Case study of a Mendelian Disorder

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Case History (AF)

- 38 year old woman attending Ob Med clinic for advice about pregnancy

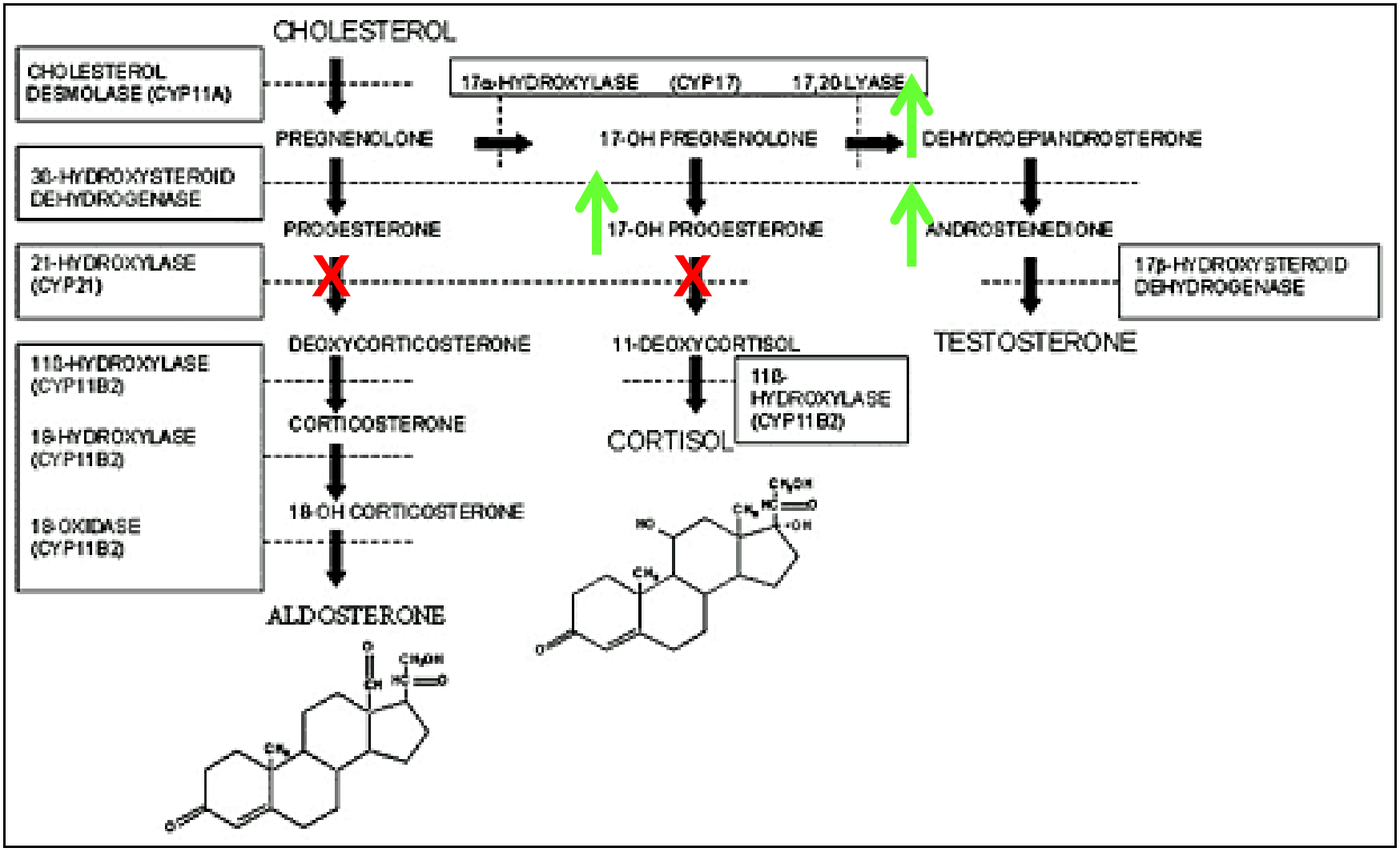
History:

- facial hirsutism and acne since her teens
- aged 24 developed hair on her chest
- USS ovaries - probable polycystic ovary syndrome

Blood tests

- Raised serum testosterone
- Raised androstenedione, DHEA sulphate, SHBG
- markedly raised 17-OH progesterone
- CT scan - bulky adrenal glands, no tumour

- Diagnosis: congenital adrenal hyperplasia


CHOLESTEROL
CHOLESTEROL DESMOLASE (CYP11A)
17α-HYDROXYLASE (CYP17)
17,20-LYASE
PREGNENOLONE
17-OH PREGNENOLONE
DEHYDROEPIANDROSTERONE
3β-HYDROXYSTEROID DEHYDROGENASE
PROGESTERONE
17-OH PROGESTERONE
ANDROSTENEDIONE
21-HYDROXYLASE (CYP21)
17β-HYDROXYSTEROID DEHYDROGENASE
TESTOSTERONE
DEOXYCORTICOSTERONE
11-DEOXYCORTISOL
11β-HYDROXYLASE (CYP11B1)
11β-HYDROXYLASE (CYP11B2)
CORTICOSTERONE
CORTISOL
18-HYDROXYLASE (CYP11B2)
18-OH CORTICOSTERONE
18-OXIDASE (CYP11B2)
ALDOSTERONE

Treatment

- Commenced on dexamethasone treatment (1mg/day)
- blood results returned to normal and symptoms improved

- Now wants advice about pregnancy and is keen to conceive ASAP

Maternal considerations

- Reduced fertility
- Important to ensure adequate GC and MC replacement
- 17-OH progesterone is not reliable
- Increased risk of hypertension and pre-eclampsia
- Require IV hydrocortisone to cover labour
- Some studies report increased frequency of caesarean section

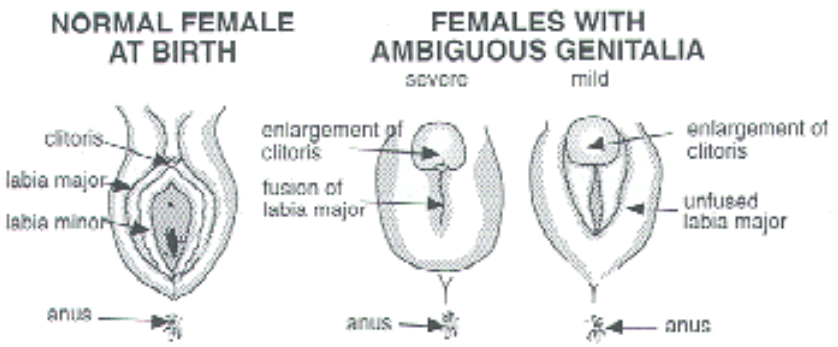
Fetal considerations

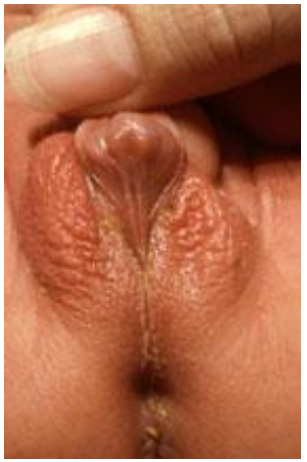
- Risk of inheriting one mutation from mother
- *Will this cause disease?*

- What is the risk of inheriting a mutation from the father?

Management of pregnancy with an affected fetus

- Aim to avoid virilisation of the female fetus

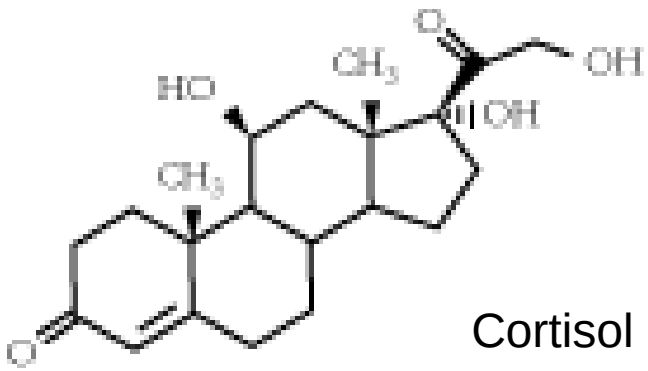




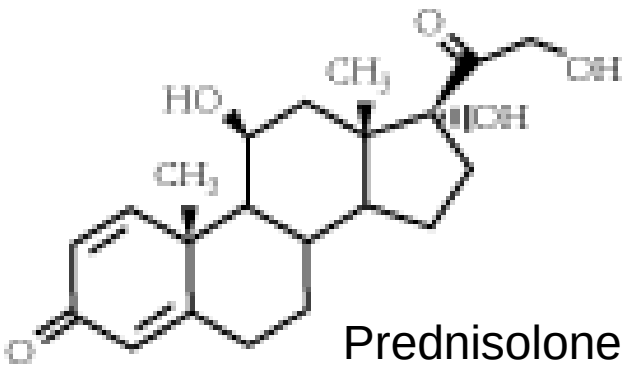
Virilisation of female fetus

- When does masculinisation first occur?
- What treatment could be used to prevent this?

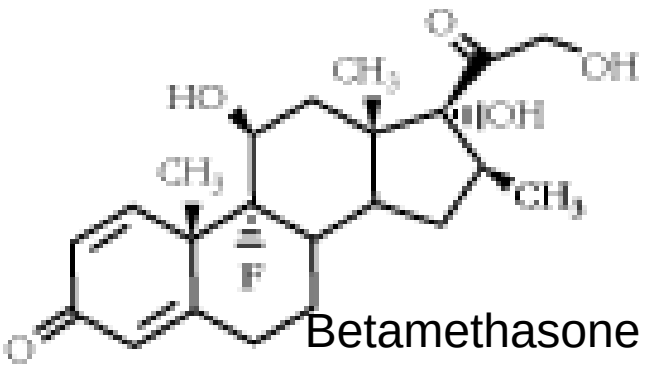
Structure of synthetic steroids



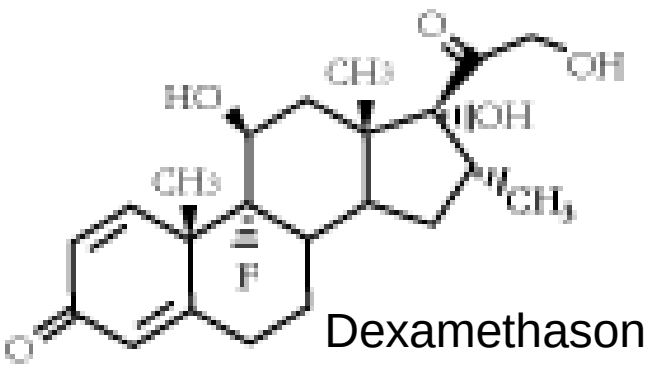
Cortisol



Prednisolone



Betamethasone



Dexamethasone

Transplacental passage of glucocorticoids

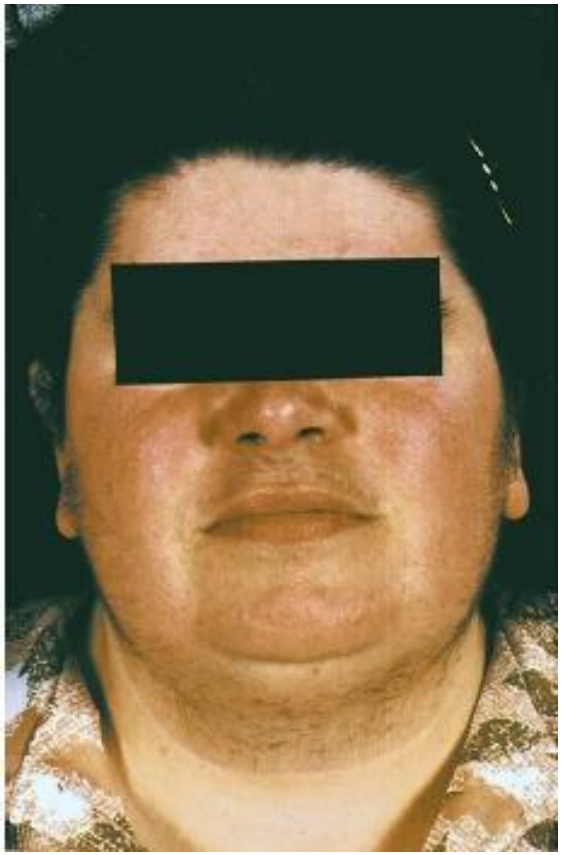
Name of GC	**Transplacental passage (%)**
Betamethsone	90
Dexamethasone	90
Hydrocortisone	50
Prednisolone	10

Potential effect of repeated courses of GC on the fetus

- Delayed brain maturation
  - Reduced cortical folding
  - Smaller brain surface area
- Hypertension in later life
- Impaired fetal growth
- Increased rates of aggressive behaviour

Potential effect of repeated courses of GC on the mother?

- Weight gain
- Glucose intolerance
- Hypertension
- Skin changes
- Cushing's syndrome



What did I suggest to this woman?

- Genetic counselling…

What is genetic counselling?

"Help... people understand and adapt to the medical, psychological and familial implications of genetic ... disease" (www.nsgc.org, www.agnc.org.uk)

- Interpret family and medical histories to assess the chance of disease occurrence or recurrence
- Inform about inheritance, testing, management, prevention, resources and research
- Counsel to promote informed choices and adaptation to the risk or condition

What did I discuss with the couple?

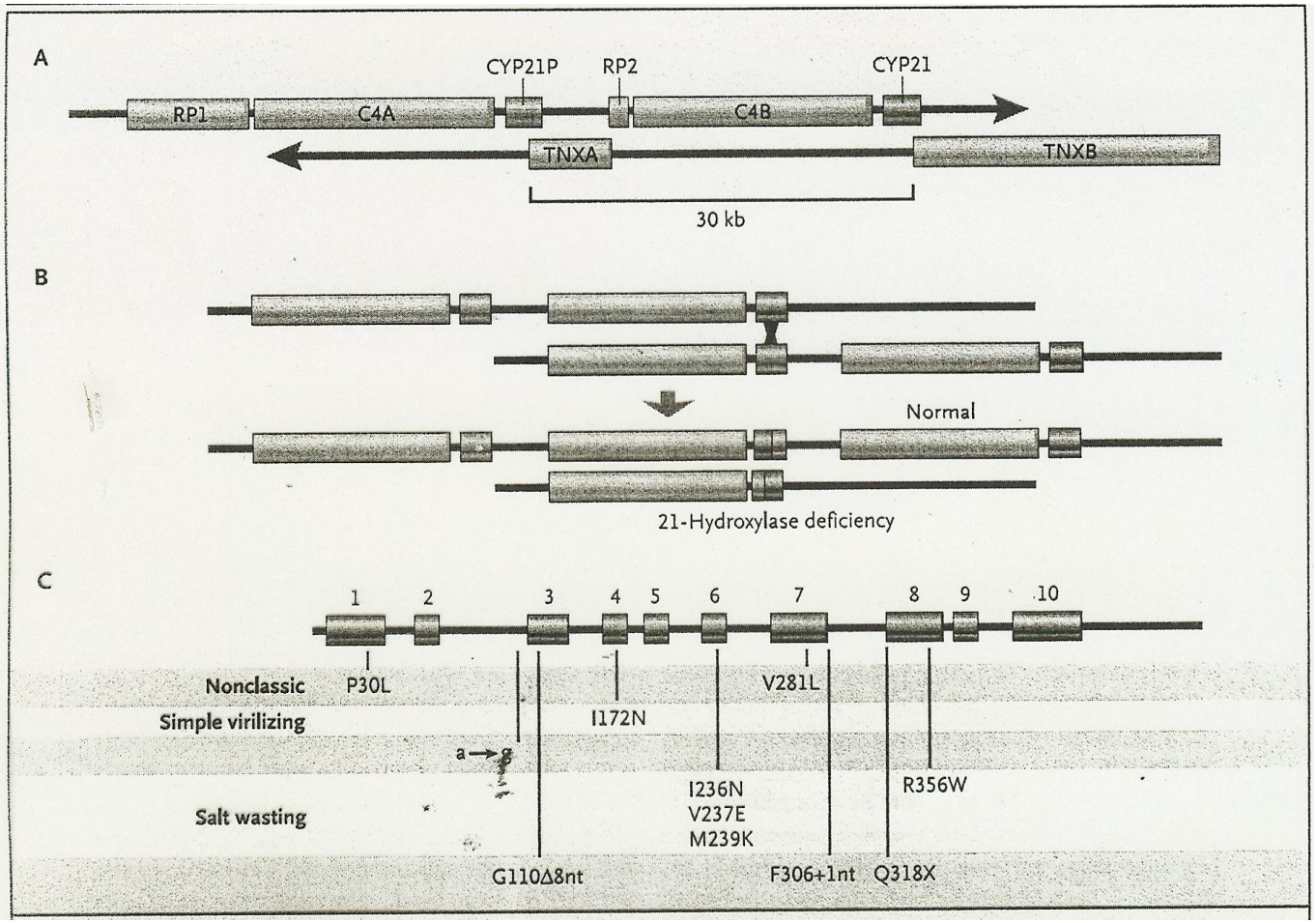
Genetic counselling session

- FHx
- Chromosomes, genes
- AR inheritance
- partner's chance to be carrier
- calculate their chance to have affected baby
- explain/offer genetic testing (pick up rate)
- take blood for test, inform lab

Genetics

- CYP21 on chromosome 6p21.3
- Duplication lead to 2 homologous genes: active gene and pseudogene
- within HLA region: recombination!
- Most mutations due to conversions (exchanges) involving pseudogene
- phenotype dependent on enzyme activity

Chromosomal region of 6p21.3



Couple's test results

21-

-HYDROXYLASE DEFICIENCY MUTATION SCREENING REPORT

S:

NAME (DoB)	STATUS	GENOTYPE		RISK ON DATA
AF	Affected –late onset 21-OH deficiency	Chimeric seq g.1683 G>T	+,chimeric T	
partner	1 in 50 prior (population)carrier risk	CYP21 Chimeric seq 707Δgagactac g.89C>T g.655A/C>G g.999T>A g.1683 G>T g.1994 C>T g.2108 C>T	No result +,+ +,+ +,+ +,+ +,+ +,T +,+ +,+	

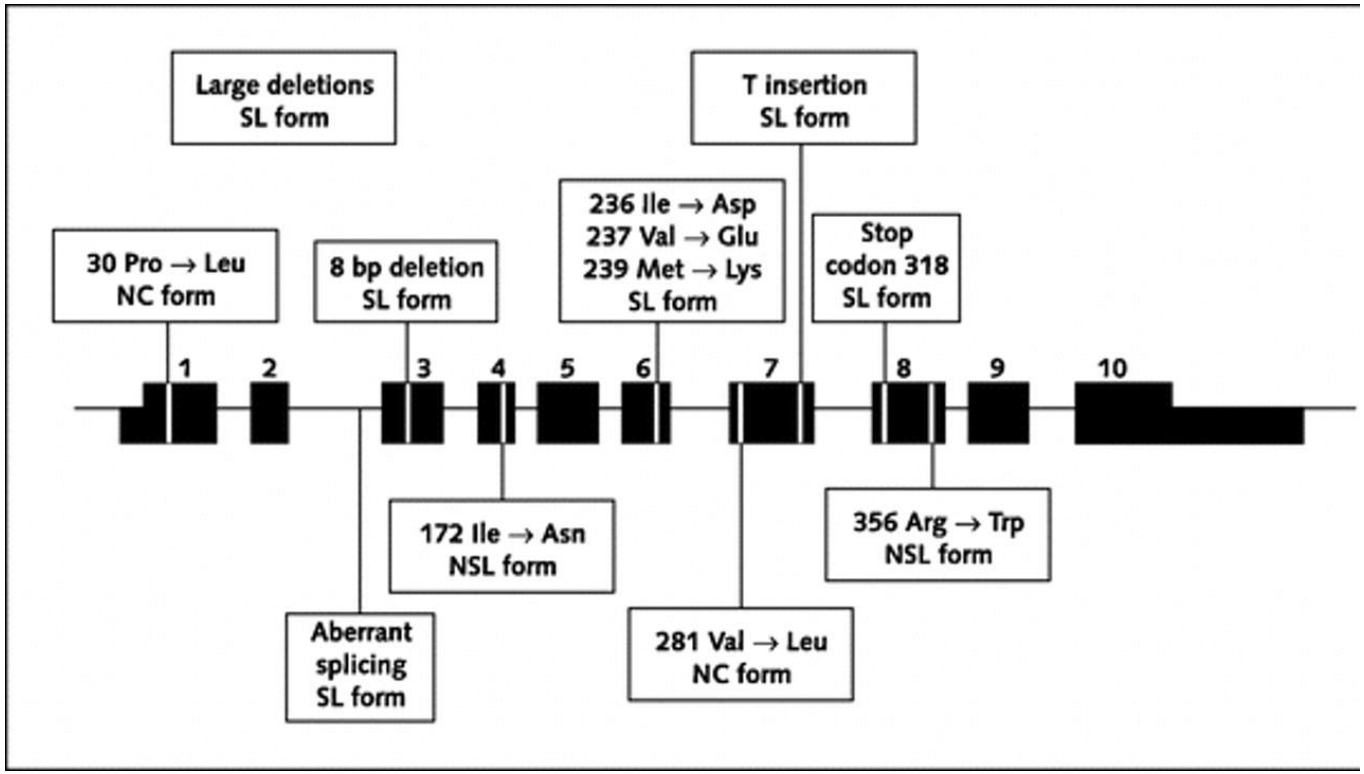
ldtype (no mutation detected)
ric = common deletion/conversion of CYP21 detected by direct ARMS test

are numbered from the A of the ATG initiation codon. Numbering is based on genomic sequence with Gen Bank umber M12792.

Test results

- Confirmed CAH due to 21CYP in AF
  - Chimeric sequence
  - “mild” mutation
- identified “mild” mutation in partner

Most common mutations in 21-Hydroxylase deficiency



Merke et. al. Ann Intern Med 2002;136:320-334

But …

- Genotype not ALWAYS correlated with phenotype (5%)
  - maybe due to modifier genes, splice site mutations, other factors

And …

- Can’t rule out partner has CAH due to 2nd mutation (could be more severe)

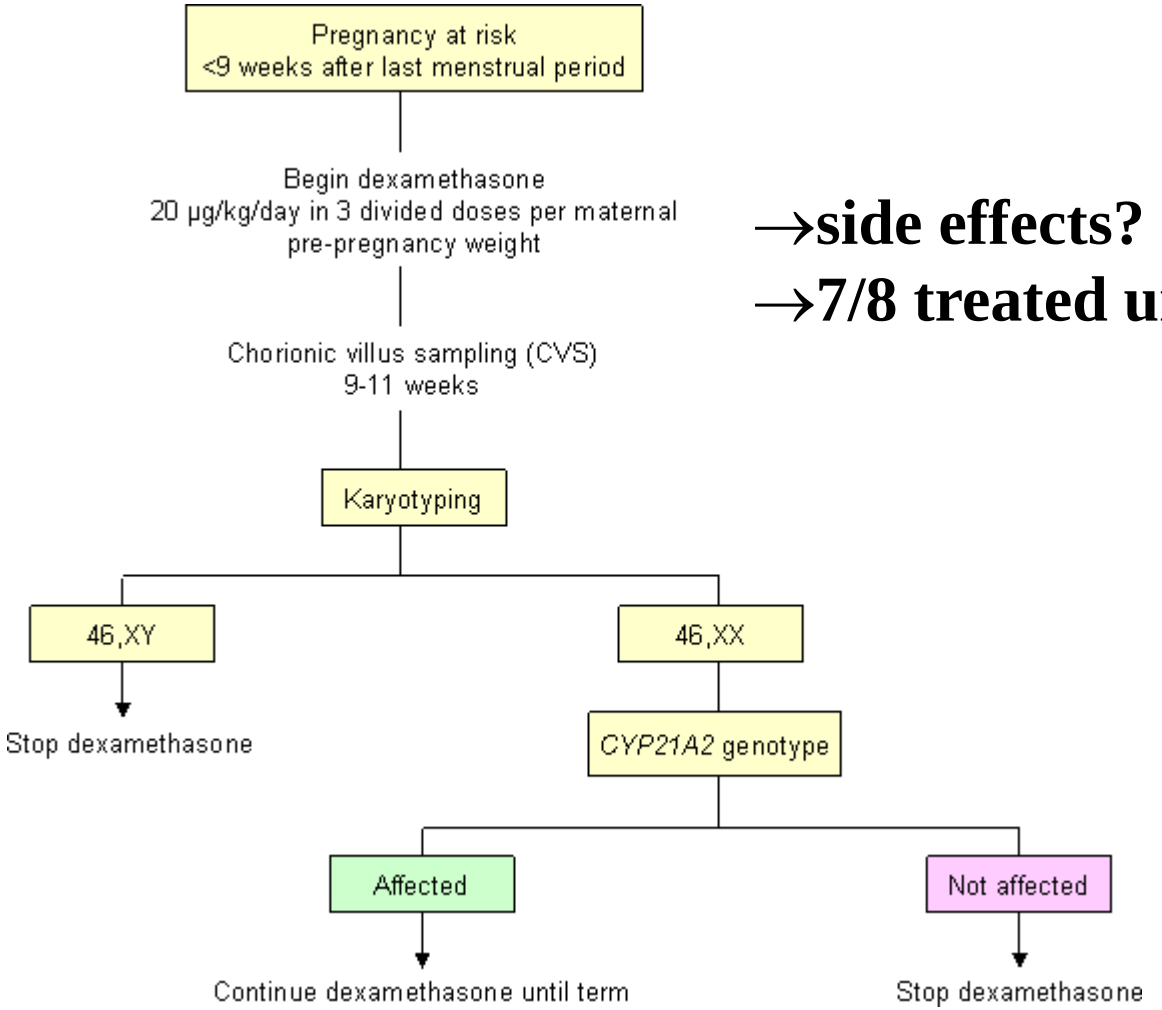
- invite couple for further genetic counselling session

2nd session

- Explain test result
- recalculate chance to have affected baby
- discuss prenatal testing options:
  - fetal sexing by blood test
  - ultrasound scan
  - CVS/amniocentesis
- … and treatment during pregnancy
- help make plan for pregnancy

5-10 years ago:

GeneReviews at http://www.ncbi.nlm.nih.gov/sites/GeneTests/



→side effects?

→7/8 treated unnecessarily

2010:

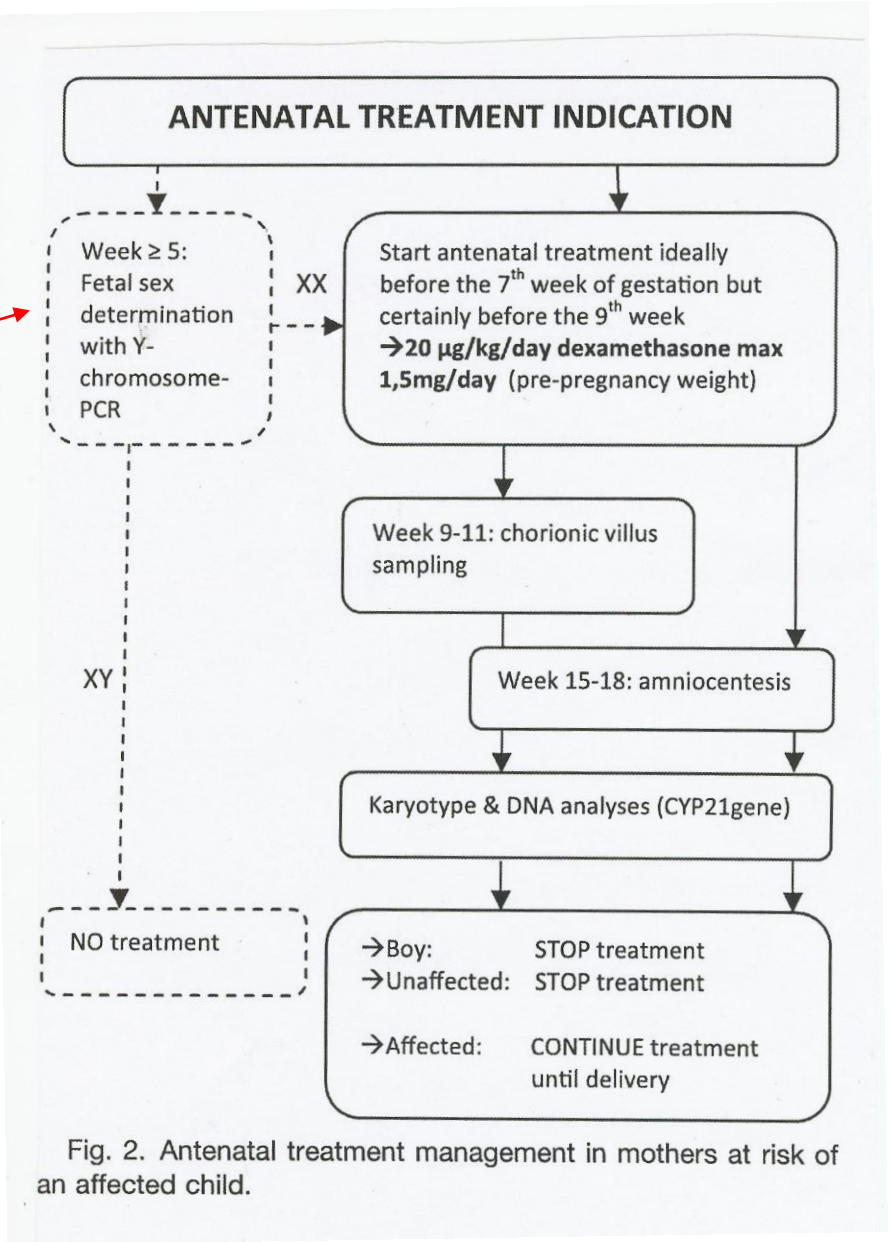


Fig. 2. Antenatal treatment management in mothers at risk of an affected child.

Vos & Bruinse, Obstet Gynecol Surv. 2010 Mar;

65(3):196-205.

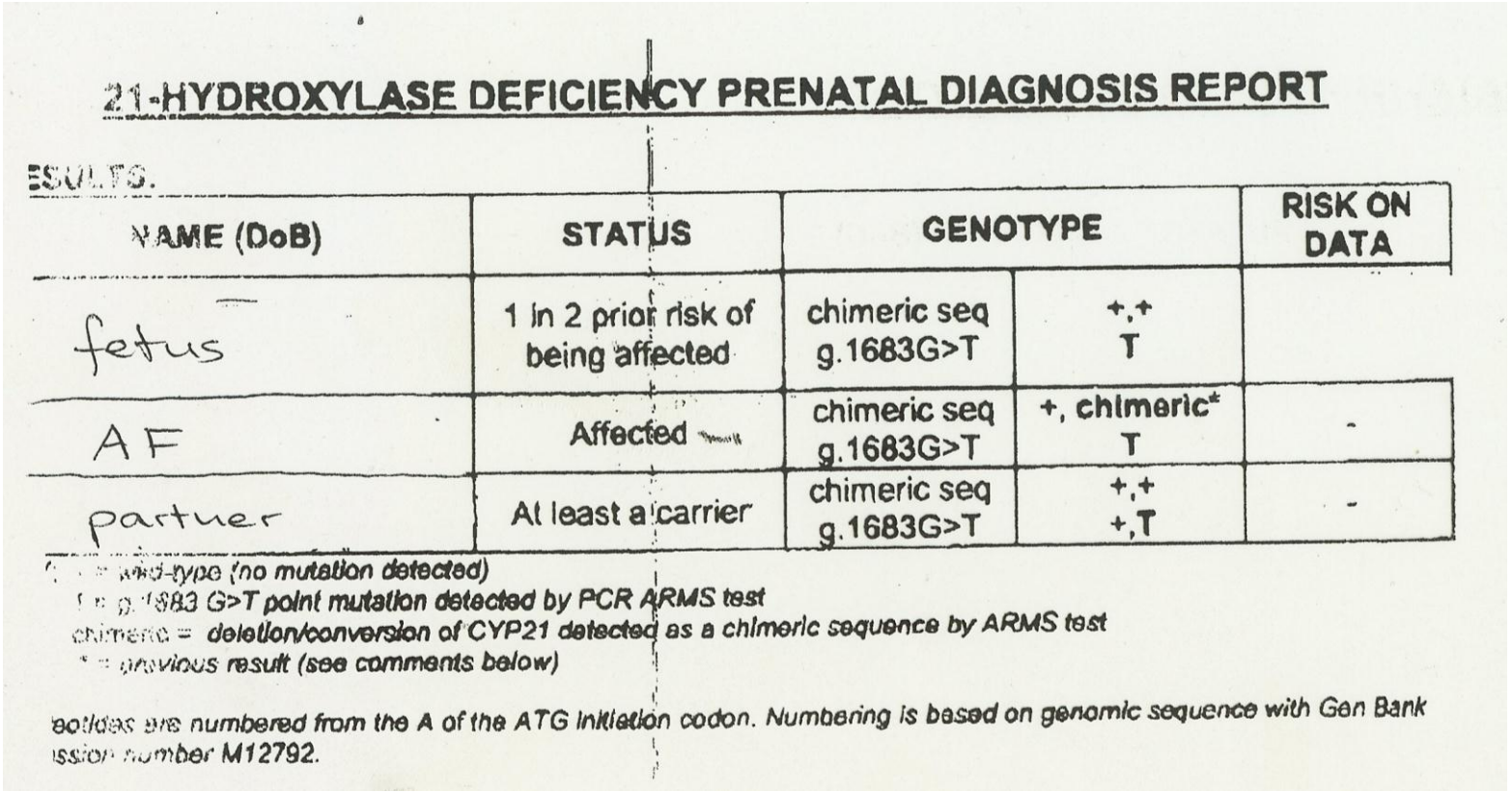
GENEReviews :

“tx to be considered experimental”

Plan

- Increase dexamethasone when pregnant
- Fetal sexing at 8 weeks
- If girl or result inconclusive: CVS at 12 weeks

Baby's genetic results



21-HYDROXYLASE DEFICIENCY PRENATAL DIAGNOSIS REPORT

RESULTS:

NAME (DoB)	STATUS	GENOTYPE		RISK ON DATA
fetus	1 in 2 prior risk of being affected	chimeric seq g.1683G>T	+,+ T	
AF	Affected	chimeric seq g.1683G>T	+, chimeric* T	-
partner	At least a carrier	chimeric seq g.1683G>T	+,+ +,T	-

wild-type (no mutation detected)
g.1683 G>T point mutation detected by PCR ARMS test
chimeric = deletion/conversion of CYP21 detected as a chimeric sequence by ARMS test
= previous result (see comments below)

Nucleotides are numbered from the A of the ATG initiation codon. Numbering is based on genomic sequence with Gen Bank accession number M12792.

Discuss results

- Change to treatment?
- Couple’s decision

Outcome of case

- Baby girl, born by C-section
- normal female genitalia, no virilisation
- growing and thriving well
- monitored for growth and androgen secretion
- treatment to start as needed