# 35 year old female LE edema and abdominal distention

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**Fellow section of Endocrinology Diabetes and Metabolism**

**06/26/2014**

# HPI

- 35 year old F with PMH of DM II, OSA, CHF (NICM)
- In her usual state of health until 1 year ago.
- c/o sweating/hot flashes, worsening of male pattern facial hair, increasing irritability, abdominal distension, early satiety, worsening LE swelling.
- Lost 40 pounds
- Secondary amenorrhea (last menstrual cycle 18 months ago)
- No headache, blurry vision, galactorrhea, skin tags/hyperpigmentation, joints enlargement or acne.

**PMH:**

- ✓CHF (EF 42%).
- ✓DM type II
- ✓PUD
- ✓Depression

**Family History:**

- ✓Father HTN
- ✓Type 2 DM (mother/father)

**Social history**

- ✓Single, 2 boys, no smoking no illicit drugs use. Drink alcohol socially

**Home medications**

- ➢ Tylenol PRN for pain

# ROS

**Constitutional:** generalized weakness, Wt loss

**HENT:** No blurred vision, no double vision, no sore throat, no headache.

**Neck:** no neck pain, no neck mass

**Cardio/pulm:** No CP, no SOB, no orthopnea or PND

**GI:** abdominal distension, early satiety, nausea. No diarrhea, constipation, melena or hematochezia

**GU:** secondary amenorrhea

**Skin** hot flashes

**Neuro** negative

# On examination

**Vitals:** BP 140/78, Pulse 88, no fever, RR 14, **BMI 42**

**General:** awake alert, comfortable

**HEENT:** normocephalic non traumatic, no pallor, no jaundice. Mild hirsutism

**Neck:** supple, no thyromegaly, no lymphadenopathy, **no supraclavicular fullness**

**CVS/Pulm:** good air entry bilateral, **fine basal inspiratory crackles** bilateral

**Abd:** mildly tender, large mass in the Lt lower abdomen, no organomegaly, audible bowel sounds.

**Skin:** normal, not diaphoretic, **no acanthosis nigricans, no hyperpigmentation**

**Neuro:** alert, no tremor, CN intact, DTR normal, **normal monofilament test and vibration sensation**

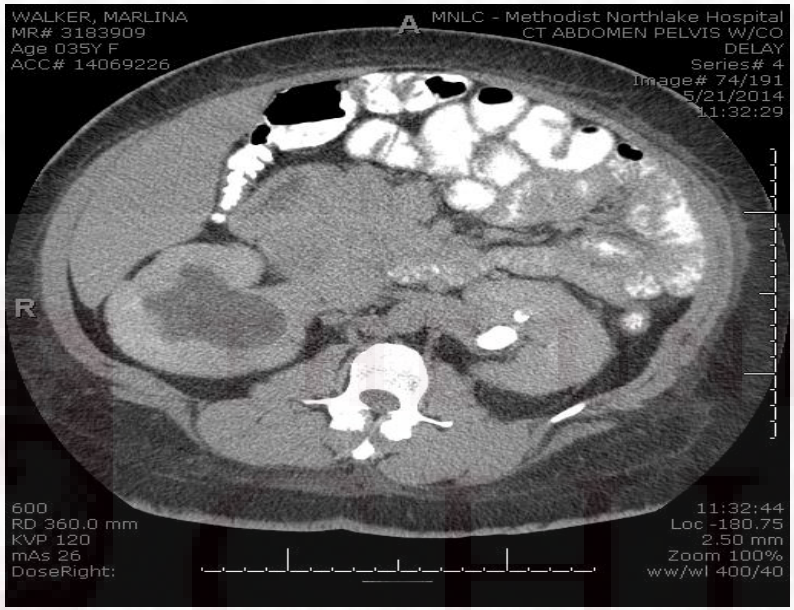
**Psych:** normal mood, and affect

***Differential diagnosis ?***

# General labs

| Test/date | 6/12/2014 |
|---|---|
| Na/K | 138/3.4 |
| Glucose | 240 |
| HbA1c | 9.0 % |
| BUN/Cr | 11/1.5 |
| eGFR | 40 |
| Albumin | 3.8 |
| ALP | 290 |
| ALT/AST | 52/42 |
| Hb | 16 |
| WBC | 7.6 |
| Plt | 223 |

# What should we do next?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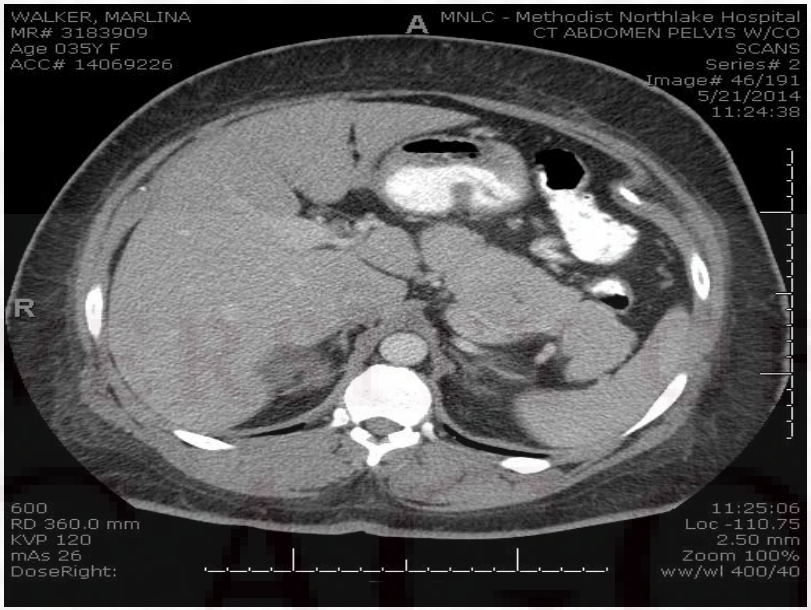
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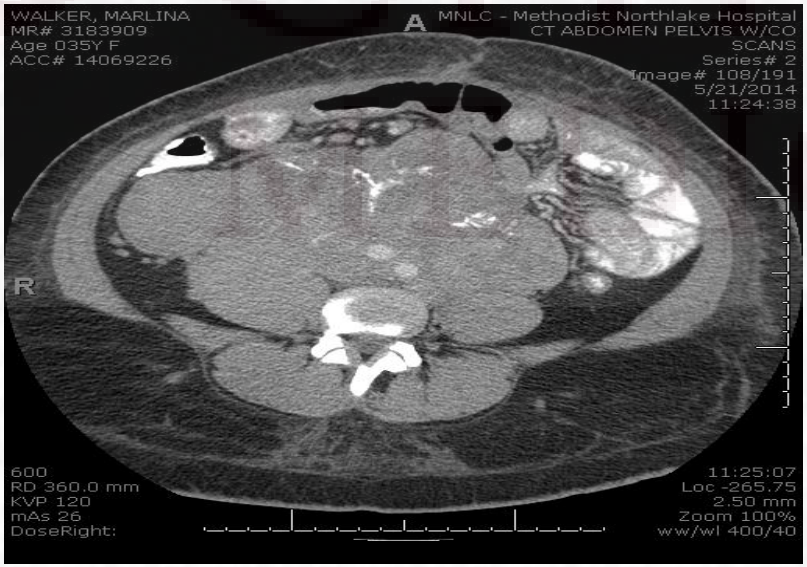
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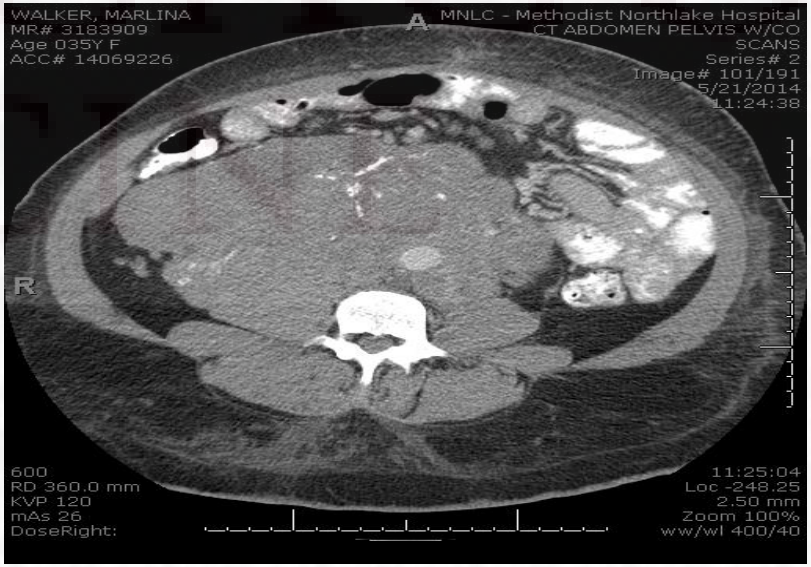
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# *Endo labs*

| Test/date | 6/12/2014 (11am) |
|---|---|
| TSH (0.4 – 4.5) | 0.99 |
| ACTH | 6.4 |
| cortisol | 46.4 |
| E2 | 413 |
| LH | < 0.1 |
| FSH | 0.5 |
| PRL (4.8 -23.3) | 27.25 |
| Total testosterone | 1832 |
| Free testosterone | 1182 |
| DHEA-S (45-270) | 32 |

# Clinical Qs

i. In a patient with high estrogen level, is an elevated cortisol level due to elevated CBG?

ii. Is diurnal variation of cortisol preserved in these cases?

# *The Increase in Plasma and Saliva Cortisol Levels in Pregnancy is not due to the Increase in Corticosteroid-Binding Globulin Levels*

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**Journal of Clinical Endocrinology and Metabolism (JCEM)**

**Vol. 71, No. 3**

- The relationships between the diurnal variations in **saliva (free) cortisol, baseline levels of total cortisol, corticosterone binding Globulin (CBG), progesterone, and estrogens** were studied in several groups of women (normal non-pregnant, taking a combined oral contraceptive pill, after superovulation therapy, during early and late pregnancy, and postpartum).

## *Six groups of women were studied*

**10 no pregnant women with regular cycles**

**8 women had been taking combined OCP (35 mcg estrogen or less)**

**10 women in mid-luteal phase → hyper-ovulation with HMG**

**9 women early pregnant (12-16 wks)**

**9 women in late pregnancy (37-39 wks)**

**6 women post partum (5-33 days post partum)**

**JCEM, Vol. 71, No. 3, 1990**

TABLE 1. Mean (±SD) saliva cortisol (hourly samples from 0800–2200 h), plasma CBG, and cortisol (0900 h) levels (nanomoles per L) in different groups of nonpregnant and pregnant women

| Group (n) | Saliva cortisol | Plasma CBG | Plasma cortisol |
|---|---|---|---|
| Normal nonpregnant (10) | 5.0 ± 1.4 | 510 ± 106 | 285 ± 72 |
| Oral contraception (8) | 6.0 ± 1.4 | 1231 ± 117[a] | 304 ± 97 |
| Superovulation (10) | 6.1 ± 0.9[b] | 550 ± 83 | 404 ± 132[b] |
| Early pregnancy (9) | 7.2 ± 1.2[c] | 929 ± 229[a] | 520 ± 115[a] |
| Late pregnancy (6) | 13.6 ± 3.6[a] | 1174 ± 193[a] | 708 ± 183[a] |
| Postpartum day 1 (4,6,6)[d] | 12.8 ± 5.3[c] | 1024 ± 232[a] | 913 ± 249[a] |
| 2 (6) | 9.1 ± 3.0[b] | 934 ± 222[a] | 736 ± 91[a] |
| 3 (6) | 9.0 ± 5.5[b] | 905 ± 225[c] | 657 ± 150[a] |
| 4 (6) | 8.1 ± 1.3[c] | 867 ± 223[c] | 569 ± 94[a] |
| 5 (6) | 6.2 ± 1.3 | 807 ± 171[c] | 486 ± 63[a] |
| 12 (4,6,6)[d] | 5.5 ± 1.7 | 678 ± 97[b] | 382 ± 82[b] |
| 19 (4,6,6)[d] | 7.1 ± 0.9[b] | 539 ± 74 | 433 ± 147[b] |
| 26 (4,6,6)[d] | 6.2 ± 1.6 | 511 ± 35 | 439 ± 181[b] |
| 33 (4,6,6)[d] | 5.5 ± 1.1 | 502 ± 59 | 389 ± 126 |

[a] $P < 0.0001$ *vs.* normal nonpregnant group.
[b] $P < 0.05$ *vs.* normal nonpregnant group.
[c] $P < 0.002$ *vs.* normal nonpregnant group.
[d] Saliva samples were provided by only four subjects (the same four) on each of these days.

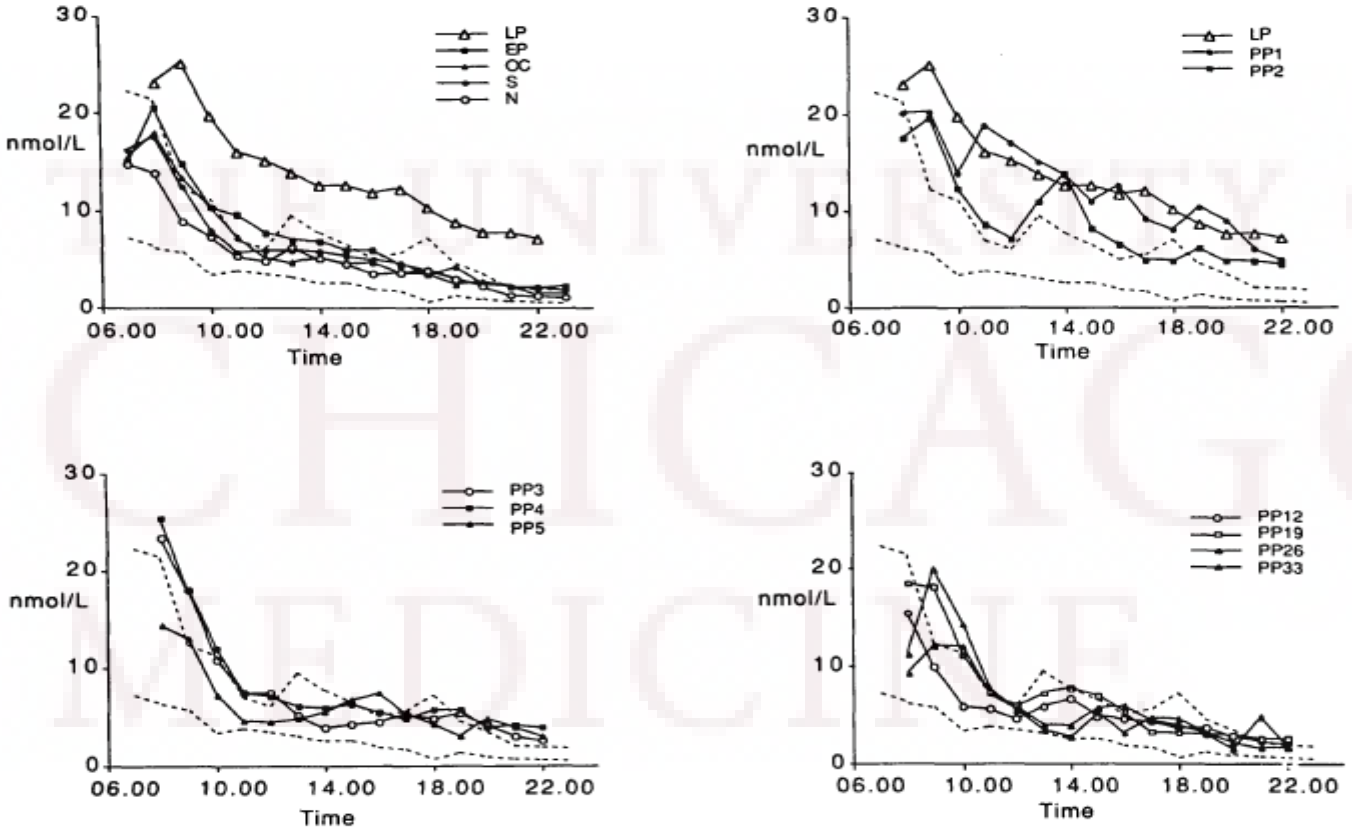
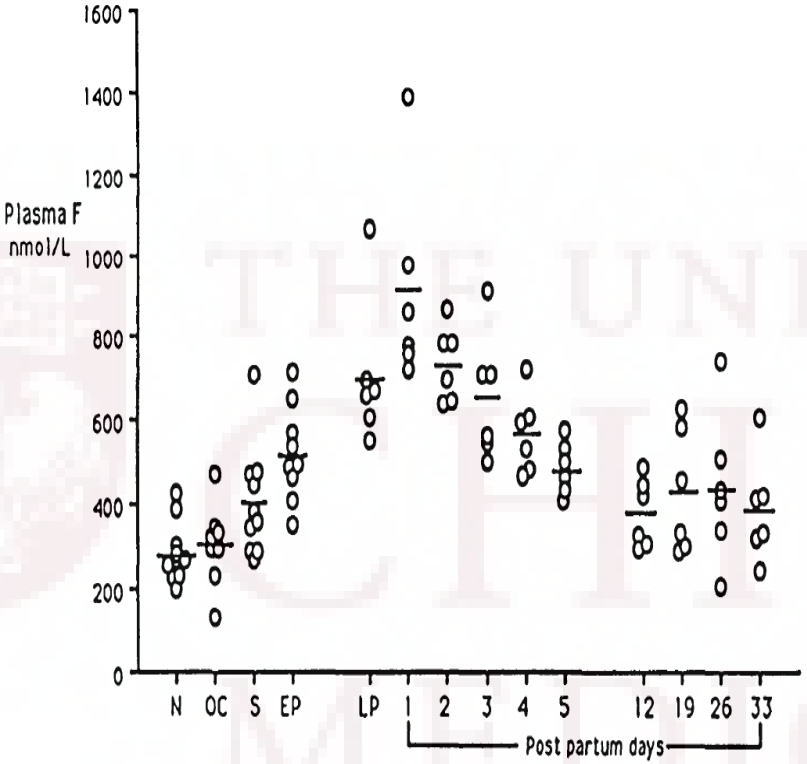
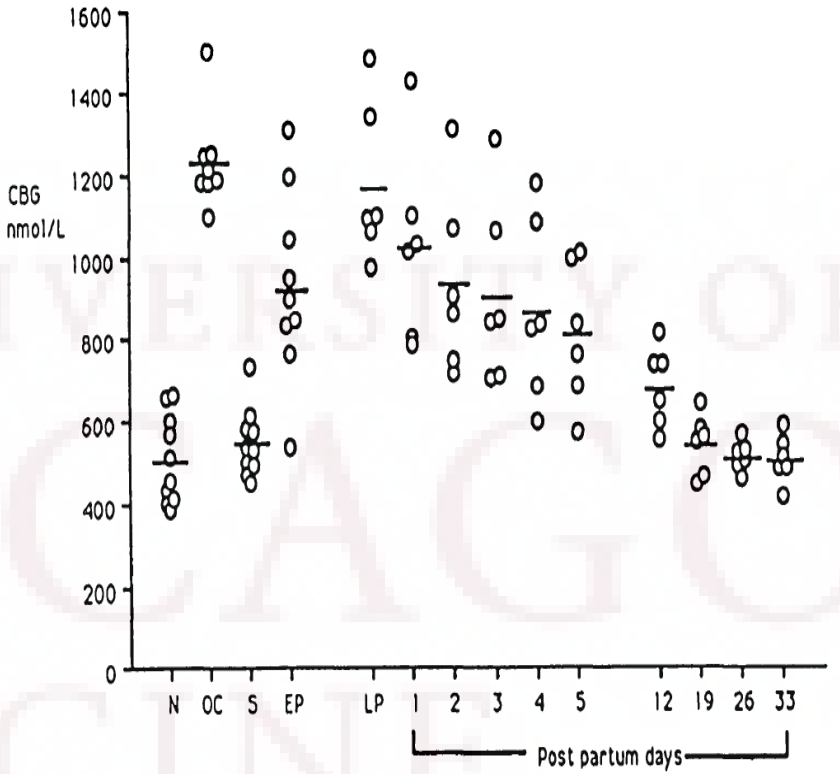



FIG. 1. Mean hourly saliva cortisol levels in different groups of women. LP, Late pregnancy (37–39 weeks gestation; n = 6); EP, early pregnancy (12–16 weeks gestation; n = 9); OC, taking combined oral contraceptive pill (n = 8); S, superovulation after hMG (n = 10); N, nonpregnant women with regular cycles (n = 10); PP1 1–33, postpartum days 1–33 (n = 4–6). The *area between the dotted lines* represents the 1–99% confidence limits of the normal mean.




***Total plasma cortisol [F]*** **in different groups of women. The *horizontal bars* indicate the mean levels for each group**




***CBG levels*** **in different groups of women. The *horizontal bars* indicate the mean levels for each group**

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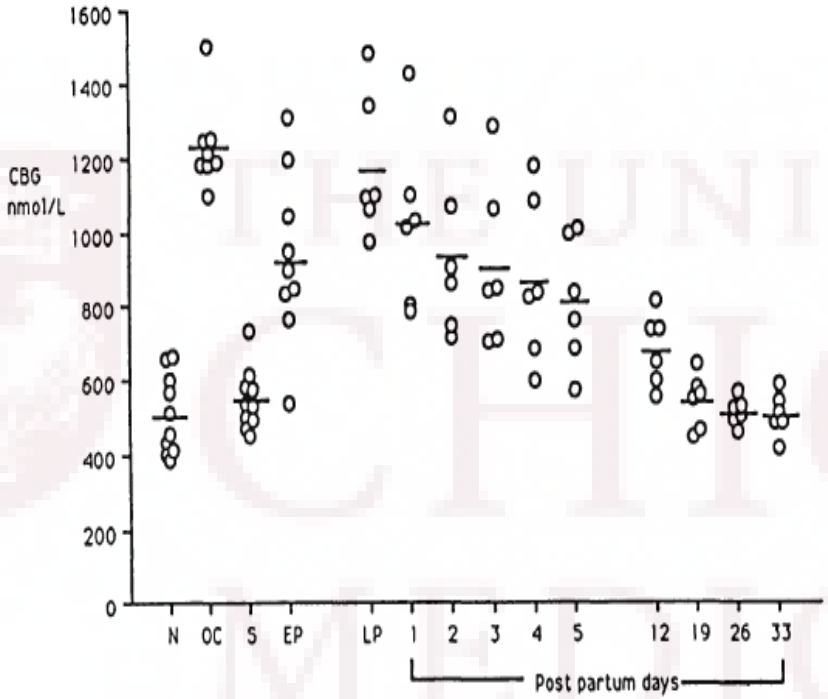
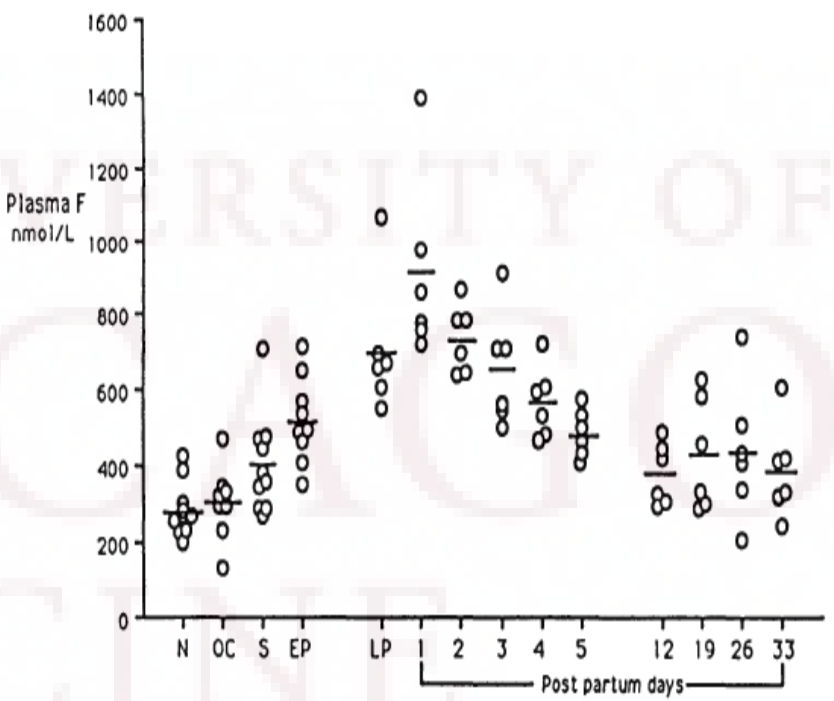



CBG levels in different groups of women. The *horizontal bars* indicate the mean levels for each group




Total plasma cortisol (F) levels in different groups of women. The *horizontal bars* indicate the mean level for each group

# Result

- Cortisol levels were significantly elevated throughout the day, with preservation of diurnal variation.
- Total cortisol and CBG levels were also significantly raised in pregnancy, but total cortisol levels were **normal in women taking a combined oral contraceptive pill in spite of significantly elevated CBG**.
- Cortisol levels fell slowly postpartum over several days, making it improbable that the increase in cortisol is solely due to elevated CRH levels
- It appears that increased free and total cortisol levels in pregnancy are related to resetting of the sensitivity of the hypothalamic-pituitary-adrenal axis and not merely to raised CBG, progesterone, or CRH levels

# Summary

- ✓ Increase in free and total cortisol levels in pregnancy is not directly due to an increase in CBG.
- ✓ It seems likely that during pregnancy there is a **resetting of the sensitivity of the hypothalamic- pituitary-adrenal axis**, probably under the influence of increasing estrogen levels concentrations. After delivery, the sensitivity of the hypothalamic-pituitary-adrenal axis slowly returns to normal.
- ✓ Although **placental production of CRH and ACTH** may lead to stimulation of cortisol production by the maternal adrenals, this **cannot explain how a normal diurnal rhythm is maintained**. Also, both plasma and saliva cortisol levels are already significantly elevated by the beginning of the second trimester, before the marked rise in CRH levels found in the second and third trimesters
- ✓ If the elevation in cortisol was solely related to placental CRH and ACTH production, it would be expected that cortisol levels would return more rapidly to normal, as the half-lives of CRH, ACTH, and cortisol are all short

# References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# Thank you

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