PROGESTERONE

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DISCLAMER

- Scientific Advisory Board Member
  Designs for Health
- Medical Advisor
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- No financial conflicts to claim

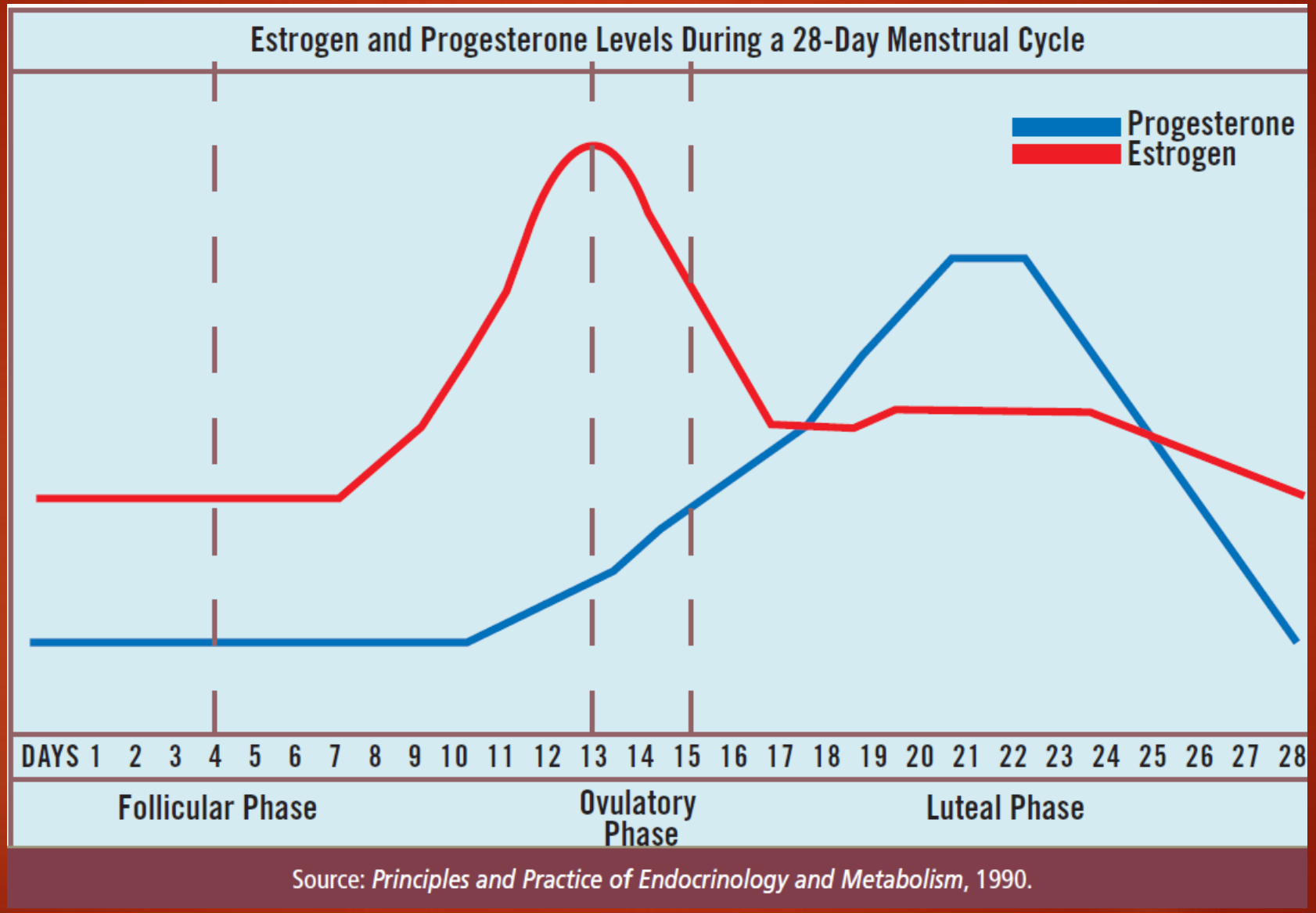
OVERVIEW

- Exogenous sources
- Endogenous production
- Factors contributing to Estrogen Dominance with “Relative” or “Absolute” Progesterone Deficiency
- Treatment Options/Case Studies

EXOGENOUS SOURCES

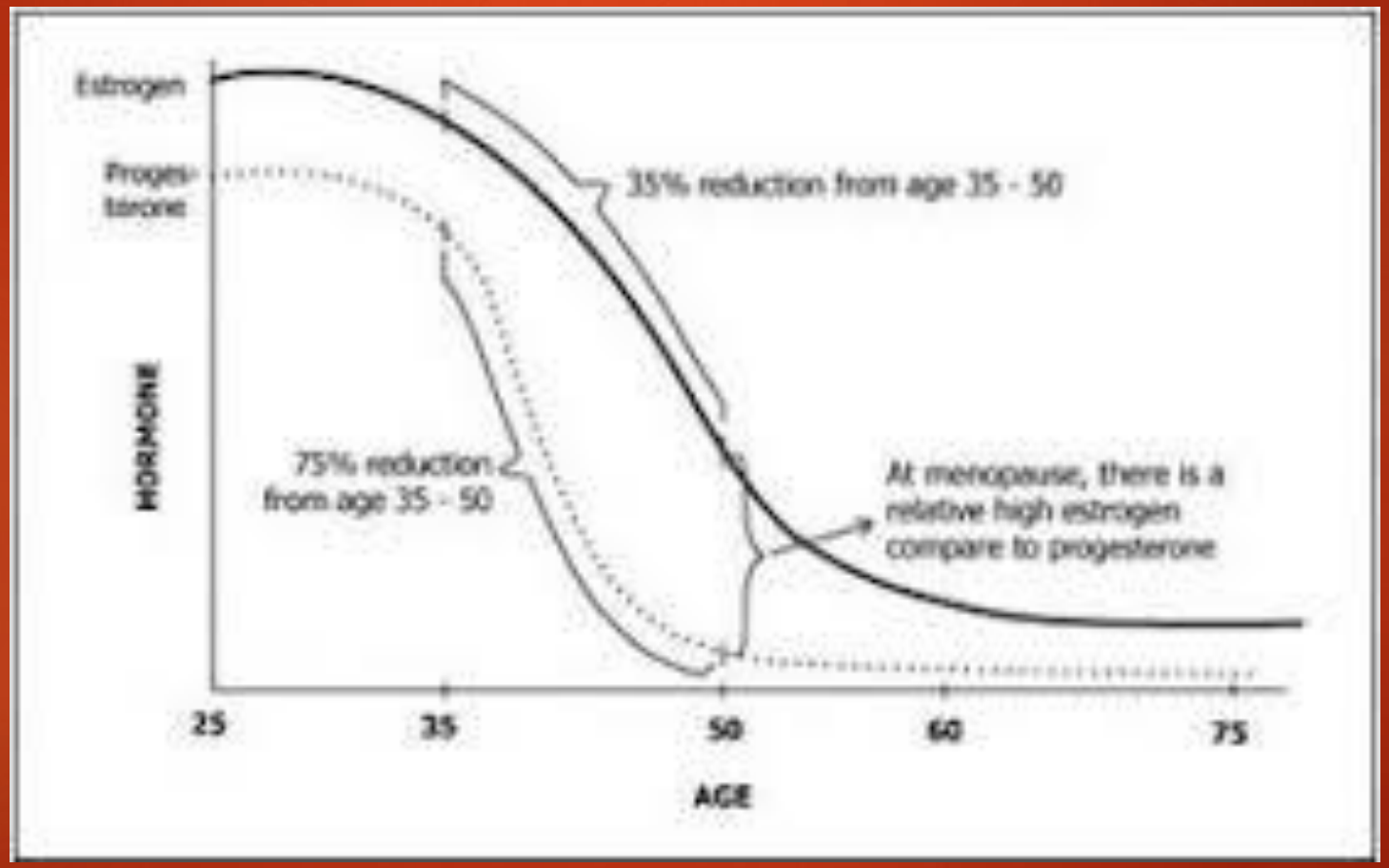
- Progesterone in oil for IntraMuscular use
- Commercially available Prometrium (generic progesterone) available in 100 and 200mg pills for oral use (goes through hepatic first pass)
- Oral micronized compounded alone or in combination with other hormones and available as ordered (does through hepatic first pass)
- Compounded for sublingual delivery (designed to avoid hepatic first pass)
- OTC transdermal cream (need to make sure it is not just "yam cream" and is usually 20-25 mg/dose
- Compounded in cream for transdermal use alone or in combination
- Nanoparticle progesterone serum for transdermal use
- Commercially available transvaginal cream/gel i.e. 4%, 8% strengths
- **PROVERA AND BCPs ARE PROGESTINS AND ARE NOT NATURAL PROGESTERONE!!!**

ENDOGENOUS PRODUCTION



Source: *Principles and Practice of Endocrinology and Metabolism*, 1990.

Progesterone Decline Compared to Estrogen



PROGESTERONE NEEDS TO BE VIEWED AS A BALANCE WITH ESTROGEN

FACTORS CONTRIBUTING TO "ESTROGEN DOMINANCE"

- Hormone Replacement Therapy (HRT) of an estrogen without a progestin/progesterone. Called "**UNOPOSED ESTROGEN**"
- Endocrine Disruptors/Xenobiotics/Xenoestrogens
- Metabolism of Estrogen→more estrogenic metabolites (ie 16a, 4OH)
- Decreased methylation of estrogen metabolites
- Decreased detoxification of estrogen through the liver
- Enterohepatic recirculation of estrogen in the gut
- Aromatization of androgens to estrogen in fat cells

SX OF ESTROGEN DOMINANCE

- Symptoms of "**Estrogen Dominance**":
  breast tenderness, fluid retention, PMS Sx, thick endometrial lining tears away from uterine lining → menorrhagia: painful cramps, clots, heavy flow
  →metrorrhagia: irregular, closer than 28 days, usually longer in length
- Immediate relief: Progesterone support
- Long term: Find the underlying problem, support ovulation and hormonal balancing

FACTORS CONTRIBUTING TO "PROGESTERONE DEFICIENCY"

- Anovulatory cycles or "suboptimal" ovulatory cycles
- Absolute verses "relative" deficiency
- Can be age related as women are born with all their eggs for lifetime
- Suboptimal follicular development→suboptimal "corpus luteum→ decreased ability to produce progesterone
- Can result in "first trimester spontaneous abortion" or preterm labor
- A decreased FSH:LH ratio
- Most common is PolyCystic Ovary Syndrome (PCOS)

Schmouder VM, et al. The rebirth of progesterone in the prevention of preterm labor. AnnPharmaco. 2013 Apr;47(4):527-38.

Diagnostic Criteria for PCOS

Androgen Excess Society 2006

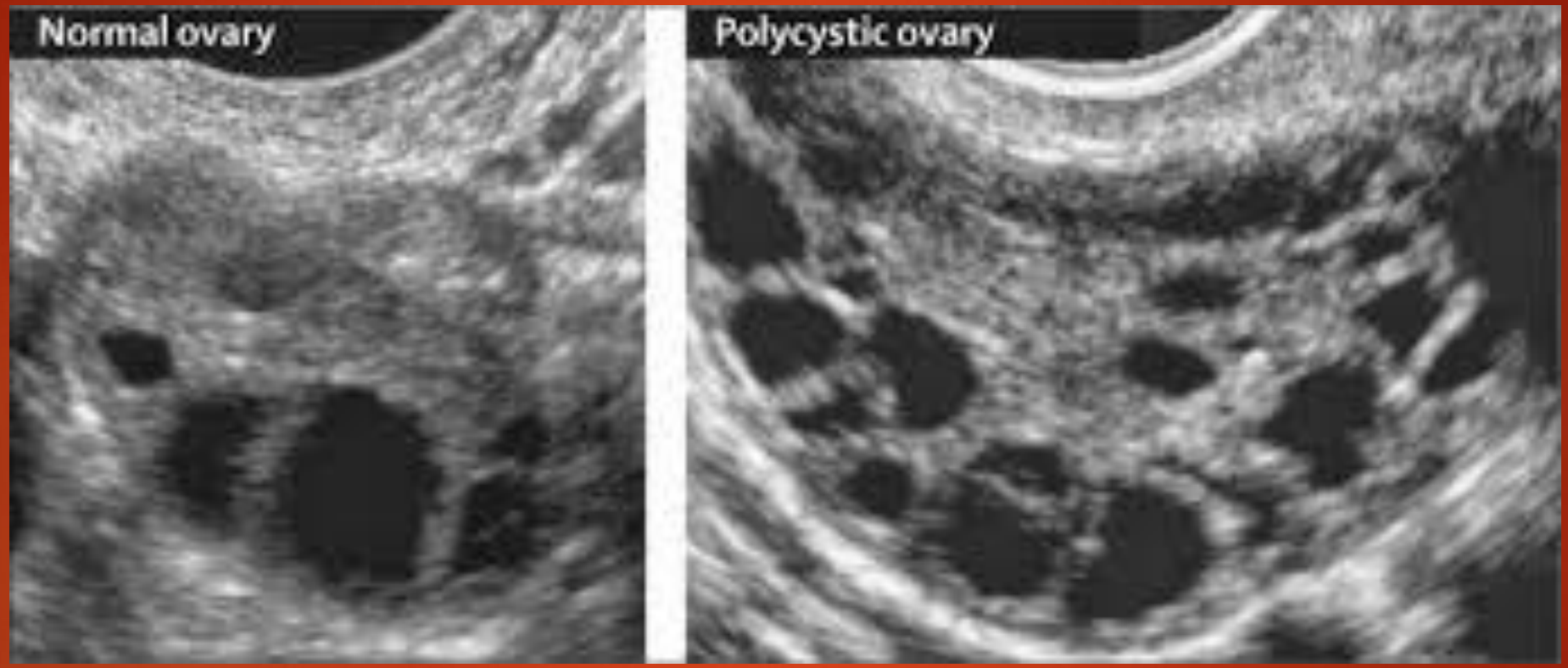
Hyperandrogenism (either clinical or biochemical)

AND

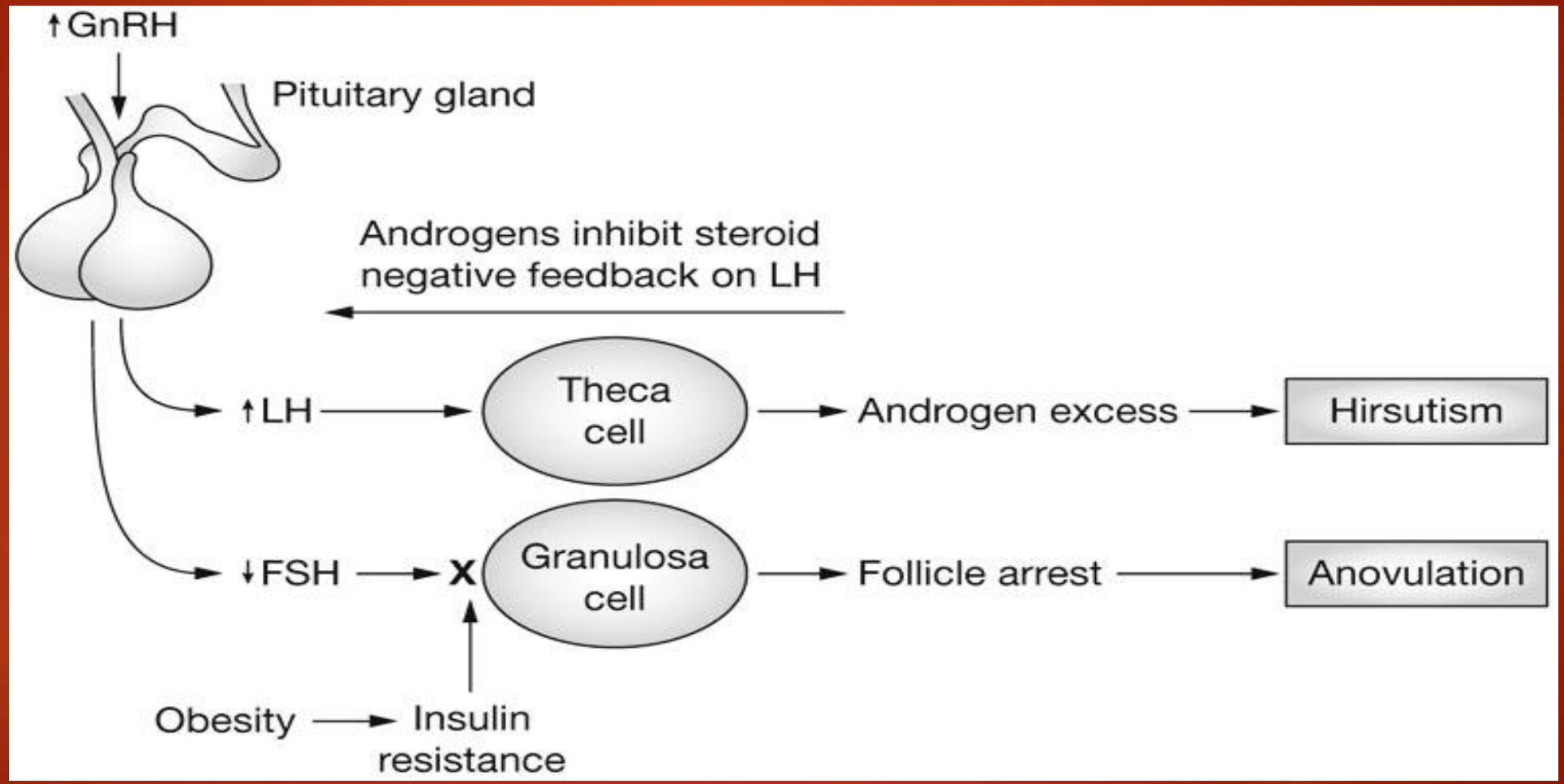
Oligomenorrhea /Signs of Anovulation OR String of Pearls on Ultrasound

*Diagnosis of exclusion that above symptoms not due to other pathology

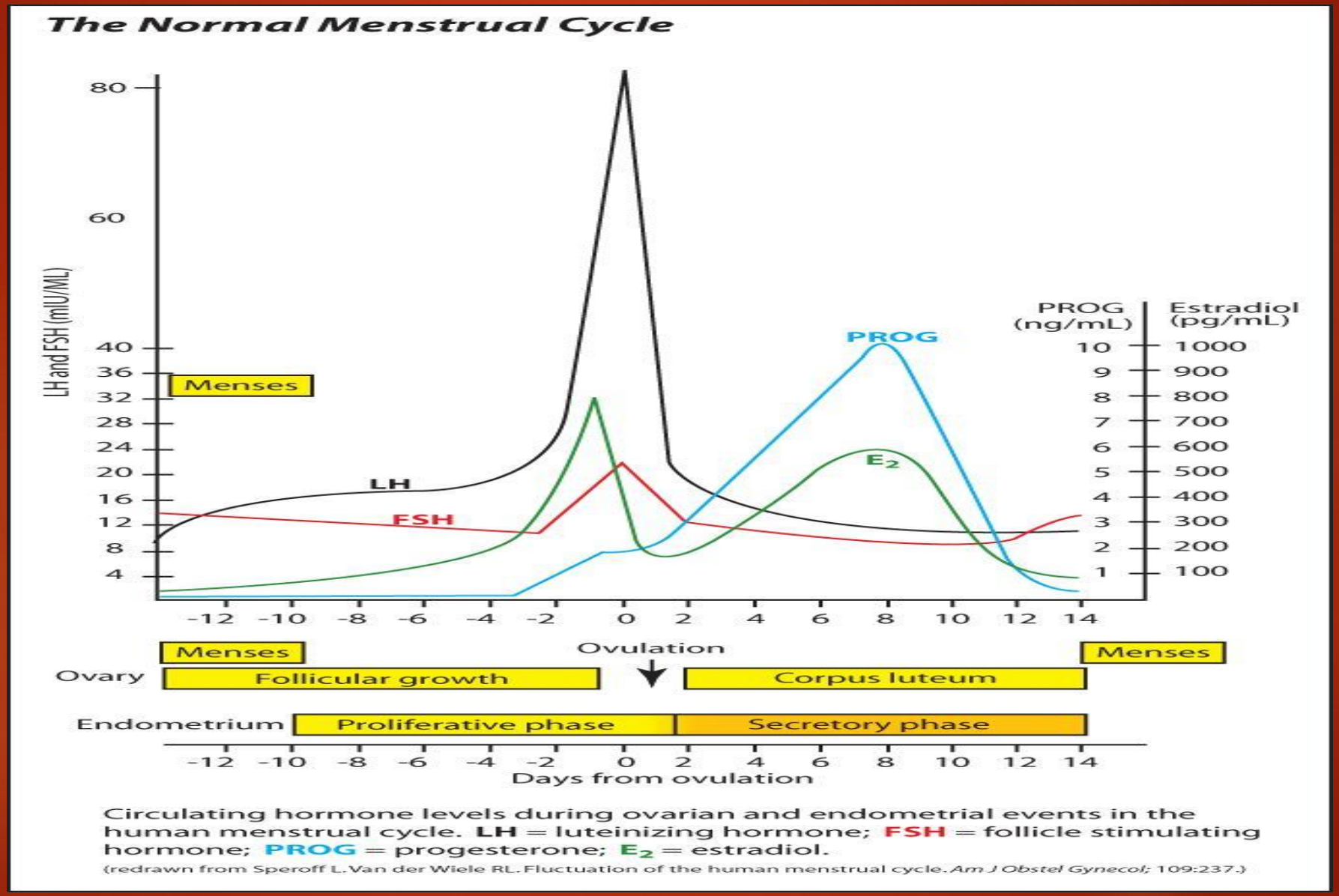
"String of Pearls" PCOS: Ultrasound



PATHOPHYSIOLOGY OF PCOS



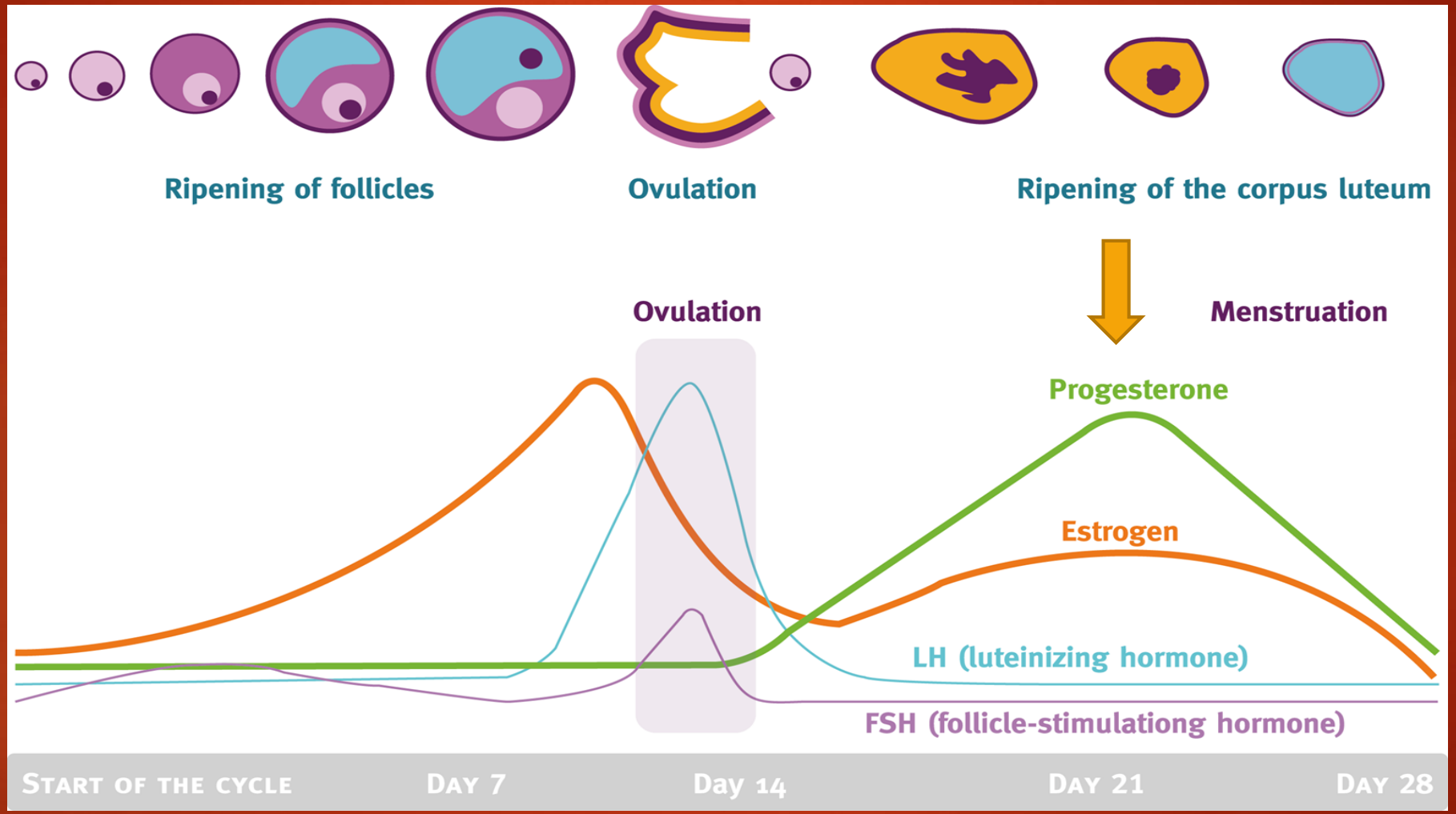
REVIEW OF MENSTRUAL CYCLE



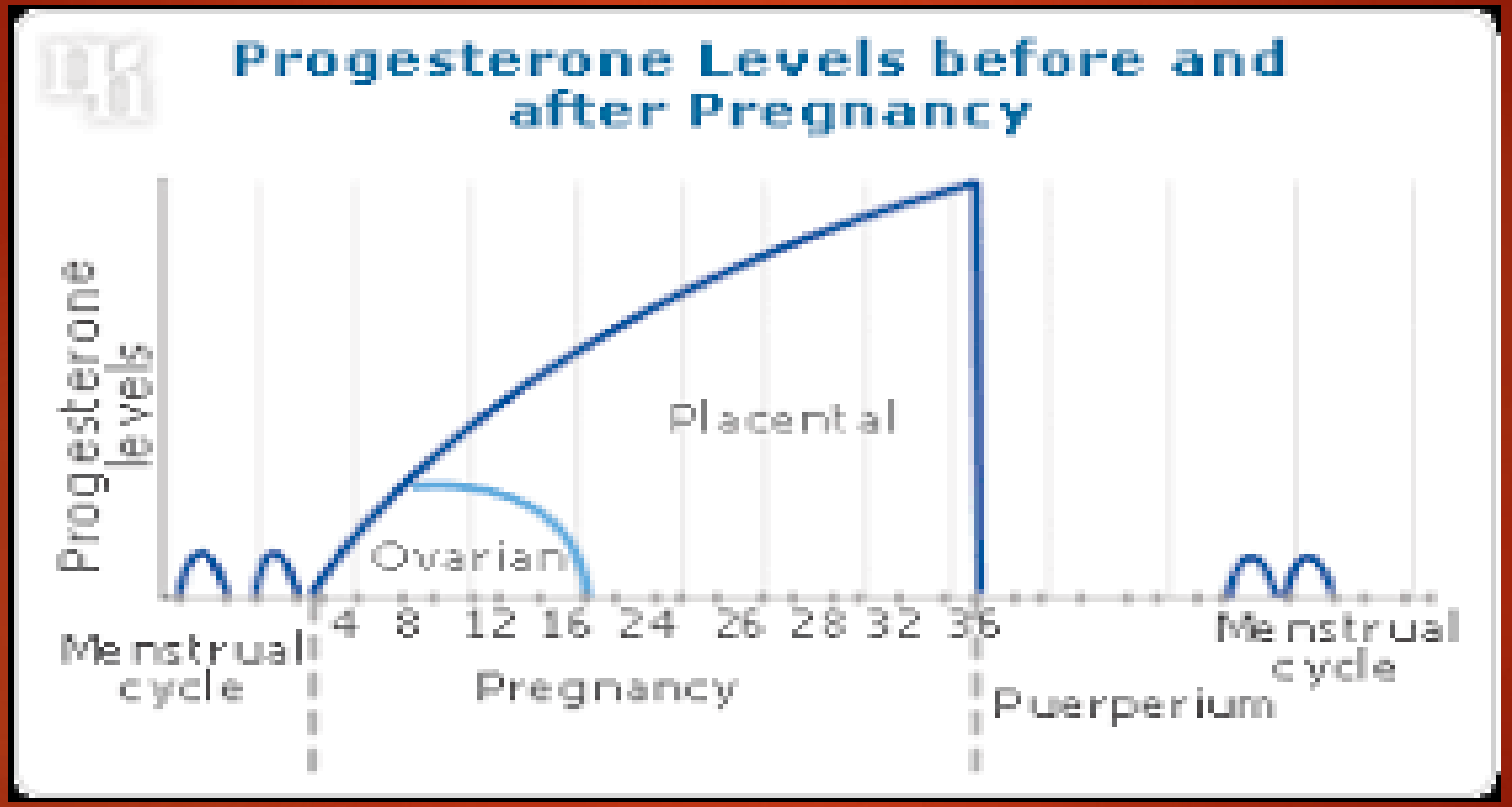
Circulating hormone levels during ovarian and endometrial events in the human menstrual cycle. **LH** = luteinizing hormone; **FSH** = follicle stimulating hormone; **PROG** = progesterone; **E_2** = estradiol.

(redrawn from Speroff L.Van der Wiele RL. Fluctuation of the human menstrual cycle. *Am J Obstel Gynecol;* 109:237.)

FOLLICULAR DEVELOPMENT



PROGESTERONE IN PREGNANCY



EVALUATING FOR LUTEAL PROGESTERONE DEFICIENCY (LPD)

- Most convenient is to measure serum level of progesterone between days 19-22 in the cycle as this is "mid-luteal" phase
- Not convenient (but optimal) is to get serum levels for 3 days in a row
- If periods are irregular, do ovulation tests at home and do serum level days 6-9 after positive ovulation test.
- If ovulation testing is never positive or serum levels are very low despite getting regular periods, confirms "anovulatory cycles
- For PCOS, treat for "insulin resistance"
  -low glycemic diet
  -insulin sensitizers if indicated

Mesen TB, et al. Progesterone and the luteal phase: a requisite to reproduction. Obstet Gyne Clin North America. 2015 Mar;42(1):135-51.

HORMONAL EFFECTS OF ANOVULATION

- **Amenorrhea** (no menses > 3 months)
- Lack of progesterone→ **unopposed estrogen** stimulation of uterine lining
- Endometrial Hyperplasia (EH)
- Increased risk for Endometrial Cancer
- Protection of uterine lining with progesterone
  -synthetic progestin vs bioidentical
  -routes of delivery: oral, sublingual, transdermal

Endometrial Cancer and PCOS

- Chittenden BG, et al. Polycystic Ovary Syndrome and the risk of gynecological cancer: a systematic review. Reproductive Biomedicine Online,19(3): 398-405, 2009
- Summary: **Women with PCOS have a 3 fold increase of developing endometrial cancer**
- Fearney EJ et al. Polycystic ovary syndrome increase the risk of endometrial cancer in women aged less than 50 years: an Australian case-controlled study. Cancer Causes and Control, 21(12):2303-8, 2010.

  Summary: **Risk of endometrial cancer increases 4 fold**

SX OF ESTROGEN DOMINANCE/ PROGESTERONE DEFICIENCY IN MENOPAUSE

- Typical history seen in middle aged women with "undiagnosed" history of PCOS/Estrogen Dominance/Progesterone Deficiency
  -Uterine fibroids
  -Uterine ablation
  -Early hysterectomy due to excessive bleeding
- Increased breast density/breast lumps/breast tenderness
- Natural progesterone does not cause increased risk of BrCA

Eden J. The endometrial and breast safety of menopausal hormone therapy containing micronized progesterone: A Short review. Aust NZ J Obstet Gyneaecol 2017 Feb;57(1):12-15.

Progesterone and Benign Breast Disease

- Barrat J, et al. **The in vivo effect of the local administration of progesterone on the mitotic activity of human ductal breast tissue: Results of a pilot study**. J Gynecol Obstet Biol Reprod (Paris) **1990**;19(3):269-74.
- Double-blinded pilot study
- Design: breast tissue samples take from premenopausal women with various benigns breast disease between days 11-13 of their menstrual cycle (before presumed ovulation and endogenous production of progesterone).

Progesterone and Benign Breast Disease

- Each patient was treated 11-13 days before surgery by daily application on breast of either:
  -placebo get
  -gel containing progesterone
  -gel containing estradiol
- Results: Mitotic activity was calculated by counting with light microscopy mitoses in the epithelial cells of normal lobular area. Mean mitotic activity was significantly lower in the progesterone treated group (0.04/1,000 cells) than in placebo (0.10/1,000 cells) or in estradiol (0.22/1,000 cells) treated group.

Progesterone and Benign Breast Disease

- **Conclusion:**
  "High concentration of ***progesterone*** sustained in human breast tissue in vivo during 11-13 days does not increase, but actually ***decreases mitotic activity*** in normal lobular epithelial cells."

Progesterone and Breast Cancer

- Fentiman IS, Gregory WM. **The hormonal milieu and prognosis in operable breast cancer**. Cancer Surv **1993**;18:149-63.
- **"Those undergoing surgery at a time of unopposed estrogen (days 3-12) had a significantly worse prognosis that those who had operations at other phases of the menstrual cycle."**
- "This was also borne out by another study that indicated that progesterone levels at the time of surgery had prognostic significance, with node positive patients in **the luteal phase (progesterone > 1.5 ng/dl) having a significantly better outcome.**"

Progesterone and Breast Cancer

- Saad Z, et al. **Timing of surgery in relation to the menstrual cycle in premenopausal women with operable breast cancer**. Br J Surg **1994** Feb;81(2):217-20.
- "The data of 96 premenopausal patients who underwent primary surgery for operable breast carcinoma between 1975 and 1988 were analyzed. **At 10 years, disease-free and overall survival rates of patients whose initial surgery was 1-12 days after the starting date of the last menstrual period (follicular phase) were significantly poorer compared with survival of those who underwent operation more that 12 days after the last menstruation (luteal phase).**"

Progesterone and Breast Cancer

- Saad Z (con't)
- "These differences in survival remained significance in a second analysis based on the menstrual phase at the time of both initial and definitive operation**. Menstrual phase had the greatest impact on the survival of patients with positive axillary nodes (P=0.009)."**
- **"Prospective studies are required to elucidate the relationship between the timing of all surgical procedures during the menstrual cycle and survival."**

Progesterone and Breast Cancer

- Badwe RA, et al. **Serum progesterone at the time of surgery and survival in women with premenopausal breast cancer**. Eur J Cancer 1994;30A(4);445-8.
- In 210 premenopausal with operable breast cancer, serum progesterone and estradiol levels were drawn 3 days prior to tumor excision. No relationship was found between estradiol level and outcomes. However, **in 93 patients with axillary positive nodes, higher progesterone levels were associated with significantly better survival.**

Progesterone and Breast Cancer

- Lemon HM, et al. **Timing of breast cancer surgery during the luteal phase may improve prognosis.** Nebr Med J **1996** Mar;81(3):73-8.
- "A meta-analysis has been performed on available retrospective reports concerning the 5-15 year disease-free survival of 5,353 premenopausal breast cancer patients operated on either during the follicular or luteal phases of the menstrual cycle."

Progesterone and Breast Cancer

- Lemon HM con't:
  "Patients with surgery during the **luteal phase (d 14-23+) had an overall mean 5% benefit** compared to those operated on the follicular phase as determined by date of their last menstrual period."
- "Patients with **positive nodes had a 34 +3% SEM increase in survival** (p=.05), including both estrogen and progesterone-receptor negative as well as positive neoplasms."

Progesterone and Breast Cancer

- Lemon HM con't:
  "In 3 of 4 reports from major cancer treatment centers, each containing 249-1175 cases, **risk of recurrent cancer and/or death increased 5 to 6-fold after 10 years for women receiving surgery during d7-14** of their cycle, compared to those resected during d21-36."
- "Improvement in prognosis was greatest for patients with the highest risk of recurrence due to node-invasive disease and receptor dysfunction."

Progesterone and Breast Cancer

- Lemon HM con't:
  "**Several cell-mediated immunologic factors inimical to metastasis are maximal in the luteal phase of the menstrual cycle**, including natural killer cell activity."
- We conclude that accurate menstrual histories should be included in the medical record from now on for all premenopausal women receiving any surgical procedure upon the breast, preferably using an **objective method of determining the date of last ovulation.**"

Progesterone and Breast Cancer

- Mohr PE, et al. **Serum progesterone and prognosis in operable breast cancer.** Br J Cancer **1996** June;73(12) :1552-5.
- "As part of a **prospective study** of prognostic factors in breast cancer, blood was taken at the time of surgery. Between 1975 and 1992 this was available from 289 premenopausal women with 3 days of tumor excision.
- "There was no significant association between E2 and survival. **Those cases with a progesterone level of 4 ng/ml or more had a significantly better survival than those with a level < 4 ng/ml."**

Progesterone and Breast Cancer

- Mohr PE con't:
  "The possibility of misclassification of menstrual cycle status, because of misreported LMP, has been minimized by applying an independent hormonal measurement (P) of cycle activity. This parameter will also identify women who may be undergoing anovular cycles."
- **"Thus this study has confirmed that a raised level of progesterone at the time of tumor excision is associated with an improvement in prognosis for women with operable breast cancer."**

Progesterone and Breast Cancer

- Cooper LS, et al. **Survival of premenopausal breast carcinoma patients in relation to menstrual cycle timing of surgery and estrogen receptor/progesterone receptor status of the primary tumor**. Cancer 1999 Nov 15;86(10):2053-8.
- Study was determine outcome in a series of 112 premenopausal women with operable breast carcinoma in relation to the timing of surgery within the menstrual cycle and the estrogen receptor (ER) and progesterone receptor (PR) status of their primary tumor as by immunohistochemistry.

Progesterone and Breast Cancer

- Cooper LS con't:
  "Those patients with ER positive tumors who underwent surgery in the early and **luteal phase of the cycle had a significantly better survival** that women with ER negative tumors. This also was true for PR status."
- **"Patients with the best prognosis had ER/PR positive tumors excised on Days 0-2 and 13-32 but even those women with ER or PR negative tumors removed during the luteal phase of their menstrual cycle fared better than patients whose tumors were removed during the follicular phase."**

Progesterone and Breast Cancer

- Cooper LS con't:
  Conclusion: "There was a **better survival rate** for patients with both ER/PR positive and negative tumors treated during the **luteal phase** of the menstrual cycle. This could be the result of **progesterone** acting on the surrounding peritumoral normal tissue, thereby **exerting a straightjacket type effect and improving cohesion of the primary carcinoma**.
- **" Unopposed estrogen in the follicular phase of the cycle may enable more tumor emboli to escape and successfully establish micrometastases."**

Progesterone and Breast Cancer

- Fentiman IS. **Time of surgery for breast cancer.** Int J Clin Pract **2002** April;56(3):188-90.
- **"Luteal phase** surgery is…associated with a **decreased risk of vascular invasion**, **implying that the tumor is more cohesive at that time."**
- "Similarly, in the **heaviest quartile** of postmenopausal patient, with the **highest endogenous estrogen levels**, there was vascular invasion around tumors in **45%** compared to only **11% of the lightest quartile**."
- **Changing the hormonal milieu may have the ability to improve prognosis.**

Local Transdermal Therapy: Chemoprevention

- Lee O, el al. Novel routes for administering chemoprevention: Local Transdermal Therapy (LTT) to the breasts. Semin Oncol **2016** Feb;43(1):107-15
- **"LLT is an approach that could be developed for any small, lipophyllic molecule with good dermal penetration, thus greatly expanding the menu of drugs that could be tested for breast cancer prevention."**

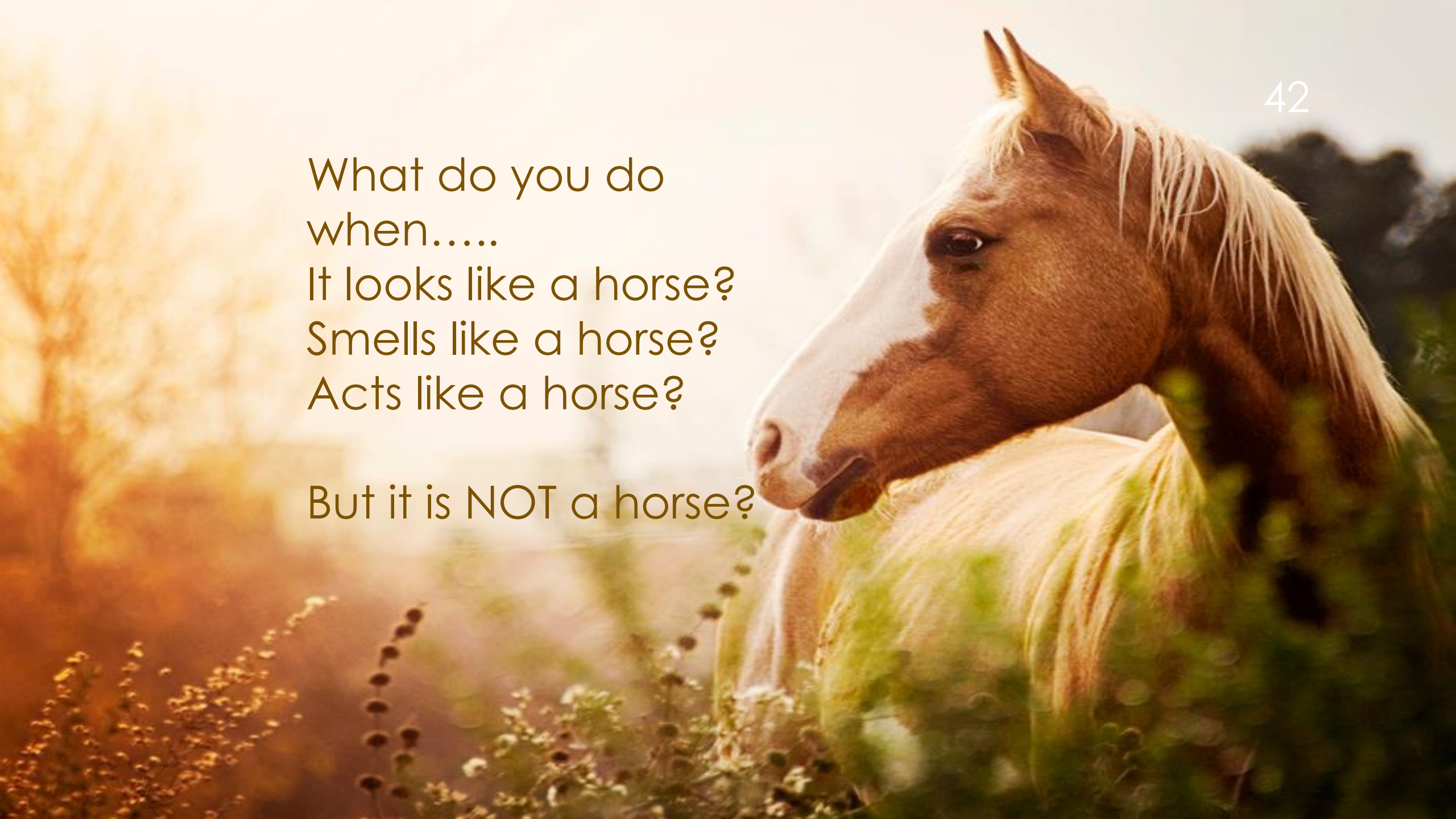
CASE PRESENTATION

Case Presentation: Megan

- 25 yo female on BCPs but wanting **"Pre-conception Evaluation"** before starting a family
  -Challenged Urine for Heavy Metals: +mercury
  -**MTHFR genetic mutation +677 and +1298**
- Detox program (while still on BCPs)
- PreNatal vitamins with **L-5-MTHF 1 mg** and iodine
- Omega 3 supplements with high DHA content

Case Presentation: Megan

- Went off BCP's
- Amenorrhea > 6 months
- Developed severe acne
- U/S done by PCP:
  -string of pearls on ovaries
- Dx: PCOS by PCP due to acne/infertility
  -started metformin w/o results

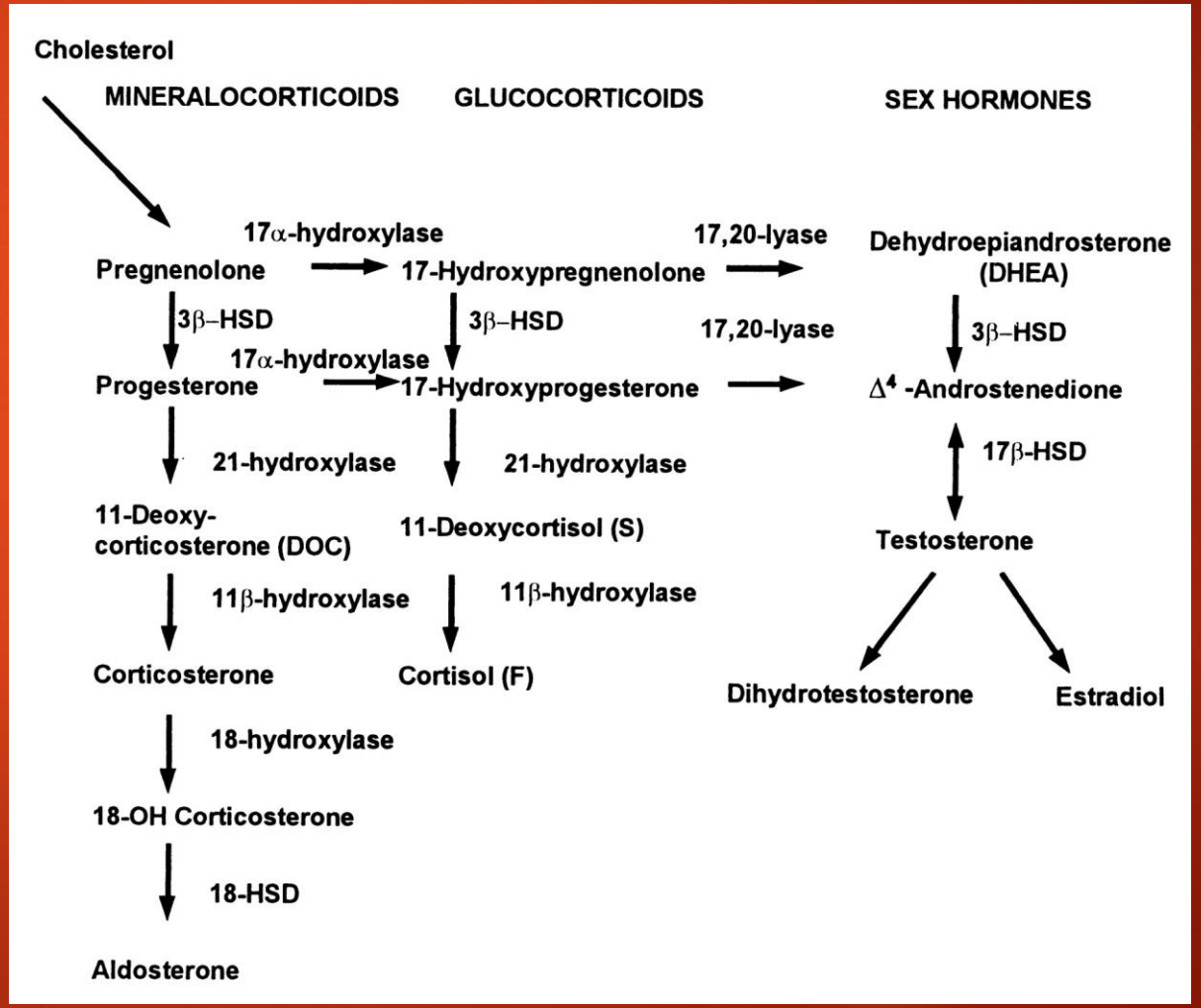


What do you do when…..
It looks like a horse?
Smells like a horse?
Acts like a horse?

But it is NOT a horse?

Case Presentation: Megan (con't) Non-Classic Congenital Adrenal Hyperplasia

- New Labs done:
  LH:FSH ratio was 6:1
  17 OHP elevated
  Androstenedione level 480 (elevated androgens)
  New Dx: **Non-Classic Congenital Adrenal Hyperplasia (genetic partial defect of the 21-hydroxylase enzyme**



Case Presentation: Megan (con't)

- Started on **physiologic replacement of natural -hydrocortisone** (HC 10 mg in AM and 5 mg noon)
- EPA/DHA: important in fetal brain development)
  -con't L-5-MTHF 1 mg daily (proper methylation imperative for early fetal organ development to prevent congenital malformations)
- Repeat labs after 6 weeks:
  -Androstenedione level cut in half
  -LH and FSH repeat levels:
  -added HCG to labs

Case Presentation: Megan (con't)

- Monitored androgen levels during pregnancy for any need to increase hydrocortisone to prevent "virilization in utero" of a female fetus due to elevated androgen levels
- Progesterone 100 mg po started prophylactically and tried wean after 12 weeks but levels decreased and progesterone was "bridged" until week 38 when it was safe for levels to drop and induce labor
- End results: full term perfectly healthy baby girl born without any signs of "virilization"


Ten perfect fingers
Ten perfect toes
Mommy's eyes
Daddy's nose
Oh, little baby
How much
You are loved!
Sophia Farren