Simposio 6

Deficit di 21-idrossilasi nella paziente adulta

Moderatori:
C. Bizzarri, A. Scoppola

Real clinical practice
A. Chiefari

Inquadramento clinico e biochimico
C. Motta

Programmazione e terapia in gravidanza
G. Spiazzi

Take home messages
A. Scoppola

Deficit di 21-idrossilasi nella paziente adulta

'Real clinical practice'

Alfonsina Chiefari

UOSD Endocrinologia
Istituto Nazionale Tumori Regina Elena - Roma

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni non ho avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario.

La prima paziente …

Laura 19 anni

- Dal menarca riferisce importante aumento della peluria (soprattutto viso e addome) ed allungamento progressivo della durata del ciclo mestruale
- Da sempre problemi di sovrappeso

- Attualmente assume integratore a base di Mioinositolo.
  Le è stata prescritta terapia con Metformina, che ha assunto senza beneficio

Laura

Anamnesi familiare

- positiva per ipertensione arteriosa e diabete mellito

Anamnesi patologica remota

- tonsillectomia

Anamnesi fisiologica

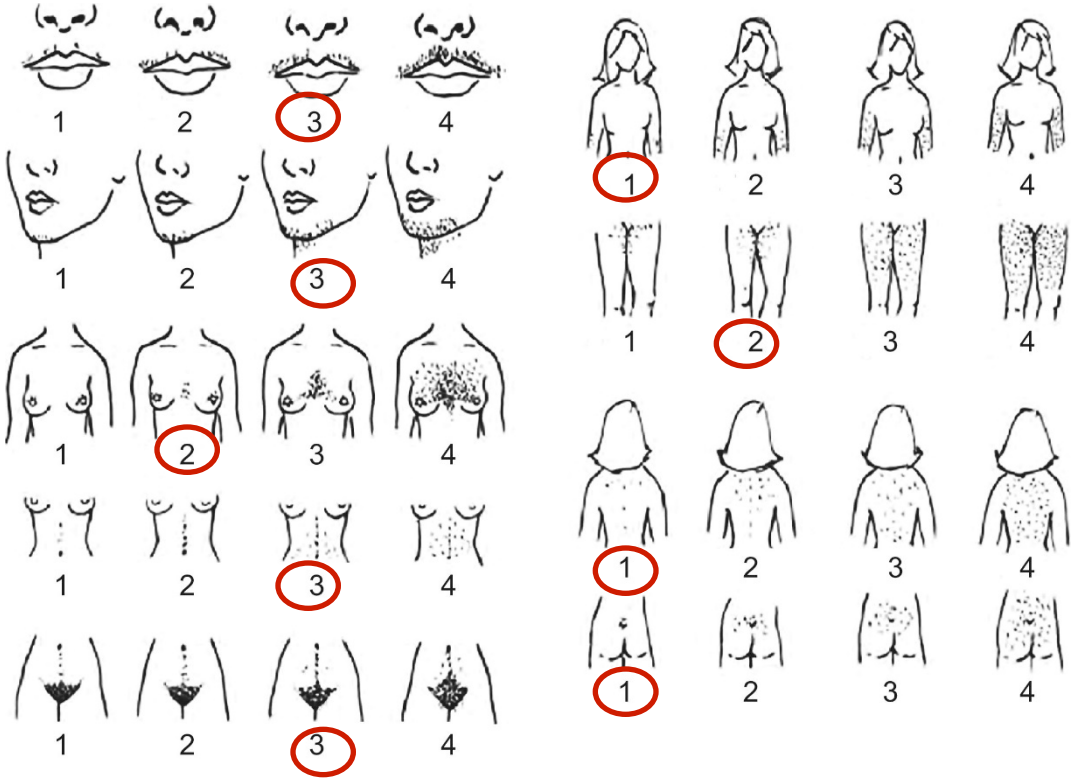
- nata a termine, peso alla nascita 3 kg
- pubarca 7 anni
- menarca 12 anni
- cicli di ritorno irregolari per oligomenorrea (circa 35-40 giorni)

Laura

Esame obiettivo:

- Peso 71 kg
- Altezza 165 cm
- BMI 26 kg/m^2
- PA 100/70 mmHg
- Non alopecia, non strie rubrae, non acantosi

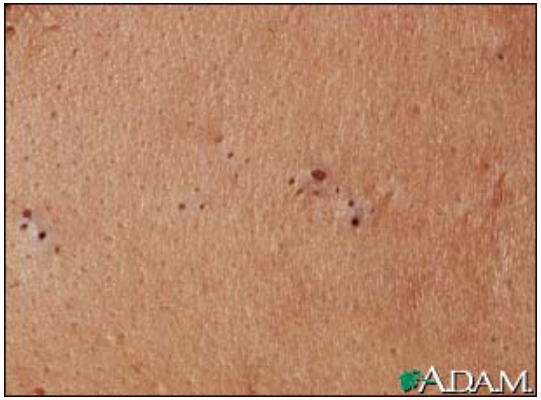
Laura

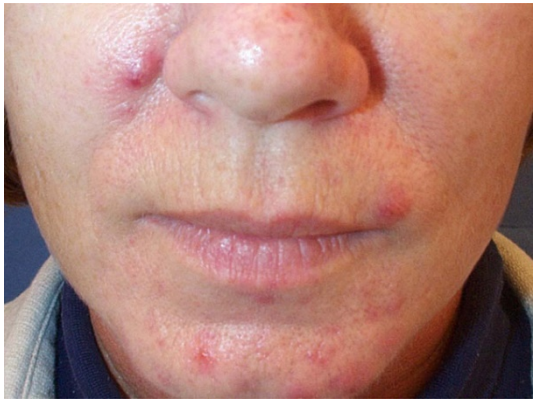


Score di Ferriman-Gallwey per irsutismo: totale 19

Laura

Grado	tipo	lesione
0	assente	assente
1	minore	comedoni 2 mm
2	medio	comedoni 10 - 20 mm
3	moderato	comedoni > 20 mm o foruncoli < 20 mm
4	severo	foruncoli > 20 mm
5	cistico	lesioni infiammatorie





Score di Lucky per Acne

Deficit di 21-idrossilasi nella paziente adulta

'Inquadramento clinico e biochimico'

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Conflitti di interesse

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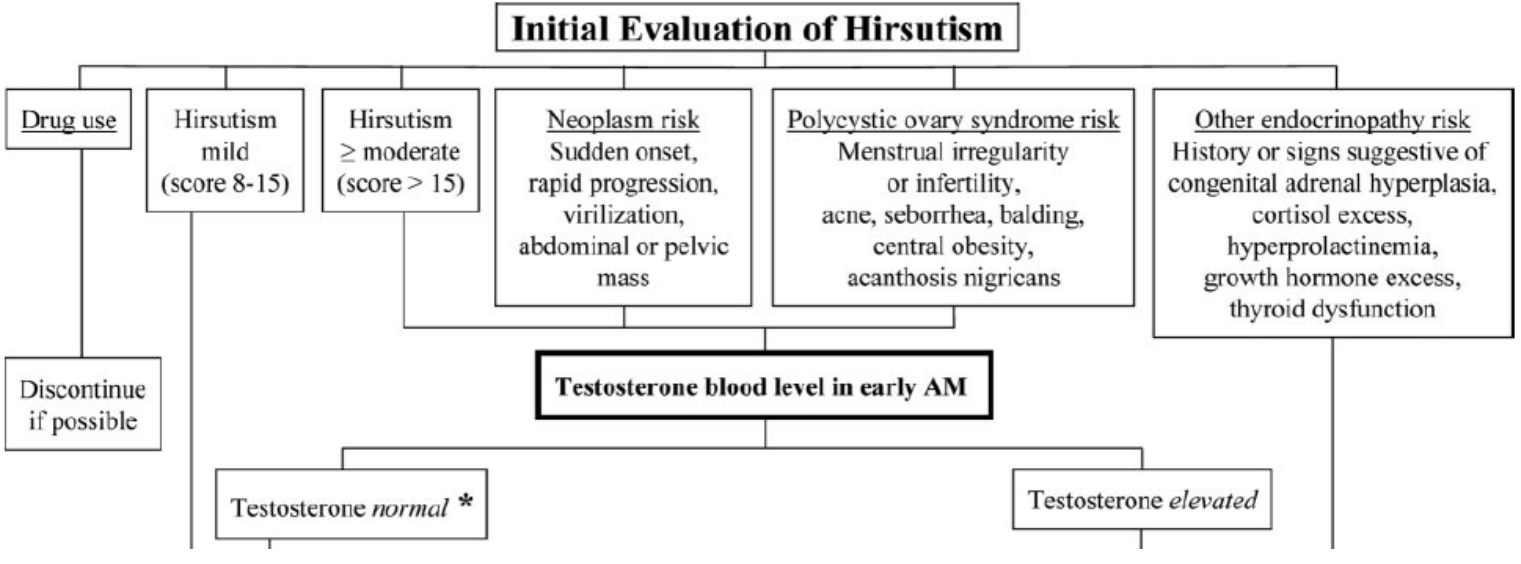
Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society Clinical Practice Guideline

Kathryn A. Martin, R. Jeffrey Chang, David A. Ehrmann, Lourdes Ibanez, Rogerio A. Lobo, Robert L. Rosenfield, Jerry Shapiro, Victor M. Montori, and Brian A. Swiglo

J Clin Endocrinol Metab, April 2008, 93(4):1105–1120



Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society* Clinical Practice Guideline

Kathryn A. Martin,[1] R. Rox Anderson,[1] R. Jeffrey Chang,[2] David A. Ehrmann,[3] Rogerio A. Lobo,[4] M. Hassan Murad,[5] Michel M. Pugeat,[6] and Robert L. Rosenfield[3]

J Clin Endocrinol Metab, April 2018, 103(4):1233–1257

Evaluation

We have broadened the suggestion for determining the serum total testosterone concentration to include all women with hirsutism and have broadened the suggestion for determining the serum-free testosterone concentration to include hirsute women whose serum total testosterone is normal in the presence of moderate to severe hirsutism or other clinical evidence of hyperandrogenemia, such as progressive growth of hair in androgen-dependent areas (sexual hair). We have added a recommendation to screen

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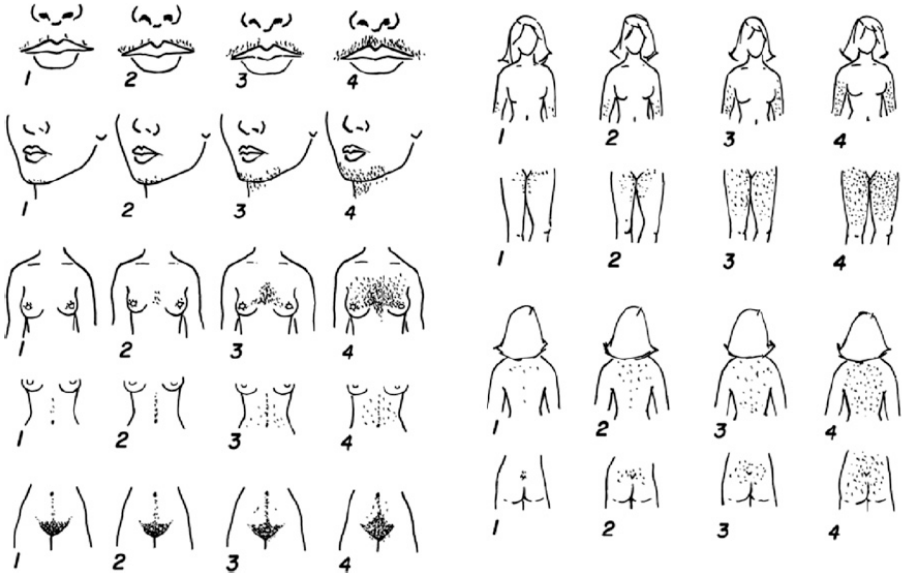
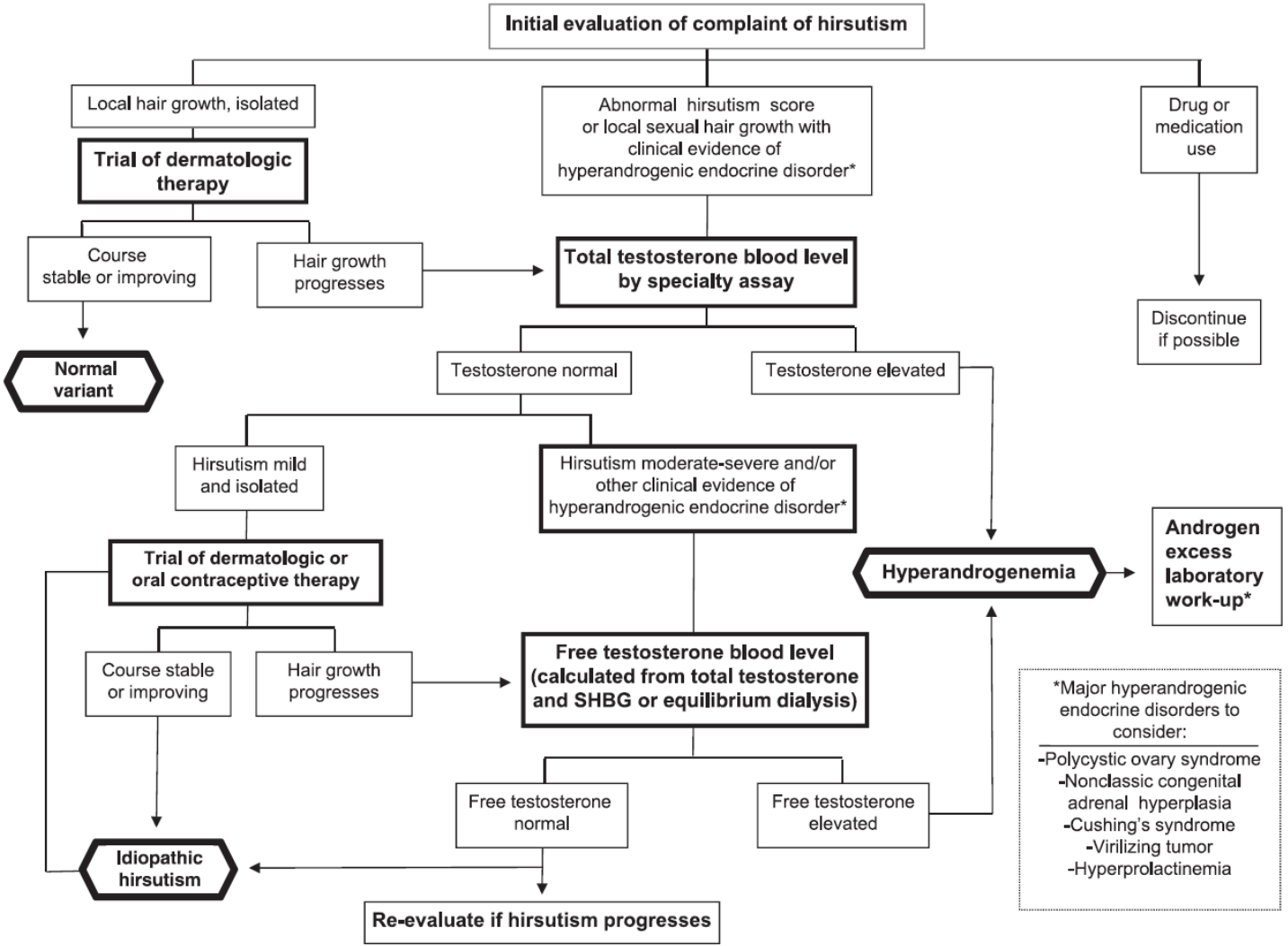
centile for the population (Fig. 1) (5, 6). Ferriman–Gallwey total scores that define hirsutism in women of reproductive age are as follows: United States and United Kingdom black or white women, ≥8 (6); Mediterranean, Hispanic, and Middle Eastern women, ≥9 to 10 (6); South American women, ≥6 (7); and Asian women, a range of ≥2 for Han Chinese women (6) to ≥7 for Southern Chinese women (8, 9). Although widely used,




Initial evaluation of complaint of hirsutism
Local hair growth, isolated
Trial of dermatologic therapy
Course stable or improving
Hair growth progresses
Normal variant
Abnormal hirsutism score or local sexual hair growth with clinical evidence of hyperandrogenic endocrine disorder*
Total testosterone blood level by specialty assay
Testosterone normal
Testosterone elevated
Hirsutism mild and isolated
Trial of dermatologic or oral contraceptive therapy
Course stable or improving
Hair growth progresses
Hirsutism moderate-severe and/or other clinical evidence of hyperandrogenic endocrine disorder*
Free testosterone blood level (calculated from total testosterone and SHBG or equilibrium dialysis)
Free testosterone normal
Free testosterone elevated
Idiopathic hirsutism
Re-evaluate if hirsutism progresses
Drug or medication use
Discontinue if possible
Hyperandrogenemia
Androgen excess laboratory work-up*
*Major hyperandrogenic endocrine disorders to consider:
-Polycystic ovary syndrome
-Nonclassic congenital adrenal hyperplasia
-Cushing's syndrome
-Virilizing tumor
-Hyperprolactinemia

Clinica

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J Clin Endocrinol Metab, April 2008, 93(4):1105–1120 jcem.endojournals.org 1105

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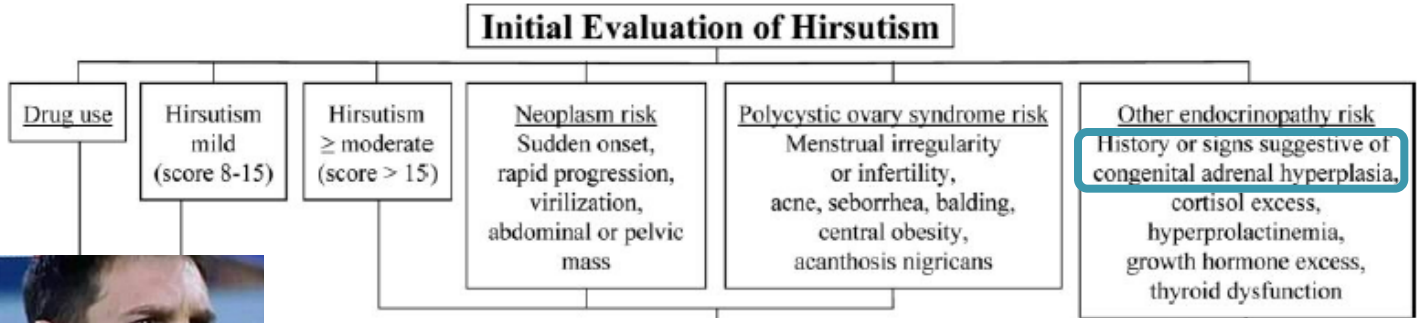


Ma quali sono i segni suggestivi di NCAH?

Iperplasia surrenalica congenita

Compromissione della ***steroidogenesi surrenalica***:

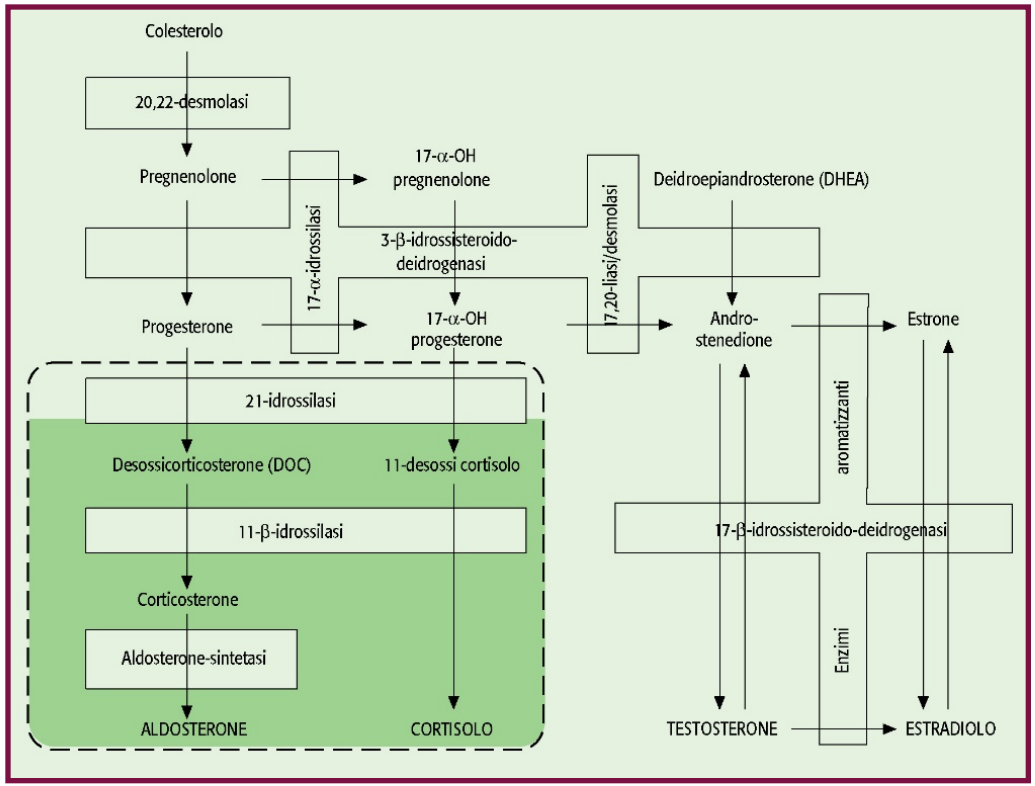
- **deficit di 21-idrossilasi 90-95% dei casi**
- deficit di 11β-idrossilasi 5-8% dei casi

Compromissione della ***steroidogenesi surrenalica e gonadica***:

- deficit di 3βOHsteroido-deidrogenasi
- deficit di 17°-idrossilasi
- deficit di P450-ossidoreduttasi

Deficit enzimatico	Clinica	Età
Grave	Forma Classica	Neonatale/Prima infanzia
Lieve	Forma Non Classica	Puberale/Adulta

Deficit 21-idrossilasi



Disordine genetico trasmesso con carattere autosomico recessivo, caratterizzato da una ridotta attività dell'enzima 21-idrossilasi, con conseguente riduzione della produzione del cortisolo ed aumento degli androgeni posti a monte del blocco della cascata enzimatica

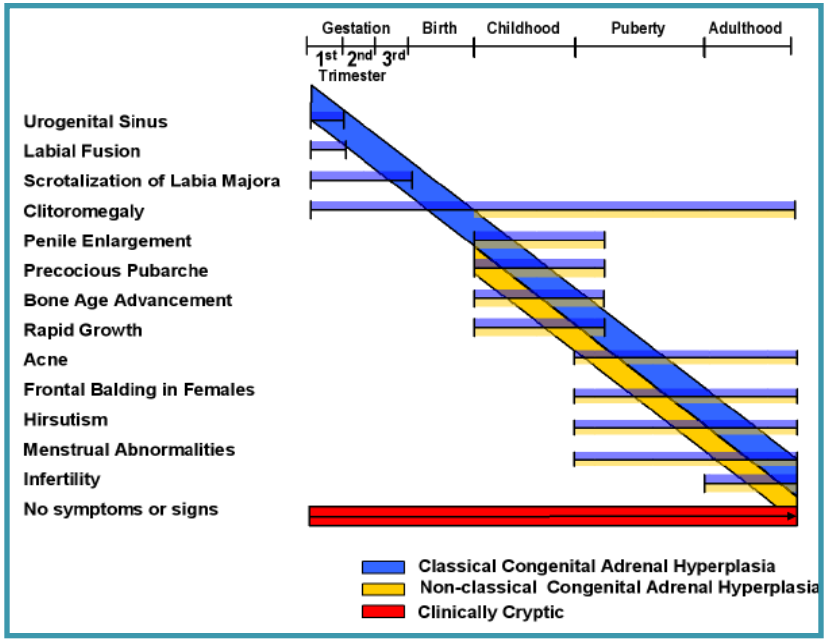
Deficit 21-idrossilasi

- **Forma classica** a comparsa neonatale (CAH): con perdita salina o virilizzante semplice

- **Forma non classica** (NCAH): late onset o a comparsa post-puberale e forma asintomatica o criptica

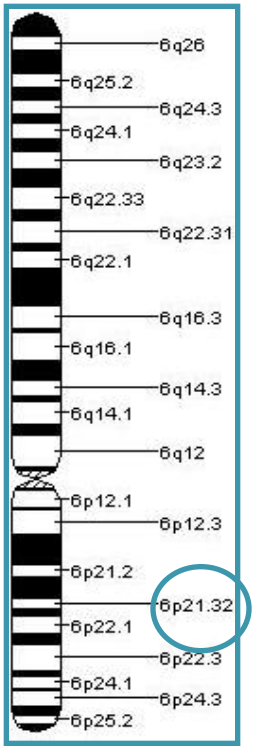
La gravità della patologia dipende dal grado di compromissione enzimatica conferita dal difetto genetico:

- CAH: 0-3 % attività enzimatica
- NCAH: 30-50% attività enzimatica



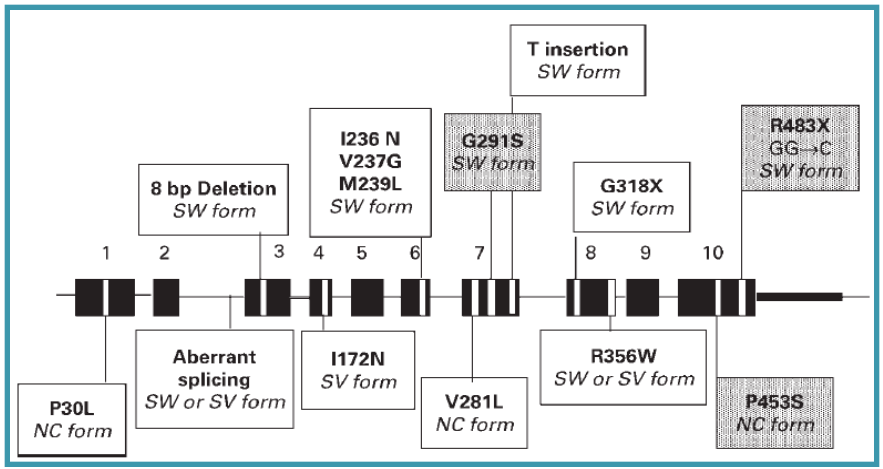
New MI, 2006, *JCEM*, 91(11):4205-14

Deficit 21-idrossilasi



Il gene CYP21 (CYP21A2) è situato sul cromosoma 6, nella regione altamente polimorfica del complesso di istocompatibilità HLA, insieme a uno pseudo-gene CYP21P (CYP21A1P), inattivo

Presentano un'omologia di circa il 98%



70-75% mutazioni puntiformi

25-30% altre mutazioni: delezioni, Inserzioni, splicing aberrante

Maguelone G et al, 2004, *Hum Reprod Update;* 10(6):469-85

Ma quali sono i segni suggestivi di NCAH?

The phenotype of hirsute women: a comparison of polycystic ovary syndrome and 21-hydroxylase–deficient nonclassic adrenal hyperplasia

Marita Pall, M.D., Ph.D.,[a] *Ricardo Azziz, M.D., M.P.H., M.B.A.,*[a,b,c] *Jorge Beires, M.D., Ph.D.,*[d] *and Duarte Pignatelli, M.D., Ph.D.*[e]

Fertility and Sterility® Vol. 94, No. 2, July 2010

In conclusion, this study suggests that nonclassic adrenal hyperplasia and PCOS present with similar clinical features and increased androgen levels. Nonclassic adrenal hyperplasia is a hyperandrogenic disease with androgen levels similar to those in obese women with PCOS but with a metabolic profile similar to that of lean women with PCOS. A few differences do exist.

TABLE 1

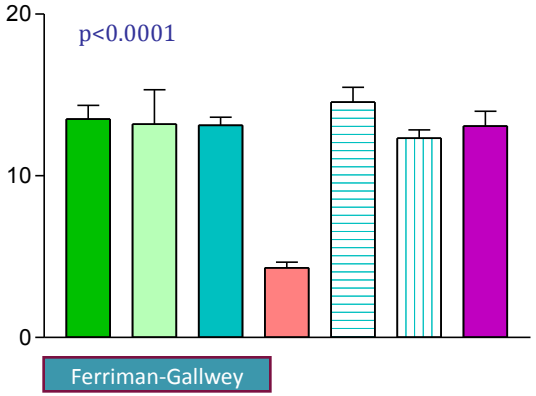
Clinical features of subjects.

	Obese patients with PCOS	Lean patients with PCOS	Patients with NCAH	Controls
No. of subjects	54	52	23	27
Age (y)	24 ± 7	22 ± 5	22 ± 8	26 ± 7
BMI (kg/m^2)	35 ± 6[a]	23 ± 2[b]	26 ± 4[a]	22 ± 2
BMI >27 kg/m^2 (%)	54/54 (100)	0/52 (0)	10/23 (43)	0/27 (0)
Degree of menstrual dysfunction				
Eumenorrhea, ovulation (%)	0/54 (0)	0/52 (0)	17/23 (74)	27/27 (100)[a]
Eumenorrhea, anovulation (%)	5/54 (9)[c,d]	6/52 (11)[c,d]	2/23 (9)	0/27 (0)[a]
Oligomenorrhea (%)	41/54 (76)[c]	41/52 (79)[c]	3/23 (13)	0/27 (0)[a]
Amenorrhea (%)	8/54 (15)	5/52 (10)	1 (4)	0/27 (0)
MFG (mean ± SD)	18 ± 5	14 ± 4[e]	16 ± 5	5 ± 2[a]
Maximum ovarian volume (cm^3)	10.7 ± 4.6[c]	9.7 ± 4.2[c]	6.1 ± 4.5	5.2 ± 2.3
Maximum no. follicles	11.9 ± 2.7[c]	11.4 ± 2.9[c]	8.1 ± 3.5	6.0 ± 2.8
Subjects with PCO (%)	46/52 (88)[c]	35/49 (71)[c]	5/21 (24)	1/24 (4)

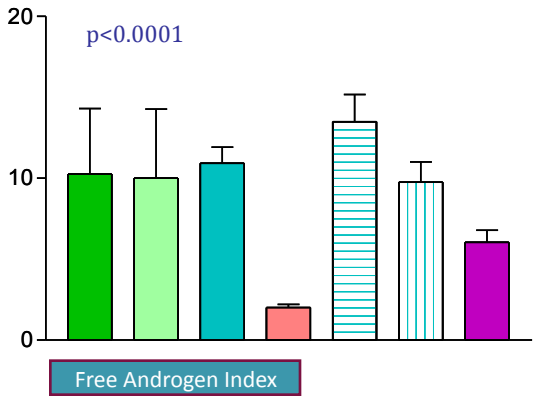
Note: Values are expressed as mean ± SD. MFG = modified Ferriman-Gallwey score; NCAH = nonclassic adrenal hyperplasia; PCO = polycystic ovaries.
[a] $P<.01$ compared with all other groups.
[b] $P<.05$ compared with obese patients with PCOS and NCAH.
[c] $P\leq.05$ compared with controls and patients with NCAH.
[d] Anovulatory, luteal-phase $P<4.0$ ng/mL.
[e] $P<.01$ compared with obese patients with PCOS.

Pall. Nonclassic adrenal hyperplasia versus PCOS. Fertil Steril 2010.

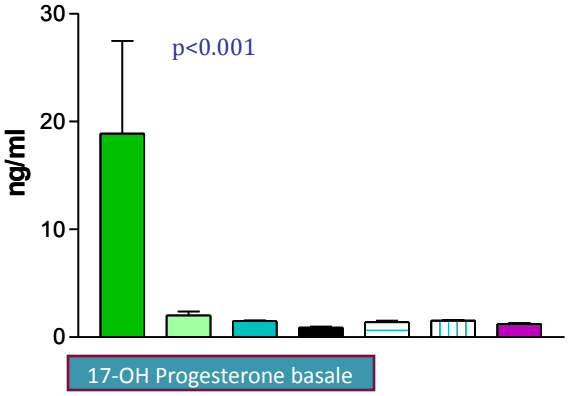
Nostra esperienza (324 pz)



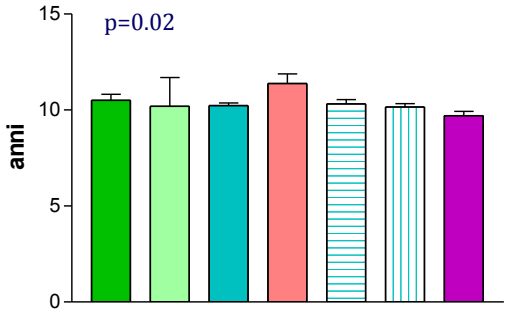
Ferriman-Gallwey



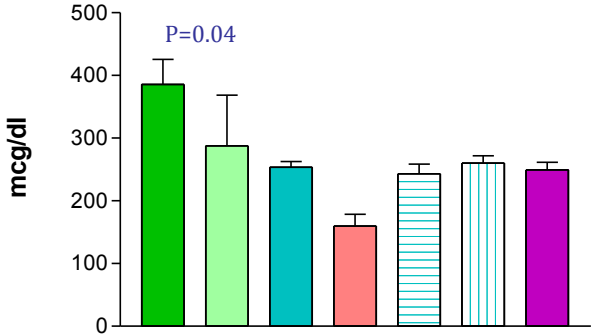
Free Androgen Index



17-OH Progesterone basale



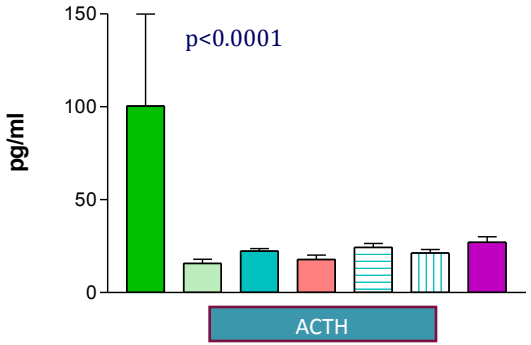
Pubarca

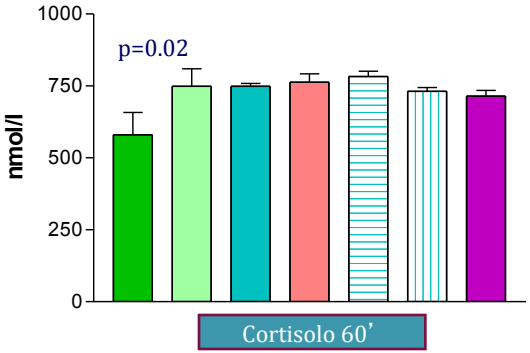


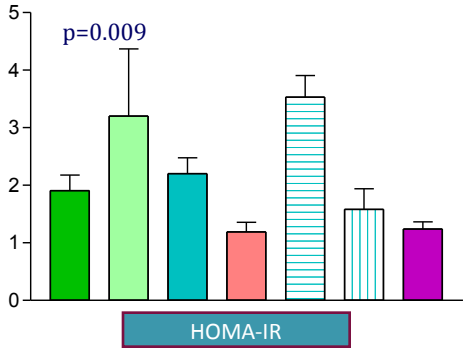
DHEA-S

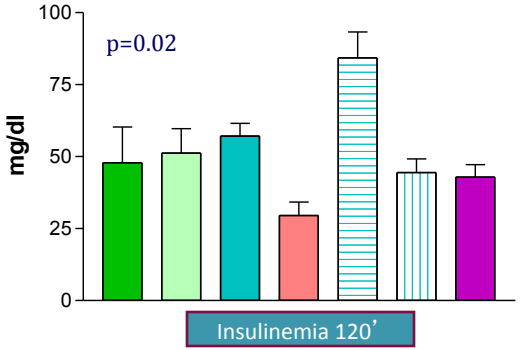
NCAH
Carrier
PCOS
Anovulaz e/o PCO
PCOS Obese
PCOS non obese
Iperandrogenismo

Nostra esperienza (324 pz)









NCAH
Carrier
PCOS
Anovulaz e/o PCO
PCOS Obese
PCOS non obese
Iperandrogenismo

Non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency revisited: an update with a special focus on adolescent and adult women

Enrico Carmina[1,*], Didier Dewailly[2], Héctor F. Escobar-Morreale[3], Fahrettin Kelestimur[4], Carlos Moran[5], Sharon Oberfield[6], Selma F. Witchel[7], and Ricardo Azziz[8]

Human Reproduction Update, Vol.23, No.5 pp. 580–599, 2017
Advanced Access publication on June 5, 2017 doi:10.1093/humupd/dmx014

ITALIAN CHAPTER

Segno/Sintomo	Prevalenza
Irsutismo	60-80%
Acne	Circa 33%
Alopecia	2-8%
Clitoridomegalia	6-20%
Irregolarità mestruali	30-50%
PCOM	24-80%
Iperplasia surrenalica-adenomi surrenalici	?

Non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency revisited: an update with a special focus on adolescent and adult women

Enrico Carmina[1,*], Didier Dewailly[2], Héctor F. Escobar-Morreale[3], Fahrettin Kelestimur[4], Carlos Moran[5], Sharon Oberfield[6], Selma F. Witchel[7], and Ricardo Azziz[8]

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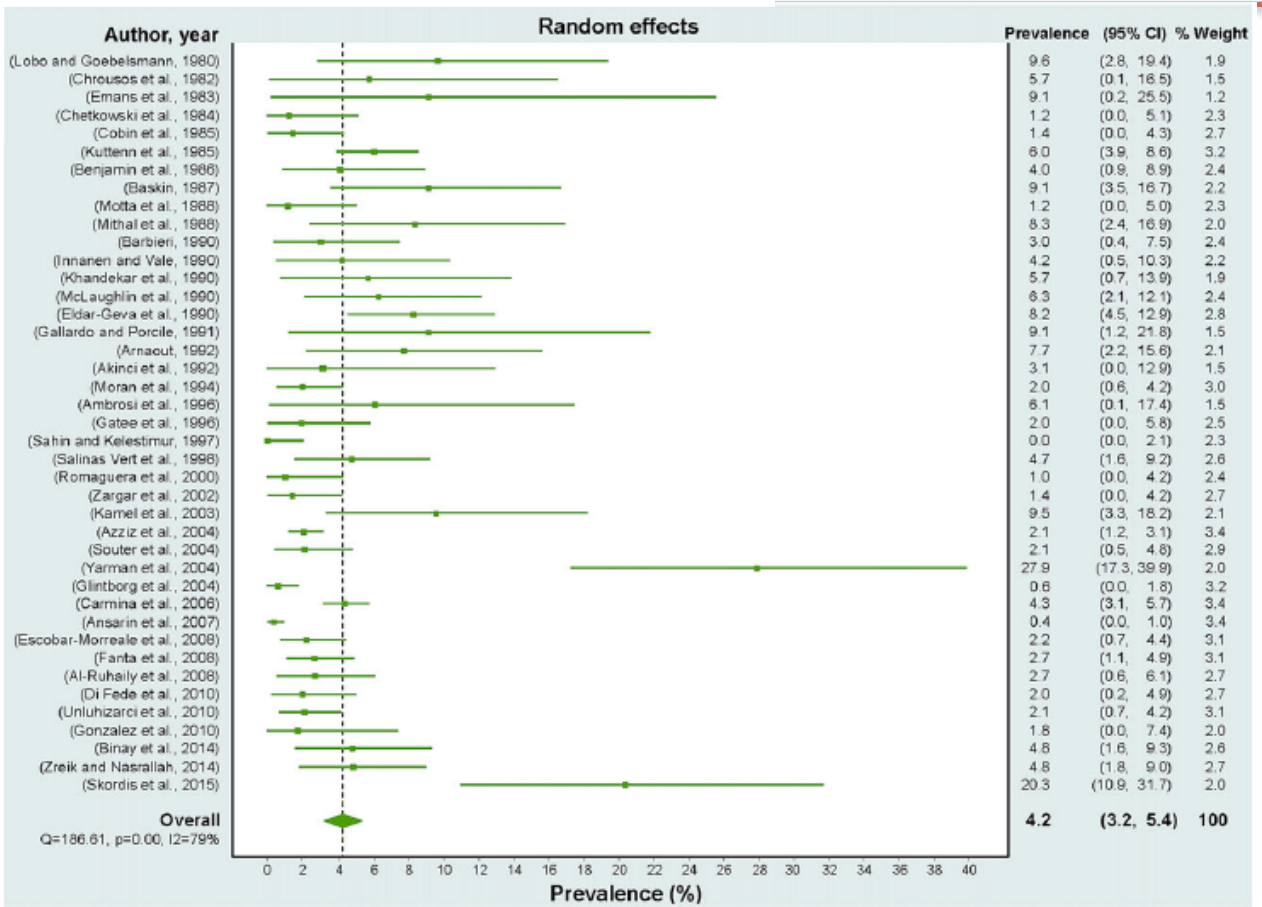
ITALIAN CHAPTER



NCAH: prevalenza

TABLE 1: Prevalence of NCAH due to 21-hydroxylase deficiency among hyperandrogenic women.

Country	Total # of Women	# NCAH (%)	Citation
USA (NE)	22*	2 (9%)	Emans et al., 1983 [8]
USA (NE)	139	2 (1.4%)	Cobin et al., 1985 [9]
USA (NE)	164	4 (2.4%)	Azziz and Zacur, 1989 [10]
USA (SE)	86	2 (2.3%)	Azziz et al., 1993 [11]
USA (SW)	83	1 (1.2%)	Chetkowski et al., 1984 [12]
USA (SE)	873	18 (1.6%)	Azziz et al., 2004 [13]
Canada	72	4 (5.5%)	Innanen and Vale, 1990 [14]
Puerto Rico	100	1 (1.0%)	Romaguera et al., 2000 [15]
Ireland	96	6 (6.2%)	McLaughlin et al., 1990 [16]
England	50	1 (2.0%)	Turner et al., 1992 [17]
France	400	24 (6.0%)	Kuttenn et al., 1985 [18]
France	69	16 (23%)	Blanché et al., 1997 [19]
Portugal	129	23 (17.8%)	Pall et al., (in press) [20]
Italy (South)	372	14 (4.0%)	Carmina et al., 1987 [21]
Italy (North)	85	1 (1.1%)	Motta et al., 1988 [22]
Italy (Palermo)	950	41 (4.5%)	Carmina et al., 2006 [23]
Spain	270	6 (2.2%)	Escobar-Morreale et al., 2008 [24]
Czech Republic	298	8 (2.7%)	Fanta et al., 2008 [25]
Greece	107	10 (9.3%)	Trakakis et al., 2008 [26]
Turkey (Ankara)	32*	1(3%)	Akinci et al., 1992 [27]
Turkey (Istanbul)	61	20 (33%)	Yarman et al., 2004 [28]
Turkey (Kayseri)	285	6 (2.1%)	Unluhizarci et al., 2010 [29]
Turkey (Central Anatolia)	63	6 (9.5%)	Kamel et al., 2003 [30]
Israel	170	14 (8.2%)	Eldar-Geva et al., 1990 [31]
India	60	3 (8.3%)	Mithal et al., 1988 [32]
India	63	3 (5.7%)	Khandekar et al., 1990 [33]

* adolescent girls.

Witchel SF, Azziz R, 2010, *J Pediat Endocrinol*: 2010:625105
Speiser PW et al, 2010, JCEM: 95(9):4133-60

Torniamo a Laura …

19 anni

- Oligomenorrea
- Lieve sovrappeso
- Irsutismo moderato
- Acne lieve

Richiesta valutazione ormonale al IV-V giorno del ciclo mestruale

Laura

Esame	Valore
LH	5.15 mcUI/ml
FSH	7 mcUI/ml
Estradiolo	28.9 pg/ml
Prolattina	11.33 ng/ml
TSH	1.5 mcUI/ml
DHEA-S	**371.6 mcg/dl (66-368)**
SHBG	45 nmol/l
Testosterone	0.9 ng/ml
17-OH Progesterone	**3.71 ng/ml (0.15-1.1)**

Free Androgen Index
6.9 (< 4.5)

Ecografia pelvica: ovaio micropolicistico bilateralmente

Laura

- Si decide pertanto di eseguire test con ACTH 250 mcg per 17-OH progesterone

ACTH test 250 mcg per 17-OH Progesterone

Tempi	0	+60’
17OH-progesterone (ng/ml)	2.46	14.3

Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society* Clinical Practice Guideline

J Clin Endocrinol Metab, November 2018, 103(11):1–46

Phyllis W. Speiser,[1,2] Wiebke Arlt,[3] Richard J. Auchus,[4] Laurence S. Baskin,[5] Gerard S. Conway,[6] Deborah P. Merke,[7,8] Heino F. L. Meyer-Bahlburg,[9] Walter L. Miller,[5] M. Hassan Murad,[10] Sharon E. Oberfield,[11] and Perrin C. White[12]

3.2 In symptomatic individuals past infancy, we recommend screening with an early morning (before 8 AM) baseline serum 17OHP measurement by LC-MS/MS. (1|⊕⊕⊕◯)

3.3 In individuals with borderline 17OHP levels, we recommend obtaining a complete adrenocortical profile (defined below) after a cosyntropin stimulation test to differentiate 21OHD from other enzyme defects. (1|⊕⊕⊕◯)

ACTH test

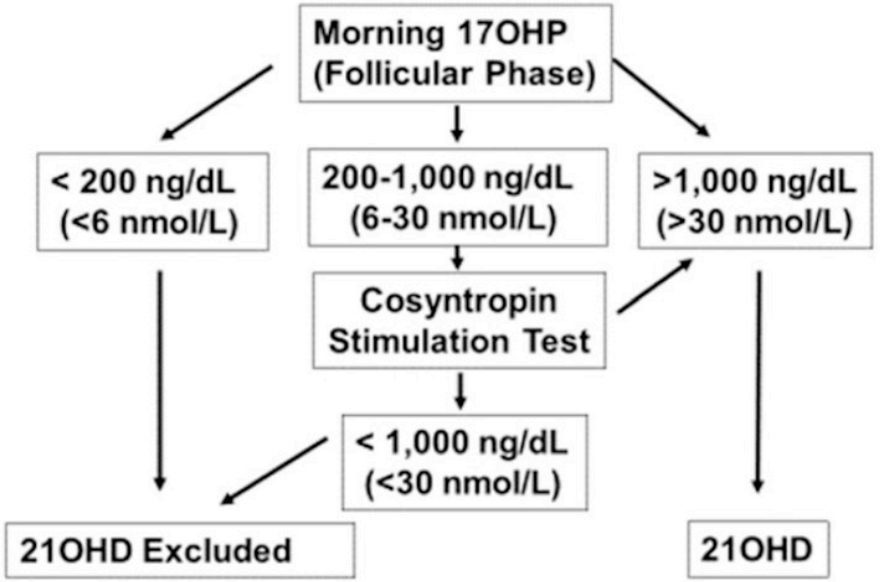
- **Cosintropina (ACTH 1-24) Synachten: 0.25 mg ev**

Prelievi al basale e dopo 60’

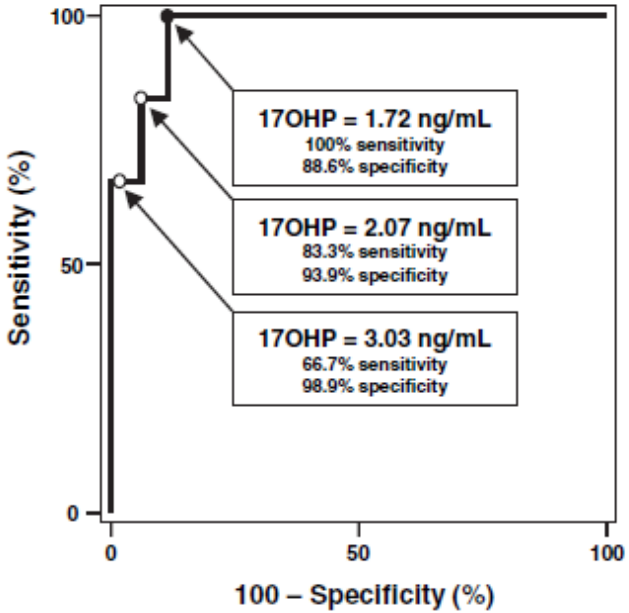
Entro le 8

In fase follicolare precoce

Idealmente dosare 17OH-progesterone, cortisolo, 11-desossicorticosterone, 11-desossicortisolo, 17OH-pregnenolone, DHEA e androstenedione tramite LC-MS/MS



17OH-progesterone basale



ORIGINAL ARTICLE
Endocrine Care

A Prospective Study of the Prevalence of Nonclassical Congenital Adrenal Hyperplasia among Women Presenting with Hyperandrogenic Symptoms and Signs

Conclusions: The prevalence of NCAH among hyperandrogenic patients from Spain is 2.2%. Basal serum 17-hydroxyprogesterone measurements have an excellent diagnostic performance, yet the cutoff value should be established in each laboratory to avoid false-negative results. (***J Clin Endocrinol Metab*** **93: 527–533, 2008)**

Escobar-Morreale HF et al. 2008, *JCEM*, 93(2):527-33

The Short Cosyntropin Test Revisited: New Normal Reference Range Using LC-MS/MS

Grethe Å. Ueland,[1,2,3] Paal Methlie,[1,2,3] Marianne Øksnes,[1,2,3] Hrafnkell B. Thordarson,[3] Jørn Sagen,[1,4] Ralf Kellmann,[4] Gunnar Mellgren,[1,4] Maria Ræder,[5] Per Dahlqvist,[6] Sandra R. Dahl,[7] Per M. Thorsby,[7] Kristian Løvås,[1,2,3] and Eystein S. Husebye[1,2,3]

J Clin Endocrinol Metab, April 2018, 103(4):1696–1703

MS/MS compared with immunoassays. We show that a stimulated 17-OHP >9.0 nmol/L after 60 minutes, which is far from the current poststimulation cutoff of 30 to 45 nmol/L, is suggestive of NCCAH. Even our patients with verified congenital adrenal hyperplasia (n = 3) did not reach that level. However, because we were only able to test a few

3 ng/ml

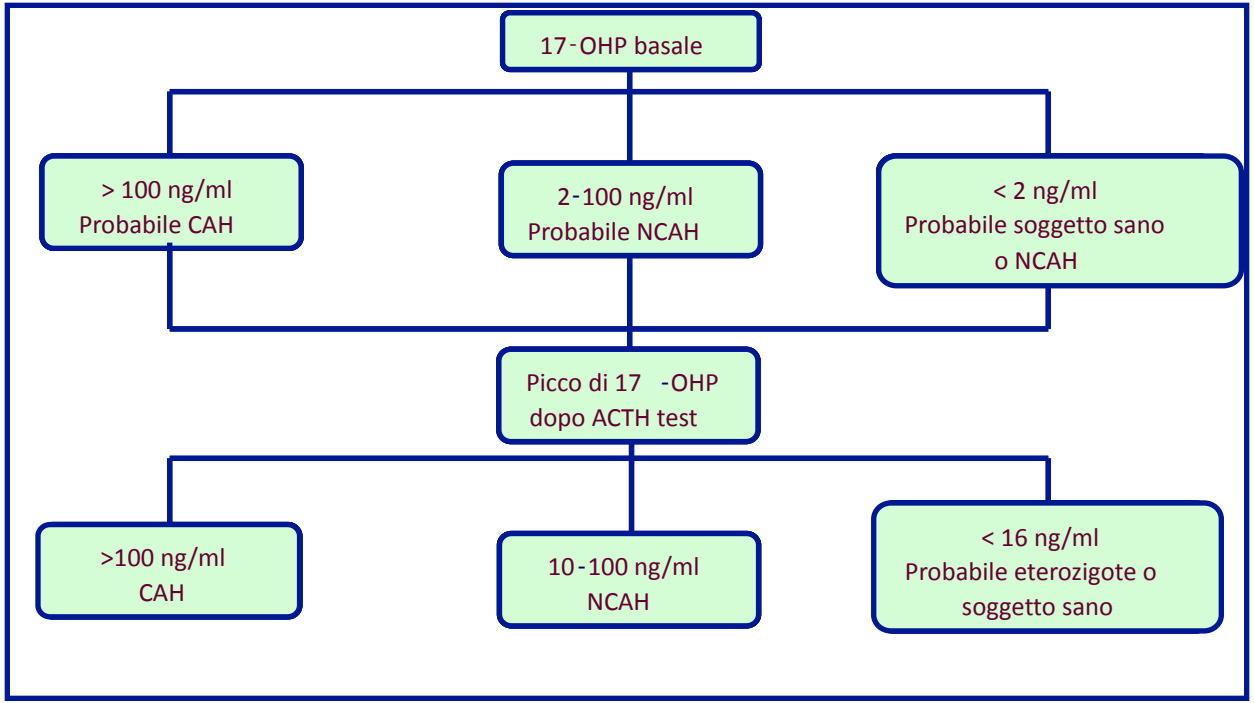
Results: Cortisol cutoff levels for LC-MS/MS were 412 and 485 nmol/L at 30 and 60 minutes, respectively. Applying the new cutoffs, 13 of 60 (22%) subjects who had AI according to conventional criteria now had a normal test result. For 17-OHP, the cutoff levels were 8.9 and 9.0 nmol/L at 30 and 60 minutes, respectively.

Conclusions: LC-MS/MS provides cutoff levels for cortisol and 17-OHP after cosyntropin stimulation that are lower than those based on immunoassays, possibly because cross-reactivity between steroid intermediates and cortisol is eliminated. This reduces the number of false-positive tests for AI and false-negative tests for NCCAH. (*J Clin Endocrinol Metab* 103: 1696–1703, 2018)

Carrier per NCAH

178, 179). Heterozygotes have slightly elevated 17OHP after ACTH stimulation, but there is overlap with unaffected subjects (173). Other analytes have been used as markers of heterozygosity (180, 181), but genotyping is a superior method of heterozygote detection. Heterozygotes do not require medical treatment but should have genetic counseling (see section 6.3).

Riassumendo …



Speiser PW et al, 2010, JCEM: 95(9):4133-60

Laura

Sindrome adreno-genitale non classica ad esordio tardivo
con iperandrogenismo biochimico e clinico

Conferma con analisi genetica

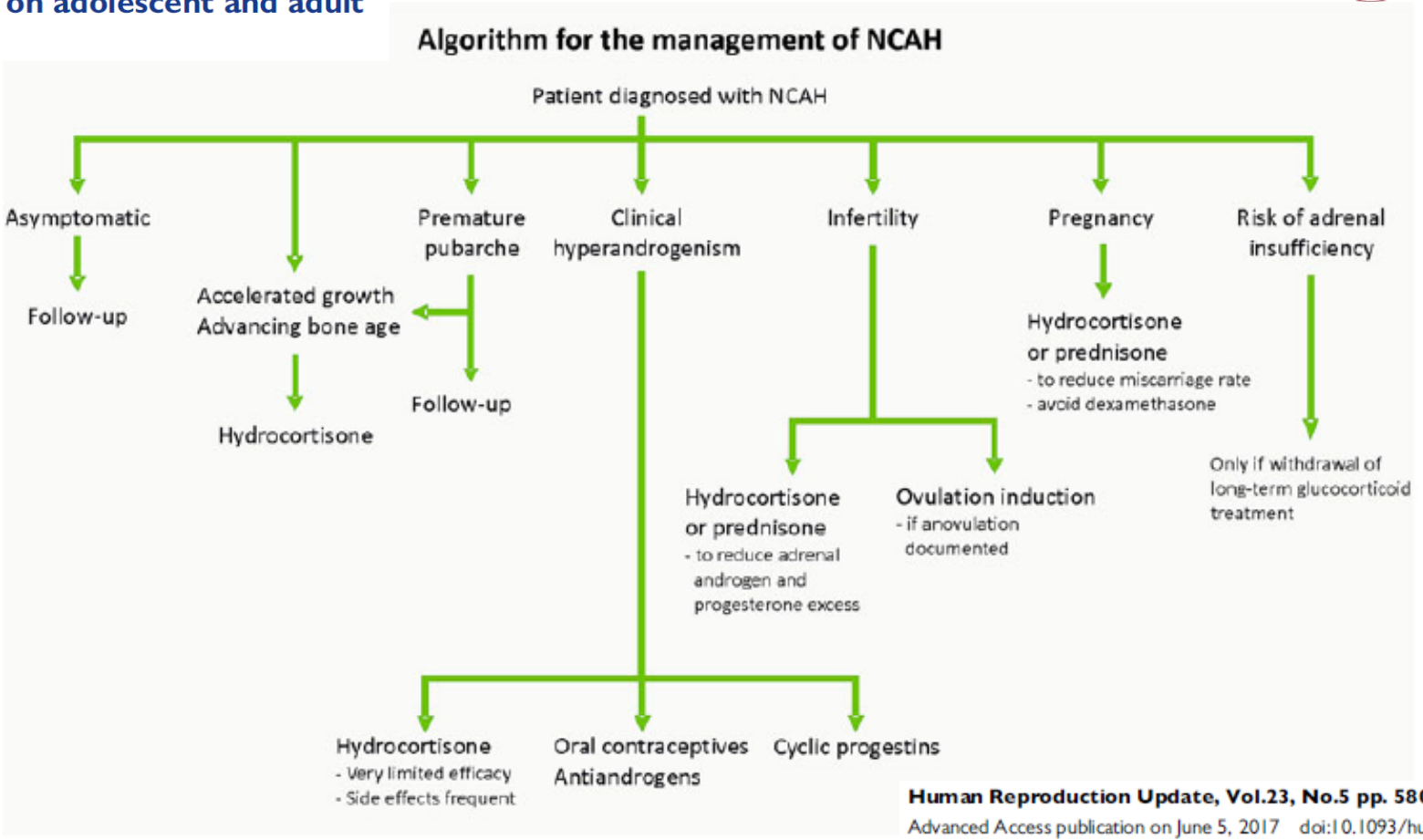
OMOZIGOSI V281L, FORMA NON CLASSICA
ATTIVITA' ENZIMATICA RESIDUA IN VITRO 50-20%

Quale terapia proporre a Laura?

Suggerita terapia con etinilestradiolo 20 mcg + drospirenone 3 mg

Non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency revisited: an update with a special focus on adolescent and adult women

Management



Human Reproduction Update, Vol.23, No.5 pp. 580–599, 2017
Advanced Access publication on June 5, 2017 doi:10.1093/humupd/dmx014

Management

5.1 In children and adolescents with inappropriately early onset and rapid progression of pubarche or bone age and in adolescent patients with overt virilization we suggest GC treatment of NCCAH. (2|⊕⊕◯◯)

Technical remark: Risks and benefits of GC therapy should be considered and discussed with the patient's family.

5.2 In asymptomatic nonpregnant individuals with NCCAH we recommend against GC treatment. (1|⊕⊕⊕◯)

5.3 In previously treated patients with NCCAH we suggest giving the option of discontinuing therapy when adult height is attained or other symptoms resolve. (2|⊕⊕⊕◯)

5.4 In adult women with NCCAH who also have patient-important hyperandrogenism or infertility we suggest GC treatment. (2|⊕⊕◯◯)

Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society* Clinical Practice Guideline

J Clin Endocrinol Metab, November 2018, 103(11):1–46

5.6 In patients with NCCAH, we suggest HC stress dosing for major surgery, trauma, or childbirth only if a patient has a suboptimal (<14 to 18 μg/dL, <400 to 500 nmol/L) cortisol response to cosyntropin or iatrogenic adrenal suppression. (2|⊕◯◯◯)

Technical remark: A range is given for cortisol cut points due to greater specificity of newer cortisol assays (see below).

Management

CLINICAL PRACTICE GUIDELINE

Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society* Clinical Practice Guideline

J Clin Endocrinol Metab, November 2018, 103(11):1–46

monitoring. In adolescents with irregular menses and acne, symptoms are usually reversed within 3 months of GC treatment, whereas hirsutism remission is more difficult with GC monotherapy. As in other androgenic disorders, an oral contraceptive with or without antiandrogens is likely the best approach for treating hirsutism in women with NCCAH (171, 207, 232, 233). For

La seconda paziente …

Anna, 24 anni

Affetta da iperplasia surrenalica congenita da **deficit di 21-idrossilasi** forma **classica con perdita salina.**

Giunge presso il nostro ambulatorio dopo essere stata seguita dalla pediatria.

Diagnosi alla nascita per ambiguità dei genitali esterni. Clitoridomegalia corretta all'età di 4 anni. Vagino-plastica all'età di 17 anni.

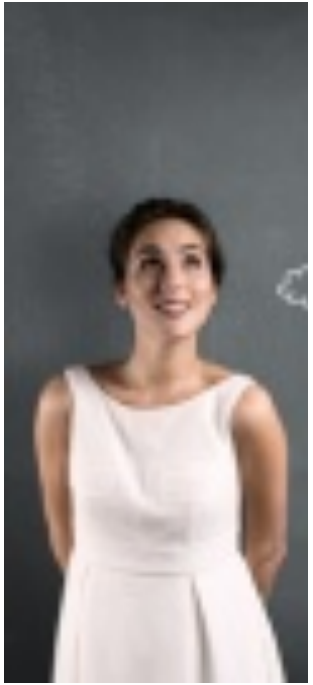
Menarca a 13 aa con cicli di ritorno regolari.

In terapia con Idrocortisone 10 mg 1½ + 1½ + 1 cp, Fludrocortisone ½ cp per 2 volte al giorno

Anna

Esame obiettivo

- Peso 63 kg
- Altezza 171 cm
- BMI 21.5 kg/m^2
- PA 130/85 mmHg
- Non irsutismo, non acanthosis nigricans
- Non stigmate cushingoidi
- Cicli regolari



Anna

Esame	Valore
ACTH	10 pg/ml
17OH-progesterone	8.7 ng/ml
Testosterone	1 ng/ml
Glicemia	85 mg/dl
Sodio	140 mmol/L
Potassio	3.7 mmol/L
Delta-4-androstenedione	0.88 ng/ml
PRA	1.7 ng/ml/h

J Clin Endocrinol Metab, November 2018, 103(11):1–46 CLINICAL PRACTICE GUIDELINE

Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society* Clinical Practice Guideline

Table 5. Utility of Various Analytes for Monitoring CAH Treatment

Patients	Analyte	Physiology	Goals and Comments
All ages	Plasma renin	Volume status	Low to normal unless hypertensive
	Potassium	MC replacement	Goal is normal
	Sodium	GC and MC replacement	Goal is normal
	Testosterone	Total androgens	Goal is at or near normal
	Androstenedione	Mostly adrenal origin	Goal is at or near normal
	Sex hormone–binding globulin	Testosterone-binding protein	For calculation of free and bioavailable testosterone
	17OHP	Variable	Normal values indicate overtreatment
Men	Testosterone	Adrenal or gonadal origin	Interpret abnormal values in context of gonadotropins and androstenedione levels
	Gonadotropins	Gonadal axis status	Low indicates poor control
	Androstenedione	Mainly adrenal	Goal is <0.5× testosterone
	Semen analysis	Fertility	Goal is normal
Women	Follicular-phase progesterone	Mainly adrenal origin when elevated	Goal is <0.6 ng/mL (<2 nmol/L) for women trying to conceive

Anna

Esame	Valore
ACTH	10 pg/ml
17OH-progesterone	8.7 ng/ml
Testosterone	1 ng/ml
Glicemia	85 mg/dl
Sodio	140 mmol/L
Potassio	3.7 mmol/L
Delta-4-androstenedione	0.88 ng/ml
PRA	1.7 ng/ml/h

Si consiglia riduzione Fludrocortisone 0.1 mg ¾ cp al mattino e Idrocortisone 10 mg 1 e ½ cp + 1 cp + ½ cp.
Si richiede MOC ed ecografia pelvica.

Anna

Torna a controllo dopo 12 mesi … è alla X settimana di gravidanza.

Gravidanza non programmata!

Porta in visione:

- Sodio 135 mEq/L
- Potassio 4 mEq/L
- ACTH 209 pg/ml
- Renina 4.8 ng/ml/h
- Delta4-androstenedione 4.5 ng/ml
- 17OH-progesterone 705 ng/ml

Si richiede screening genetico del partner

Anna non vuole sottoporsi a procedure invasive di diagnosi prenatale

Anna

Dopo due settimane torna a controllo …

Partner: assenza di mutazioni

Monitoraggio clinico e biochimico durante la gravidanza (glicemia ed elettroliti)

Parto cesareo. Ha partorito un figlio maschio in buona salute.

Peso alla nascita 3.6 kg

Anna

Quale probabilità di avere un figlio affetto?

Necessario eseguire screening genetico del partner?

Utile effettuare una diagnosi prenatale?

Anna era in terapia con Idrocortisone e Fludrocortisone: necessario modificarla?

Deficit di 21-idrossilasi nella paziente adulta

‘Programmazione e terapia in gravidanza’

Giovanna Spiazzi

U.O.C. di Endocrinologia, Diabetologia e Malattie del Metabolismo
Azienda Ospedaliera Universitaria Integrata Verona

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni non ho avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario.

Fertilità nella donna

- **Cause biologiche**:
  Iperproduzione androgeni e precursori, esposizione prenatale
  Irregolarità mestruali e anovulazione: 30-75% (PCOS secondarie)
  Ovarian adrenal rest tumours (raro)
- **Cause meccaniche**: chirurgia dei genitali
- **Cause psicologiche**

Suboptimal Psychosocial Outcomes in Patients With Congenital Adrenal Hyperplasia: Epidemiological Studies in a Nonbiased National Cohort in Sweden

A. Strandqvist, H. Falhammar, P. Lichtenstein, A. L. Hirschberg, A. Wedell, C. Norrby, A. Nordenskjöld, L. Frisén, and A. Nordenström

N: 588 253

Table 3. ORs for All the Studied Measures, Assessed for the Whole Cohort of Patients, Women and Men

	All Patients	All Women	All Men
All born 1982–1991			
Complete education	**0.5 (0.3–0.9)**	**0.3 (0.2–0.6)**	0.9 (0.4–2.1)
All born 1925–1991			
Primary education (10 y)	0.8 (0.6–1.1)	0.8 (0.5–1.4)	0.8 (0.5–1.3)
Higher education	0.7 (0.4–1.2)	0.9 (0.4–1.7)	0.5 (0.2–1.3)
Working 3–7 y	1.3 (0.7–2.2)	1.4 (0.7–2.8)	1.3 (0.5–3.6)
Working > 7 y	1.8 (0.99–3.2)	1.6 (0.8–3.2)	**3.1 (1.1–8.8)**
High income	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.8 (0.6–1.2)
Low income	0.9 (0.6–1.4)	0.8 (0.5–1.4)	1.0 (0.5–2.0)
Sick leave	**1.7 (1.2–2.4)**	1.3 (0.8–2.0)	**2.8 (1.6–4.8)**
Disability pension	**1.5 (1.0–2.2)**	1.4 (0.9–2.4)	1.6 (0.8–3.2)
Social welfare	1.0 (0.7–1.4)	1.1 (0.7–1.7)	0.9 (0.5–1.6)
Marriage	1.0 (0.8–1.4)	0.7 (0.5–1.0)	**1.6 (1.0–2.5)**
Children	**0.3 (0.2–0.3)**	**0.2 (0.1–0.3)**	**0.4 (0.2–0.6)**

Odds ratios (OR) for all the studied measures, assessed for the whole cohort of patients, men and women separately. OR with 95% confidence interval in parenthesis is given. Significant differences in bold characters.

J Clin Endocrinol Metab, April 2014, 99(4):1425–1432

Fertilità nella donna con iperplasia surrenalica: nati vivi

Forma Classica con perdita di sali (CHA-SW): 0-10% (n = 64)
Forma Classica (CHA): 33-50% (n = 83)
Forma Non Classica (NCHA): 63-90% (n = 18)

Popolazione Generale: 65-91%

Journal of Pediatric Endocrinology & Metabolism, 19, 677-685 (2006)

Meccanismi di infertilità nella donna con iperplasia surrenalica

CLINICAL STUDY European Journal of Endocrinology (2012) **167** 499–505

Influence of hormonal control on LH pulsatility and secretion in women with classical congenital adrenal hyperplasia

Anne Bachelot, Zeina Chakhtoura, Geneviève Plu-Bureau[1], Mathieu Coudert[2], Christiane Coussieu[3], Yasmina Badachi[4], Jérome Dulon, Beny Charbit[5] and Philippe Touraine on behalf of the CAHLH study group[†]

LH pulsatility pattern eterogenei
Cluster 2: ridotti profili di pulsatilità LH

Table 3 Comparison of clinical characteristics between patients in clusters 1 and 2.

	CAH patients		
	Cluster 1 ($n=7$)	Cluster 2 ($n=9$)	*P*
Age (years)	33.0 (24.0–40.0)	24.0 (19.0–40.0)	NS
Menarche (years)	12 (11–15)	13 (10–17)	NS
BMI (kg/m^2)	24.2 ± 5.2	27.3 ± 8.2	NS
W/H ratio	0.87 (0.83–0.95)	0.85 (0.64–1.15)	NS
Regular menstrual cycles	5	1	0.03
Genotype O/A/B	0/4/3	1/4/4	NS
Hydrocortisone (mg/day)	20 (15–35)	20 (10–30)	NS

Table 4 Comparison of hormonal characteristics between patients in clusters 1 and 2.

	CAH patients		
	Cluster 1 ($n=7$)	Cluster 2 ($n=9$)	*P*
17-OH progesterone (ng/ml)	1.0 (0.2–2.5)	60.0 (2.8–475.0)	0.005
Progesterone (ng/ml)	0.05 (0.05–0.44)	5.78 (0.55–27.02)	0.004
Testosterone (ng/ml)	0.06 (0.06–0.26)	0.39 (0.06–4.24)	0.01
Androstenedione (ng/ml)	0.6 (0.4–1.5)	3.1 (0.3–29.6)	0.05
SHBG (nmol/l)	90.9 (49.1–191.9)	61.4 (14–98)	NS
Estradiol (pg/ml)	64 (34–84)	98 (27–221)	NS
FSH (IU/l)	6.1 (4.7–9.6)	3.5 (0.1–8.3)	0.02
LH (IU/l)	6.2 (4.8–9.5)	2.3 (0.1–10.1)	0.01
FSH/LH ratio	1.0 (0.5–2.0)	1.2 (0.8–9.6)	NS

Health Status of Adults with Congenital Adrenal Hyperplasia: A Cohort Study of 203 Patients

Wiebke Arlt, Debbie S. Willis, Sarah H. Wild, Nils Krone, Emma J. Doherty, Stefanie Hahner, Thang S. Han, Paul V. Carroll, Gerry S. Conway, D. Aled Rees, Roland H. Stimson, Brian R. Walker, John M. C. Connell, Richard J. Ross, and the United Kingdom Congenital Adrenal Hyperplasia Adult Study Executive (CaHASE)

TABLE 1. Glucocorticoid treatment in the 21-hydroxylase deficiency patients in the United Kingdom CaHASE cohort (n = 199)

Glucocorticoid treatment	Male classic CAH (n = 62)	Female classic CAH (n = 103)	Female nonclassic CAH (n = 31)
26% Hydrocortisone only			
n (%)	24 (39%)	21 (20%)	5 (16%)
Median dose (range) (mg/d)	25 (10–60)	20 (10–32.5)	20 (10–25)
Administration (od/bd/tds) (n = 51)		13/61/26%	
Reverse circadian administration (n = 51)		11%	
43% Prednisolone only			
n (%)	18 (29%)	50 (49%)	17 (55%)
Median dose (range) (mg/d)	7.5 (2.5–10)	6 (2.5–10)	5 (1–7.5)
Administration (od/bd/tds) (n = 88)		24/75/1%	
Reverse circadian administration (n = 88)		60%	
19% Dexamethasone only			
n (%)	15 (24%)	17 (17%)	5 (16%)
Median dose (range) (mg/d)	0.5 (0.25–0.75)	0.375 (0.25–0.75)	0.25 (0.25–0.5)
Administration (od/bd/tds) (n = 37)		78/22/0%	
Reverse circadian administration (n = 37)		44%	
10% Combination of glucocorticoid preparations[a]	4 (6%)	14 (14%)	2 (6%)
No glucocorticoids		1 (1%)	2 (6%)
41% Reverse circadian glucocorticoid administration	21 (34%)	51 (50%)	11 (35%)
Fludrocortisone			
n (%)	51 (82%)	74 (72%)	3 (10%)
Median dose (range) (μg/d)	125 (10–500)	150 (50–500)	50 (50–250)

203 CAH: 138 donne

Norm 36%

Ridotto 38%

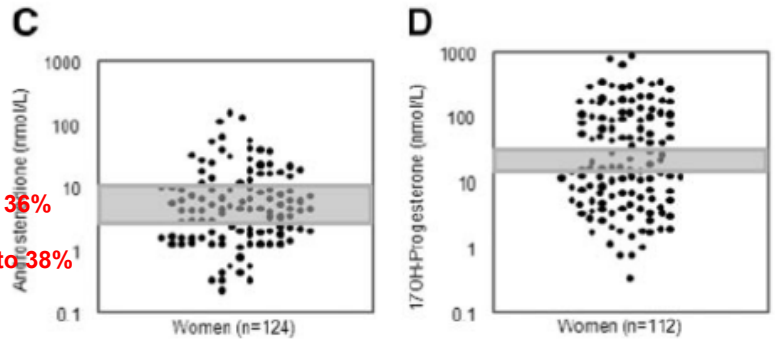


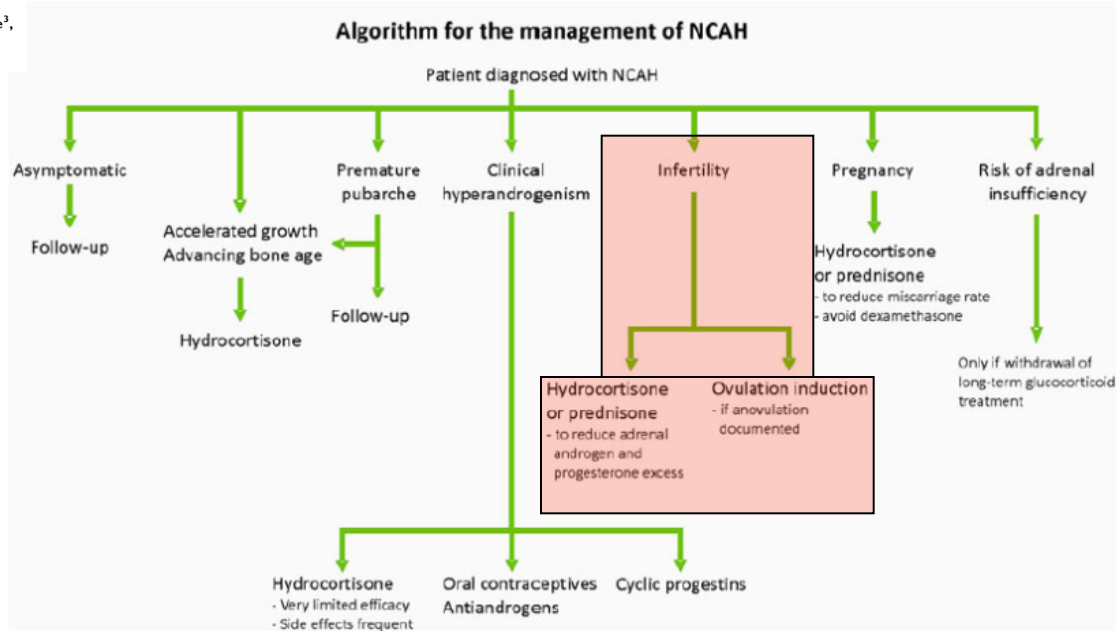
FIG. 2. Serum levels of the androgen precursor androstenedione (A, C) and the glucocorticoid precursor 17OHP (B, D) in male and female CAH patients sampled in the morning after intake of the usual glucocorticoid morning dose. The *shaded areas* represent recommended target range (2). Note the logarithmic scale used for representing the serum hormone concentrations.

J Clin Endocrinol Metab, November 2010, 95(11):5110–5121

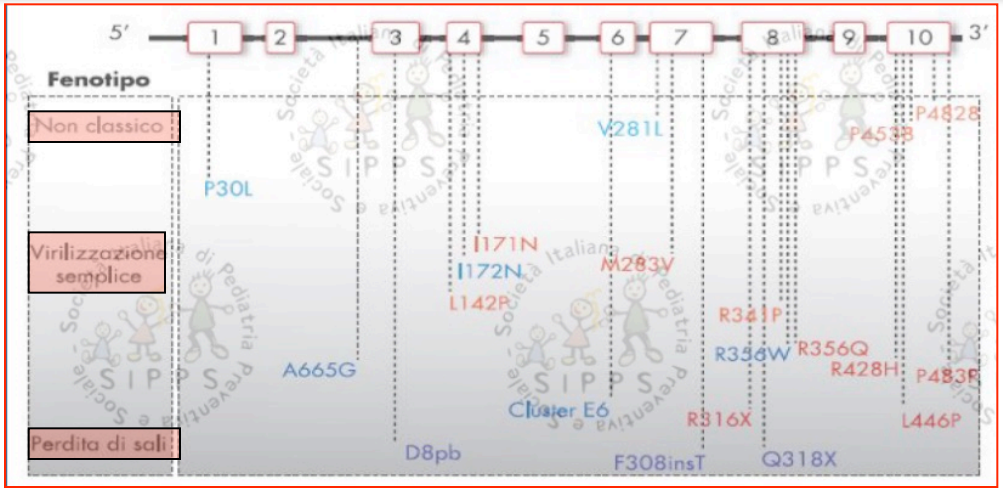
Infertilità nelle donne con NCAH

Non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency revisited: an update with a special focus on adolescent and adult women

Enrico Carmina[1,*], Didier Dewailly[2], Héctor F. Escobar-Morreale[3], Fahrettin Kelestimur[4], Carlos Moran[5], Sharon Oberfield[6], Selma F. Witchel[7], and Ricardo Azziz[8]



Human Reproduction Update, Vol.23, No.5 pp. 580–599, 2017

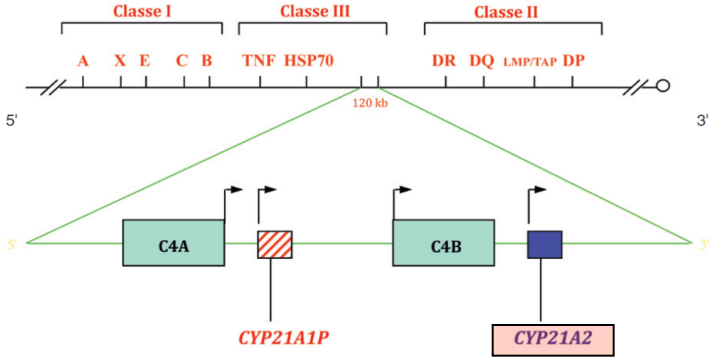


Fenotipo determinato da allele con mutazione meno grave

Tabella I. Frequenza del deficit di 21-idrossilasi, forma classica in alcune popolazioni (dati ottenuti da screening neonatali).

Regione	Incidenza	Riferimenti bibliografici
Alaska, Esquimesi	1:280	Pang, 1982
Isola La Reunion	1:2100	Pang, 1988
Svezia	1:9800	Thil'en, 1998
Stati Uniti (Wisconsin)	1:11000	Allen, 1997
Francia	1:13000	Cartigny, 1999
Giappone	1:18000	Tajima, 1997
Stati Uniti (Texas)	1:16000	Therrel, 1998
Scozia	1:17000	Pang, 1988
Italia	1:18000	Balsamo A, 1996
Nuova Zelanda	1:23000	Cutfield, 1995

Deficit 21-idrossilasi - gene CYP21A2



Attività enzimatica	Varianti Patogenetiche comuni in *CYP21A2*
0%	Delezione 30kb Conversione genica estesa p.Gly110Valfs*21 [Ile236Asn;Val237Glu;Met239Lys] p.Gln318* p.Arg356Trp Arg483Pro
<1%	c.293-13A-C>G[a]
2-11%	p.Ile172Asn
20-50%	p.Pro30Leu p.Val281Leu p.Pro453Ser p.Arg339His

a: associata sia a SW che SV.

Genotipo	Fenotipo
Severa/ Severa	Classico SW
Severa/ Intermedia	Classico SV
Intermedia/ Intermedia	Classico SV
Severa/ Lieve	NON-CLASSICO CRIPTICO
Intermedia/ Lieve	NON-CLASSICO CRIPTICO
Lieve/ Lieve	NON-CLASSICO CRIPTICO

Genitori a rischio

1) Affetti da CHA: 1:15.000

Portatore sano CHA: 1:60

2) Affetti da NCHA: 1:1000

Portatore sano NCHA: 6:60

Coppia con figlio affetto:

1:4 CHA

1:2 ♀

1:8 ♀ con CHA

Donna affetta CHA + Partner

1:60 1:120 CHA (feto affetto)

1: 240 ♀ con CHA

Probabilità di un genitore con **NCHA** (eterozigote con mutazione severa) di avere un figlio con CHA:

1:250

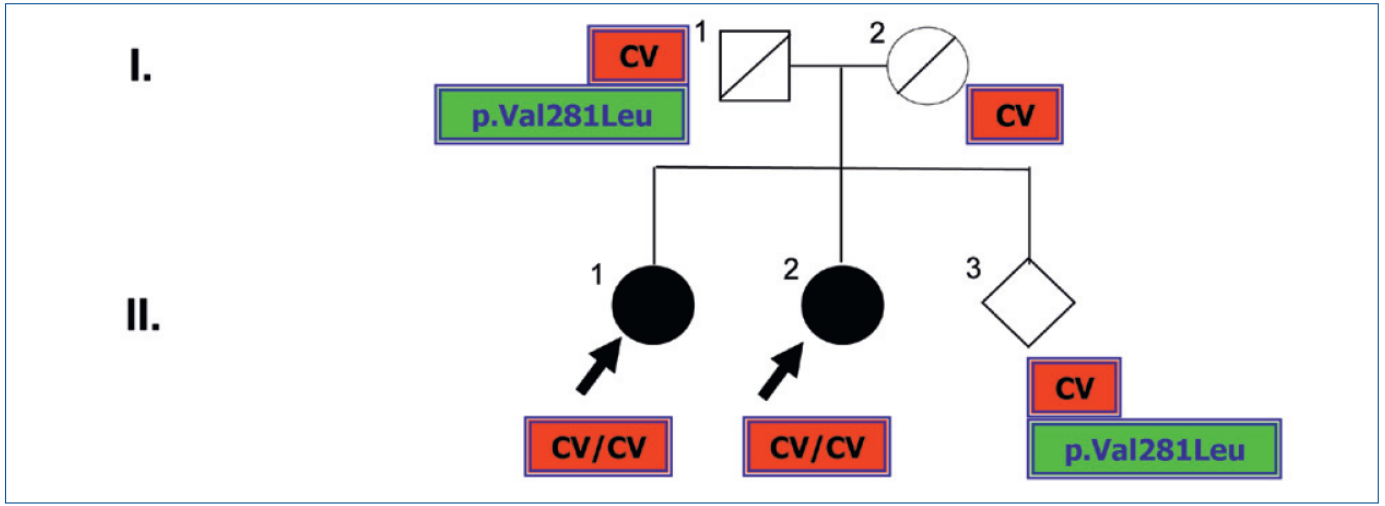


Figura 5. Studio familiare: famiglia con due figli affetti da forma classica SW (II.1, II.2), inviata al test genetico per conferma diagnostica. Identificate le mutazioni: padre asintomatico con genotipo criptico (combinazione di una variante severa, CV, con una variante lieve, p.Val281Leu). Madre eterozigote per la mutazione severa CV. Figli affetti entrambi omozigoti per la variante severa CV (conversione genica estesa). Questo caso evidenzia l'importanza dello studio familiare; se avessimo fatto il test genetico solo ai due soggetti affetti non avremmo definito correttamente il rischio riproduttivo della famiglia.
Diagnosi prenatale (II.3): in una gravidanza successiva, la madre ha iniziato la terapia per la prevenzione della virilizzazione. La DPN: risultato genotipo non-classico (combinazione della variante paterna lieve, p.Val281Leu, con la variante materna severa, CV); fenotipo atteso: forma non-classica, quindi sospensione terapia desametasone.

Se desiderio di gravidanza:

1) Vista l'elevata prevalenza di eterozigosi per mutazioni di CYP21A2, è fondamentale il counseling genetico
2) Se in una coppia che desidera figli è nota la presenza di un portatore di mutazione severa (forma classica, non classica o eterozigosi severa), è necessario eseguire lo studio genetico nel partner
3) Lo studio genetico non può essere sostituito dalla valutazione ormonale

Management of congenital adrenal hyperplasia and nonclassic congenital adrenal hyperplasia during pregnancy

NCAH

6.5 In women with nonclassic congenital adrenal hyperplasia who are infertile or have a history of prior miscarriage, we recommend treatment with a glucocorticoid that does not traverse the placenta. (1|⊕⊕◯◯)

6.6 In women with congenital adrenal hyperplasia who are pregnant, we advise management by an endocrinologist familiar with congenital adrenal hyperplasia. (Ungraded Good Practice Statement)

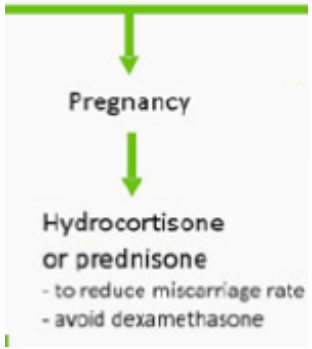
6.7 In women with congenital adrenal hyperplasia who become pregnant we recommend continued prepregnancy doses of hydrocortisone/prednisolone and fludrocortisone therapy, with dosage adjustments if symptoms and signs of glucocorticoid insufficiency occur. (1|⊕⊕◯◯)

Technical remark: Clinicians should evaluate the need for an increase in glucocorticoid during the second or third trimester and administer stress doses of glucocorticoids during labor and delivery.

6.8 In women with congenital adrenal hyperplasia who are pregnant, or trying to become pregnant, we recommend against using glucocorticoids that traverse the placenta, such as dexamethasone. (1|⊕⊕◯◯)

6.9 In women with congenital adrenal hyperplasia who are pregnant, we advise that the birthing plan includes an obstetric specialist. (Ungraded Good Practice Statement)

Algorithm for the management of NCAH



J Clin Endocrinol Metab, November 2018, 103(11):1–46

Trattamento prenatale con DEX

Ridurre la virilizzazione dei genitali esterni

Ridurre la necessità di chirurgia ricostruttiva dei genitali

Ridurre lo stress emotivo nei genitori

Questioni etiche: esporre inutilmente 7 feti ad alte dosi di DEX nel primo trimestre per trattare 1 feto affetto?

Embriogenesi

4 WG: formazione corteccia surrenalica

6-7 WG: inizia secrezione di steroidi

7-12 WG: formazione genitali esterni

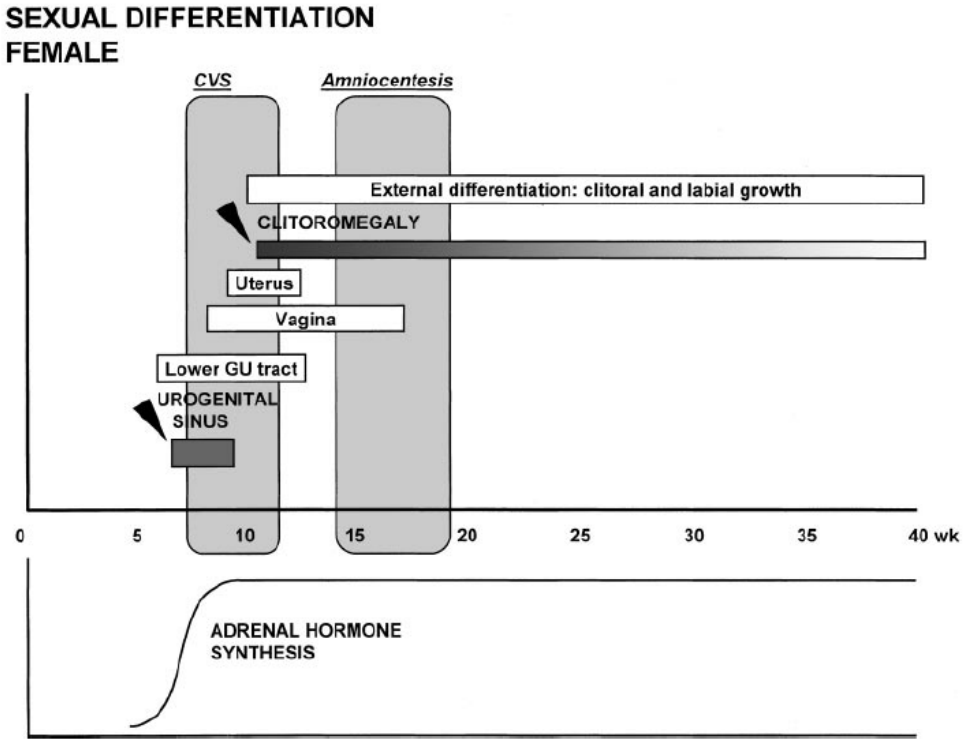
6-7 WG: timing ideale?

10-12 W: test villi coriali

12-13 W: amniocentesi

4-5 W: SRY test

(Fetal Y-chromosome DNA in maternal blood)



Early SRY test

New Management Strategy of Pregnancies at Risk of Congenital Adrenal Hyperplasia Using Fetal Sex Determination in Maternal Serum: French Cohort of 258 Cases (2002–2011)

Véronique Tardy-Guidollet, Rita Menassa, Jean-Marc Costa, Michel David,‡ Claire Bouvattier-Morel, Clarisse Baumann, Muriel Houang, Françoise Lorenzini, Nicole Philip, Sylvie Odent, Agnès Guichet, and Yves Morel

2002-2011
258 feti a rischio (134 M/124 F)
Test sensibile (96%) dalla 4 WG+5 gg
No DEX nel 68% dei M

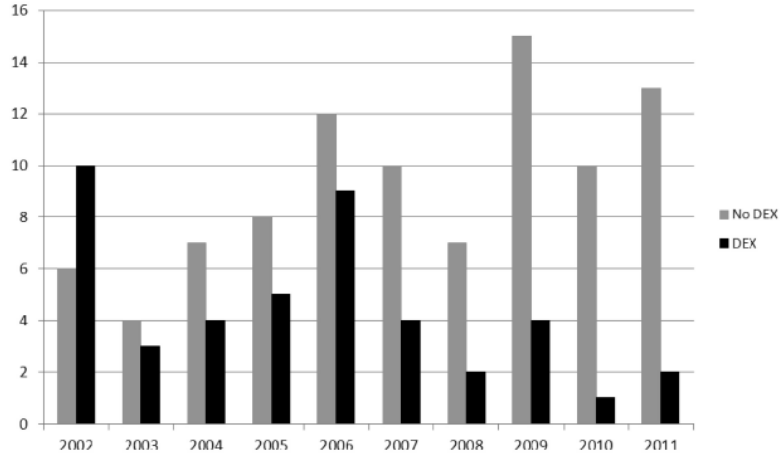


Figure 4. Number of untreated males vs number of treated males per year. The percentage of untreated males increased from 38% in 2002 to 90% in 2010 and 2011.

J Clin Endocrinol Metab, April 2014, 99(4):1180–1188

An Update on Prenatal Diagnosis and Treatment of Congenital Adrenal Hyperplasia

Maria I. New, M.D.[1,2] Moolamannil Abraham, M.D.[1,2] Tony Yuen, Ph.D.[2,3] Oksana Lekarev, D.O.[1,2]

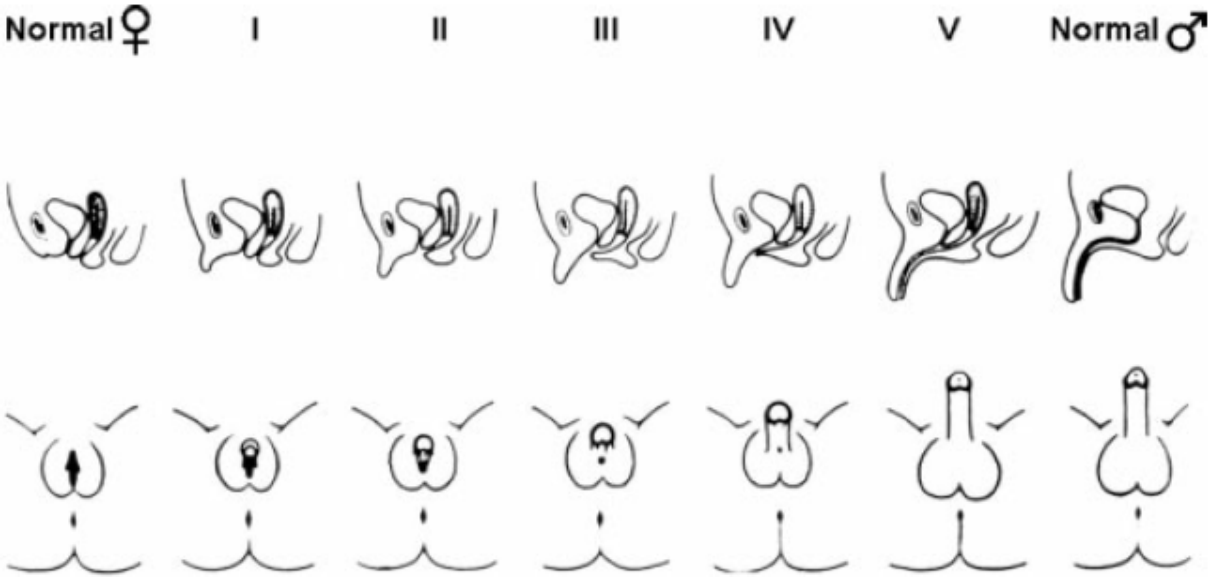
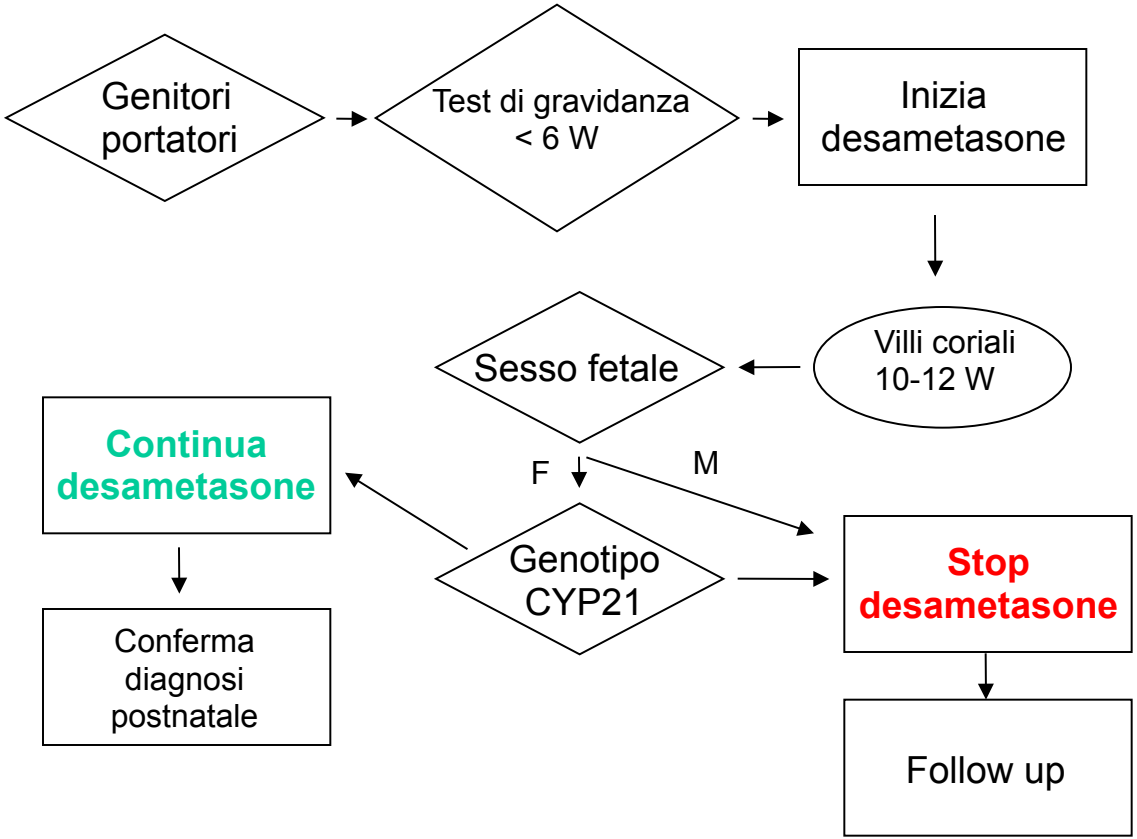


Figure 3 Depiction of Prader scores.

Semin Reprod Med 2012;30:396–399

Diagnosi e trattamento prenatale



2. Prenatal Treatment of CAH

2.1 We advise that clinicians continue to regard prenatal therapy as experimental. Thus, we do not recommend specific treatment protocols. (Ungraded Good Practice Statement)

2.2 In pregnant women at risk for carrying a fetus affected with CAH and who are considering prenatal treatment, we recommend obtaining prenatal therapy only through protocols approved by Institutional Review Boards at centers capable of collecting outcomes from a sufficiently large number of patients, so that risks and benefits can be defined more precisely. (1|⊕⊕⊕◯)

2.3 We advise that research protocols for prenatal therapy include genetic screening for Y-chromosomal DNA in maternal blood to exclude male fetuses from potential treatment groups. (Ungraded Good Practice Statement)

Schema terapeutico usuale

Desametasone (non disat da 11OHasi2):

0.02 mg/kg peso pre-gravidico in 2-3 somm/die (max 1.5 mg/die)

Secrezione fisiologica cortisolo: 6-7 mg/m^2 al dì

Dex 50-80 volte più potente: dose fisiol ~0.1 mg/m^2 al dì

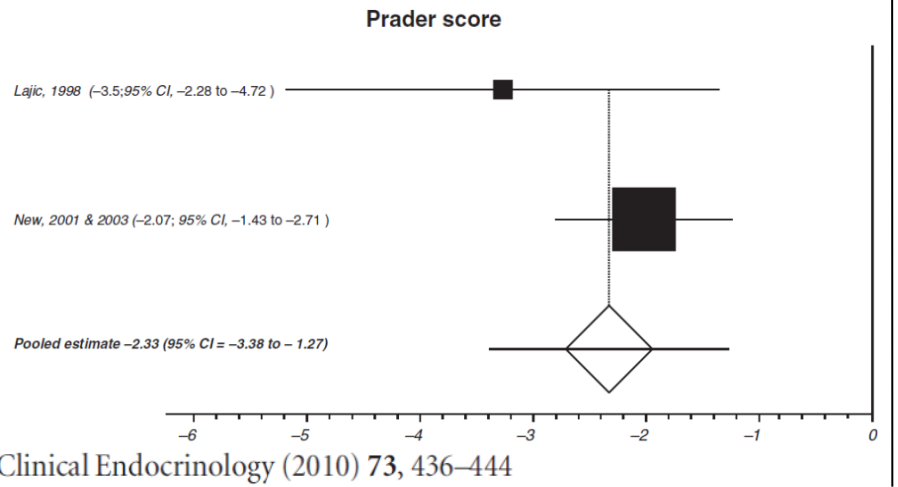
Es: Donna di 60 kg = 1.6 m^2: 0.2 mg/die vs 1.2 mg/die (~6 volte)

Livelli fisiol feto: 1/10 dei livelli materni → feto trattato:~60 volte

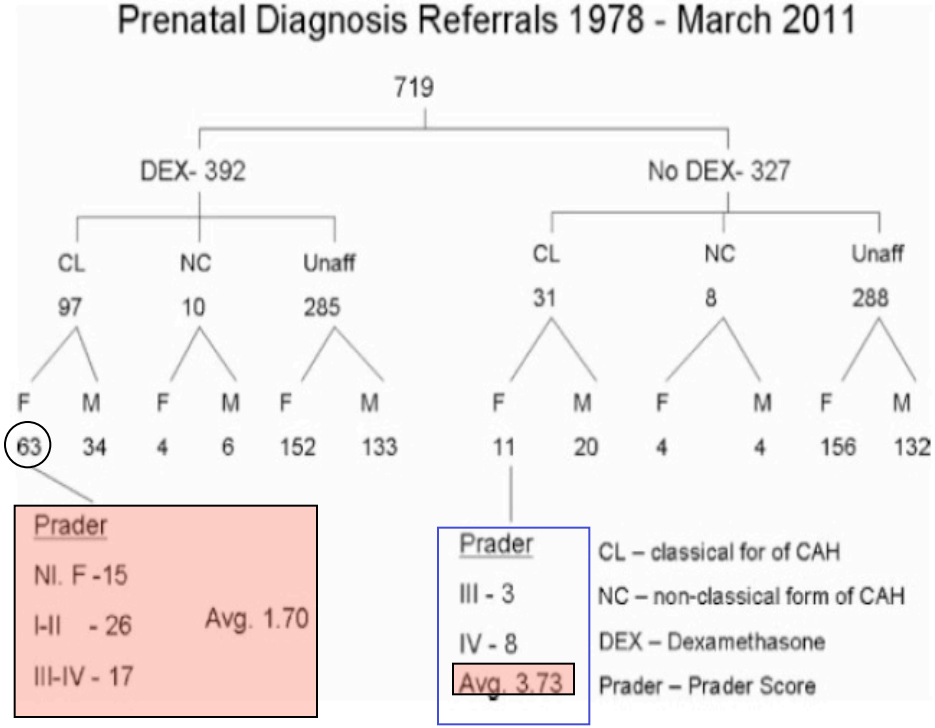
Efficacia sul feto (80%)

Studio francese:
112 madri trattate, 17 casi
12 genitali normali
3 virilizzazione moderata
2 severa (DEX > 6W)

J Clin Endocrinol Metab, April 2014, 99(4):1180–1188

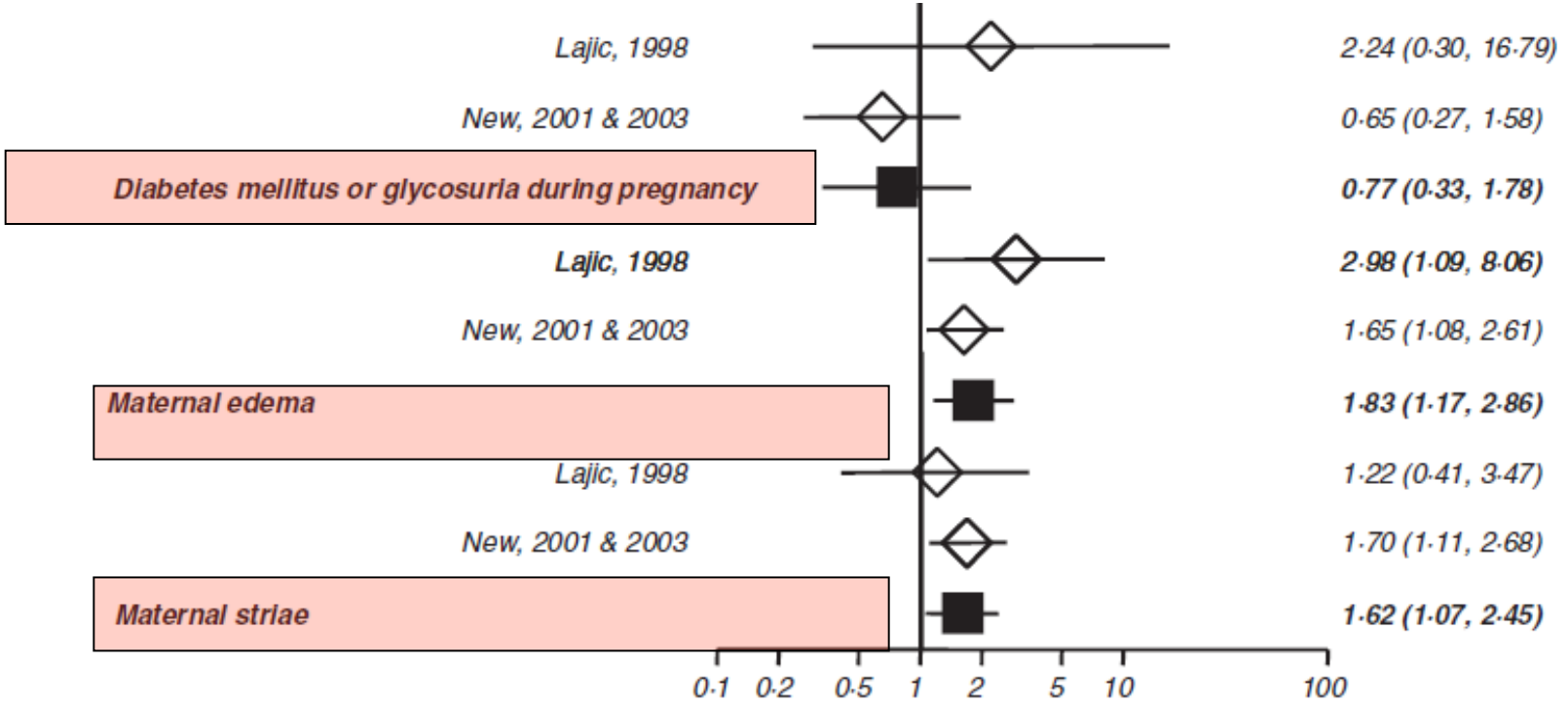


Clinical Endocrinology (2010) 73, 436–444



Semin Reprod Med 2012;30:396–399

Sicurezza materna



Clinical Endocrinology (2010) **73**, 436–444

Sicurezza feto: teratogenicità

TABLE 2
Association of risk of orofacial clefts among offspring born to women who used maternal corticosteroid medications from 4 weeks before through 12 weeks after conception, by route of administration and component corticosteroid

				OR (95% CI)†	
Route of administration and component	CLP (n)*	CP (n)*	Control (n)*	CLP	CP
Any use	33	6	72	1.7 (1.1-2.6)	0.5 (0.2-1.3)
Any systemic use	9	2	16	2.1 (0.9-4.7)	0.8 (0.2-3.6)
Prednisone	8	2	11	2.7 (1.1-6.7)	1.2 (0.3-5.4)
Any nasal spray/inhaled use	19	5	47	1.5 (0.9-2.5)	0.7 (0.3-1.8)
Beclomethasone	5	2	11	1.7 (0.6-4.8)	1.2 (0.3-5.4)
Budesonide	3	2	4	2.8 (0.6-12.3)	3.3 (0.6-17.9)
Fluticasone	8	0	23	1.3 (0.6-2.9)	—
Triamcinolone	5	1	9	2.0 (0.7-6.1)	—
Any topical use	2	0	8	0.9 (0.2-4.3)	—
Other/not otherwise specified use	4	0	5	2.9 (0.8-11.0)	—

Am J Obstet Gynecol 2007;197:585.e1-585.e7.

OR 7.3 (95% CI: 1.8-29.4)
Esposizione < 8 WG

Desametasone: Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks (NIH)

Sicurezza feto: peso alla nascita

TABLE 1. Birth weights of dexamethasone (Dex)-treated and untreated newborns, affected or unaffected with CAH

	Dex treated		Untreated	
	Affected (n = 73)	Not affected (n = 158)	Affected (n = 22)	Not affected (n = 135)
Birth weight (mean kg)	3.17	3.41	3.59	3.40

$P = 0.167$.

- 400 g, simile a quello di feti di donne che fumano 40 sigarette/die

Rischio aumentato di: ipertensione in età adulta
DMT2, CVD, rigidità aortica

J Clin Endocrinol Metab, December 2001, 86(12):5651–5657

Cognitive Functions in Children at Risk for Congenital Adrenal Hyperplasia Treated Prenatally with Dexamethasone

J Clin Endocrinol Metab, February 2007, 92(2):542–548

Tatja Hirvikoski, Anna Nordenström, Torun Lindholm, Frank Lindblad, E. Martin Ritzén, Anna Wedell, and Svetlana Lajic

1985-95
40 feti
Funz neuropsicologiche
Performance scolastica

TABLE 3. Results on child-completed questionnaire of Social Anxiety Scale for Children–Revised (SASC-R) summarized separately for the three groups

	CAH-unaffected, short-term treated (n = 13)	CAH-affected, prenatally treated (n = 8)	Control group (n = 26)	*P*	
SASC-FNE	19.77 (5.9)	13.87 (6.10)	14.85 (6.99)	0.062	NS
SASC-New	17.15 (3.76)	14.5 (5.5)	13.73 (4.56)	0.094	NS
SASC-General	8.69 (2.6)	5.12 (2.47)	6.88 (3.05)	0.026	*a*
SASC-Total	45.62 (10.19)	33.50 (12.75)	35.46 (12.75)	0.034	*a*

TABLE 1. Results on neuropsychological tests[a]

	DEX-treated group (n = 25)	Control group (n = 35)	*P*	
Psychometric intelligence				
Verbal comprehension, index score	102.44 (12.75)	107.40 (11.07)	0.114	NS
Perceptual organization, index score	101.64 (11.88)	105.09 (14.10)	0.324	NS
FSIQ	101.24 (12.96)	106.86 (11.36)	0.080	NS
Handedness				
Manual preference, raw score	5.96 (0.20)	5.57 (1.20)	0.067	NS
Memory encoding				
Faces, scaled score	11.6 (3.40)	10.89 (2.90)	0.385	NS
Names, scaled score	11.24 (2.92)	11.74 (2.67)	0.492	NS
Narrative memory,[b] scaled score	11.33 (2.76)	11.03 (2.54)	0.667	NS
Word list, raw score (maximum 5 × 15 = 75 words)	51.32 (8.31)	51.34 (10.96)	0.993	NS
Spatial encoding, raw score (maximum 9 locations)	8.88 (0.33)	8.66 (0.97)	0.275	NS
Long-term memory				
Faces, scaled score	11.40 (2.90)	11.34 (2.07)	0.929	NS
Names, scaled score	11.68 (2.64)	11.42 (2.09)	0.682	NS
Word list, raw score (maximum 15 words)	11.64 (2.12)	11.29 (2.99)	0.613	NS
Spatial memory, raw score	8.6 (0.58)	8.66 (0.77)	0.754	NS
Working memory				
Freedom of Distractibility Index, index score	92.08 (13.56)	101.43 (13.10)	0.009	*f*
Freedom of Distractibility, log-transformed	4.51 (0.15)	4.61 (0.13)	0.007	*f*
Arithmetic, scaled score	9.08 (3.01)	9.83 (2.81)	0.328	NS
Digit Span, scaled score	8.36 (2.40)	10.69 (2.47)	0.001	*f*
Span Board Test,[c] scaled score	10.79 (3.56)	12.34 (3.13)	0.083	NS
Impulse inhibition				
Interference, Stroop,[d] T-score[e]	53.23 (4.32)	52.58 (4.65)	0.610	NS
Speed of processing				
Processing Speed Index, index score	105.88 (13.84)	112.86 (17.98)	0.110	NS
Speeded reading, Stroop,[d] T-score	46.36 (6.27)	50.32 (7.19)	0.043	*e*
Speeded naming of colors, Stroop,[d] T-score	40.59 (6.39)	44.52 (5.03)	0.016	*e*

TABLE 2. Results on child-completed questionnaire of the Scholastic Competence subscale from the Self-Perception Profile for Children[a]

	DEX-treated group (n = 21)	Control group (n = 26)	*P*
Scholastic competence	3.04 (0.50)	3.4 (0.37)	0.007[b]

Data are expressed as mean (SD).

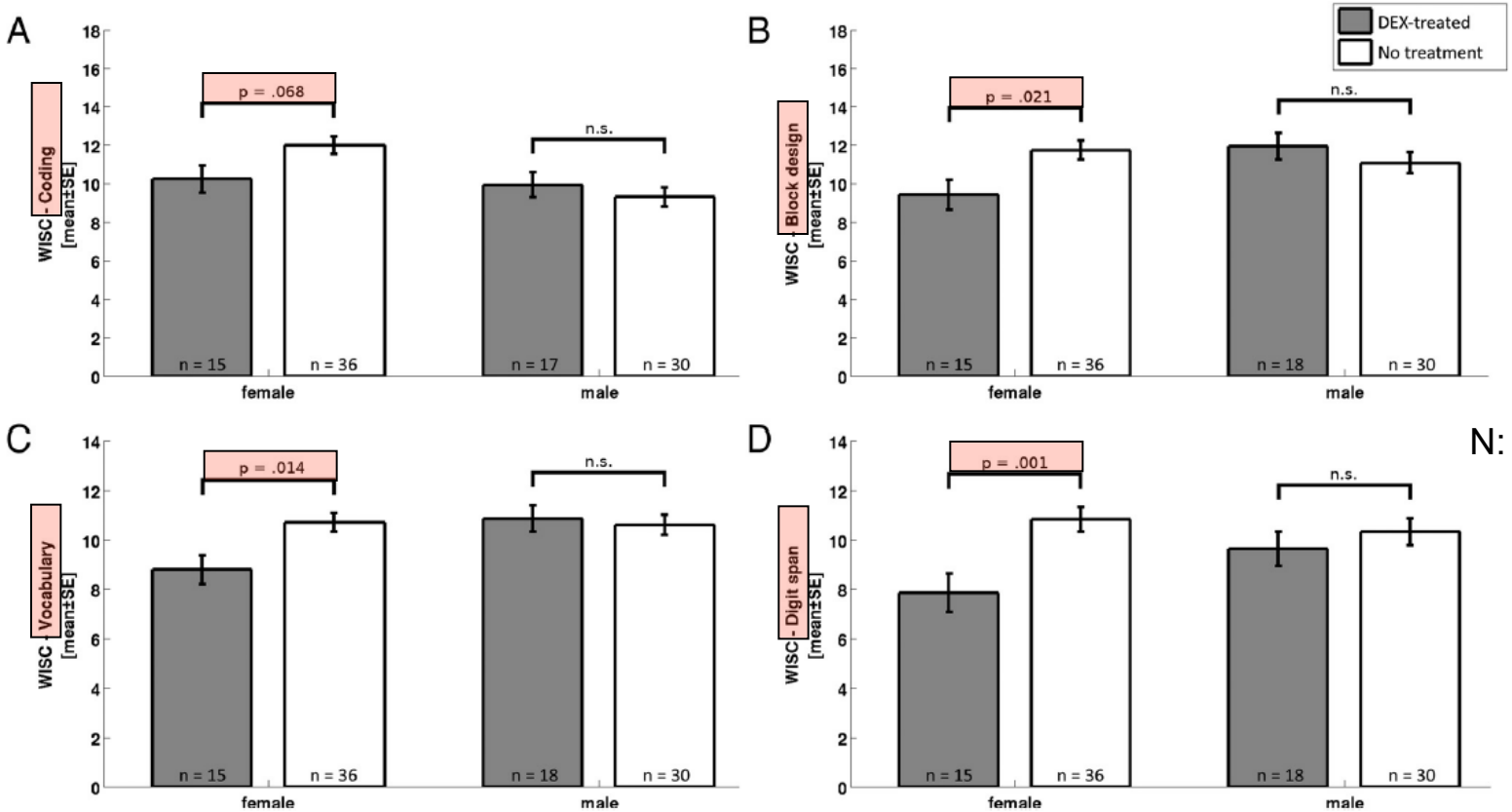
Sex-Dimorphic Effects of Prenatal Treatment With Dexamethasone

J Clin Endocrinol Metab, October 2016, 101(10):3838–3846

Lena Wallensteen,* Marius Zimmermann,* Malin Thomsen Sandberg, Anton Gezelius, Anna Nordenström, Tatja Hirvikoski, and Svetlana Lajic

Sicurezza feto

WISC-III, Wechsler Intelligence Scales for Children-III



N: non-CAH 34 vs 66

Questioni aperte

1. Trattamento prenatale con DEX a dosi inferiori rispetto a quelle oggi utilizzate?
2. Determinazione sistematica del sesso fetale attraverso l'analisi del DNA fetale nel sangue materno (cromosoma Y)?
3. Diagnosi genetica pre-impianto?


Thank you!

Deficit di 21-idrossilasi nella paziente adulta

Take Home Messages

Alessandro Scoppola

UOSD di Endocrinologia

Ospedale Santo Spirito in Sassia - Roma

SISTEMA SANITARIO REGIONALE
ASL ROMA 1

REGIONE LAZIO

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni non ho avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

Diagnosi

Deficit enzimatico della 21-idrossilasi

Grave (CAH) – neonatale/prima infanzia

Lieve (NCAH) – puberale adulta

Iperplasia surrenale congenita

Quadro clinico

Irsutismo 60-80%
PCO 24-80%
Irr. Mestr. 30-50%
Acne 30%

In fase follicolare precoce:

Testosterone totale entro le ore 8 (…/MS)

17OH-progesterone entro le ore 8 (LC-MS/MS)

> 100 ng/ml: CAH probabile
2-100 ng/ml: NCAH probabile
< 2 ng/ml: normale/NCAH

Dopo ACTH

> 100 ng/ml: CAH
10-100 ng/ml: NCAH
< 16 ng/ml: eterozigote/normale

Trattamento delle pazienti adulte

Forma Classica (CAH)

- ✓ Evitare la soppressione completa della secrezione steroidea
- ✓ Durante la gravidanza il trattamento con idrocortisone o prednisone e mineralcorticoidi va adeguato ad eventuali sintomi di insufficienza cortico-surrenalica (II e III trimestre)
- ✓ Considerare per tutti l'incremento del dosaggio di glucocorticoide in condizioni particolari (febbre > 38.5, chirurgia, gravi malattie, ecc.)

Forma Non Classica (NCAH)

- ✓ I casi asintomatici e fuori dalla gravidanza non necessitano di terapia
- ✓ La terapia (idrocortisone o prednisone) è indicata in presenza di iperandrogenismo e infertilità
- ✓ Offrire l'opzione della sospensione del trattamento in funzione dell'età
- ✓ Considerare per tutti il trattamento con idrocortisone in condizioni particolari (intervento chirurgico, gravi malattie, ecc.)

Controlli durante il trattamento

Forma Classica (CAH)

- ✓ Controllo annuale di:
  - ✓ P.A., B.M.I., valutazione clinica, esami ematochimici per funzione mineralcorticoide e glucocorticoide
- ✓ Valutazione MOC e del metabolismo osseo
- ✓ Valutazione cardiologica
- ✓ Valutazione del metabolismo glico-lipidico
- ✓ Non è indicata la valutazione morfologica surrenalica di routine

Gravidanza

Diagnosi nota di CAH/NCAH

- ✓ **È fondamentale il counseling genetico**
- ✓ **Se in una coppia un genitore è portatore di mutazione severa (forma classica, non classica o eterozigosi severa), è necessario eseguire lo studio genetico nel partner**
- ✓ **Lo studio genetico non può essere sostituito dalla valutazione ormonale**

Diagnosi non nota di CAH/NCAH

- ✓ **Considerare la possibile causa di infertilità**

Prima della gravidanza: questioni aperte

Terapia prenatale con desametasone (dopo valutazione del DNA fetale cromosoma Y nel sangue materno)

- Ridurre la virilizzazione dei genitali esterni
- Ridurre la necessità di chirurgia ricostruttiva dei genitali
- Ridurre lo stress emotivo nei genitori

Effettuare sistematicamente la determinazione del sesso fetale da DNA fetale nel sangue materno (cromosoma Y)?


Grazie!