

A fluorescence microscopy image of a cell. The cell is stained with a green fluorescent marker, likely a nucleus stain like DAPI, and a red fluorescent marker, possibly a cytoplasmic or membrane stain. The cell is elongated and has a central region where the green signal is more intense. The background is dark, with some other cells visible in the distance.

# Factors that Regulate Hormone Therapy Efficacy

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# Factors Regulating Efficacy of Estrogen or Hormone Therapy

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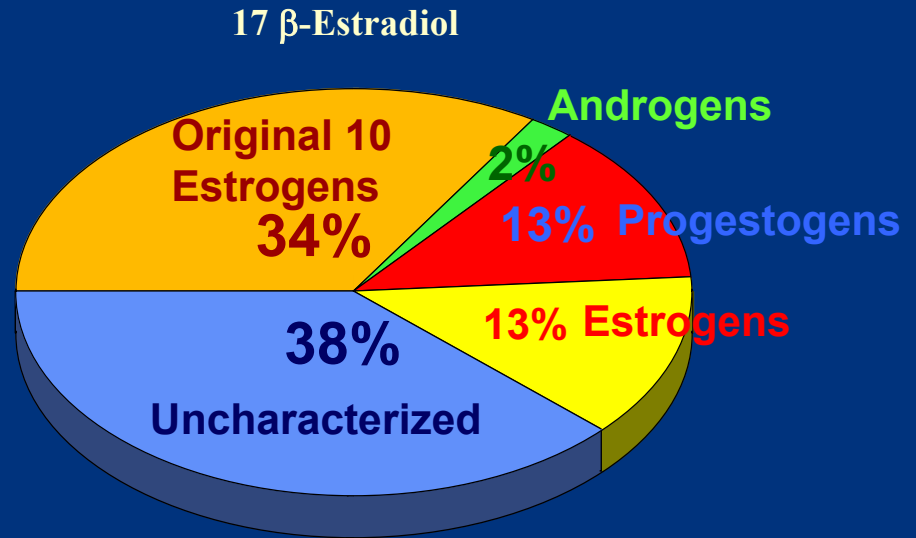
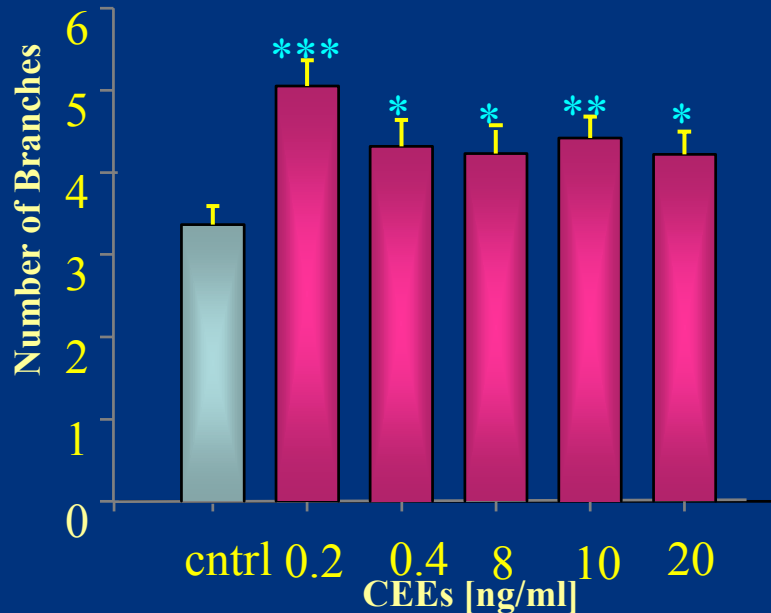
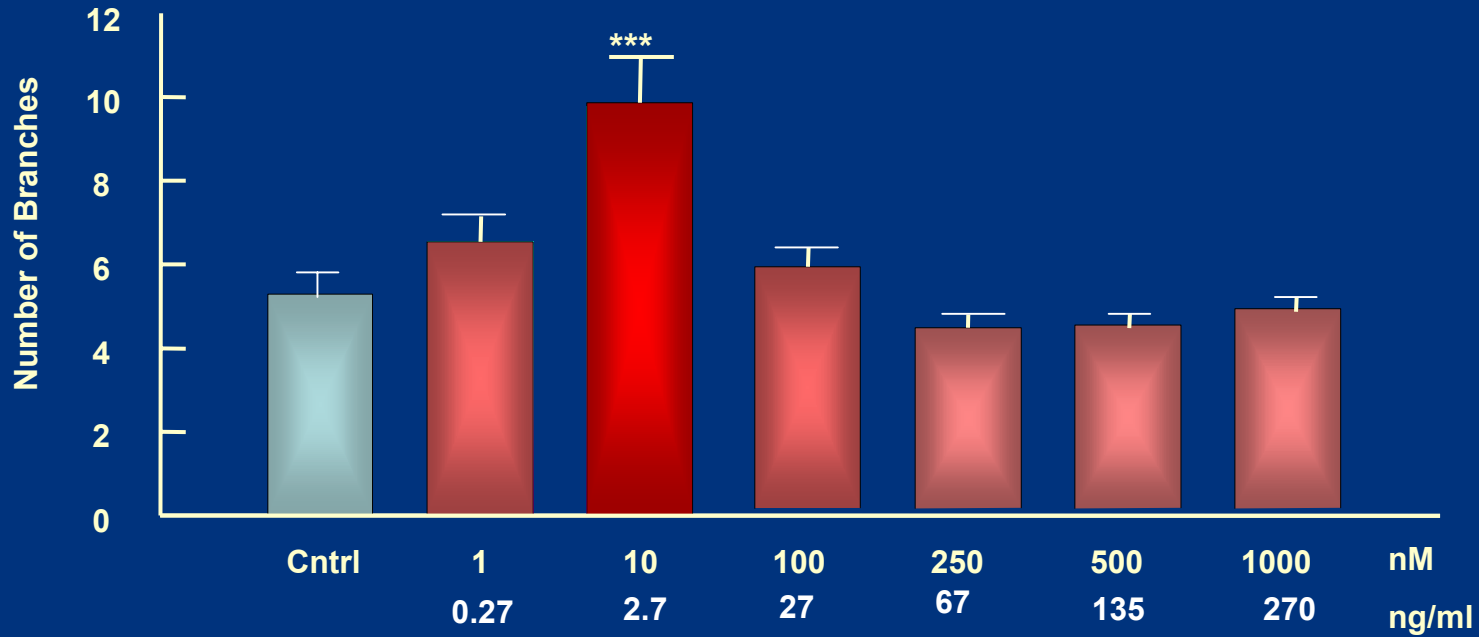
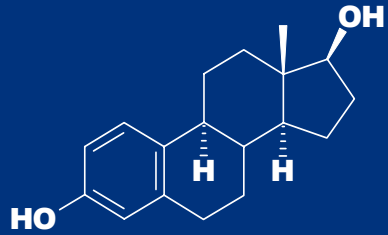
- **Receptor and Ligand Properties**
- **Dose**
- **Formulation**
- **Route of Administration**
- **Timing of therapeutic intervention**

# FDA Regulatory Process: Biologics/Drug Development

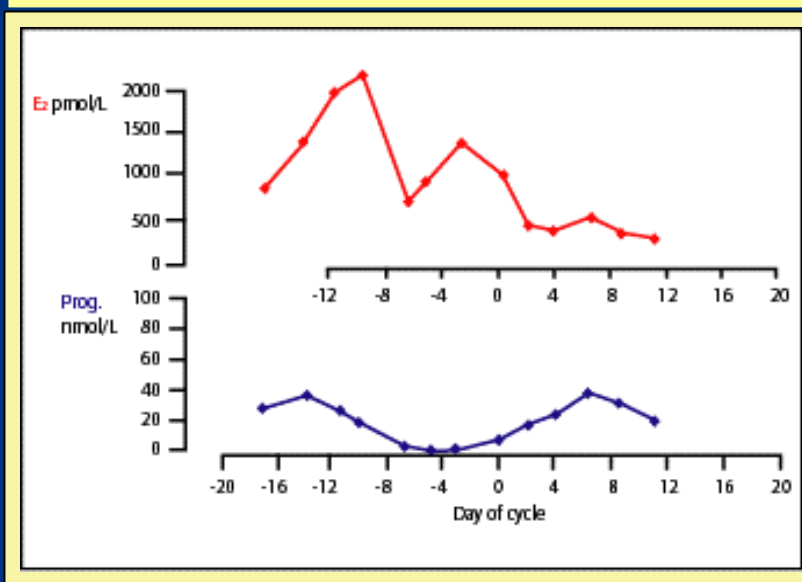
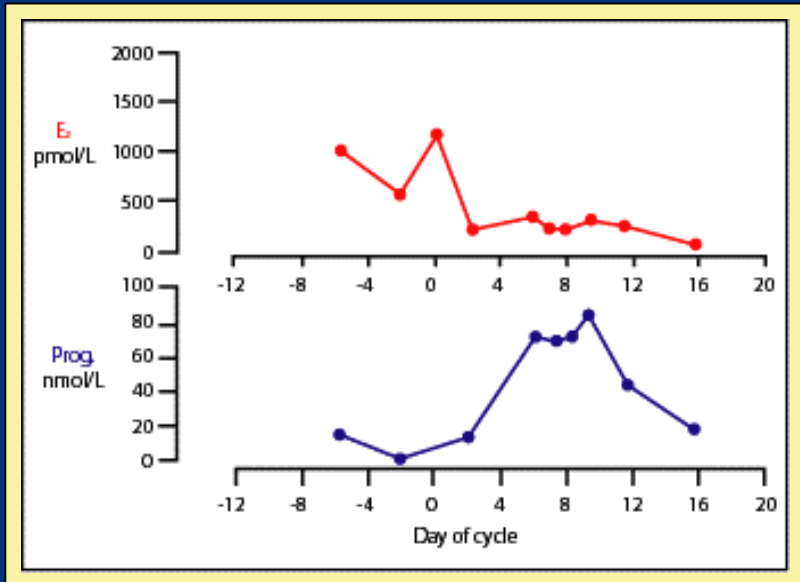
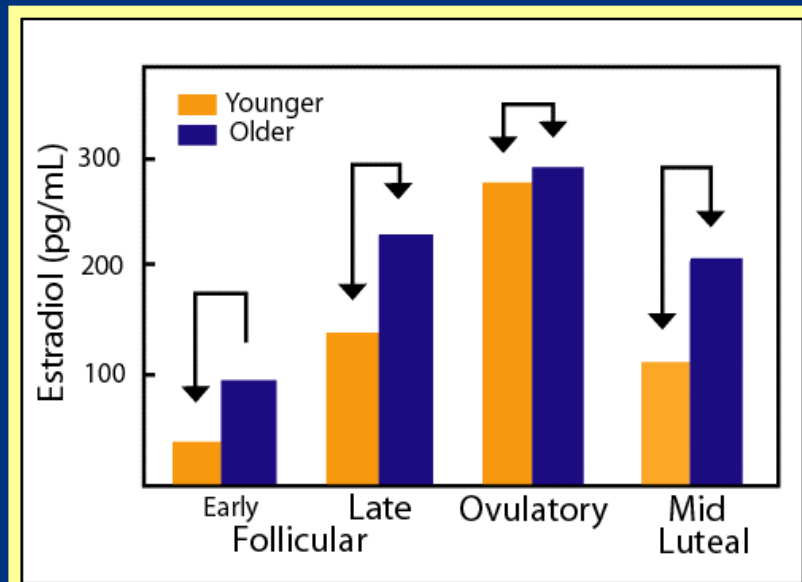
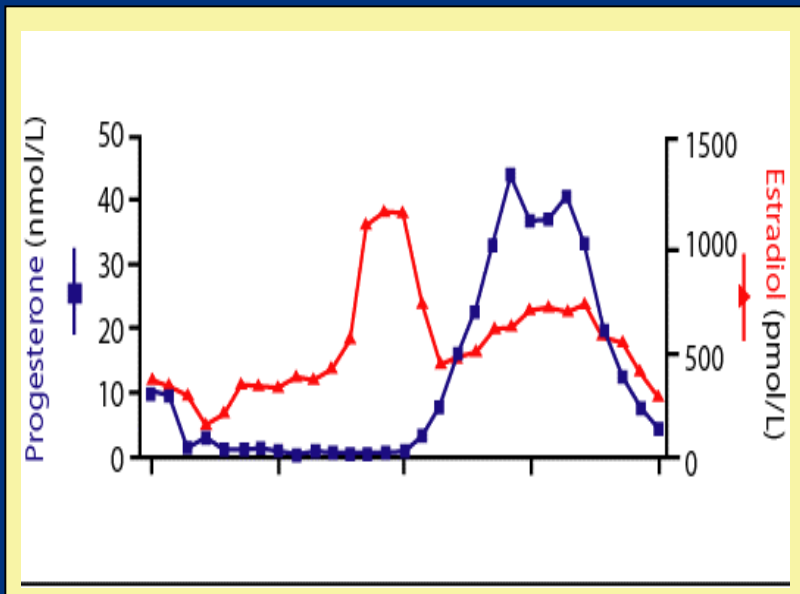
## Preclinical

- **Pharmacology Characterization:**
  - Determines potential effects on body organs/systems
  - **Predicts therapeutic window for dosing**
  - Multiple biological models
    - -In vitro (cell culture, tissue slices, isolated organs)
    - -In vivo (various animal models)

# Different Estrogens Generate Different Dose Responses



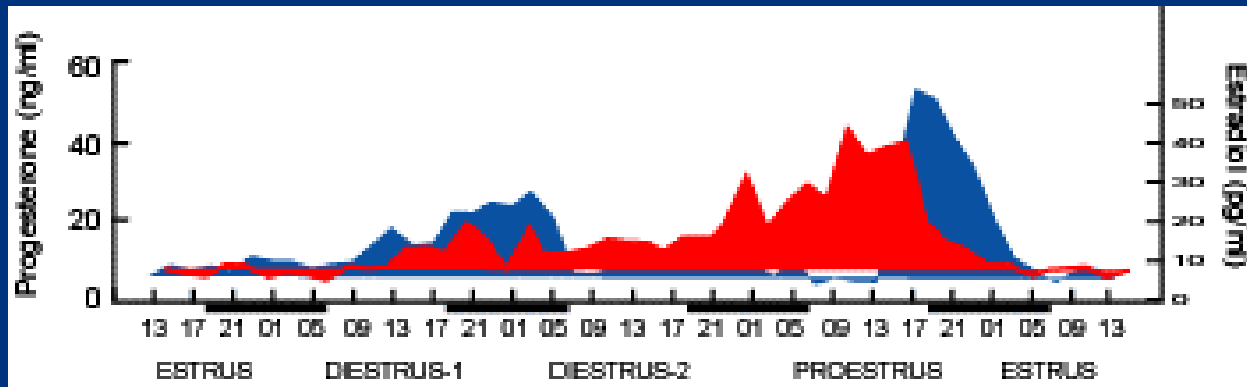
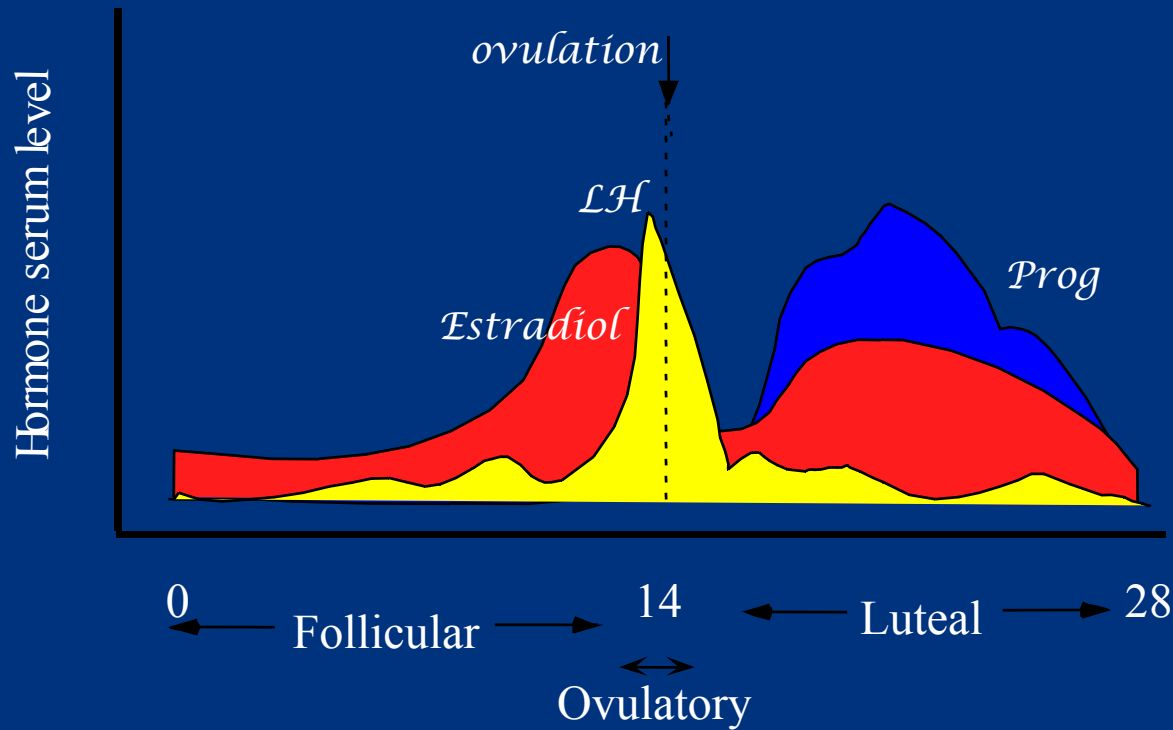
# Dosing of E2 and P4 during Perimenopause



1. Groome NP, Illingworth PJ, O'Brien M, et al. *J Clin Endocrinol Metab* 1996;81:4:1401-1405

2. Buckler HM. The perimenopausal state and incipient ovarian failure. *Treatment of the Postmenopausal Woman: Basic and Clinical Aspects* 1999;2:47-60

# Dosing of E2 and P4 for Human versus Rat



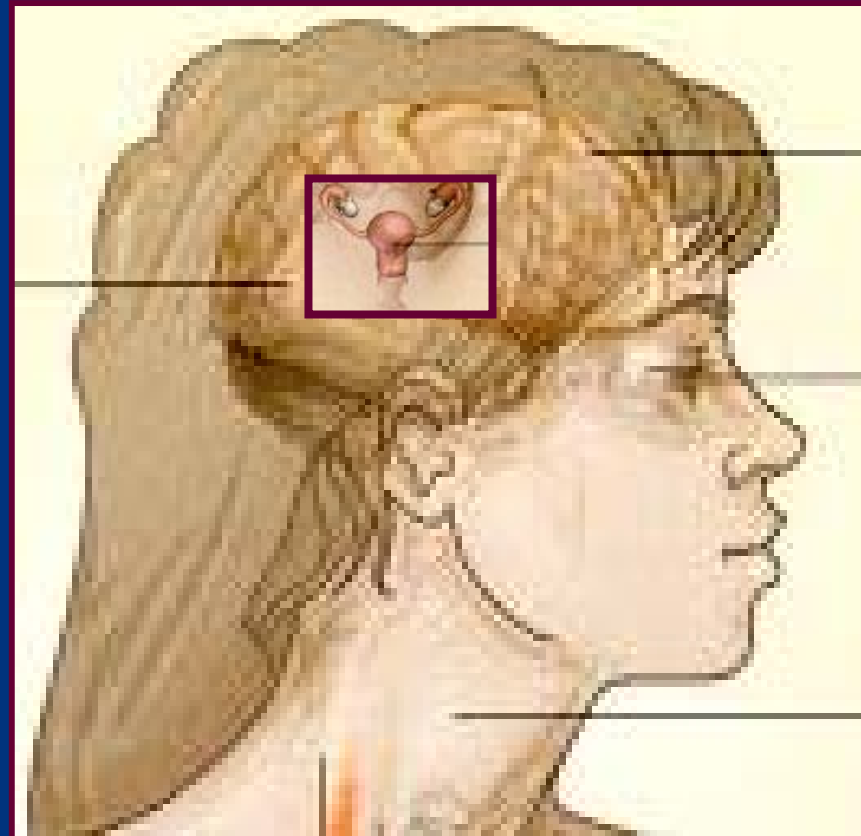
# Impact of Route Of Administration on Health Markers

**Table 2. Estrogen replacement.**

Liver protein target	Transdermal	Oral	Potential effects	Ref.
Angiotensin precursor	No change	↑	Sodium retention, vasoconstriction	(9)
C-reactive protein	No change	↑	Risk for atherosclerosis, ischemic stroke	(18, 49)
GH-induced IGF-1	No change	↓	Decrease in lean body mass	(49)
Serum binding proteins	No change	↑	Change in hormone bioavailability	(9)
Activated protein C	No change	↑ Resistance	Increased blood coagulation	(50)

From: Turgeon, J.L., McDonnell, D.P., Martin, K.A. & Wise, P.M. Hormone Therapy: Physiological Complexity Belies Therapeutic Simplicity. *Science*, 304:1269-1273, 2004

# Hormone Therapy Formulation: Is the Uterus a Predictor of Brain Response To Progestogens?





# FDA Regulatory Process: Biologics/Drug Development

## Preclinical

- **Pharmacology Characterization:**
  - Determines potential effects on body organs/systems
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# Unresolved Issues for the Brain

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- **Receptor and Ligand Properties**
  - Estrogen and Progesterone Receptors in Brain?
- **Dose**
  - Goldilocks Effect or Broad Spectrum?
- **Route of Administration**
  - Are plasma markers predictive of brain response?
- **Formulation**
  - Which progestogens and which estrogens are optimal and in what ratio and in what regimen?
- **Timing of therapeutic intervention**
  - Can peripheral mitochondria provide a window into the brain?

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