

Altogether  
to Beat  
Cushing's  
Syndrome



Viaggio alla  
(ri)scoperta  
della **Sindrome  
di Cushing**

Terza Edizione

Sorrento, 27-30 maggio 2014

La gestione del  
Cushing in  
gravidanza:

Il ruolo  
dell'endocrinologo

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# SINDROME DI CUSHING

## Gravidanza?

Aum  
Ip  
D  
Dica  
s  
E  
Sn  
Fac

Fosse sovraclavari occupate  
Dislipidemia  
PCO/ipерandrogenismo  
osteoporosi  
Debolezza muscolare  
Calcoli renali

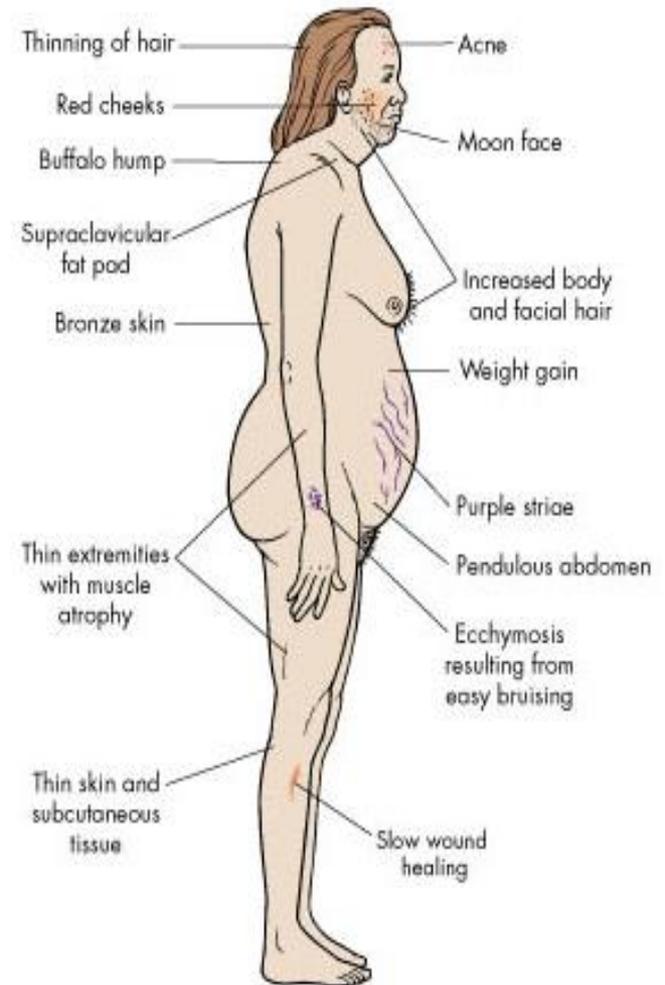
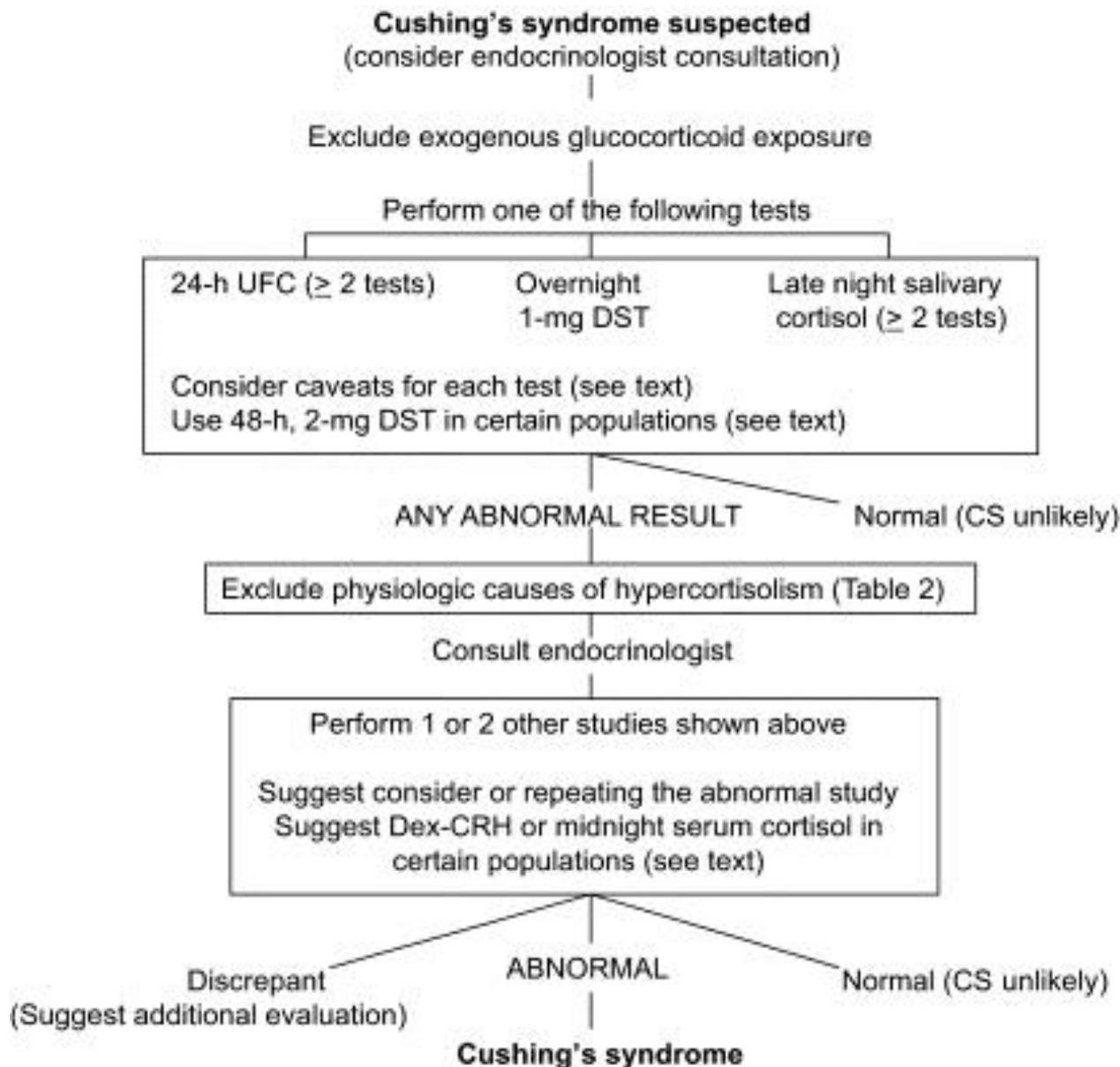
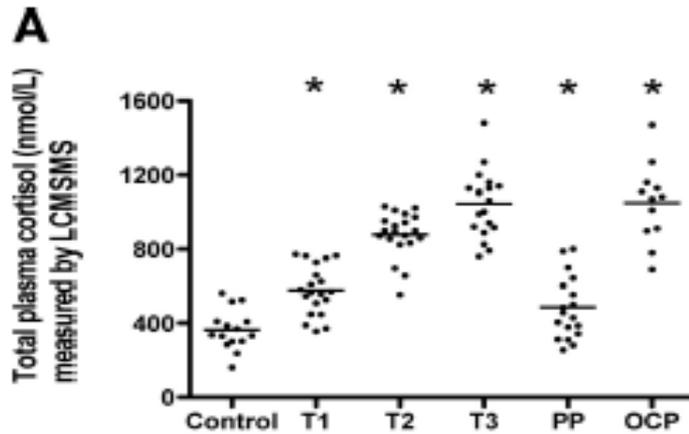


Figure 47-9 Common characteristics of Cushing's syndrome.

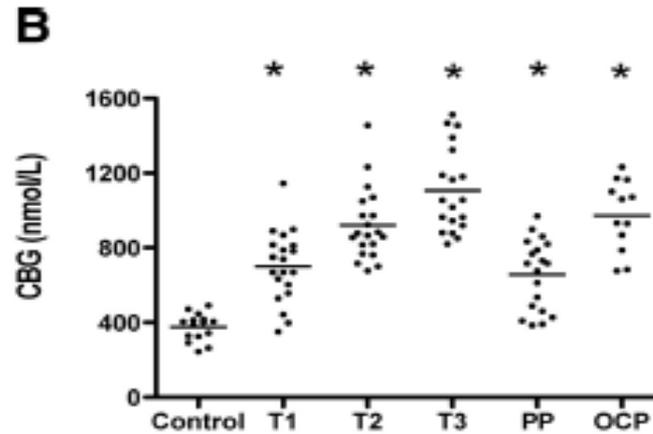


# A Longitudinal Study of Plasma and Urinary Cortisol in Pregnancy and Postpartum

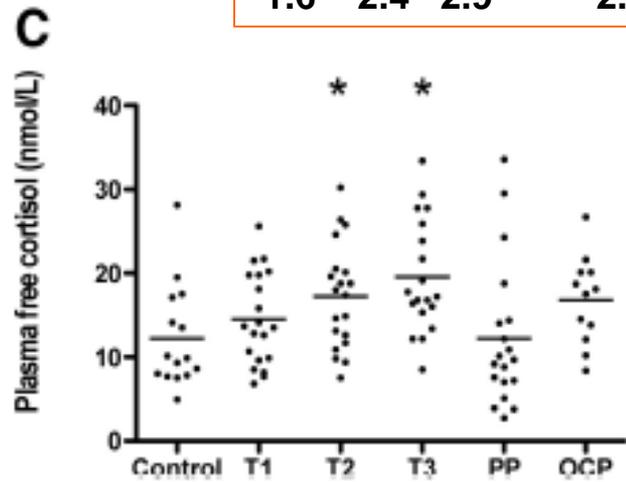
Caroline Jung, Jui T. Ho, David J. Torpy, Anne Rogers, Matt Doogue, John G. Lewis, Raymond J. Czajko, and Warrick J. Inder



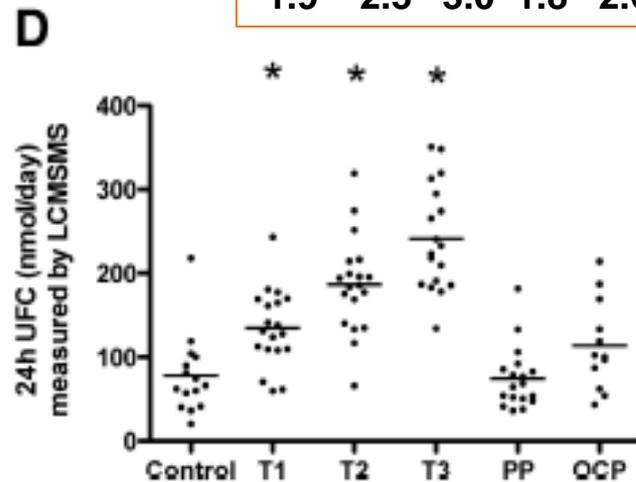
1.6 2.4 2.9 2.9



1.9 2.5 3.0 1.8 2.6



1.2 1.4 1.6

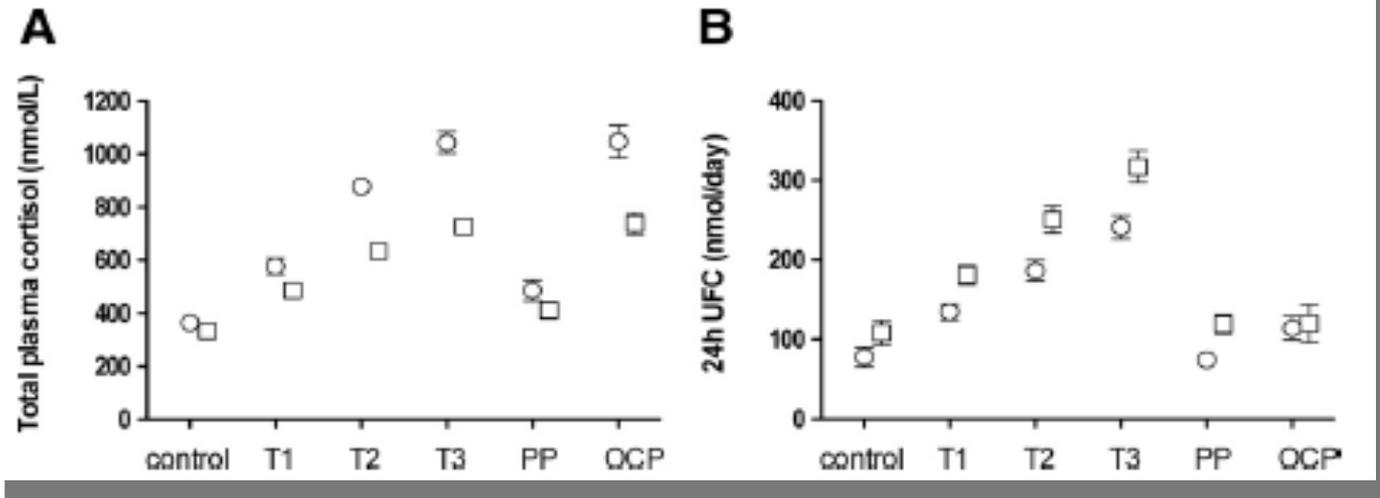


1.7 2.4 3.1

- 20 gravide  
- 12 EE <= 35 ug  
- 15 controllli

> ULN

# Media del cortisolo plasmatico e urinario misurati con LCMSMS e Immunoassay

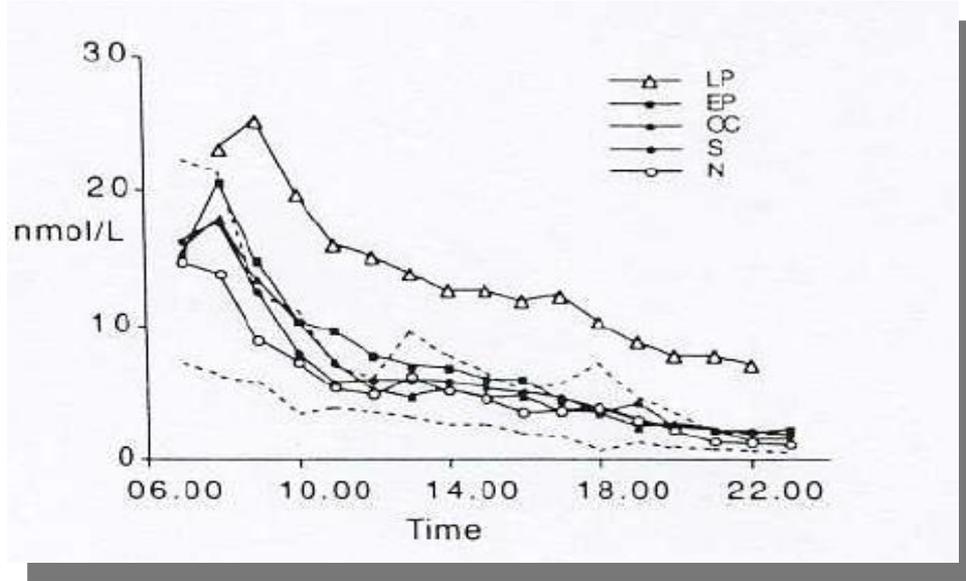


Immunoassay:  
<15% 1°T  
< 30% nel 2° e 3° T

Immunoassay 30-35% superiori

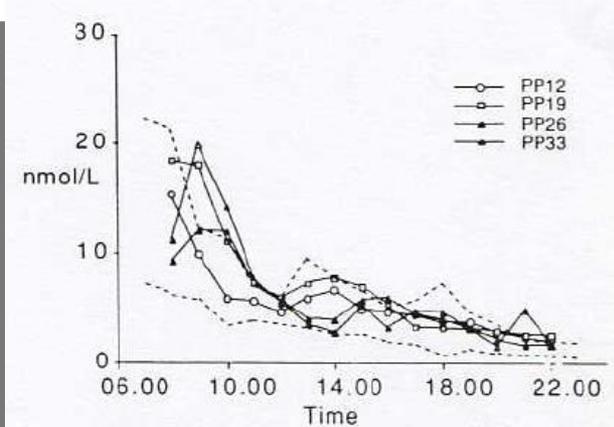
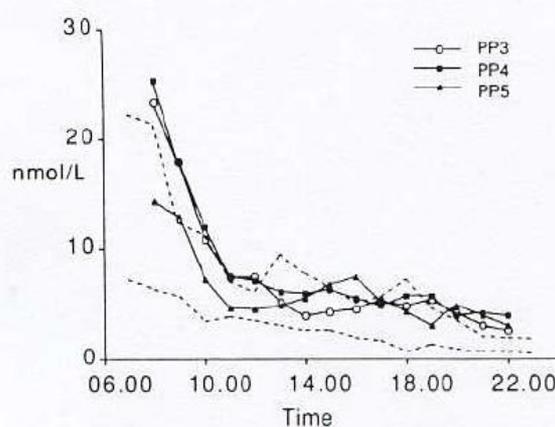
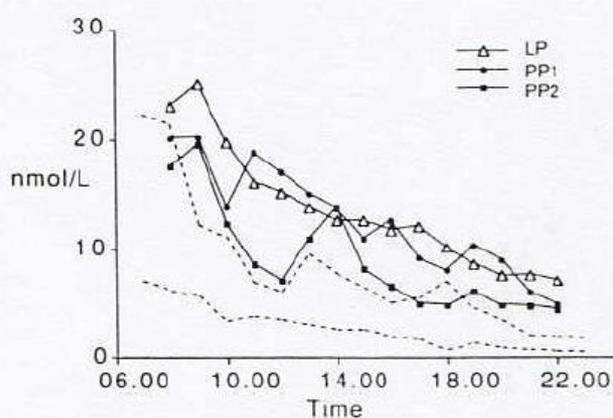
□ Immunoassay    ○ LCMSMS

# Cortisolo salivare in donne in gravidanza ed altre situazioni



LP: gravidanza avanzata (n=9)  
EP: 9-16° SG (n=9)  
OC: pillola (n=8)  
S: superovulazione (hMG) (n=10)  
N: normale (n=10)

## Postpartum



# Usefulness of salivary cortisol in the diagnosis of hypercortisolism: comparison with serum and urinary cortisol

Luca Manetti, Giuseppe Rossi<sup>1</sup>, Lucia Grasso, Valentina Raffaelli, Ilaria Scattina, Simone Del Sarto<sup>1</sup>, Mirco Cosottini<sup>2</sup>, Aldo Iannelli<sup>2</sup>, Maurizio Gasperi<sup>3</sup>, Fausto Bogazzi and Enio Martino

**Table 2** Test results (mean  $\pm$  s.d. and range) of the study population.

	CD untr (n=27)	P	OCP (n=21)	P	Pregnancy (n=18)	P	Controls (n=89)
SC <sub>0800 h</sub> (ng/ml)	14.0 $\pm$ 9.29 4.32–42.6	<0.0001	8.27 $\pm$ 3.71 3.80–18.8	0.9	8.35 $\pm$ 2.93 4.37–14.4	0.8	8.23 $\pm$ 3.52 1.20–19.5
SC <sub>1600 h</sub> (ng/ml)	11.0 $\pm$ 6.96 2.83–29.6	<0.0001	2.81 $\pm$ 0.98 1.43–5.96	0.5	3.49 $\pm$ 1.85 1.60–9.13	0.1	2.98 $\pm$ 1.19 0.97–6.78
MSC (ng/ml)	10.8 $\pm$ 9.10 3.88–49.1	<0.0001	1.51 $\pm$ 0.70 0.70–3.74	0.3	2.41 $\pm$ 1.33 0.68–6.80	<0.0001	1.37 $\pm$ 0.57 0.16–3.00

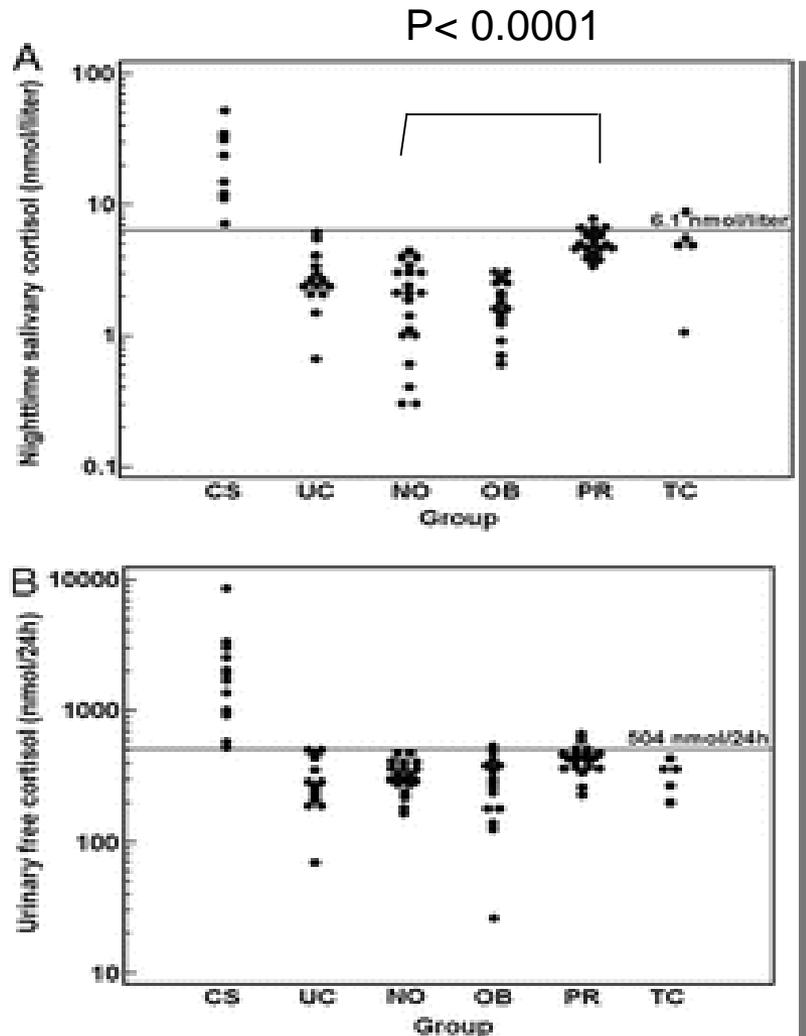


CD untr: active Cushing's disease  
 OCP: pillola  
 SC0800 h: cortisolo salivare ore 8  
 SC1600 h: cortisolo salivare ore 16  
 MSC: cortisolo salivare notturno

Cortisolo salivare notturno, cut-off: 2.7 ng/ml  
 CD vs control: Sens: 100% spec: 97.7% con  
 Donne in Pillola: specificità: 95.2%  
 Gravidanza: specificità: 83.3% (3/18 donne  
 valori più alti)

# Reproducibility of Nighttime Salivary Cortisol and Its Use in the Diagnosis of Hypercortisolism Compared with Urinary Free Cortisol and Overnight Dexamethasone Suppression Test

Alexander Viardot, Peter Huber, Jardena J. Puder, Henryk Zulewski, Ulrich Keller, and Beat Müller



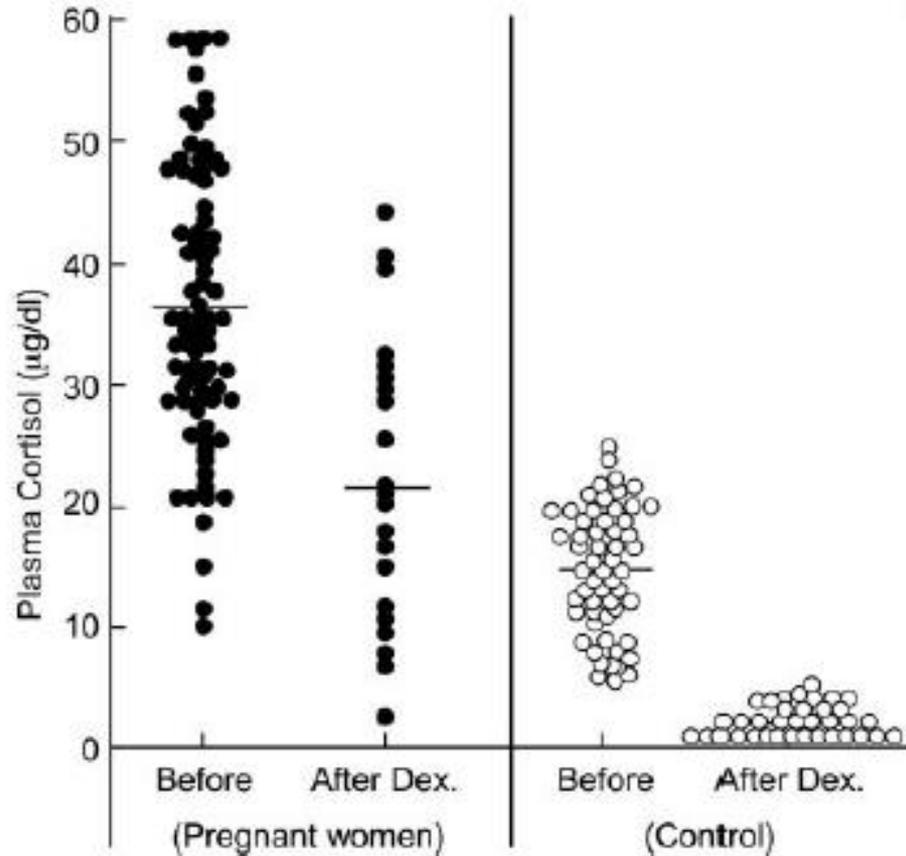
Cut-off: 6.1 nmol/l (0.22 ug/dl)

specificità per NSC: 75%

CS: Cushing's  
UC: Cushing escluso  
NO: normali  
OB: obesi  
PR: gravide media 38° SG  
TC: Cushing's trattati

## Ipercortisolismo e resistenza alla soppressione con basse dosi di desametasone in gravidanza

- 87% in donne non gravide
- 83% nel primo trimestre
- 44% nel secondo trimestre
- 37% nel terzo trimestre



## DIAGNOSI DI SINDROME DI CUSHING IN GRAVIDANZA

Un CLU > 3 volte ULN può essere indicativo di CS nel 2°3°T (indicazione fatte su piccole series e diverse metodologie)

*Lindsay JR, JCEM 2005*

Ritmo di cortisolo salivare conservato ma con un valore assoluto maggiore in confronto con i normali (manca la soglia diagnostica in gravidanza)

*Scott JM, JCEM 1990, Yaneva JCEM 2004, Manetti L, EJE 2013*

Il test di soppressione con 1 mg di desametasone ha un valore limitato per la diagnosi di CS in gravidanza perchè la soppressione di cortisolo è ridotta in particolare negli ultimi mesi

*(Odagiri et al 1988)*

## CORTISOLO ed ACTH IN GRAVIDANZA

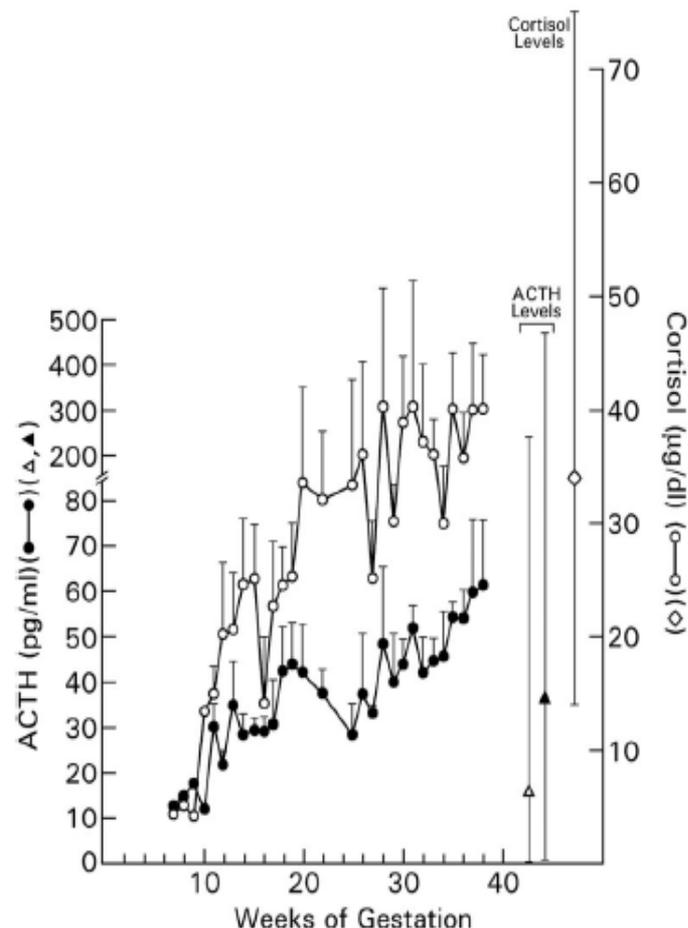
Gli estrogeni stimolano la produzione epatica di CBG legando il cortisolo e riducendo il feedback negativo.

L'ACTH aumenta per mantenere il cortisolo libero normale che è anche aumentato dovuto a:

- effetto antigluco corticoide del progesterone,
- alterato set-point al feedback negativo
- l'ACTH placentare

L'aumento di ACTH è parallelo all'aumento del cortisolo dovuto a:

- sintesi placentare
- perdita di sensibilità ipofisaria al feedback
- ed altri stimoli dal CRH come l'AVP e urocortina (che comparte omologia con il CRH)



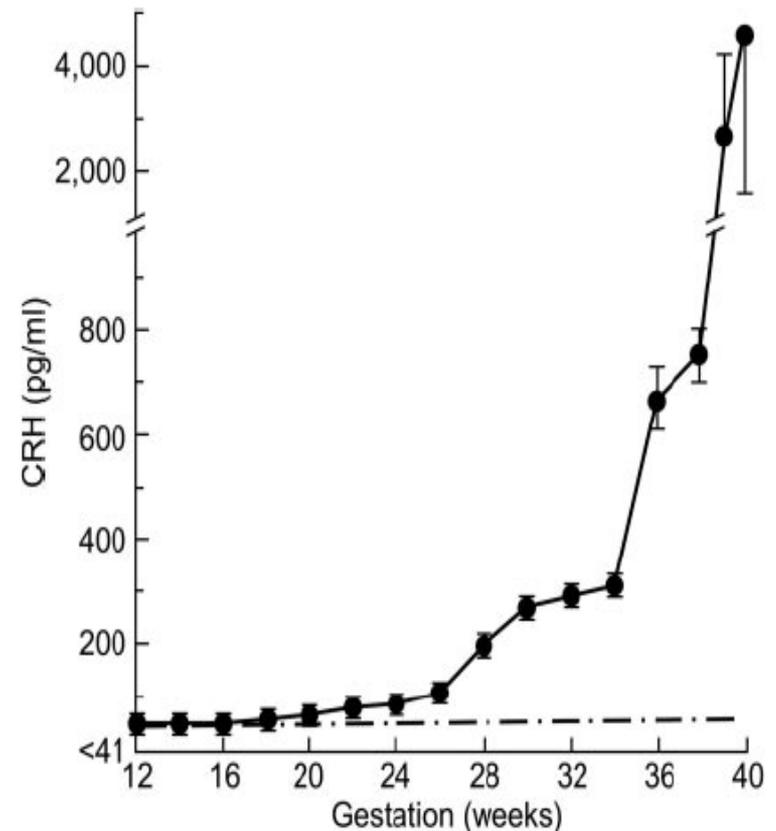
## CRH IN GRAVIDANZA

La placenta produce anche CRH che è identico a quello ipotalamico ed entrambi modulano la secrezione di ACTH.

La sua regolazione non è ben compresa ma potrebbe esserci un meccanismo di feedback positivo dei GC sul CRH placentare

I maggiori livelli sono nelle 5 settimane prima del parto

La mancanza di correlazione tra CRH, ACTH e cortisolo suggerisce che l'ACTH viene anche stimolato da altri secretagoghi quali AVP e urocortina



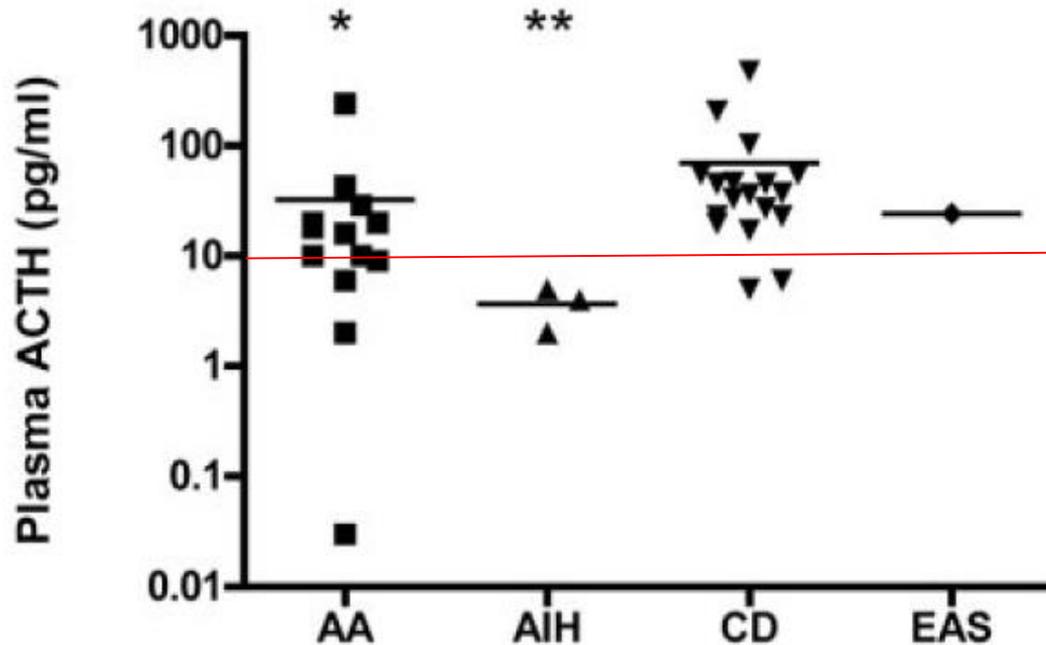
## CAUSE DEL RIDOTTO EFFETTO SOPPRESSIVO DEL DESAMETASONE?

- Effetto del CBG sul cortisolo
- Ripristino del meccanismo di feedback materno
- Effetti anti-glucocorticoidi del progesterone (non dimostrato)
- ACTH e CRH non placentare non rispondente al meccanismo di feedback
- Refrattarietà tissutale ai glucocorticoidi
- Ridotta biodisponibilità del desametasone

## POSTPARTO

- CRH e ACTH si normalizzano dopo 2 ore del parto mentre il cortisolo si normalizza più tardivamente
- CBG si normalizza dopo 12 giorni
- Nel periodo postparto, 82% delle donne mantengono una soppressione anormale del cortisolo dopo desametasone che può persistere fino a 2-3 settimane e ricuperarsi dopo la 5° settimana.

Livelli di ACTH in 39 soggetti con sindrome di Cushing in gravidanza



\*  $p < 0.05$ ; \*\*  $p < 0.01$  vs CD

# Diagnosi differenziale

## **Test di soppressione con 8 mg desametasone (HDST):**

Lindsay et al (2005) 14 pazienti studiati. Usando il criterio di soppressione di 80% tutti i pazienti con SC ACTH-indipendente sono stati identificati

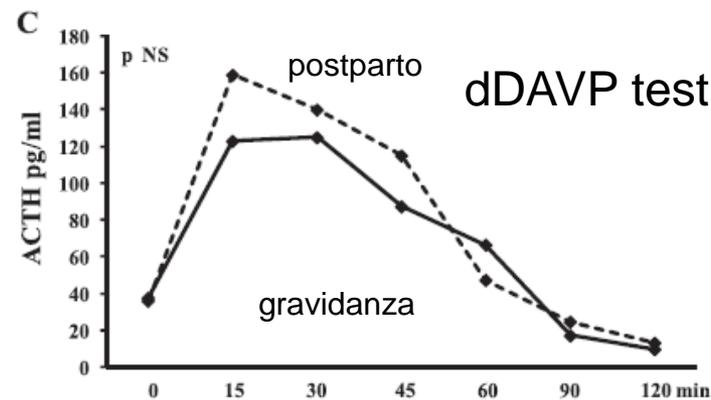
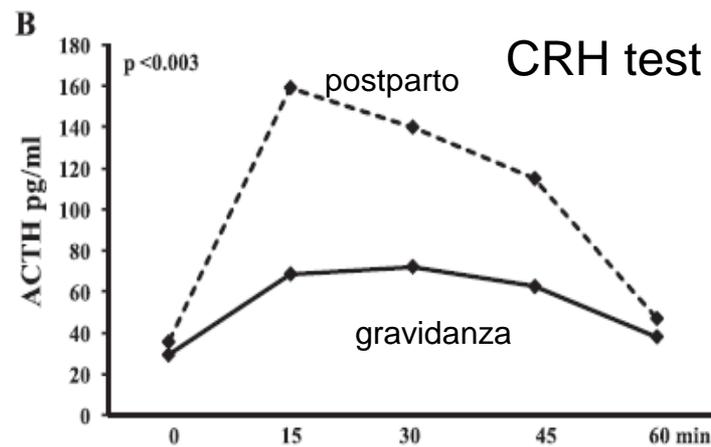
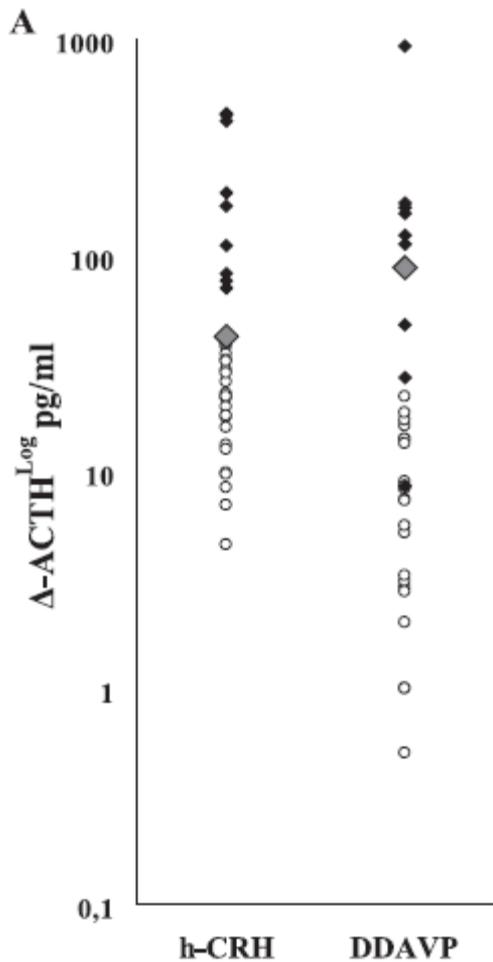
## **CRH test:**

Schulte et al Clin Endo (1990) 7 donne gravide studiate con h-CRH test (1 ug/kg), no risposta dell'ACTH.

Lindsay et al JCEM (2005) aumento sostanziale dei valori di cortisolo (44-130%) in 5 pazienti studiati consistente con la diagnosi chirurgica di malattia di Cushing.

# How to diagnose and manage Cushing's disease during pregnancy, when hypercortisolism is mild?

Marta Ragonese, Oana Ruxandra Cotta, Francesco Ferraù, Francesco Trimarchi & Salvatore Cannavò



$\diamond$  Paziente gravida  $\circ$  22 donne non gravide  
 $\blacklozenge$  9 donne con CD

# Diagnosi differenziale

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## **IPSS:**

Qualche caso descritto (Nieman et al JCEM 2005) eseguito con protezione dell'addome, torace e schiena e seguendo un approccio giugulare diretto sotto la guida con ultrasuoni, per ridurre al minimo l'esposizione fetale alle radiazioni

**Imaging:** La RMN senza gadolinio è preferita durante la gravidanza. Controindicata nel primo trimestre, tra la 12° e 32° valutare rischio beneficio, è sicura dopo la 32° SG

## EXTENSIVE CLINICAL EXPERIENCE

### Cushing's Syndrome during Pregnancy: Personal Experience and Review of the Literature

John R. Lindsay, Jacqueline Jonklaas, Edward H. Oldfield, and Lynnette K. Nieman

136 gravidanze

Diagnosi alla  $18.4 \pm 10$  SG (n=92)

CLU aumento di 8 volte il ULN (1° T: 725, 2° T: 1061; 3° T: 942  $\mu\text{g}/\text{day}$  ( $M \pm 85\%IC$ ))

Ritmo assente: cortisolo (16-01h)  $36 \pm 2,8$   $\mu\text{g}/\text{dl}$

LDST 1 mg o 2 mg x 2 gg: mancata soppressione (5.5-55  $\mu\text{g}/\text{dl}$ )

#### Diagnosi differenziale:

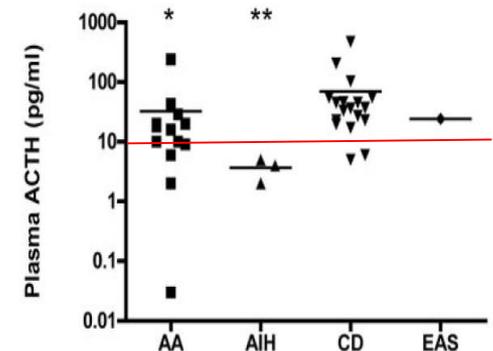
ACTH era non soppresso nel 50% dei Cushing surrenalici

HDST 14 casi identificava bene le forme surrenaliche

#### Imaging:

13/40 (32%) con CD la RMN dava qualche informazione

53/69 (76%) dei surrenalici (eco, RMN, TAC, pielografia)



## **EXTENSIVE CLINICAL EXPERIENCE**

### **Cushing's Syndrome during Pregnancy: Personal Experience and Review of the Literature**

John R. Lindsay, Jacqueline Jonklaas, Edward H. Oldfield, and Lynnette K. Nieman

<b>Diagnosi</b>	<b>casi</b>
Malattia di Cushing	40
Adenoma surrenalico	56
Carcinoma surrenalico	12
ACTH ectopico	4
Carney's complex	1
AIMAH	4

## EXTENSIVE CLINICAL EXPERIENCE

### Cushing's Syndrome during Pregnancy: Personal Experience and Review of the Literature

John R. Lindsay, Jacqueline Jonklaas, Edward H. Oldfield, and Lynnette K. Nieman

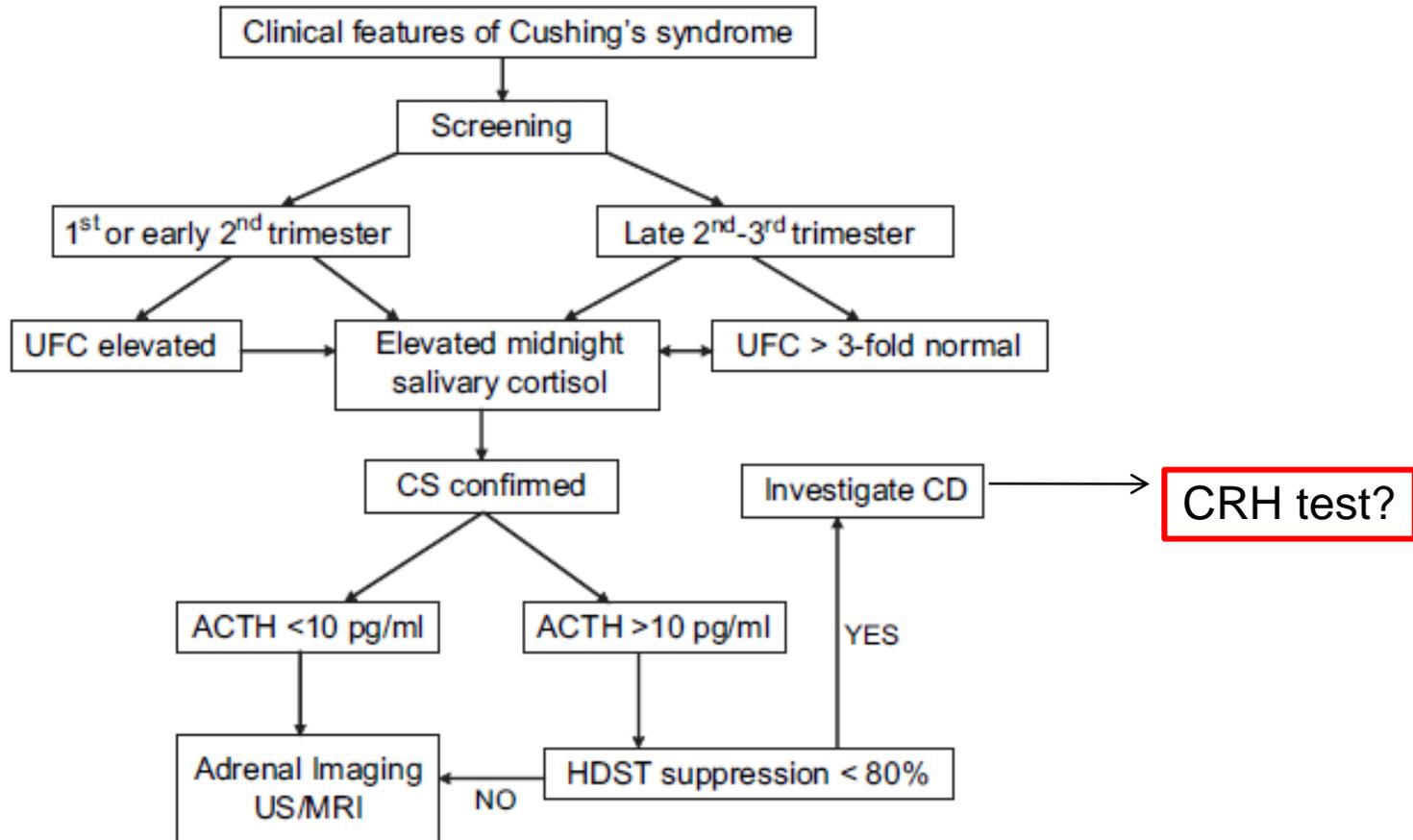
Morbidity materna	Morbidity fetale
Iperensione (68%)	Prematurità (43%)
Diabetes or IGT (25%)	Nati morti (6%)
Preeclampsia (14%)	Aborto spontaneo/IUD (5%)
Osteoporosi e fratture (5%)	Ritardo di crescita intrauterino (21%)
Insufficienza cardiaca (3%)	Morte postnatale 2 casi (epatite, sepsis, gastroenterite)
Problemi psichiatrici (4%)	Insufficienza surrenalica (2%)
Infezioni di ferite (2%)	Single reports (labbro leporino, pervietà del dotto, coartazione)
Morte (2%)	Emorragia intraventricolare postpartum (2 casi)

Nati vivi: 76% senza terapia, 89% con terapia

# Adrenal Disorders in Pregnancy

John R. Lindsay, MD, Lynnette K. Nieman, MD\*

Endocrinol Metab Clin N Am  
35 (2006) 1-20



## **The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline**

*Nieman LK, et al*

*JCEM* 2008; 93(5): 1526–1540.

### **4.0 Special populations/considerations**

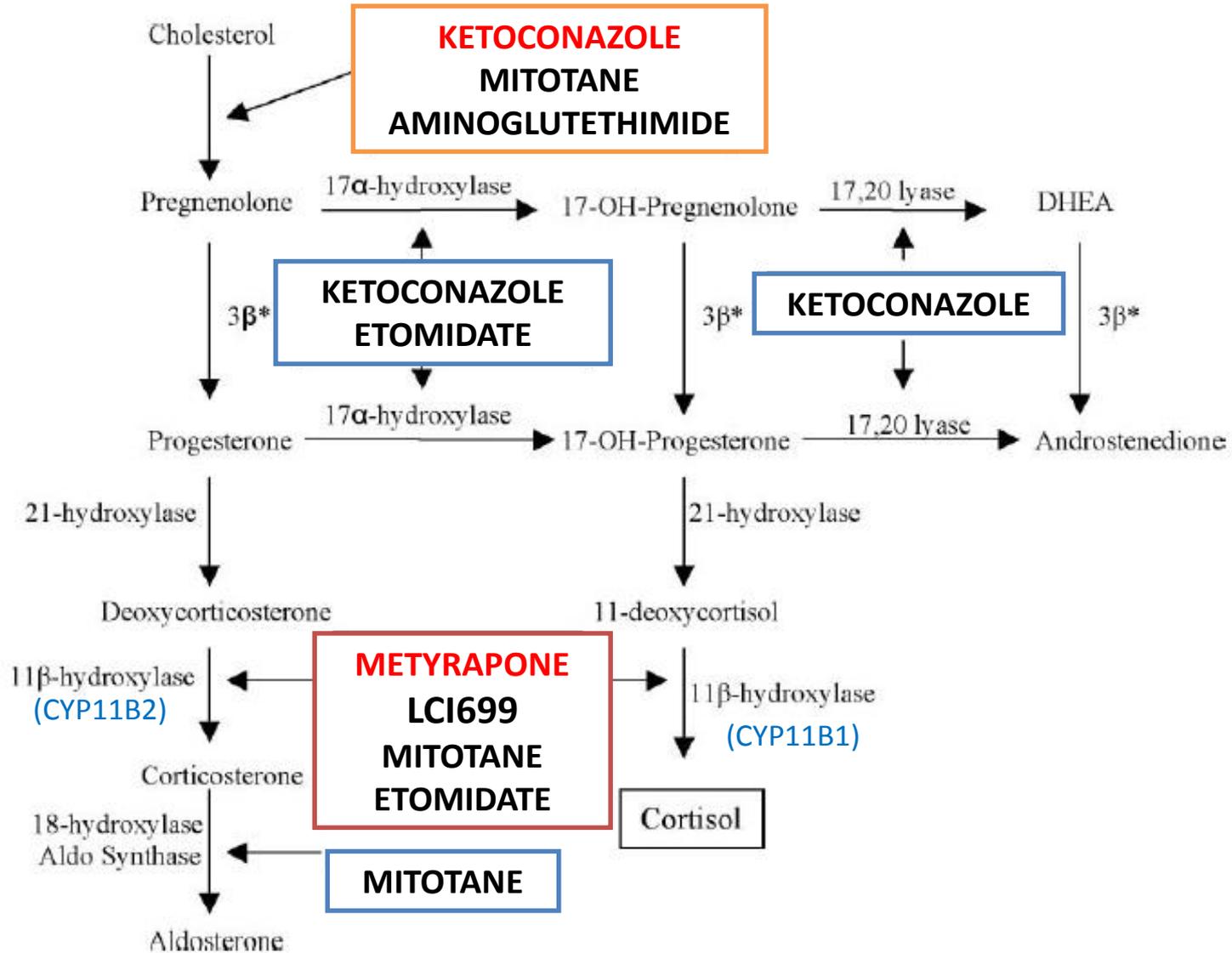
4.1 Pregnancy: We recommend the use of UFC and against the use of dexamethasone testing in the initial evaluation of pregnant women

(1⊕⊕⊕○)

### **4.1 Evidence for choice of tests in pregnant women**

Only UFC values in the second or third trimester greater than 3 times the upper limit of normal can be taken to indicate Cushing's syndrome. Serum cortisol circadian variation is preserved in normal pregnancy, albeit with a higher midnight nadir. Whereas loss of circadian variation is characteristic of Cushing's syndrome, diagnostic thresholds for evening serum or salivary cortisol in pregnant patients are not known

# Steroidogenesis Inhibitors



# The medical management of Cushing's syndrome during pregnancy

Wei How Lim<sup>a,b,\*</sup>, David J. Torpy<sup>c,d</sup>, William S. Jeffries<sup>d,e</sup>

**Table 2**

Published reports of hypercortisolism during pregnancy that were managed exclusively with metyrapone or ketoconazole.

Authors	Aetiology	Rational for medical treatment	Medication	Dose (mg/day)	Period	Outcome	Foetal outcome	Birthweight (g)	Apgar scores
Achong et al. [9]	Pregnancy-induced	Refused surgery	Metyrapone	NS	18–32 weeks	Caesarean section for PET at 32 weeks	Liveborn male	2150	7, 9
	Pregnancy-induced	Refused surgery	Metyrapone	NS	17–32 weeks	IUFD	Stillborn	NS	0, 0
	Pregnancy-induced	Refused surgery	Metyrapone Enoxaparin Aspirin	NS 40 mg 100 mg	7–30 weeks	Caesarean section for IUGR at 30 weeks	Liveborn female	1449	6, 8
Hána et al. [10]	Pregnancy-induced	Nil surgical pathology identified	Metyrapone	2250 mg	17–34 weeks	Caesarean section for PET at 34 weeks	Liveborn female	1070	6, 8
Connell et al. [19]	Adrenal carcinoma	Late gestation for surgery	Metyrapone	750 mg	26–28 weeks	Caesarean section for PET at 28 weeks	Liveborn <sup>b</sup>	1200	NS
Wallace et al. [21]	Pregnancy-induced	Nil surgical pathology identified	Metyrapone	3000 mg	14–32 weeks	Caesarean section for placenta abruption at 32 weeks	Liveborn female	1690	9, 9
	Pregnancy-induced	Nil surgical pathology identified	Metyrapone	2500 mg	14–37 weeks	Spontaneous vaginal delivery at 37 weeks	Liveborn female	2905	8, 9
Cabezón et al. [22]	Cushing's disease	Nil surgical pathology identified antepartum	Metyrapone	1000 mg	24–28 weeks	Caesarean section for preterm labour and malpresentation (twin pregnancy) at 28 weeks	Liveborn female <sup>a</sup>	830	NS
							Liveborn male	1020	NS
Berwaerts et al. [24]	Pregnancy-induced	Refused surgery	Ketoconazole Carbergoline	600–1000 mg 0.12–0.25 mg	8–37 weeks	Spontaneous vaginal delivery at 37 weeks	Liveborn male	2400	8, 9
Prebtani et al. [26]	Adrenal adenoma	NS	Ketoconazole	600 mg	33–35 weeks	Caesarean section at 35 weeks	Liveborn male	2600	NS
Amado et al. [27]	Adrenal adenoma	Nil surgical pathology identified antepartum	Ketoconazole	600 mg	32–37 weeks	Elective Caesarean section at 37 weeks	Liveborn female	2080	9, 9
Mundra et al. [31]	Adrenal adenoma	Refused surgery	Metyrapone	250 mg	22–34 weeks	Caesarean section for foetal distress at 34 weeks	Liveborn	NS	NS
Kasperlik-Zaluska et al. [32]	Pregnancy-induced	Nil surgical pathology identified	Metyrapone	750–1000 mg	5–32 weeks	Caesarean section for placental abruption at 32 weeks	Liveborn male	1800	8, 9
Close et al. [33]	Pregnancy-induced	Nil surgical pathology identified	Metyrapone	3000 mg	23–34 weeks	Caesarean section for IUGR at 34 weeks	Liveborn female	NS	NS
Gormley et al. [34]	Adrenal adenoma	Not suitable for surgery	Metyrapone	NS	27–37 weeks	Caesarean section for maternal risks at 37 weeks	Liveborn female	NS	4, 7
Present case	Adrenal adenoma	Late gestation for surgery, previous history of preterm delivery	Metyrapone	500–1000 mg	27–35 weeks	Spontaneous pre-term vaginal delivery at 35 weeks	Liveborn male	2850	6, 8

# The medical management of Cushing's syndrome during pregnancy

Wei How Lim<sup>a,b,\*</sup>, David J. Torpy<sup>c,d</sup>, William S. Jeffries<sup>d,e</sup>

**21 donne in terapia medica** Ipercortisolismo indotto dalla gravidanza (n=9=  
Adenoma surrenalico (n=8)  
Malattia di Cushing (n=3)  
Carcinoma (n=1)

## TERAPIA MEDICA:

**Metirapone** (n=16) dose 250 a 3000 mg/dì

**Chetoconazole** (n=3) 400-1000 mg/dì non associato a malformazioni (1°T)

**Chetoconazole + cabergolina** 0.12-0.25 mg/sett (n=1)

**Cabergolina** fino a 5 mg 2 volte/sett (Woo et al, Obstet Gynecol 2013)

**Motivazione** prima dell'intervento (n=5) TTS 2, adrenalectomia 3

rifiuto della chirurgia (n=5)

Lesione non identificata (n=7)

Gravidanza avanzata (n=1) e non condizione di chirurgia (n=1)

66% parto prima della 34 SG (pre-eclampsia distacco di placenta)

80% parto cesareo (n=12), preclampsia, IUGR, distacco placenta,  
grav gemellare, distress.

2 morte fetale, prematurità, distress respiratorio, ittero

# Adrenalectomy for adrenocortical adenoma causing Cushing's syndrome in pregnancy: a case report and review of literature

Rami N. Sammour<sup>a,\*</sup>, Leonard Saiegh<sup>b</sup>, Ibrahim Matter<sup>c</sup>, Ron Gonen<sup>a</sup>, Carmela Shechner<sup>b</sup>, Max Cohen<sup>a</sup>, Gonen Ohel<sup>a</sup>, Gabriel Dickstein<sup>b</sup>

Summary of all cases of adrenalectomy performed during pregnancy for Cushing's syndrome caused by adrenocortical adenoma.

Author, year (Ref.)	Case no.	Age (years)	Side of tumor	Maximal diameter (cm)	Urinary free cortisol (nmol/day)	Gestational age at surgery (weeks)	Approach
Eisenstein, 1963 [4]	1	24	L	N/R	N/R	18	Open, anterior
Abrahamson, 1968 [5]	2	25	R	3.3	3100	17	Open
Grimes, 1973 [6]	3	25	R	7.5	N/R	16	Open, anterior
Blumsohn, 1978 [7]	4	25	R	3	N/R	18	Open, anterior
Bevan, 1987 [8]	5	27	L	4	4600	29	Open, posterior
Barasch, 1988 [9]	6	30	L	4.2	9660	24	Open, lateral
Cook, 1989 [10]	7	36	R	2.8	11,600	20	Open
Pricolo, 1990 [11]	8	34	R	3.5	3935		Open, anterior
	9	28	L	4.5	N/R		Open, posterior
Pickard, 1990 [12]	10	33	R	7	4893		Open
Da Motta, 1991 [13]	11	25	R	3	N/R	4	Open
MacGibbon, 1995 [14]	12	38	L	2.8	3814	23	Open, anterior
Kamiya, 1998 [15]	13	29	R	N/R	2644	28	Open, transflank
Lo, 1998 [16]	14	29	L	4	952	24	Open
Nakashima, 2000 [17]	15	31	L	3	5133	31	Laparoscopy
Aishima, 2000 [18]	16	31	L	3	5133	31	Laparoscopy
Lo, 2001 [19]	17	28	L	3.5	1460	14	Laparoscopy
Shaw, 2002 [20]	18	18	L	5	2450	31	Open, posterior
Doshi, 2003 [21]	19	22	L	5	N/R	17	Open
Blanco, 2006 [22]	20	30	L	3	3670	16	Laparoscopy
Terhune, 2009 [23]	21	35	L	3.6	N/R	21	Laparoscopy
Rask, 2009 [24]	22	27	R	6.4	4500	26	Laparoscopy
Pollack, 2010 [25]	23	26	L	4.2	4714	26	Laparoscopy
Present case	24	32	R	4	1900	32	Laparoscopy

2° T (n=15)  
3° T (n=6)

R = right; L = left; N/R = not reported.

# OUTCOME

Outcome of the cases presented in Table 1.

Case	Manifestations	Patient outcome	Pregnancy outcome	Neonatal outcome	Surgery complications	Steroid replacement therapy (duration)
1	Hypertension, emotional lability, weakness	Weight loss, resolution of symptoms	Premature labor at 35 weeks	1660 g, healthy	None	Yes (19 weeks)
2	Face swelling, weight gain, hyperpigmentation	No antepartum complications	SVD at 38 weeks	1850 g, healthy	None	Yes
3	Congestive heart failure, blurred vision, hyperglycemia, Cushingoid features	N/R	PROM with SVD at term	2750 g, healthy	UTI	Yes (29 weeks)
4	Severe hypertension, pulmonary edema, peptic ulcer	Resolution of symptoms	Spontaneous abortion at 21 weeks	Stillbirth, 500 g	None	N/R
5	Myopathy, conjunctival edema	Resolution of myopathy and conjunctival suffusion	SVD at 36 weeks.	1870 g, healthy	None	Yes (12 months)
6	Weight gain, weakness, restlessness, Cushingoid features, hypertension	Resolution of symptoms, normalization of blood pressure	SVD at 37 weeks	2500 g, healthy	None	Yes
7	Hypertension, hirsutism	N/R	Delivery at 34 weeks	2200 g, healthy	None	Yes
8	Psychosis, hypertension, fatigue	Resolution of psychosis after delivery	PROM at 32 weeks, emergency CS at 33 weeks	1880 g, 3 weeks at NICU for prematurity, no congenital anomalies	None	Yes (at least 14 weeks)
9	Weakness, fatigue, hypertension	N/R	SVD at term	2450 g, healthy	None	Yes
10	Muscle weakness, hypertension, hyperglycemia	N/R	Emergency CS at 31 weeks	1500 g, healthy, required supplemental oxygen	Signs of fetal distress 12 h after adrenalectomy	N/R
11	Obesity, acne	N/R	CS at term due to breech presentation	4000 g, healthy	None	Yes (at least 60 months)
12	DM, Cushingoid features	Reduction in insulin requirement	Induction of labor at 37 weeks due to GDM, with SVD	Healthy	None	Yes (at least 14 weeks)
13	Cardiac failure	Improvement of symptoms, reversal of cardiac hypertrophy	PROM at 33 weeks, CS	1744 g, Apgar 9 at 1 min	None	Yes (at least 5 weeks)
14	Pulmonary edema, hypertension	Progression to severe preeclampsia and HELLP syndrome at 31 weeks	Emergency CS at 31 weeks	1465 g, grade 1 IVH, moderate RDS. Discharged at 1 month in good condition	None	Yes (at least 7 weeks)
15	Hypertension, edema	N/R	Delivery at 36 weeks	Healthy	Pulmonary edema	N/R
16	Hypertension, facial swelling	N/R	SVD at 40 weeks	2470 g, healthy	Pulmonary edema	N/R
17	Cushingoid features, uncontrolled DM and hypertension	Control of glucose and hypertension	PROM at 33 weeks with SVD	1850 g, healthy	None	N/R
18	Weight gain, easy bruising, Cushingoid features	Resolution of symptoms	SVD at 36 weeks	2470 g, healthy	None	Yes (15 months)
19	Hypertension, Cushingoid features	Normalization of blood pressure. Disappearance of Cushingoid features after delivery	Emergency CS at 31 weeks due to signs of fetal distress in CTG	Discharged from NICU at 7 weeks, healthy thereafter	Laceration of spleen requiring splenectomy	N/R
20	Cushingoid features, facial swelling, acne	N/R	PROM and SVD at 30 weeks	1280 g, low grade RDS, healthy thereafter	None	Yes (at least 18 months)
21	Weight gain and fatigue before pregnancy	Resolution of hyperglycemia	SVD at 37 weeks	Healthy	None	Yes (1 week)
22	Hypertension, DM	Reduction in insulin and in antihypertensive drug requirement	CS at 35 weeks due to intrauterine growth restriction	1795 g, healthy	None	Yes (at least 42 months)
23	DM, weight gain, fatigue, weakness, hypertension	Reduction in insulin requirement	Preterm labor at 36 weeks, emergency CS	2800 g, healthy	None	Yes (at least 10 weeks)
24	DM, Cushingoid features	Improved glucose control	SVD at 39 weeks	2480 g, healthy	None	Yes (24 months)

PROM = premature rupture of membranes; N/R = not reported; NICU = neonatal intensive care unit; CS = cesarean section; SVD = spontaneous vaginal delivery; RDS = respiratory distress syndrome; HELLP = hemolysis, elevated liver enzymes, low platelets; IVH = intraventricular hemorrhage; CTG = cardiotocography; DM = diabetes mellitus; UTI = urinary tract infection; GDM = gestational diabetes mellitus.

# Adrenalectomy for adrenocortical adenoma causing Cushing's syndrome in pregnancy: a case report and review of literature

Rami N. Sammour <sup>a,\*</sup>, Leonard Saiegh <sup>b</sup>, Ibrahim Matter <sup>c</sup>, Ron Gonen <sup>a</sup>, Carmela Shechner <sup>b</sup>, Max Cohen <sup>a</sup>, Gonen Ohel <sup>a</sup>, Gabriel Dickstein <sup>b</sup>

## **OUTCOME MATERNO**

93% risoluzione del Cushing o miglioramento dei valori pressori e DBT  
1 paziente con severa preclampsia 7 settimane dopo chirurgia  
36% parto cesareo con 5 urgenze (distacco placentare, distress)

## **OUTCOME FETALE E PERINATALE**

1 aborto spontaneo  
61% di nati vivi dopo la 37 SG  
30% nati prima della 34 SG  
35% SGA

## **COMPLICANZE CHIRURGICHE**

1 lacerazione della milza  
1 edema polmonare, infezione urinaria  
1 aritmia fetale

## Management of Cushing's syndrome secondary to adrenal adenoma during pregnancy.

Pricolo VE et al. Surgery 1990108:1072-7.

	operati durante la gravidanza (n=7)	operati post parto (n=19)
Morte fetale	14%	32%
Sopravvivenza non complicata	87%	37%
Complicanze materna	57%	84%

## TERAPIA MEDICA

- Teratogenicità
- Alterazione della differenziazione sessuale
- Alterazione del pattern ormonale....la riduzione del cortisolo può influenzare lo sviluppo polmonare fetale alla fine della gravidanza?
- Insufficienza surrenalica fetale-perinatale?

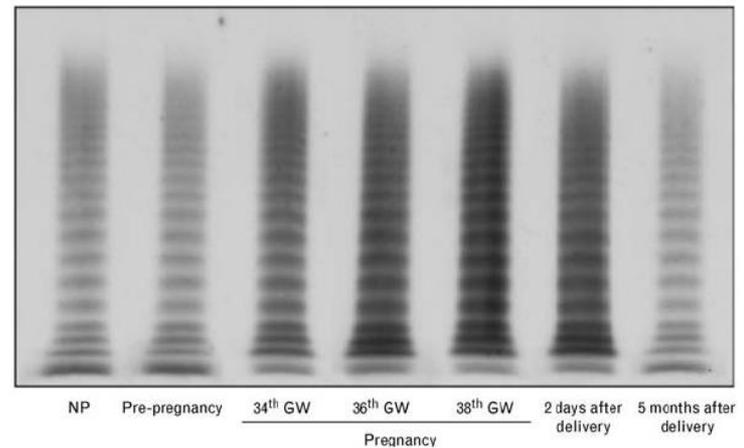
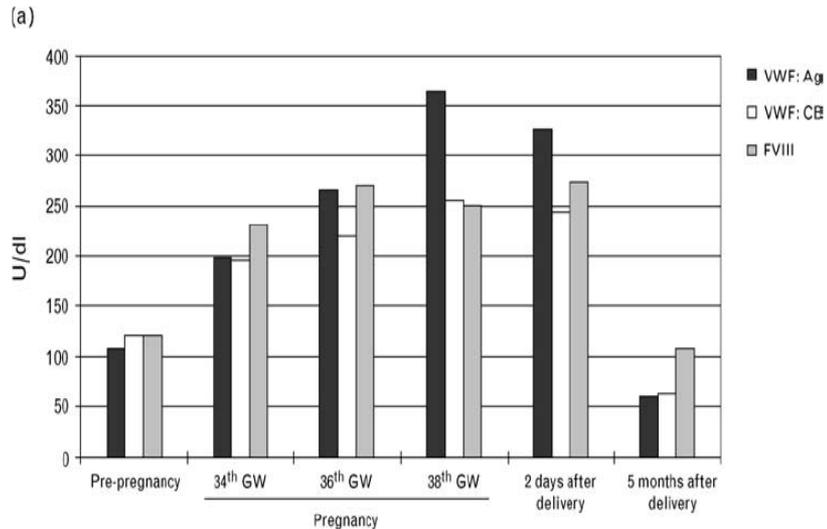
## TERAPIA CHIRURGICA

- Numero ridotto di pazienti
- Gruppi di pazienti non confrontabili
- Bias: possibilità di più pubblicazioni con esito positivo
- Necessità di terapia sostitutiva post-chirurgica
- Preclampsia, prematurità e IUGR sembrano non essere diversi tra trattati e non trattati

Influenza del timing e della severità del quadro nella scelta terapeutica

# Hypercortisolism and pregnancy upregulate von Willebrand factor through different mechanisms: report on a pregnant patient with Cushing's syndrome

Alessandra Casonato<sup>a</sup>, Viviana Daidone<sup>a</sup>, Elena Pontara<sup>a</sup>, Nora Albiger<sup>b</sup>, Maria G. Cattini<sup>a</sup> and Carla Scaroni<sup>b</sup>



Polimorfismo del promotore del VWF: haplotype 2 che protegge contro l'aumento del VWF indotto dal cortisolo

Differenti meccanismi di upregulation dei VWF nel Cushing e la gravidanza

# Pregnancy-induced Cushing's syndrome in recurrent pregnancies: Case report and literature review

Naomi ACHONG, Michael D'EMDEN, Narelle FAGERMO and Robin MORTIMER

*Royal Brisbane and Women's Hospital, Herston, Brisbane, Qld, Australia*

Sindrome di Cushing ACTH-indipendente di insorgenza in gravidanza

## **10 casi**

6 senza anomalie morfologiche o istologiche

1 bilateral micronodular adrenal hyperplasia

1 bilateral macronodular adrenal hyperplasia

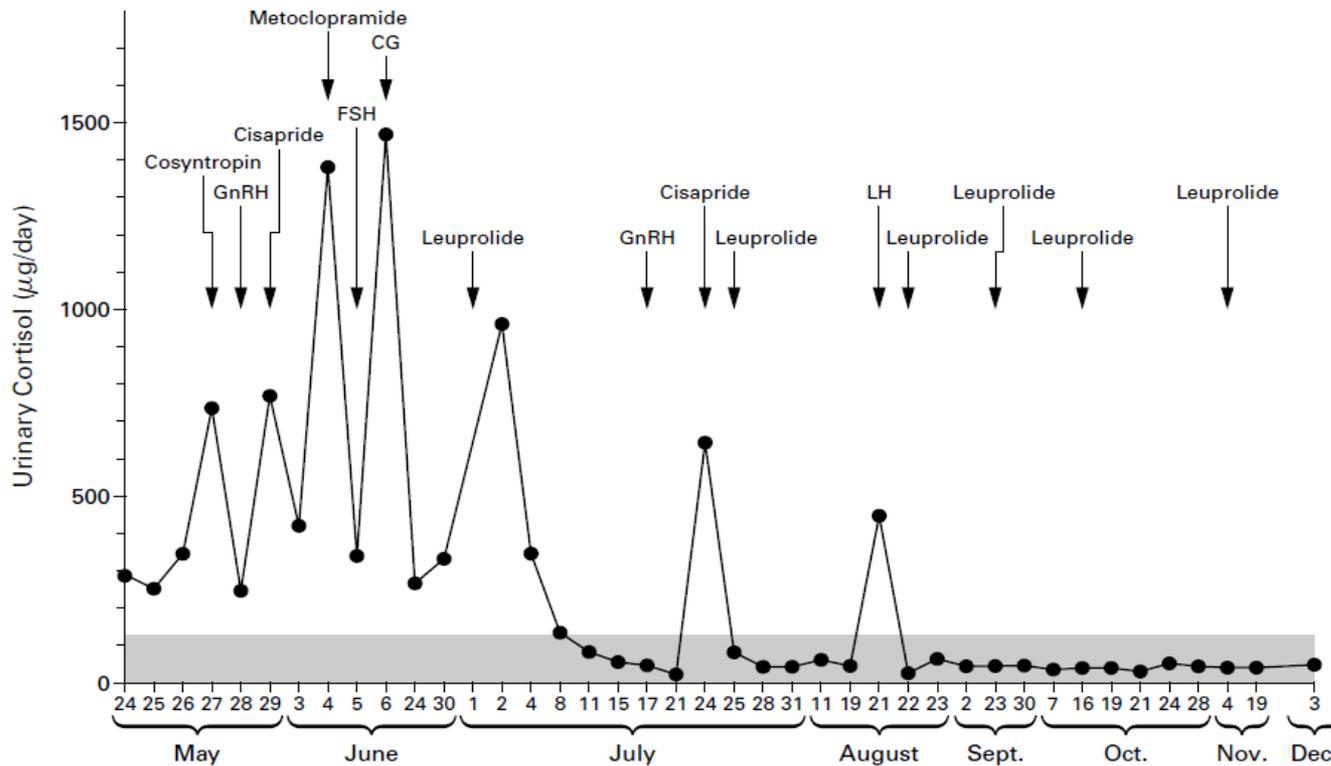
1 adenoma

Meccanismo di upregulation del Rc LH/HCG eutopico

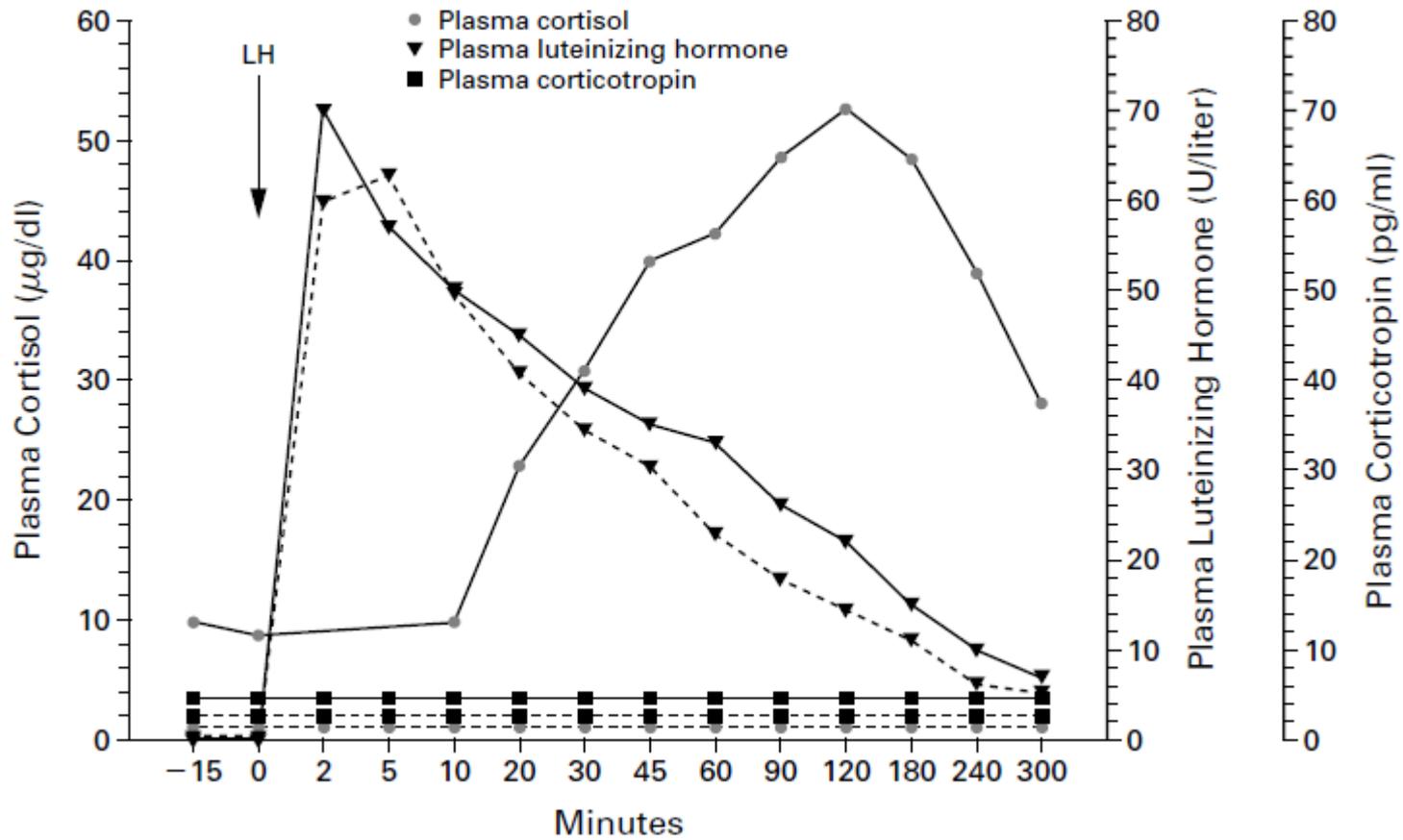
# LEUPROLIDE ACETATE THERAPY IN LUTEINIZING HORMONE-DEPENDENT CUSHING'S SYNDROME

ANDRÉ LACROIX, M.D., PAVEL HAMET, M.D., PH.D.,  
AND JEAN-MARIE BOUTIN, M.D., PH.D.

SC transitorio durante le gravidanza.  
Diagnosi di AIMAH costante in  
menopausa

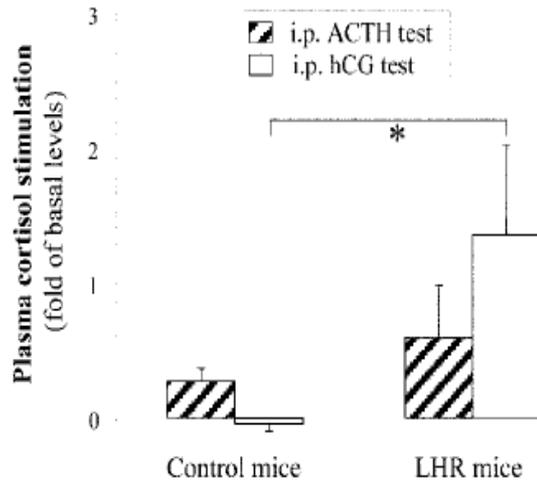
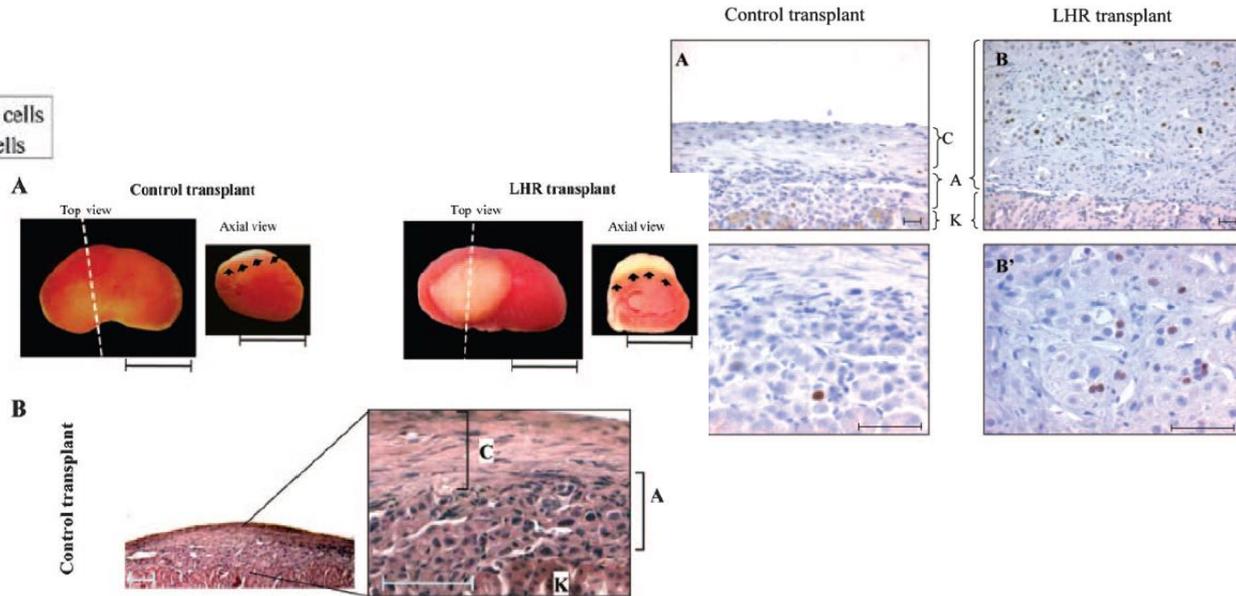
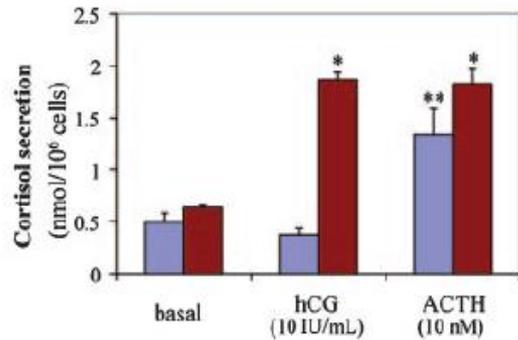


## Risposta del cortisolo a LH recombinante



# Aberrant Expression of Human Luteinizing Hormone Receptor by Adrenocortical Cells Is Sufficient to Provoke Both Hyperplasia and Cushing's Syndrome Features

Tânia L. Mazzuco, Olivier Chabre, Jean-Jacques Feige, and Michaël Thomas



**Conclusions:** These results demonstrate that a single genetic event such as the inappropriate expression of the nonmutated LH/hCG receptor gene is sufficient to initiate the phenotypic changes that cause the development of a benign adrenocortical tumor. (*J Clin Endocrinol Metab* 91: 196-203, 2006)

Grazie  
dell'attenzione



