La gestione della gravidanza nella sindrome di Cushing: il ruolo del ginecologo

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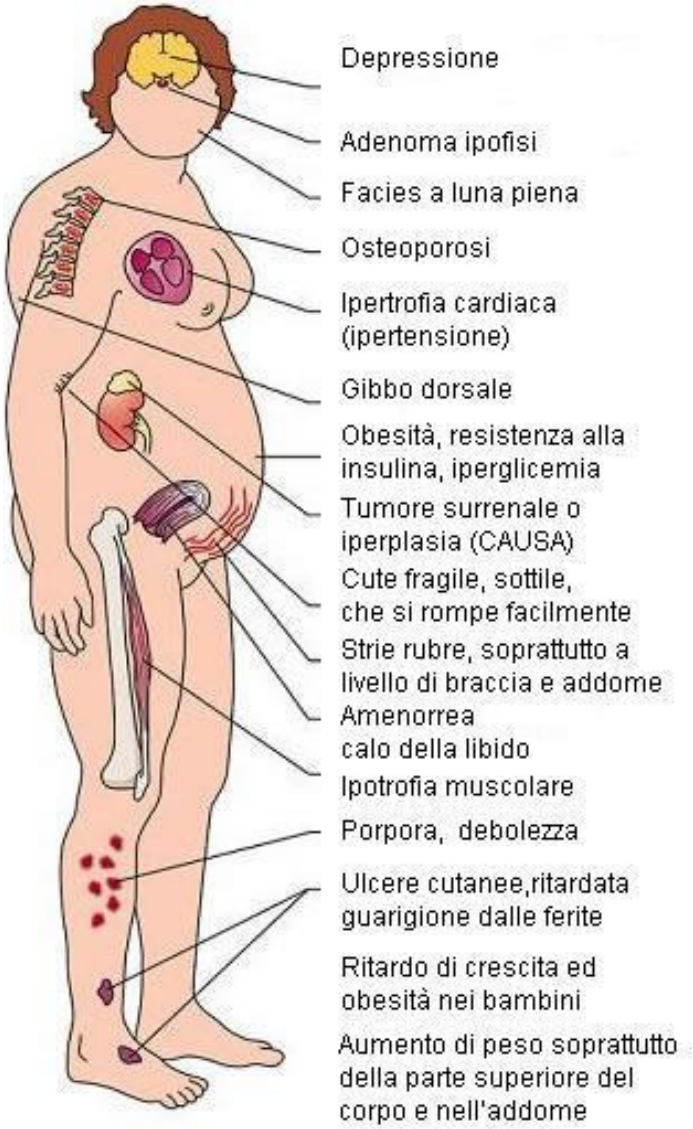
CUSHING

La gran parte delle pazienti è affetta da sterilità



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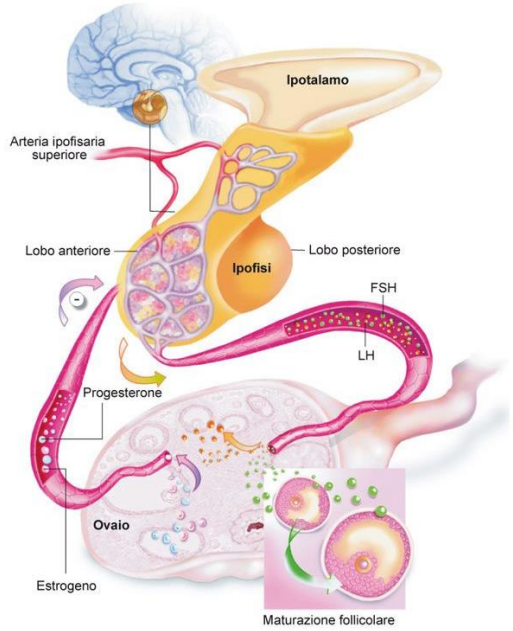
- Iperandrogenismo
- ⇩ SHBG
- ⇧ Attività aromatasica
- Alterazione pulsatilità GnRH
- Alterazione produzione estrogenica

Cook et al., 2004

Background



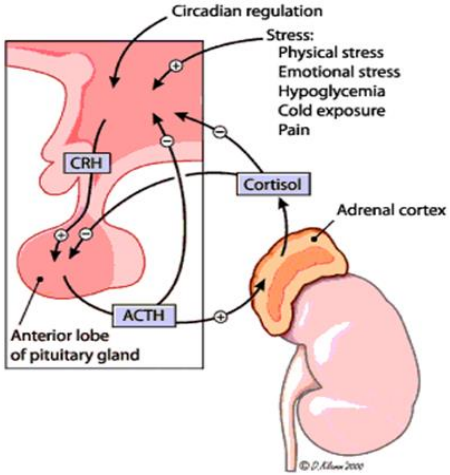
Cushing during pregnancy is a rare condition with fewer than 150 cases reported in the literature

Cushing is associated with a high incidence of ovulatory failure due to hypercortisolism and hyperandrogenism

A diagnostic challenge to physicians not only because of its rare occurrence but also due to overlapping clinical features with preeclampsia and gestational diabetes

Holgado Galicia et al., BMJ Case Rep, 2011; Borna et al., Acta Med Iran, 2012

Background



The incidence of adrenal and pituitary disease in pregnant women is quite different from non-pregnant women.

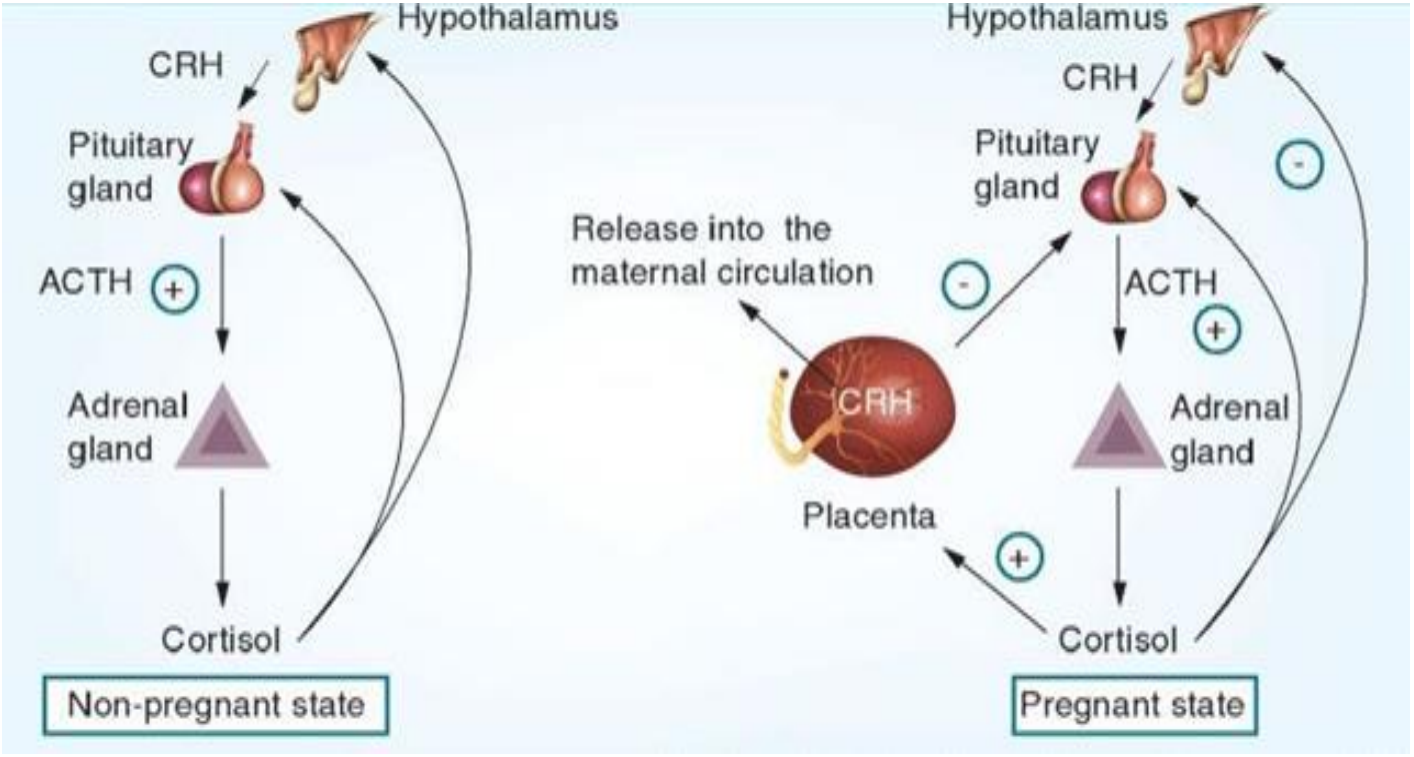
Of the total number of **Cushing's syndrome** cases, adrenal adenomas comprise approximately 40–50% of cases in pregnancy, compared with approximately 15% of cases in non - pregnant women.

Cushing's disease comprises only over 30% of cases in pregnant women compared with 58–70% in non - pregnant women.

Of the remaining cases, about 10% are due to adrenal carcinoma, with the rest due to ACTH - independent hyperplasia, ectopic ACTH secretion, and unspecified causes.

Lekarev et al., Best Practice & Research Clinical Endocrinology & Metabolism, 2011

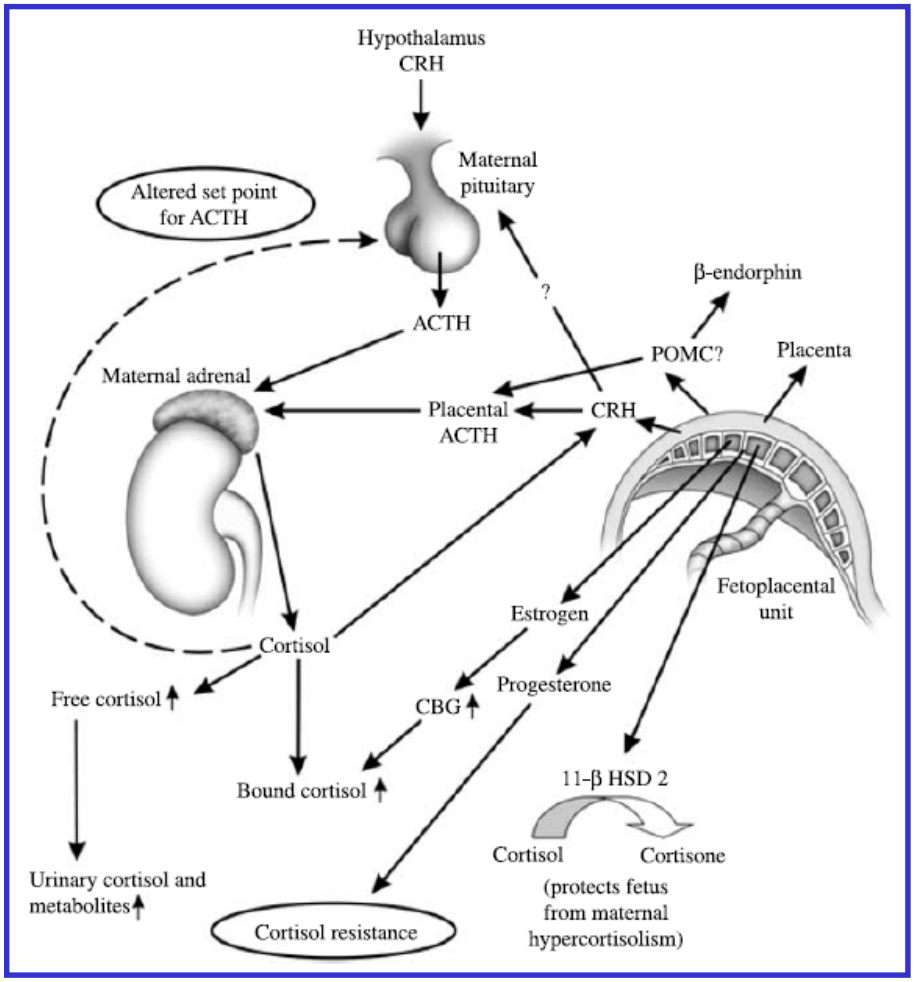
Pathogenesis



The theory is that the placental rise in CRH is instrumental in manifestation and exacerbation of symptoms!!!

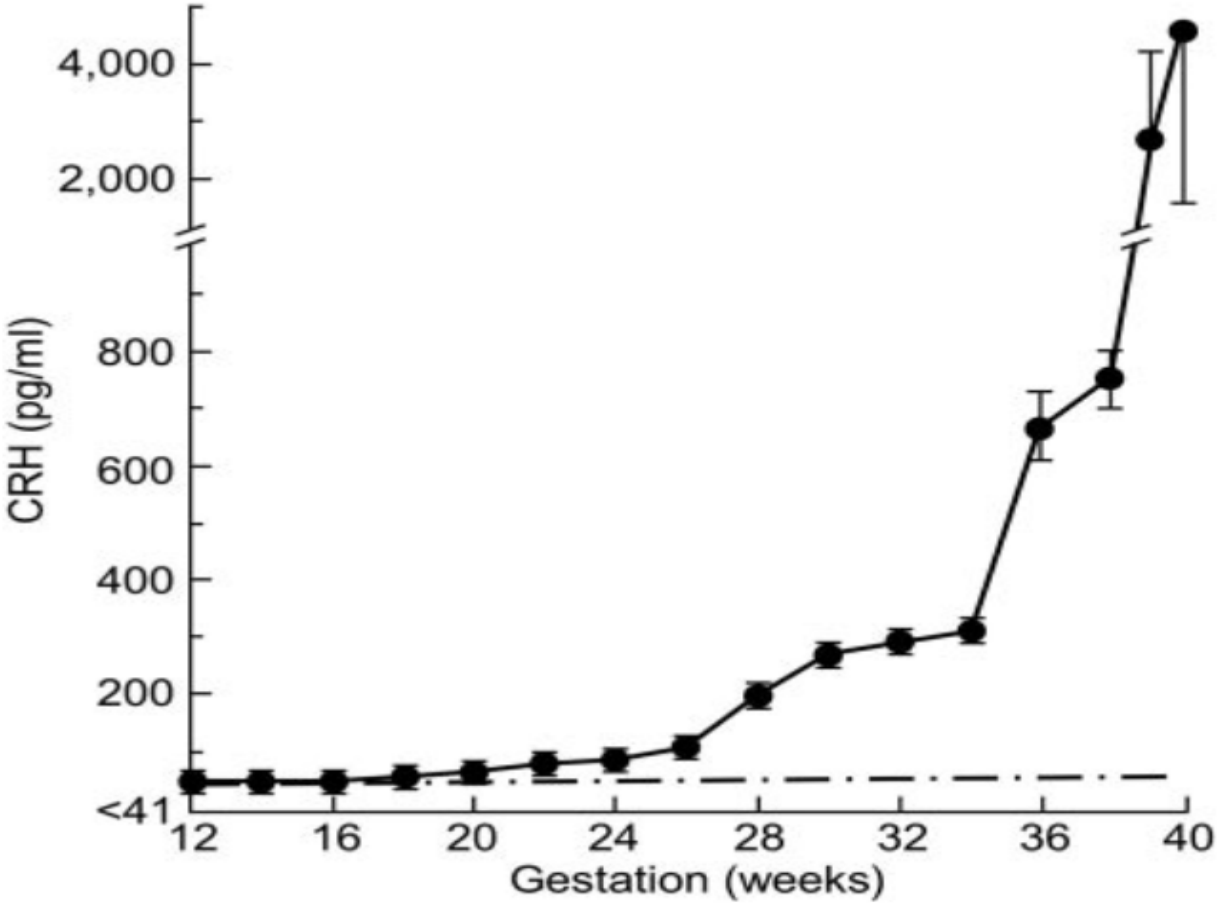
Lekarev et al., Best Practice & Research Clinical Endocrinology & Metabolism, 2011; Expert Rev Endocrinol Metabol, 2012

ACTH and pregnancy



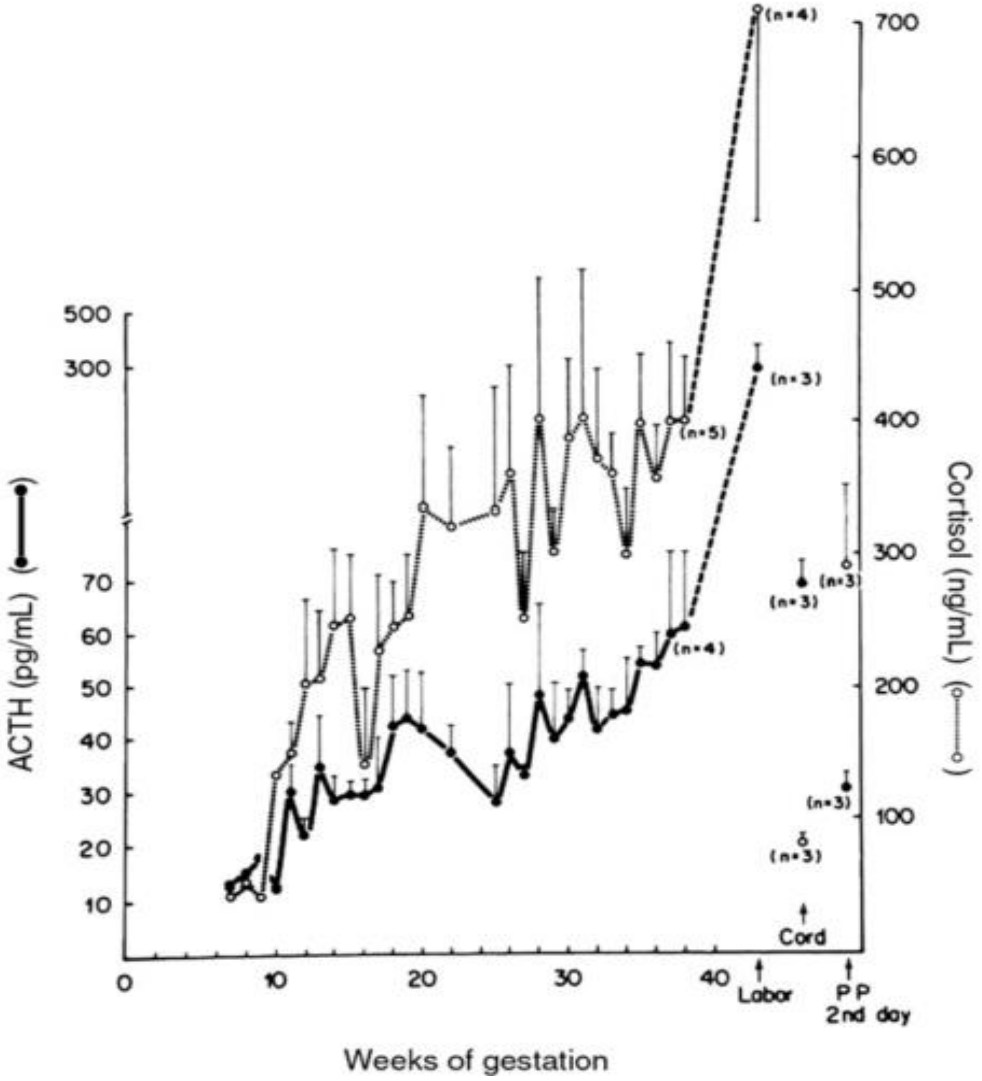
- Increase of Cortisol Binding Globulin (CBG) with reduction of free cortisol and compensatory increase of ACTH;
- Increase of serum cortisol (2-3 times); altered set-point pituitary;
- Placental CRH stimulates secretion of placental ACTH; increase of ACTH in the third trimester with peak during labor and delivery;
- Placental 11β-OHSD protects the fetal-placental unit from excess of maternal cortisol.

Increase of CRH concentrations during pregnancy



Lindsay and Nieman, Endocrine Reviews, 2005

Serial increases in serum cortisol and ACTH during pregnancy in normal controls throughout pregnancy



Lekarev et al., Best Practice & Research Clinical Endocrinology & Metabolism, 2011

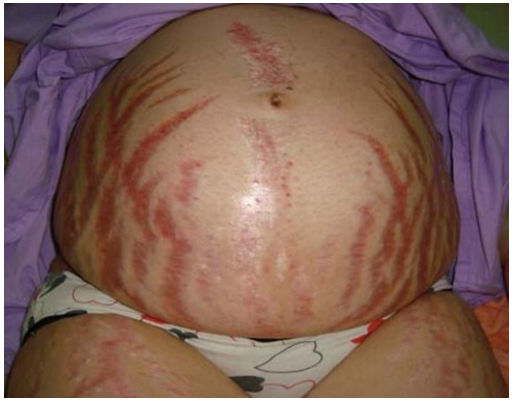
Diagnosis

The diagnosis of Cushing's syndrome during pregnancy may pose a challenge because the typical symptoms of the disorder and pregnancy may overlap.

These include central weight gain, edema, fatigue, emotional upset, hypertension and glucose intolerance.

Clinical: sign and sympton

The signs and symptoms that can help differentiate Cushing's syndrome from normal physiologic pregnancy include hyperpigmented violaceous striae as opposed to skin-colored striae, easy bruising, as well as the pathologic findings of acne and hirsutism due to a significant elevation of adrenal androgens.



Lekarev et al., Best Practice & Research Clinical Endocrinology & Metabolism, 2011

Diagnosis

Urine free cortisol: in the II and III trimester values three times higher then maximum are suspected

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ACTH levels have been reported to be in the normal to elevated range in all pregnant patients with Cushing's syndrome, irrespective of the etiology.
This is likely due to both the placental ACTH production and the placental CRH-stimulated pituitary ACTH production.

Therefore patients with adrenal adenomas have ACTH levels in the "normal" range, while non pregnant patients with the same condition would have suppressed ACTH levels.

Identifying a lack of diurnal variation of free and total cortisol is helpful in establishing the diagnosis of Cushing's syndrome.

Midnight plasma or salivary cortisol levels would therefore be helpful, but unfortunately no normative data have been established

Lekarev et al., Best Practice & Research Clinical Endocrinology & Metabolism, 2011

Diagnosis

Liddle test: Test with low-dose dexamethasone (1-mg)
during the third trimester these values are suppressible with high-dose dexamethasone (8-mg)

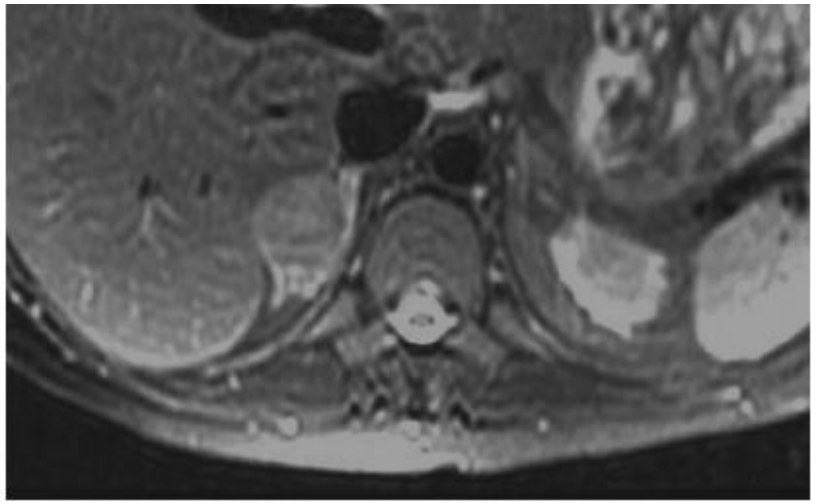
↓

used to distinguish between Cushing's and ectopic ACTH overproduction (in Cushing's disease cortisol is suppressed more of 50%)

No catheterization (risks from radiation and risk of thrombosis) except when there is a discrepancy between morphological and biochemical tests; when strictly necessary jugular approach is preferred;

Imaging: Ultrasounds - RMN

can be safely performed for adrenal or pituitary tumour



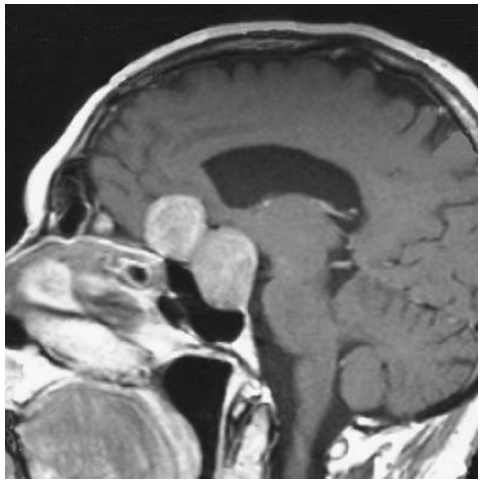
The use of magnetic resonance imaging (MRI) in the obstetric patient

MRI without the use of contrast agents in the obstetrical patient is safe for mother and fetus in the **second and third trimesters**

Use of magnetic resonance imaging during **the first trimester** of pregnancy should be restricted to maternal indications for which the information is considered clinically imperative.

Gadolinium contrast may be used in pregnant women when the benefits outweigh the potential risks. (III-C)

Inadvertent exposure to magnetic resonance imaging during the first trimester has not been associated with any long-term sequelae and should not raise clinical concern. (III-C)



Patenaude Y et al., J Obstet Gynaecol Can 2014

Maternal and fetal morbidity

Maternal morbidity	Fetal morbidity
Hypertension (68%)	Prematurity (43%)
Diabetes or IGT (25%)	Stillbirths (6%)
Preeclampsia (14%)	Spontaneous abortion/IUD (5%)
Osteoporosis and fracture (5%)	Infant death in two cases (acute hepatitis; sepsis and gastroenteritis)
Cardiac failure (3%)	IUGR (21%)
Psychiatric disorders (4%)	Hypoadrenalism (2%)
Wound infection (2%)	Single reports of cleft lip, patent ductus and coarctation
Maternal death (2%)	Intraventricular hemorrhage in two cases postpartum

Vilar L et al, Arq Bras Endocrinol Metab 2007

Maternal complications

Pregnancies ware complicated by uncontrolled **hypertension and gestational diabetes**, two co-morbidities that are associated with adverse risks to both maternal and foetal.

Elevated blood pressure caused by high cortisol levels is usually severe and when uncontrolled may lead to multiple complications including pre-eclampsia, pulmonary haemorrhage, and acute cardiac as well as renal failure

Lim et al. European Journal of Obstetrics & Gynecology and Reproductive Biology 2013

and effects of pregnancy on tumor (ACTH- secreting)

- **no increase of tumor size;**

Vilar L et al, Arq Bras Endocrinol Metab 2007

Fetal complications

25% fetal mortality (spontaneous abortion or neonatal mortality from extreme prematurity).

50% preterm delivery.

early pregnancy: 11-beta-hydroxysteroid dehydrogenase type-2 enzyme converts the majority of maternal cortisol to the biologically inactive cortisone.

second and third trimesters levels of cortisol increase drastically to abnormal levels which are harmful to the foetus, and have been associated with spontaneous pregnancy loss, prematurity, oligohydramnios, intrauterine growth restriction (IUGR) and intrauterine foetal demise.

Lim et al. European Journal of Obstetrics & Gynecology and Reproductive Biology 2013

Management

Active management of patients with CS during pregnancy, either surgically or medically, is associated with a reduction in maternal symptoms and neonatal complications.

Anti-hypertensives are used in conjunction: controlling blood pressure to ensure a safer outcome during pregnancy.

Blood glucose control

Lim et al. European Journal of Obstetrics & Gynecology and Reproductive Biology 2013

Treatment of Cushing Syndrome during pregnancy

Treatment of CS during pregnancy must be individualized.

During first trimester, the first line of treatment is medical with surgical resection to follow.

Among drugs, either metyrapone or ketoconazole can be used though both have side effects, but metyrapone is preferred.

Mitotane is teratogenic and therapeutic abortion is required in case of exposure.

Bashir A. Laway and Shahnaz A. Mir Indian J Endrocrinol Metab, 2013

Treatment of Cushing disease in pregnancy

NHC first line in the second trimester;

Adiuvant drug therapy, transient (first trimester) or second choice in inoperable tumors;

Metyrapone (first line!); ketoconazole (teratogenic in the rats) when a rapid effect is required or in case of intollerance to metyrapone;

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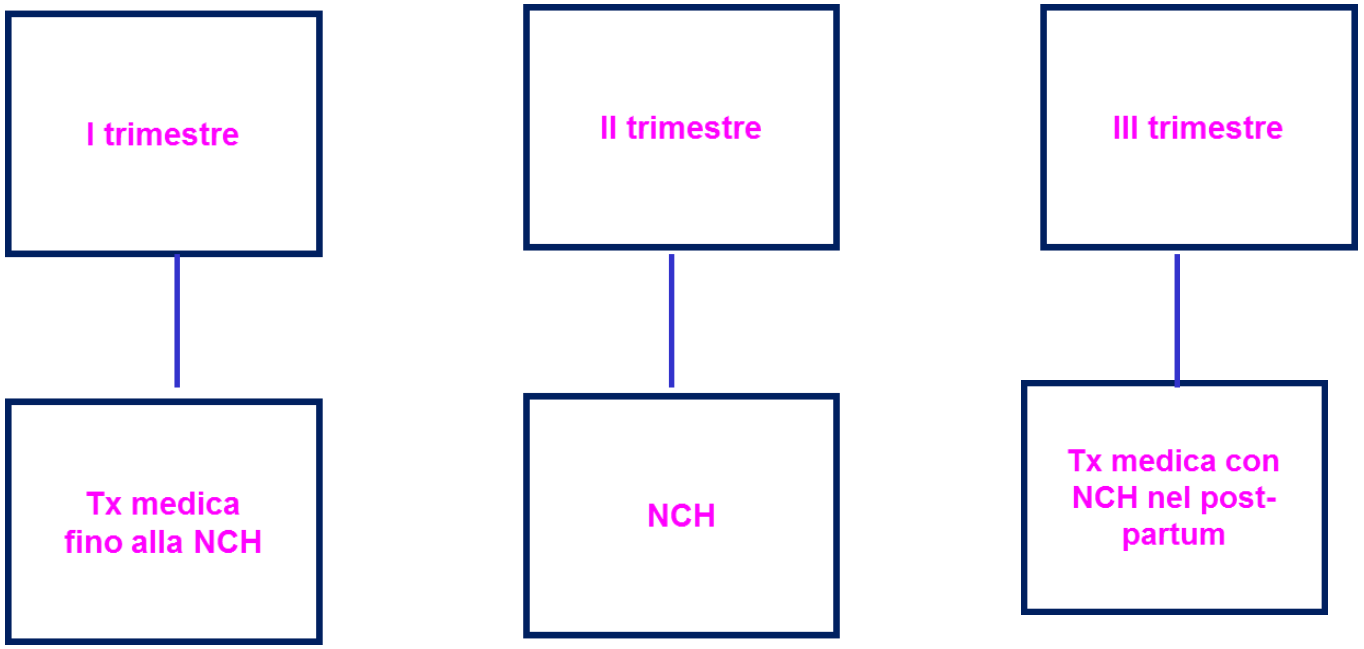
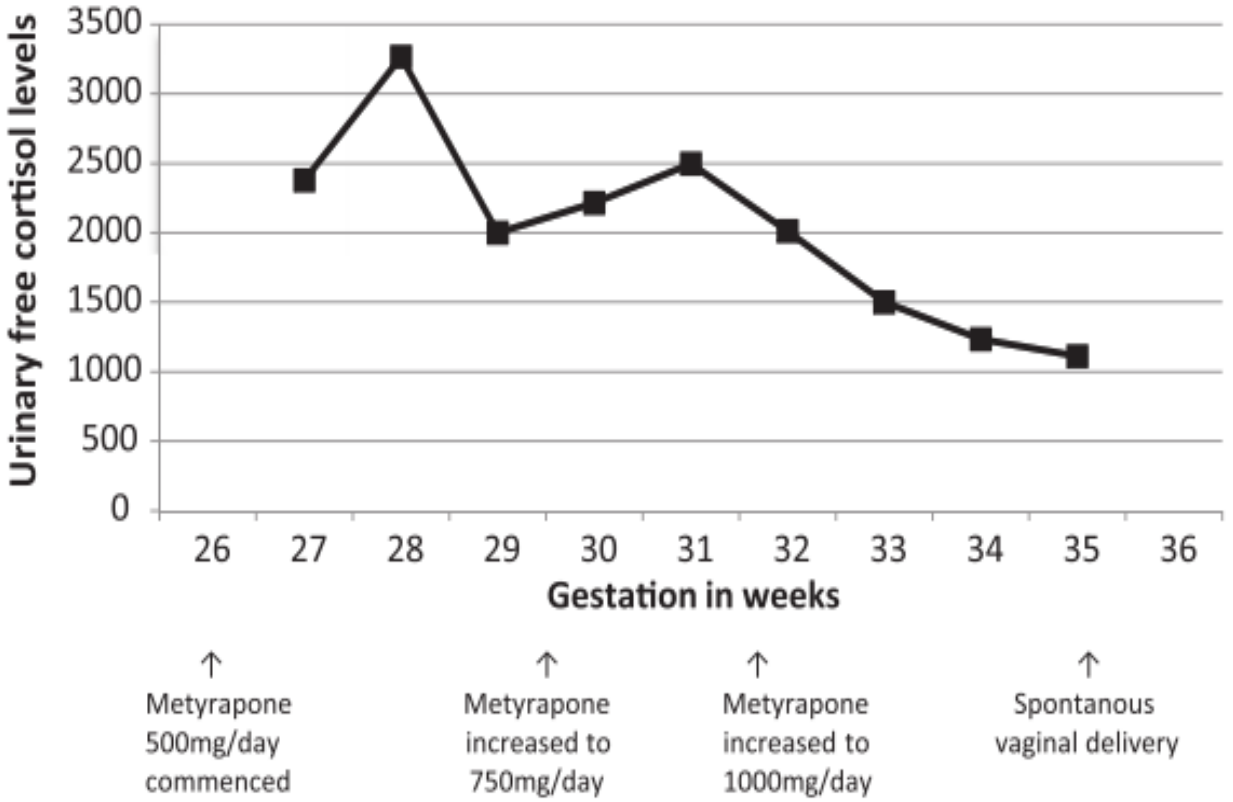


Biochemical course of 24-h UFC levels during the second and third trimester with metyrapone treatment



Lim et al., European Journal of Obstetrics & Gynecology and Reproductive Biology, 2013

Published reports of hypercortisolism during pregnancy that were managed exclusively with drugs.

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	Livebom 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	Livebom female	1449	6, 8
Hána et al. [10]	Pregnancy-induced	Nil surgical pathology identified	Metyrapone	2250 mg	17–34 weeks	Caesaren section for PET at 34 weeks	Livebom 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	Livebom[b]	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	Livebom female	1690	9, 9
	Pregnancy-induced	Nil surgical pathology identified	Metyrapone	2500 mg	14–37 weeks	Spontaneous vaginal delivery at 37 weeks	Livebom 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	Livebom female[a]	830	NS
							Livebom 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	Livebom male	2400	8, 9
Prebtani et al. [26]	Adrenal adenoma	NS	Ketoconazole	600 mg	33–35 weeks	Caesarean section at 35 weeks	Livebom 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	Livebom 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	Livebom	NS	NS
Kasperlik-Załuska et al. [32]	Pregnancy-induced	Nil surgical pathology identified	Metyrapone	750–1000 mg	5–32 weeks	Caesarean section for placental abruption at 32 weeks	Livebom 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	Livebom 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	Livebom 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	Livebom male	2850	6, 8

Lim et al. 2013

Published reports of hypercortisolism during pregnancy that were managed with medical and surgery therapy.

Authors	Aetiology	Rational for medical treatment	Medication	Dose (mg/day)	Period	Outcome	Foetal outcome	Birthweight (g)
Lindsay et al. [5]	Cushing's disease	In preparation for surgery	Metyrapone	500 mg	14–18 weeks	TSS at 18 weeks Vaginal delivery at 34/40 due to PET and IUGR post induction of labour	Liveborn male	1712
Boronat et al. [25]	Cushing's disease	Treatment prior to conception	Ketoconazole Metyrapone	400 mg 500–1000 mg	0–13 weeks 20–34 weeks	TSS at 16 weeks Vaginal delivery at 34 weeks post induction	Liveborn male	2480
Blanco et al. [35]	Adrenal adenoma	In preparation for surgery	Metyrapone	750–2000 mg	8–16 weeks	Adrenalectomy at 16 weeks Preterm vaginal delivery at 30 weeks	Liveborn male	1280
Shaw et al. [36]	Adrenal adenoma	In preparation for surgery	Metyrapone	1500 mg	30–31 weeks	Adrenalectomy at 31 weeks Spontaneous vaginal delivery at 36 weeks	Liveborn female	2470
Hanson et al. [37]	Adrenal adenoma	Treatment prior to conception	Amino-glutethimide	2500 mg	0–21 weeks	Adrenalectomy at 27 weeks Vaginal delivery at term	Liveborn female	3130

Lim et al. 2013

Cesearean or vaginal delivery?

Mode of delivery must be individualized

- considering the tie;
- the course of pregnancy;
- the possible surgical treatment for the syndrome / disease of Cushing;
- size of tumor ACTH-secreting

Take home messages

Cushing's syndrome during pregnancy is a rare condition

Diagnosis is difficult because typical symptoms of the disorder and pregnancy may overlap and biochimical tests may be normal for pregnancy

Continous interactions between gynecologist and endocrinologist is crucial for diagnosis, management of pregnancy and estabilishing modality of delivery

No sufficient literature for defining protocols and guidelines for timing/modality of delivery