:10-20 (6-10%), respectively
- A patient with classic CAH would have 1:120 probability of having a child with classic CAH and 1:240 of having a girl with classic CAH
- A patient with NC21OHD will have 1:500 risk of having a child with classic CAH and 1:20-30 (3-5%) of having a child with NC21OHD
- However, in a retrospective analysis of two large series of children born to NC21OHD women, the prevalence of classic and NC21OHD was much higher at 1-1.5% and 14.2-24%

  Moran C, Azziz R, Weintrob N et al., 2006 JCEM 91:3451-3456
- *Ayalon et al , IES 2015*

ב"ית "דנה-דואק" לילדים

Outline

- Background
- Prenatal therapy
- Complications and mortality
- **Newborn Screening**

Newborn Screening

- 21OHD is common and potentially fatal
- Early diagnosis and treatment can prevent morbidity and mortality
- Females outnumber males in most retrospective studies in which 21OHD was diagnosed clinically

  Lebovitz RM et al., 1984, Am J Dis Child 138:571
  Nordenstrom A et al., 2005, Horm Res 63:22

- Retrospective analysis of sudden infant death in the Czech republic and Austria identified three (1%) genotype-proven cases of classic 21OHD among 242 samples screened

  Strnadova KA et al., 2007, Eur J Pediatr, 166:1

- The death rate in salt-wasting CAH without screening is between 4 and 10%

  Grosse SD et al., 2007 Horm Res 67:284

Newborn Screening (NS)

- 17- hydroxy progesterone on dried blood spots on the same filter paper of other NS programs
- Screening markedly reduced the time to diagnosis and gender assignment of virilized girls
- Morbidity and mortality are reduced due to early diagnosis and prevention of severe salt wasting or late diagnosis of males with SV CAH
- Salt wasting 21OHD patients ascertained through screening programs are equally likely to be male, have less severe hyponatremia and hyperkalemia
- Initiated in Israel at 2008, eight patients/year
  1:23000 in Jews, 1:9500 in Arabs
  80% salt wasting

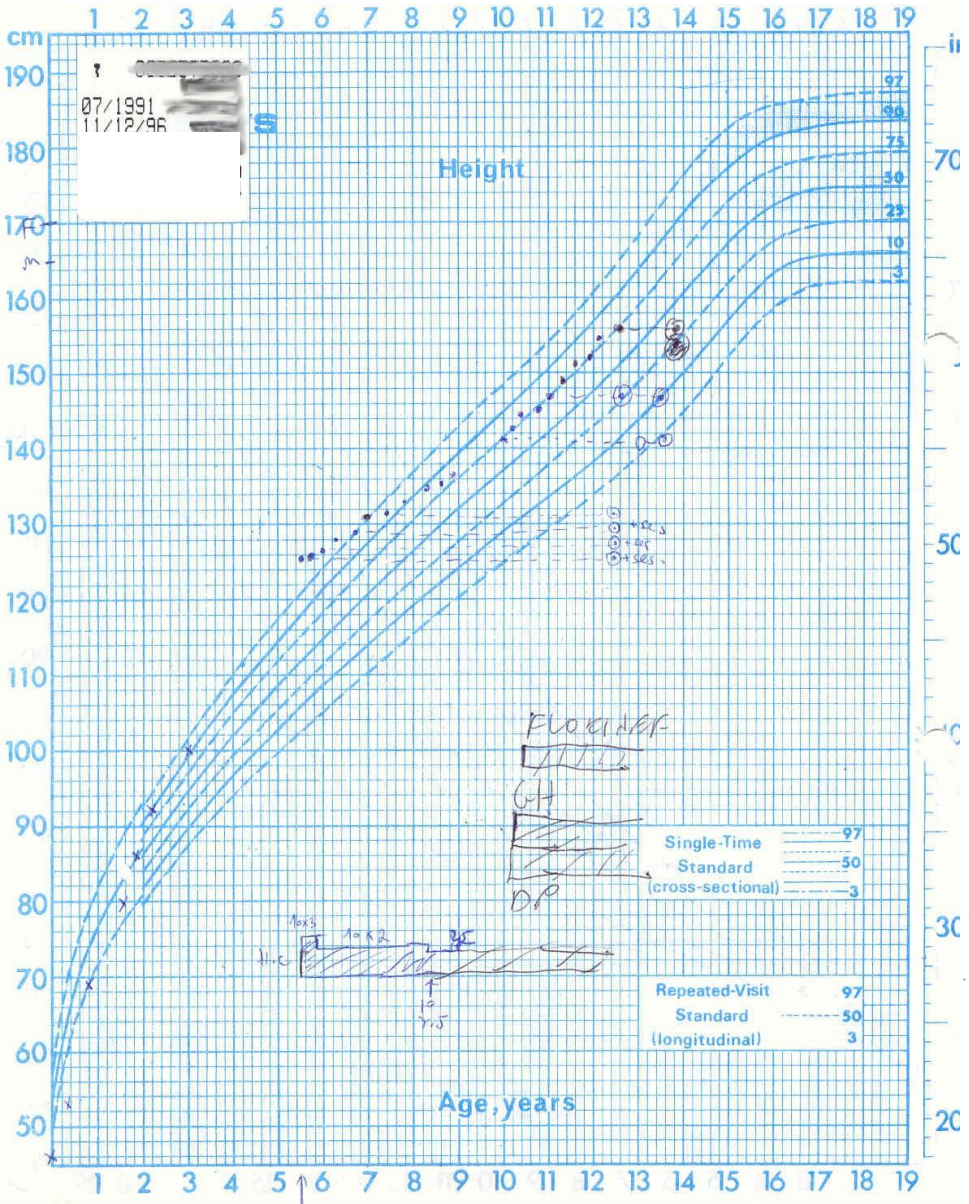
Jak J et al., IES 2011, Nazaret, Israel
Gidlof S. et al., 2014 JAMA Pediatr. 168:567
Heather NL et al.,2015 J JCEM 100:1002
Shlomo Almashanu, Head of Israel National Screening program, Personal Comunication,03.15

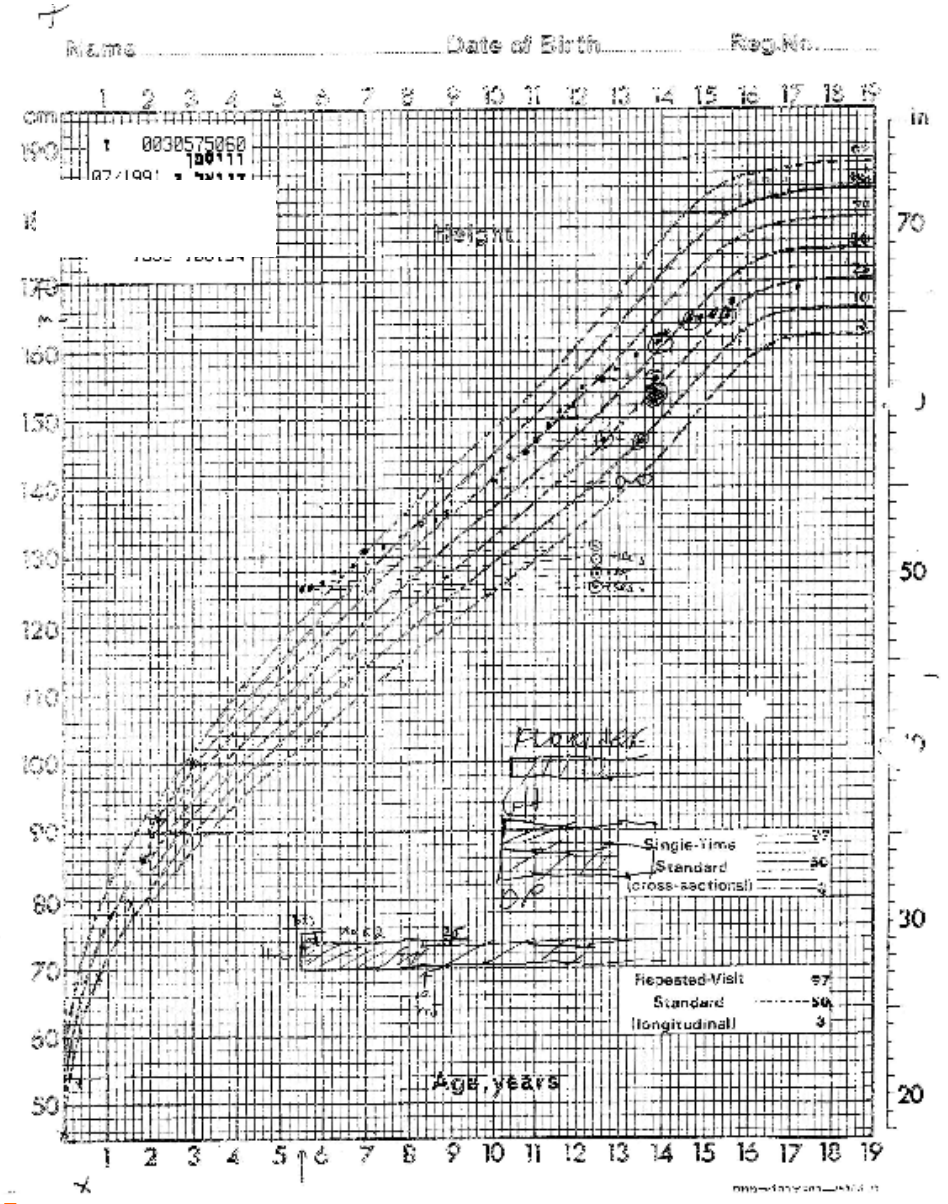
Newborn Screening-Pitfalls

- 17-OHP level are normally high at birth, decrease rapidly during the first post natal days. Diagnostic accuracy is poor in the first 2 days
- Premature, sick or stressed infants have even more elevated 17-OHP. Antenatal corticosteroid treatment might reduce 17-OHP
- Specificity is improved by using different cutoff levels according to gestational age and birth weight
- Positive predictive value 25% in full term and 1.4% in preterm. False negative 0-10% in SW and 20% in SV
- Repeat test for every positive result
  Perform test for any suspicious child

Van Der Kamp HJ, 2005, JCEM 90:3904-3907
Jak J et al., IES 2011, Nazaret, Israel
Gidlof S. et al., JAMA Pediatr. 2014, 168:567

Classic 21 Hydroxylase Deficiency
Simple Virilizing Form





Non-Classic 21-Hydroxylase Deficiency

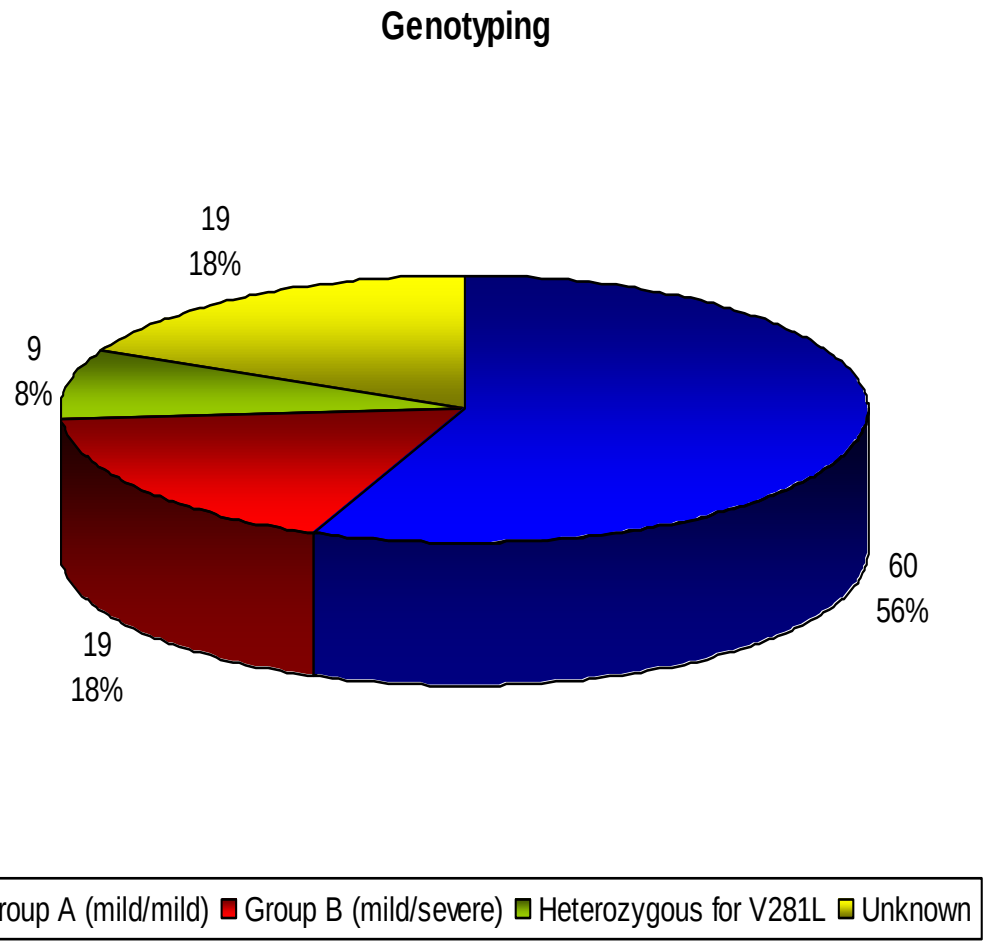
- **Prevalence**
  - Estimated to occur in: ~1/1000-2000 Caucasian non-Jewish individuals
    ~1:400 Ashkenazic Jews, carrier rate 1:10
    ~1:600 Ethiopian Jews, carrier rate 1:15
    ~1:800 Moroccian Jews, carrier rate 1:20
    Israel S. - personal communication

In hyperandrogenic women

- 1-2% in USA and Puerto Rico
- 4-6% in Canada, France, Ireland and Italy
- 6-10% in India, Jordan and Israel

Eldar-Geva T et al., 1990 N Engl J Med 323:855
Azziz et al, JCE&M , 69:577, 1989, 78:810, 1994
Moran et al, J Endocrinol Invest 21:707, 1998

Genotype Distribution among 107 Patients with Non-classical 21 Hydroxylase Deficiency



Weintrob N et al, Eur J Endocrinol 2000 143: 397-403

Eyal O et al, Acta Pædiatrica 2013 102: 419-423

Cortisol Levels (nmol/L) at Diagnosis in Relation to Genotype

	Group A (n = 39)	Group B (n = 15)
Basal level	358 ± 149	335 ± 145
Stimulated level	556 ± 119	531 ± 120
Increment	198 ± 115	237 ± 85
% of test failures	48	70

Group A: Homozygous mild mutations, Group B: Compound heterozygous mild/severe

The Pediatric Endocrinology and Diabetes Unit

ב"ית "דנה-דואק" לילדים

תודה לכל הצוות.. ולכם על ההקשבה

Mental Health

Quality of life (QoL)

- CAH patients, both children and adults, men and women, usually did not differ from controls in measures of QoL and psychological adjustment
- Significant impairment were found concerning body image and attitude toward sexuality
- CAH women were more often single and fewer of them had children
- Impaired bodily self-image associated with short stature, overwieght and hirsutism

Berenbaum SA et al., 2004 J pediatr 144:741-746
Jaaskelainen J et al., 2000 Acta Paediatr 89:183-187
Kuhnle U et al., 1997 Pediatr Surg Int 12:511-515

Phenotype-genotype Correlation in 56 Unrelated French Women with Nonclassical CAH

	Group A: mild/mild (n=18)	Group B: mild/severe (n=33)
Age at diagnosis	20.8 ± 5.3	22.1 ± 7.6
Age at menarche	12.7 ± 1.5	12.5 ± 1.5
Primary amenorrhea	0	18%[1]
Secondary amenorrhea	22%	3%[1]
Oligomenorrhea	44%	48.5%[1]
Regular	33%	30.5%[1]
Hirsutism	94%	97%
Adult height	161.2 ± 4.1	159.9 ± 5.9

[1] $p < 0.05$

Deneux et al, JCEM 2001 86: 207-213

Homozygous Mild Mutations vs Compound Heterozygous Severe/Mild Mutations

Parameter	Group A (N 60, F 46)	Group B (N 19, F 14)	*p* Value t-test
Age at diagnosis	11.2 (±7.5)	7.0 (±4.2)	0.0033
Age at initiation of therapy	12.3 (±7.29)	7.8 (±3.83)	0.0014
Mid parental height SDS	-0.31 (±0.67)	-0.62 (±0.77)	0.094
Final height SDS	-0.47 (±0.99)	-1.05 (±0.65)	0.005
Corrected height SDS	-0.16 (±0.73)	-0.45 (±0.78)	0.14

Eyal O et al., IES 2011, Nazaret, Israel

Prenatal Treatment

- **Efficacy:**

  Effective in reducing or eliminating external genitalia virilization in 80-85% of affected females

  Lajic S et al., 1998 JCEM 83:3872-3880
  Forest MG, 2004 Hum Reprod update 10:469-485
  New MI et al., Seminars in Reprod. Medicine 2012 30:396

- **Maternal safety (n=253):**

  Excessive weight gain. In 9-30% mood swings, mild gastric distress, pedal edema, mild hypertension. In 1.5% striae, hypertension, preeclampsia and gestational diabetes

  Forest MG et al.,1998, Trends Endocrinol Metab 9:284
  New MI et al., 2001, JCEM 86:5651-5657