

# Women's Fracture Prevention: Co-therapy of an Anti-resorptive Osteoporosis Therapy with Progesterone

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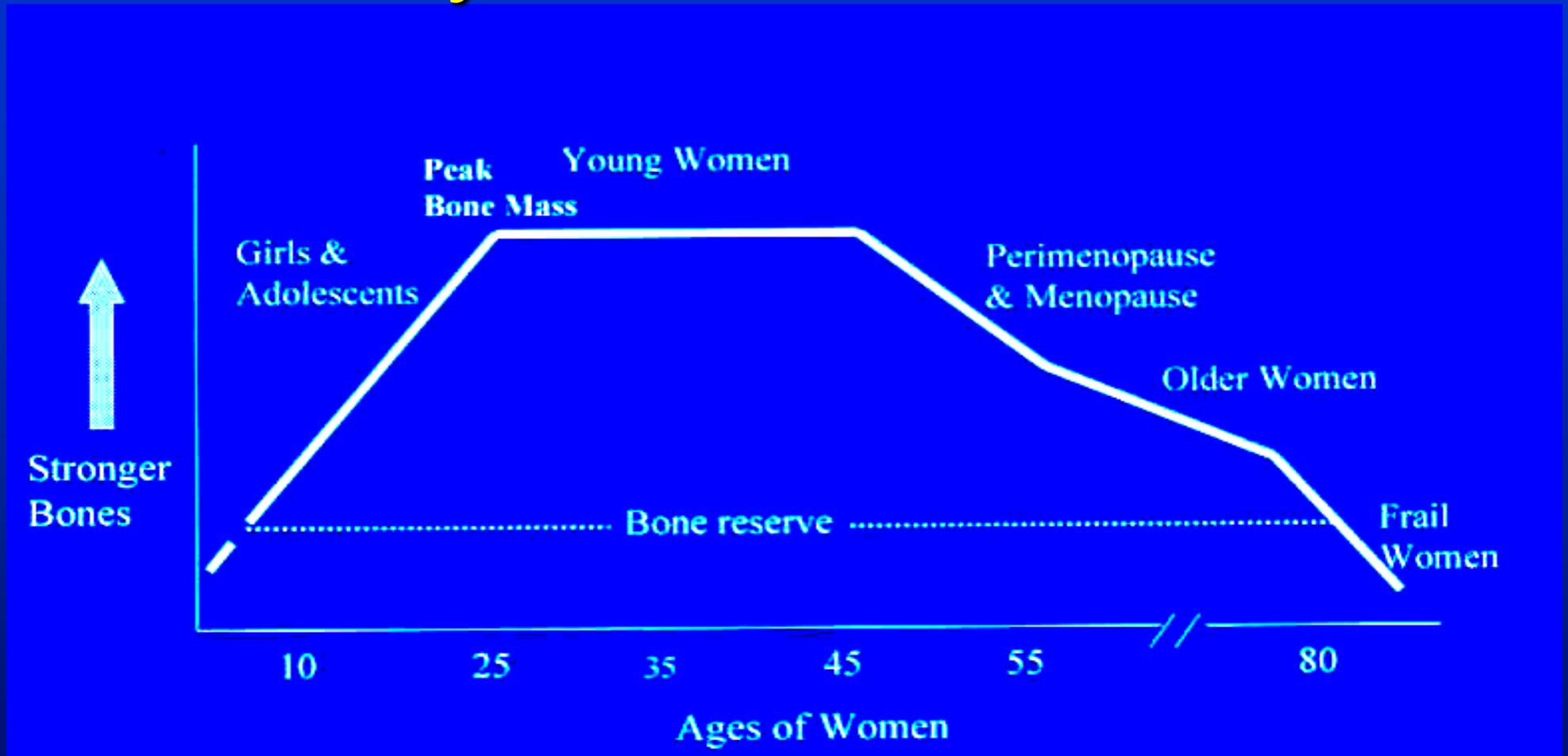


# Progesterone with Antiresorptives

## What we will learn:

- ◆ How does bone **renovation**/remodeling work?
  - ◆ Linkage between bone loss and formation
  - ◆ Different rates of work and jobs for different cells
- ◆ How are women's hormones (estrogen and progesterone) related to bone remodeling?
- ◆ Could progesterone added to anti-resorptive therapy help prevent fractures?

# Life Cycle of Bone—Women



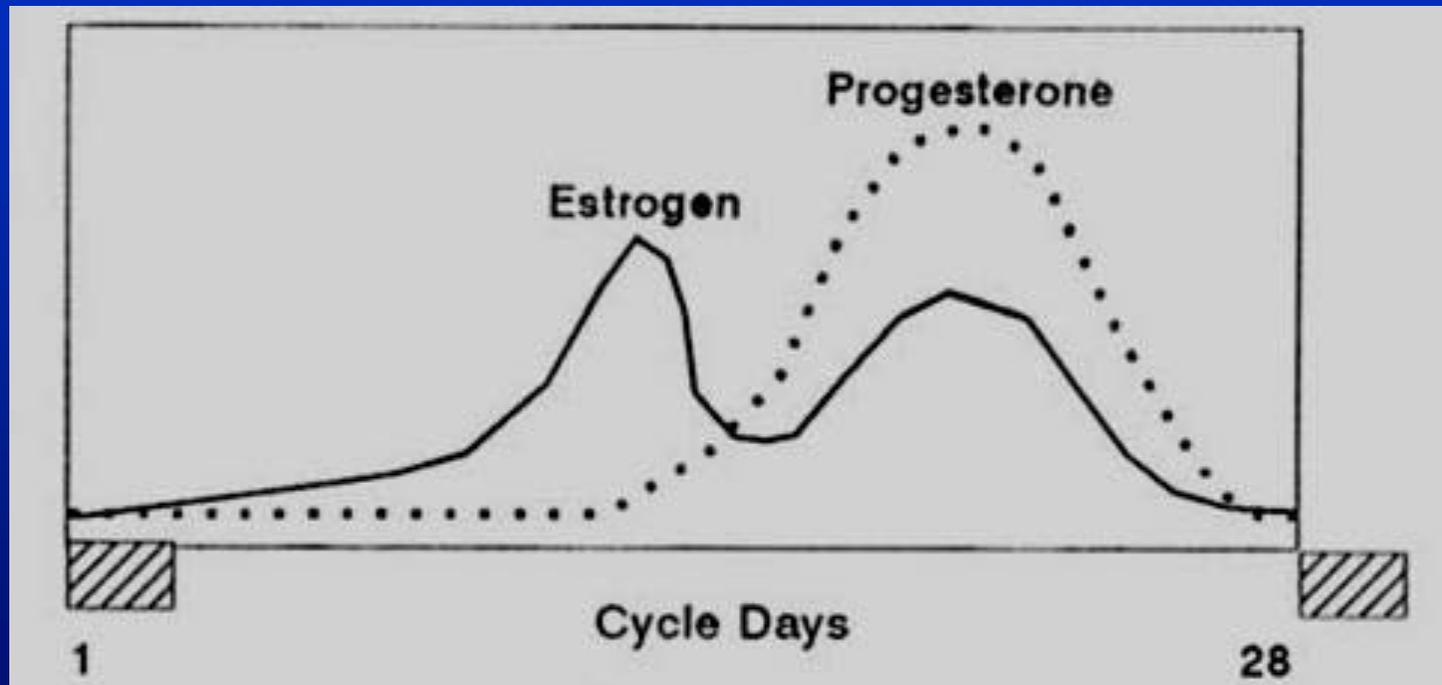
Note that, with normal peak bone mass and its maintenance to perimenopause, women don't have increased risks for fractures until their 80s

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# Overview of Progesterone and Estrogen

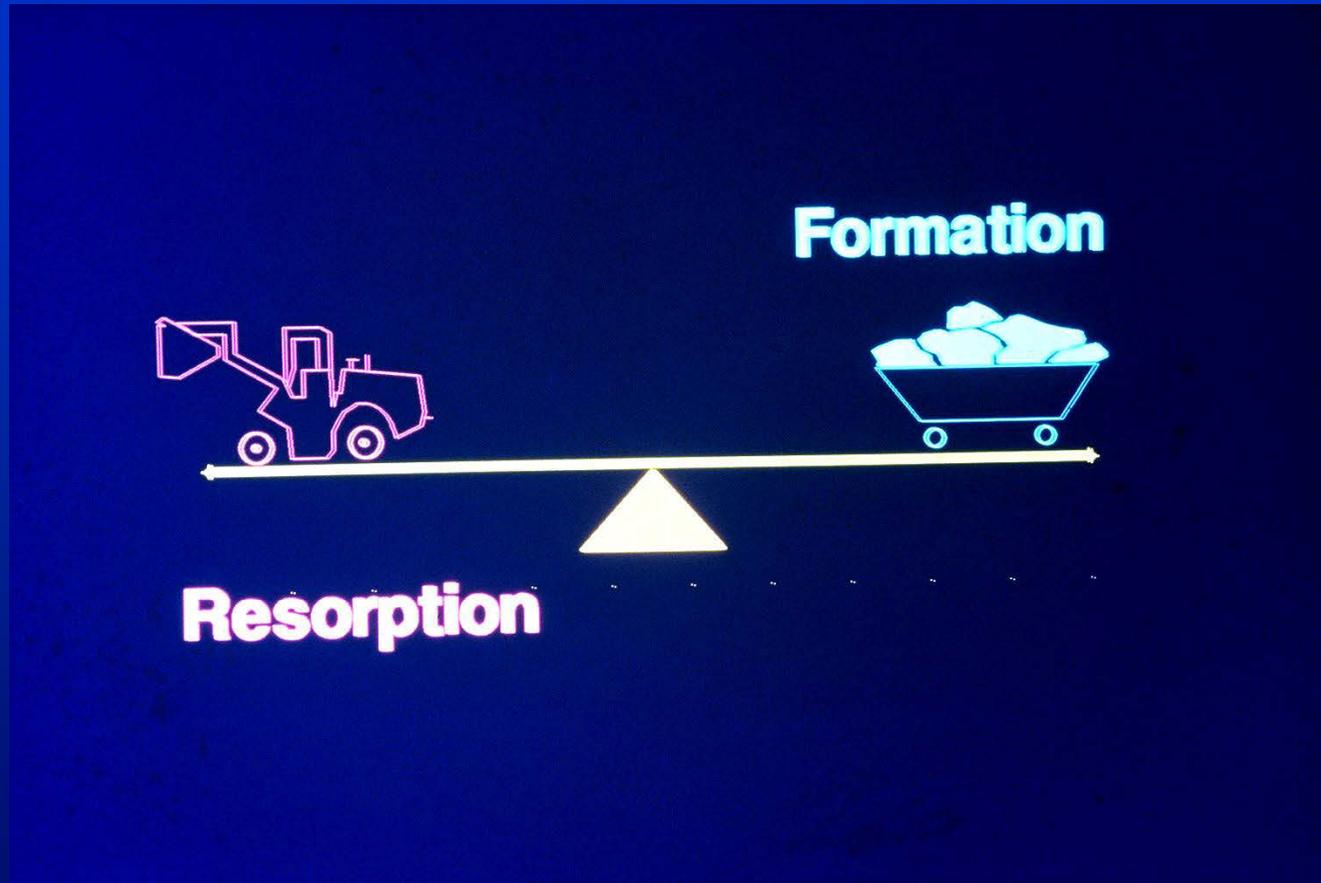


Flow

Flow

The “Estrogen Deficiency”  
(menopause) idea  
led to the importance of bone  
loss-stopping therapies for  
Osteoporosis

# Bone Remodeling BALANCE



# Bone Remodeling (renovation)

**Bone resorption**

**Bone formation**

haematopoietic stem cell

mesenchymal stem cell

pre-osteoclast

pre-osteoblast

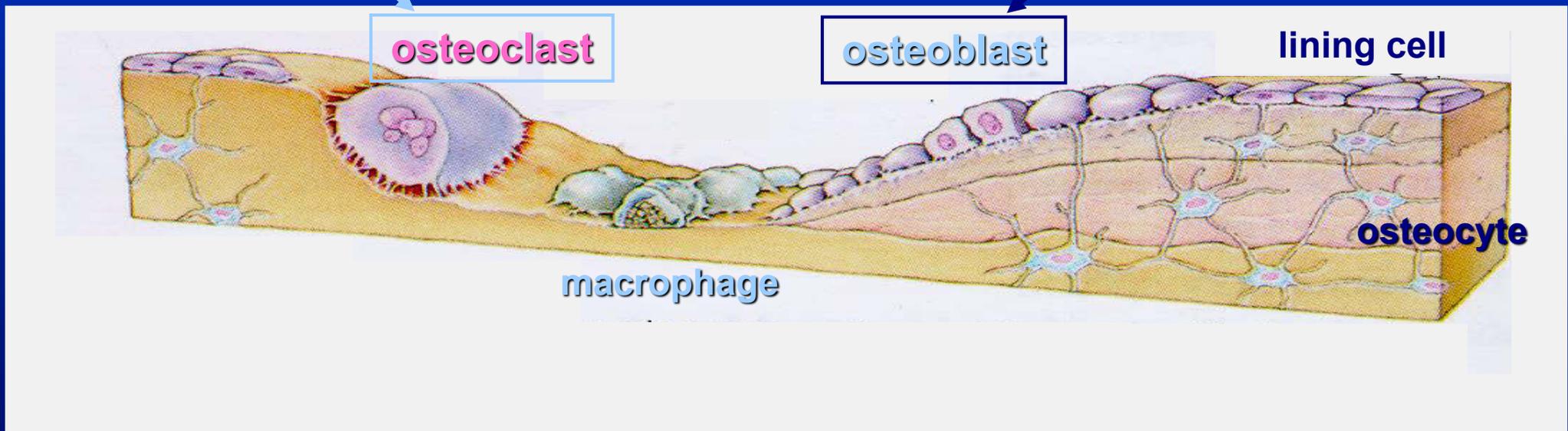
osteoclast

osteoblast

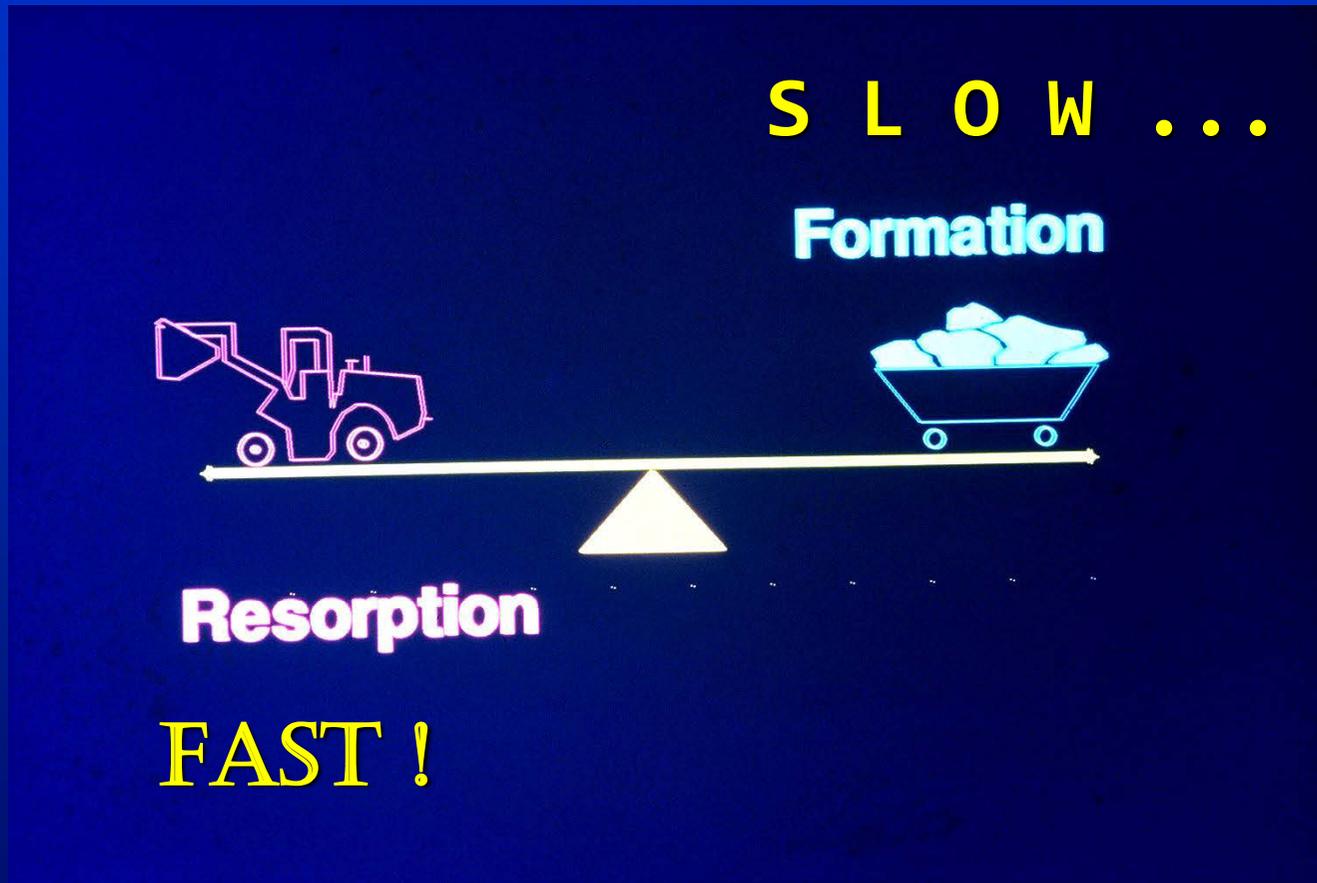
lining cell

osteocyte

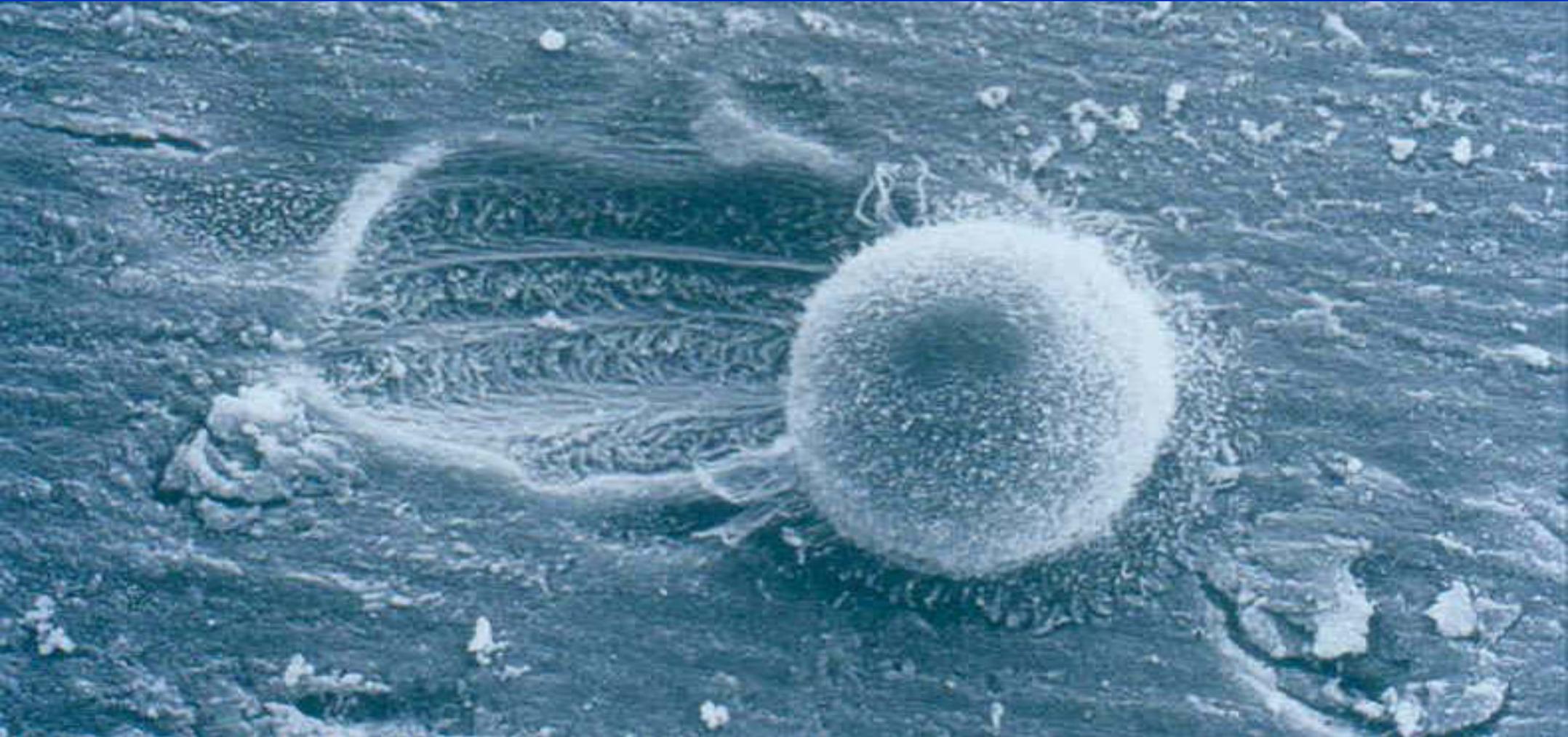
macrophage



# Bone Remodeling BALANCE



# Osteoclast—Resorption



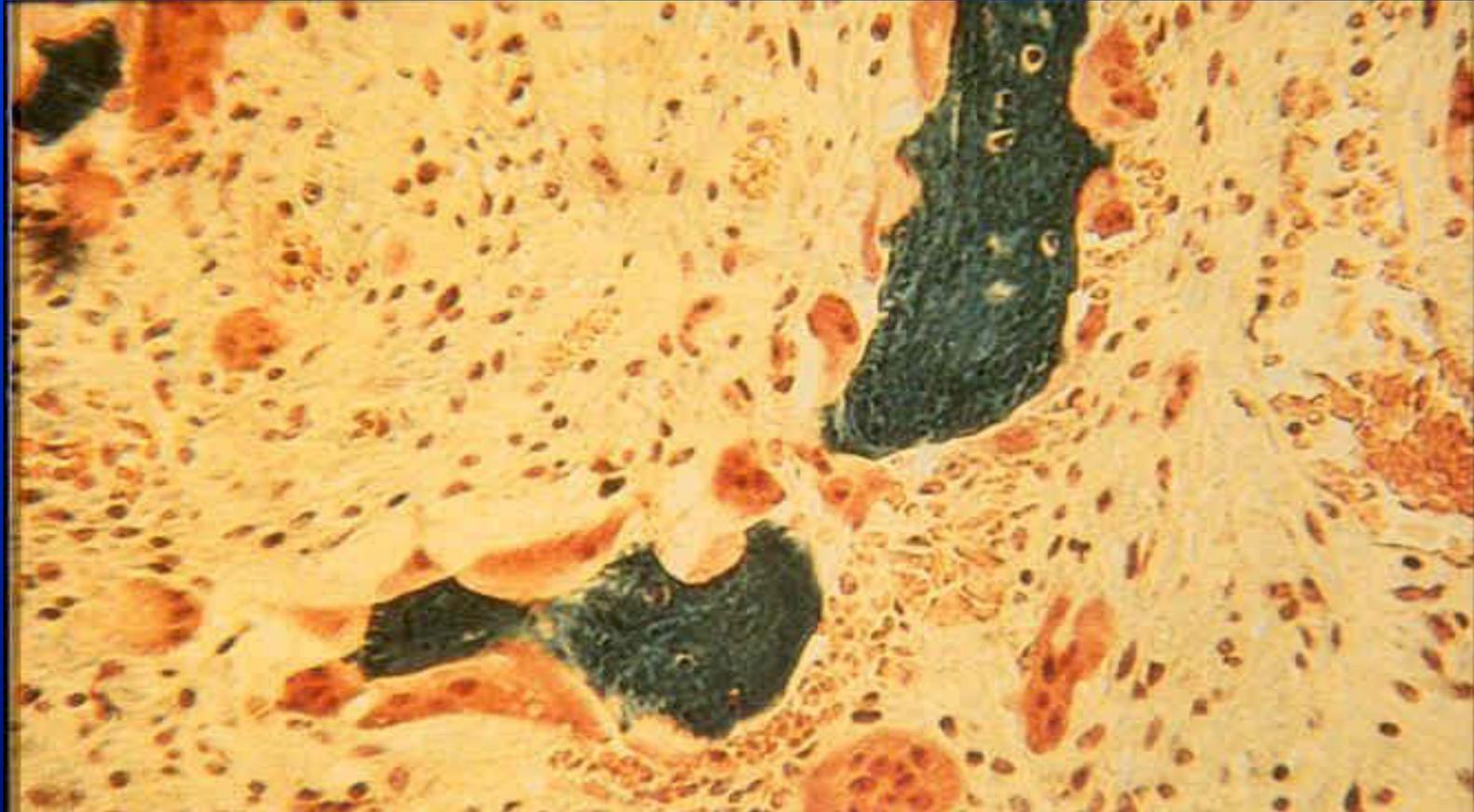
# Trabecular perforation—photomicrograph



Dempster DW [J. Bone Miner. Res. 1986; 1: 15](#)

# Trabecular perforation—microscopic

● is  
bone



Eriksen EF Bone Histomorphometry ASBMR 1994, Raven Press

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**Bone formation**

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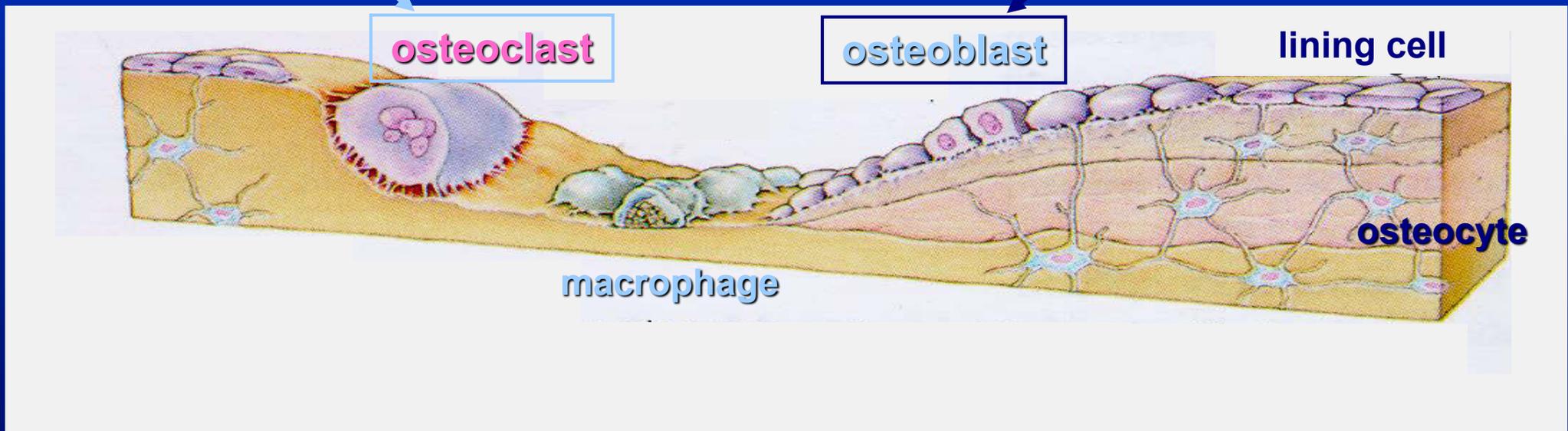
osteoclast

osteoblast

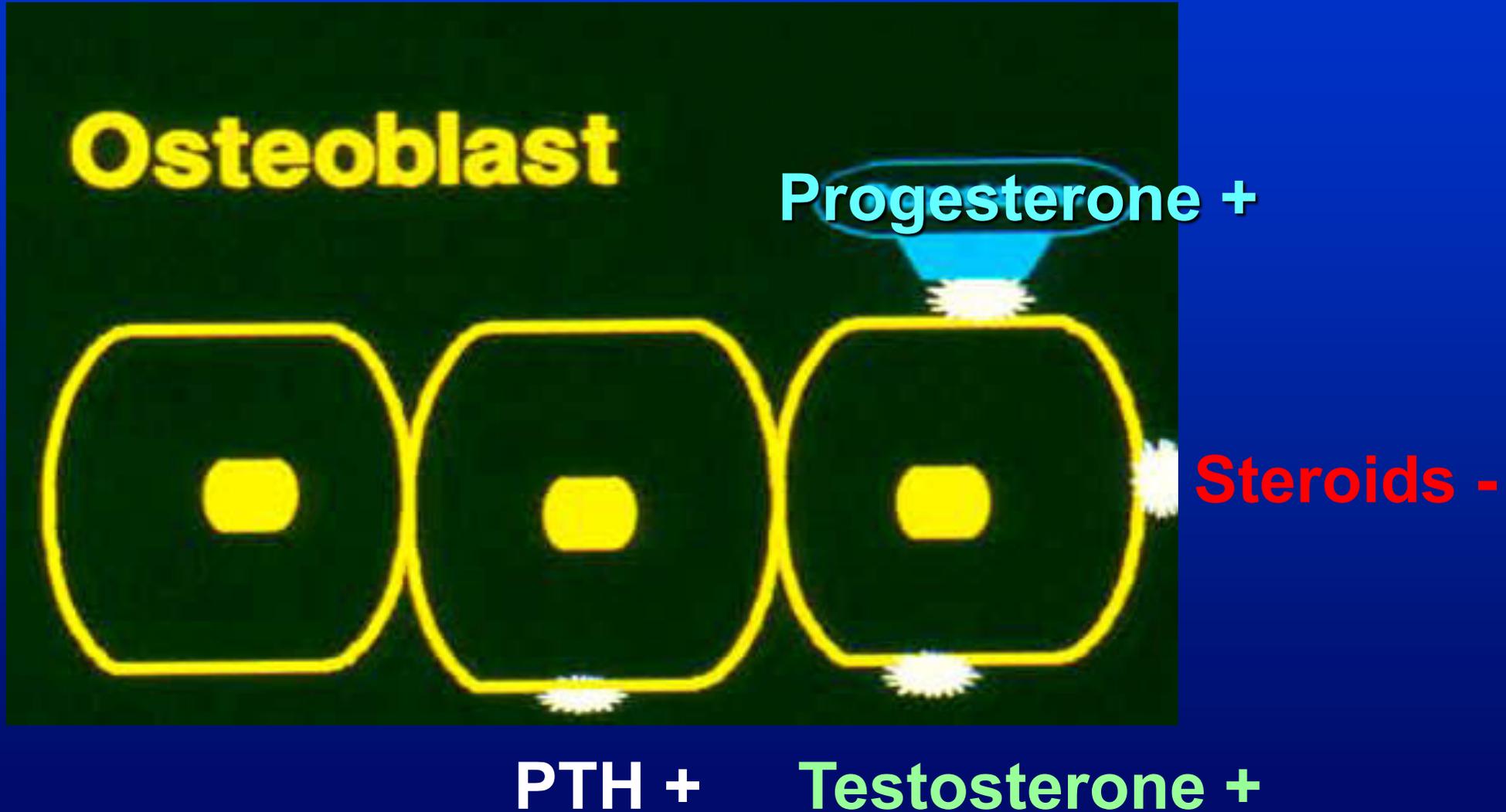
lining cell

osteocyte

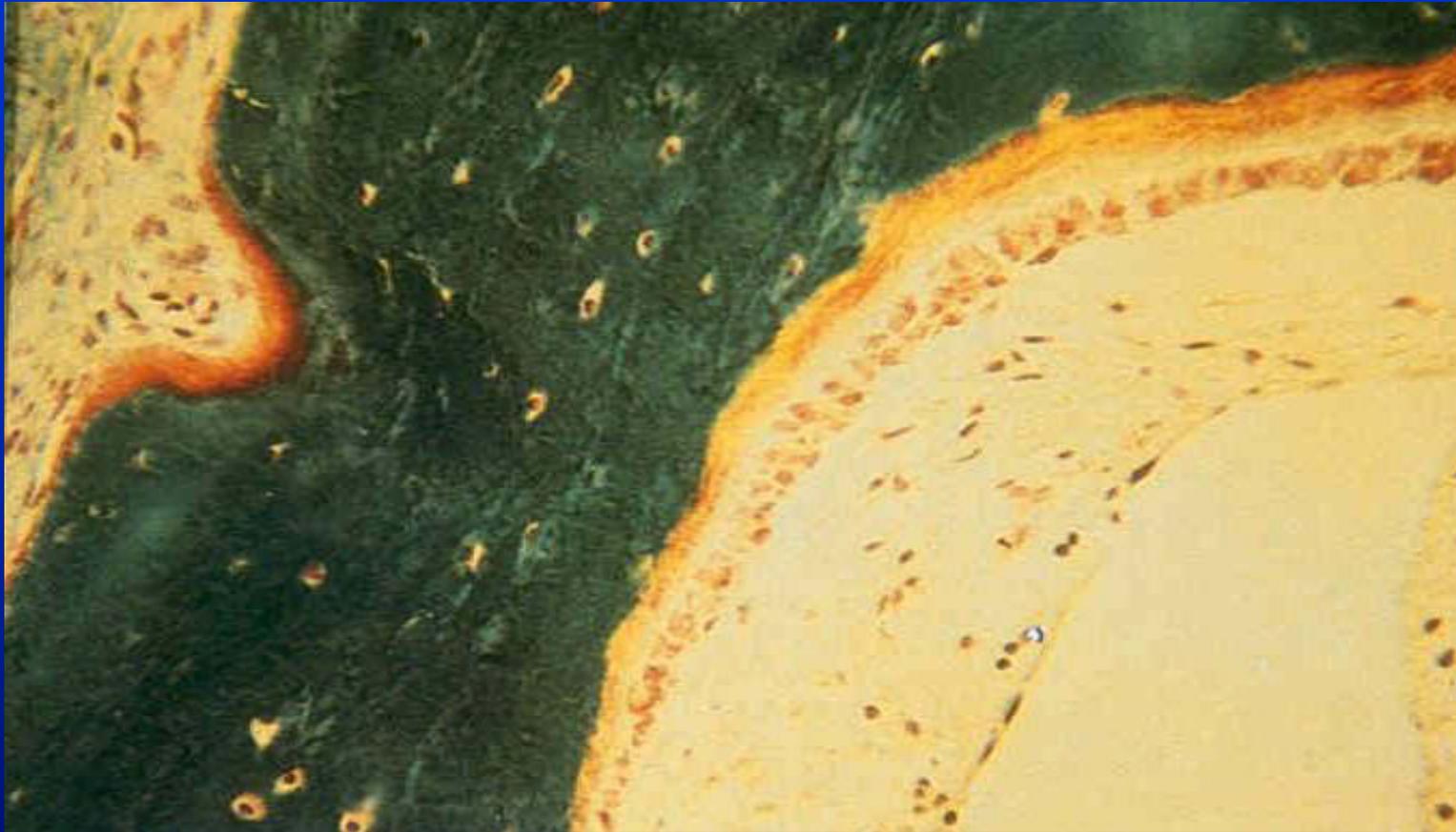
macrophage



# Osteoblast—Bone Formation



# Bone remodeling—formation



←osteoid

←osteoblasts

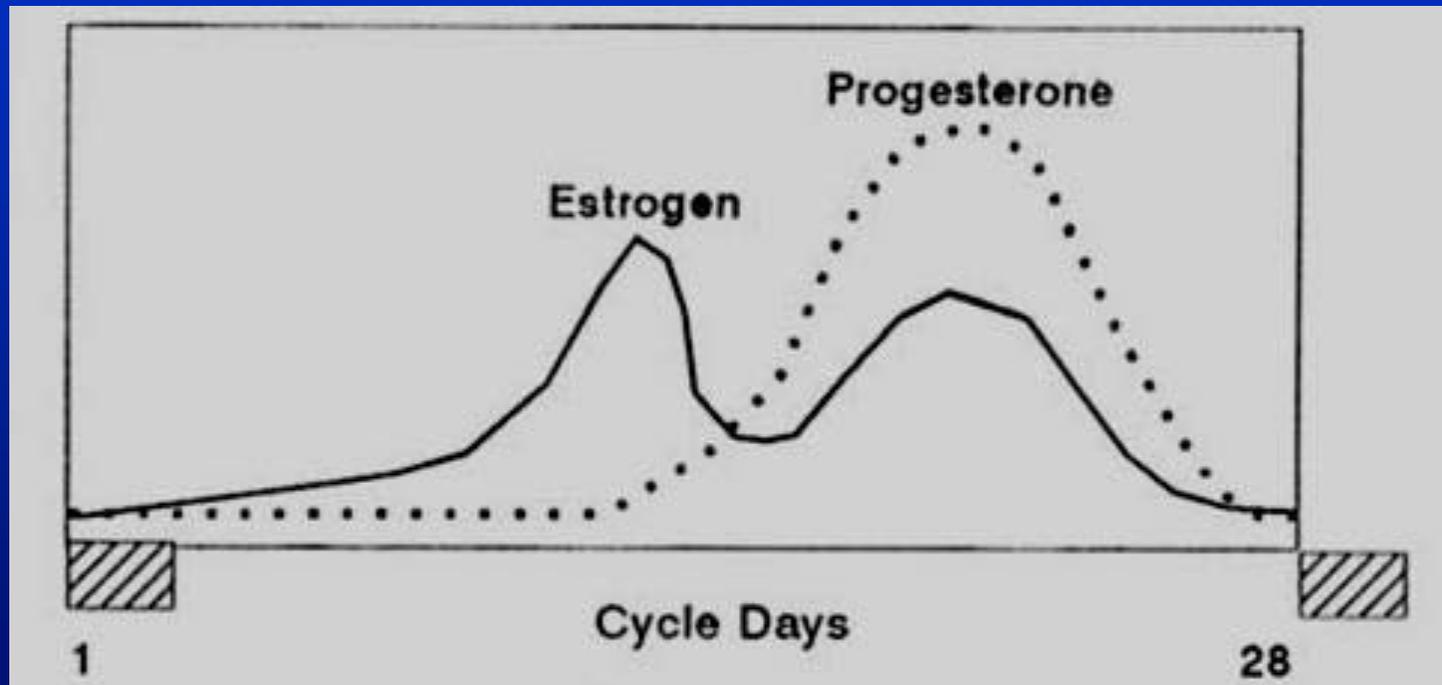
Eriksen EF *Bone Histomorphometry* ASBMR 1994, Raven Press

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- ◆ Could added progesterone therapy help prevent fractures? *Will progesterone plus anti-resorptive therapy stop its long-term use from being bad for bones?*

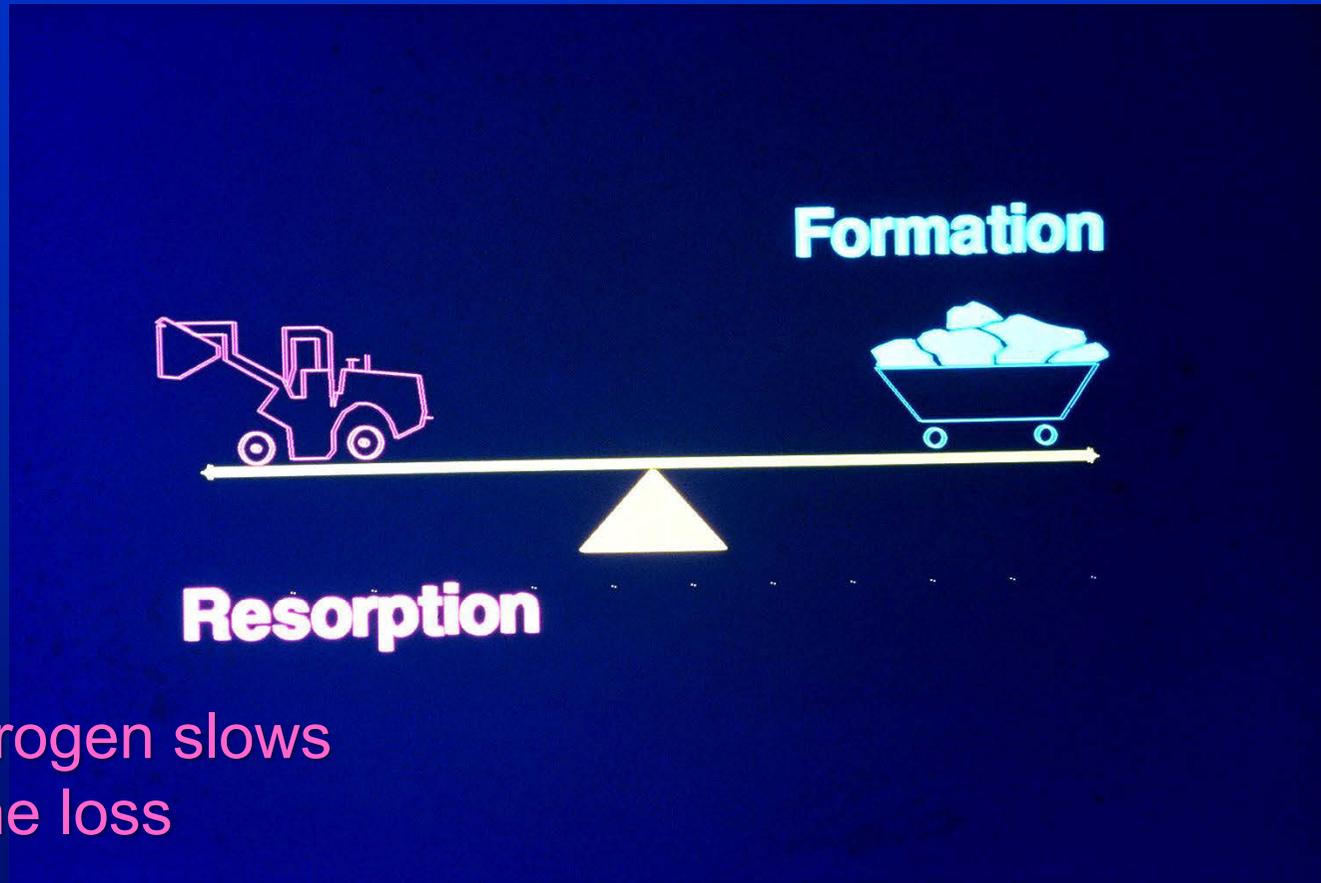
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Flow

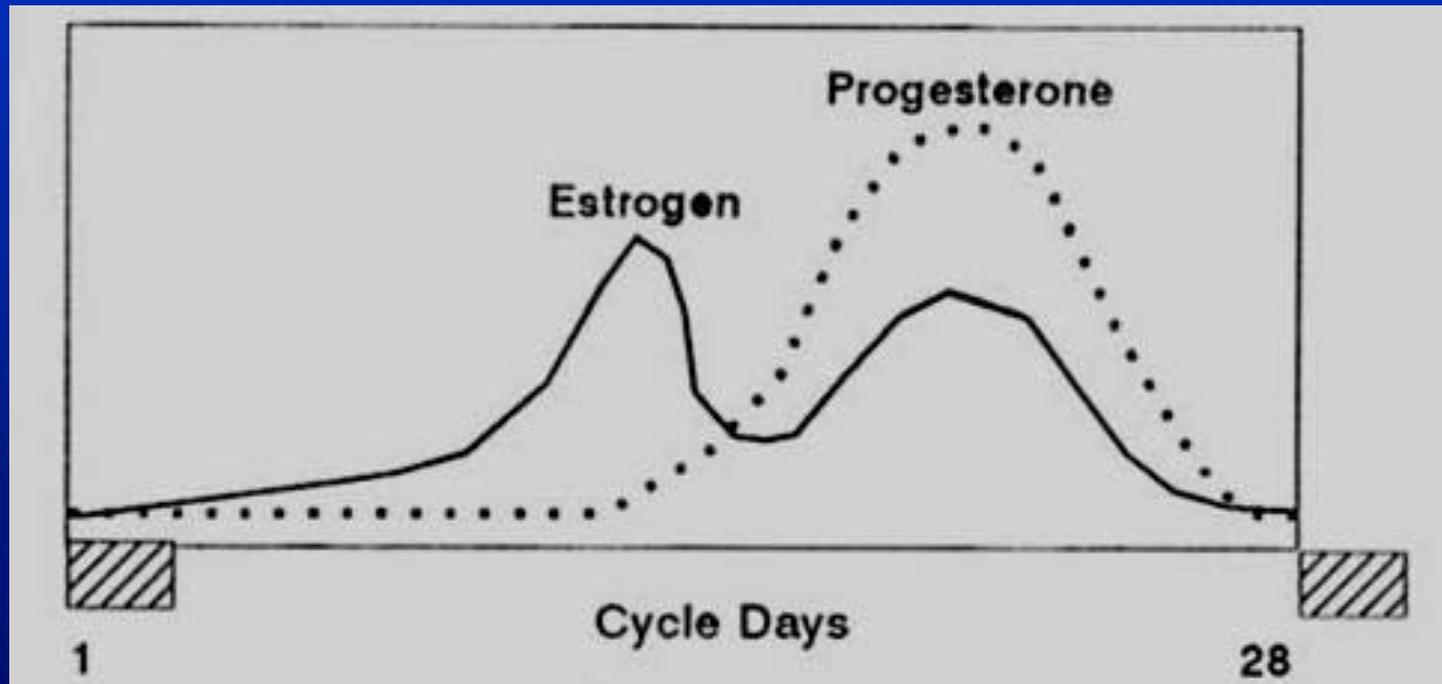
Flow

# Bone Remodeling BALANCE



# Premenopausal Bone Remodelling

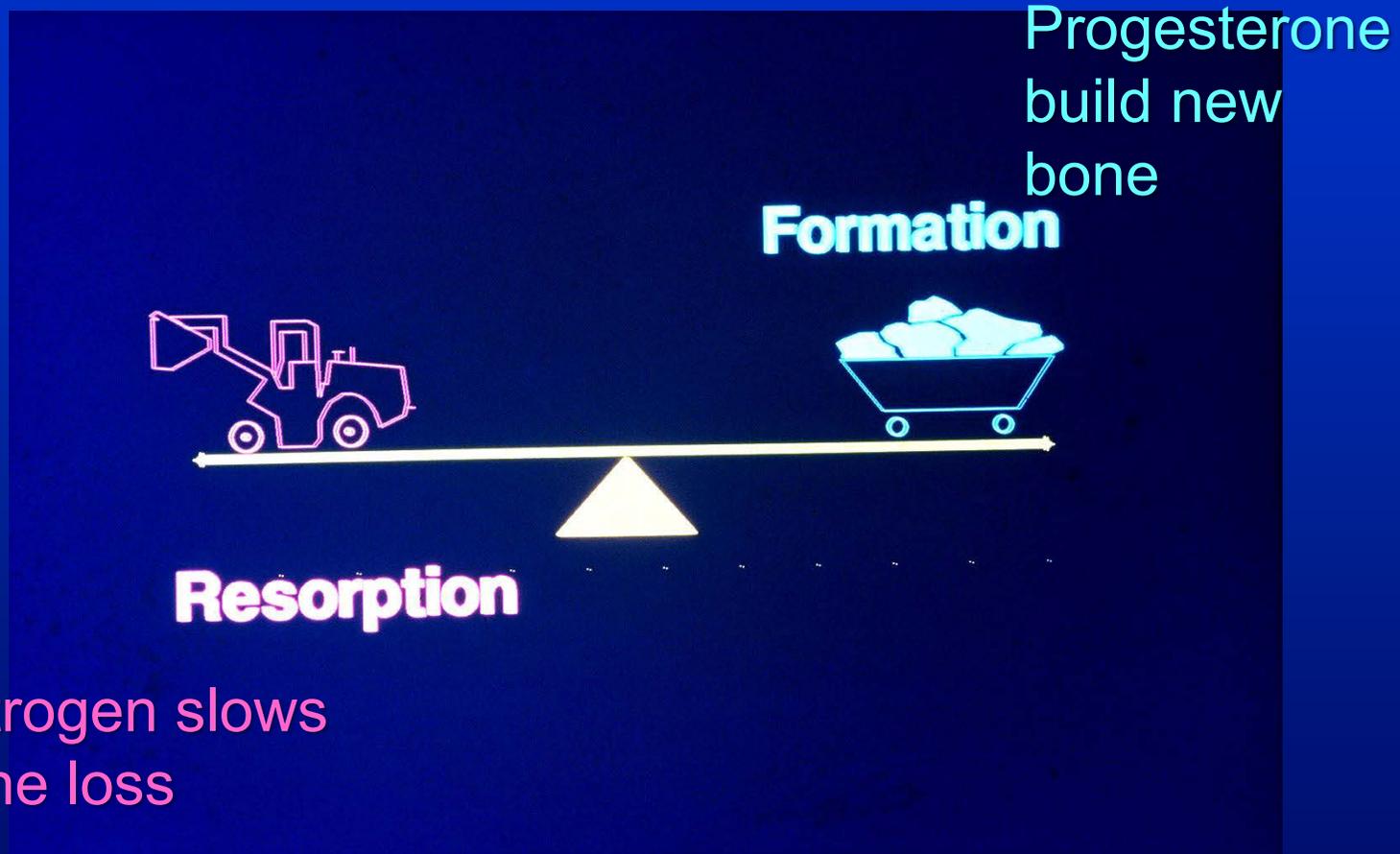
↓ Estrogen peak



Flow

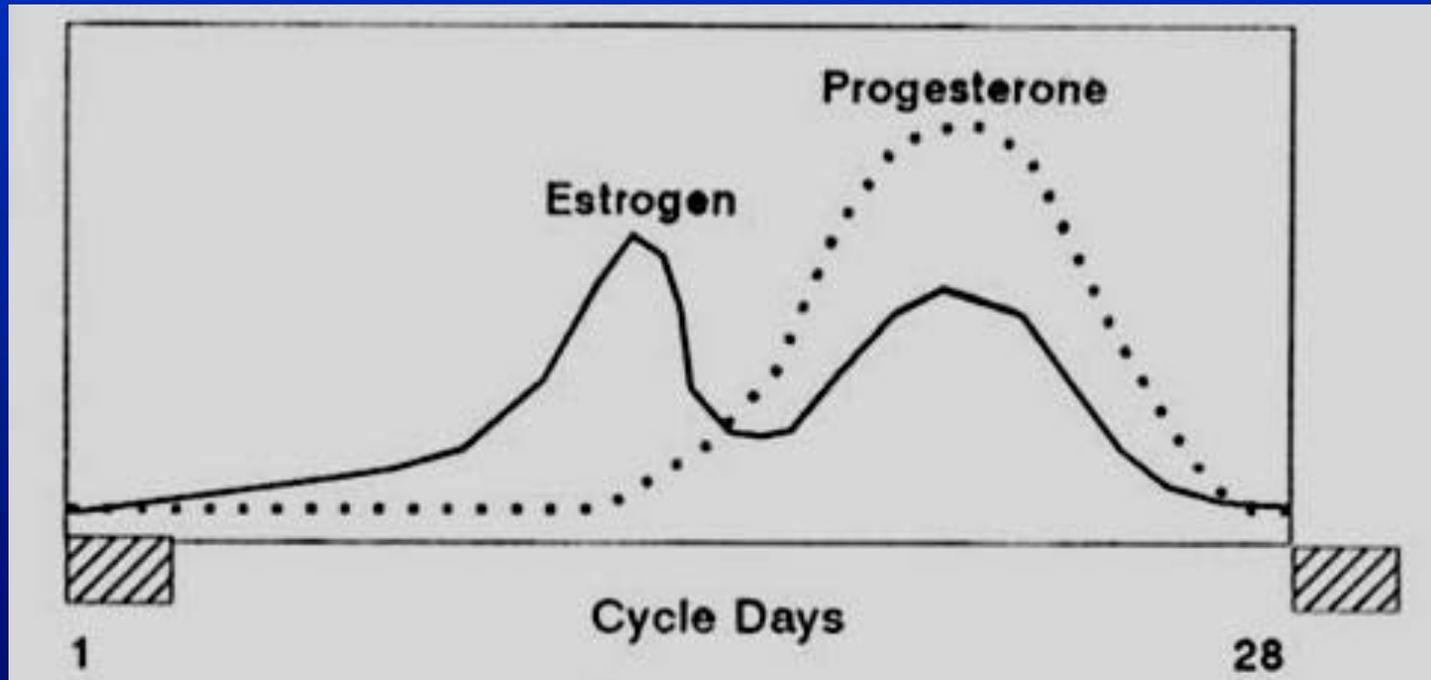
Flow

# Bone Remodeling BALANCE



# Premenopausal Bone Remodelling

↓ Luteal Phase ↓

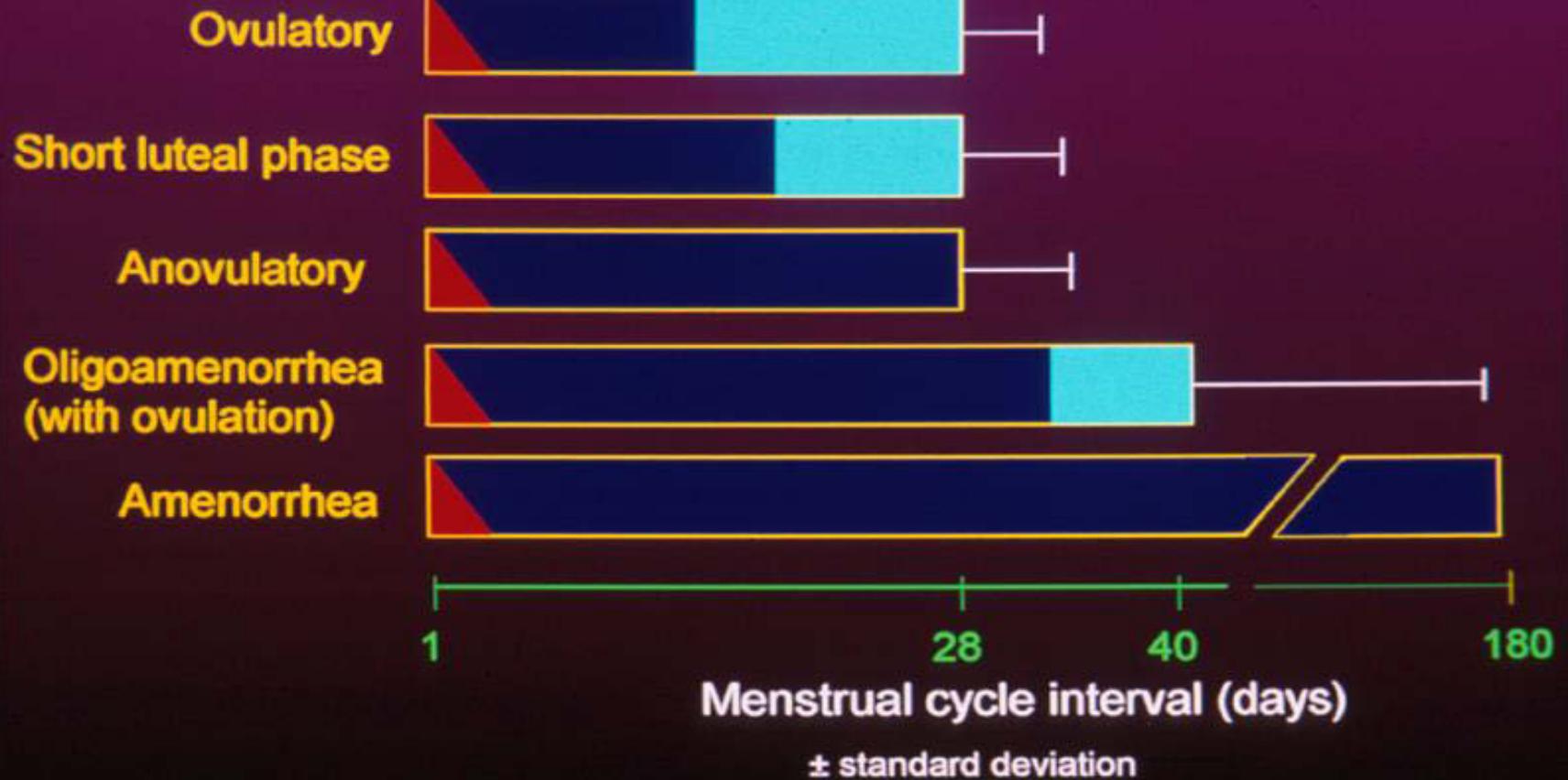


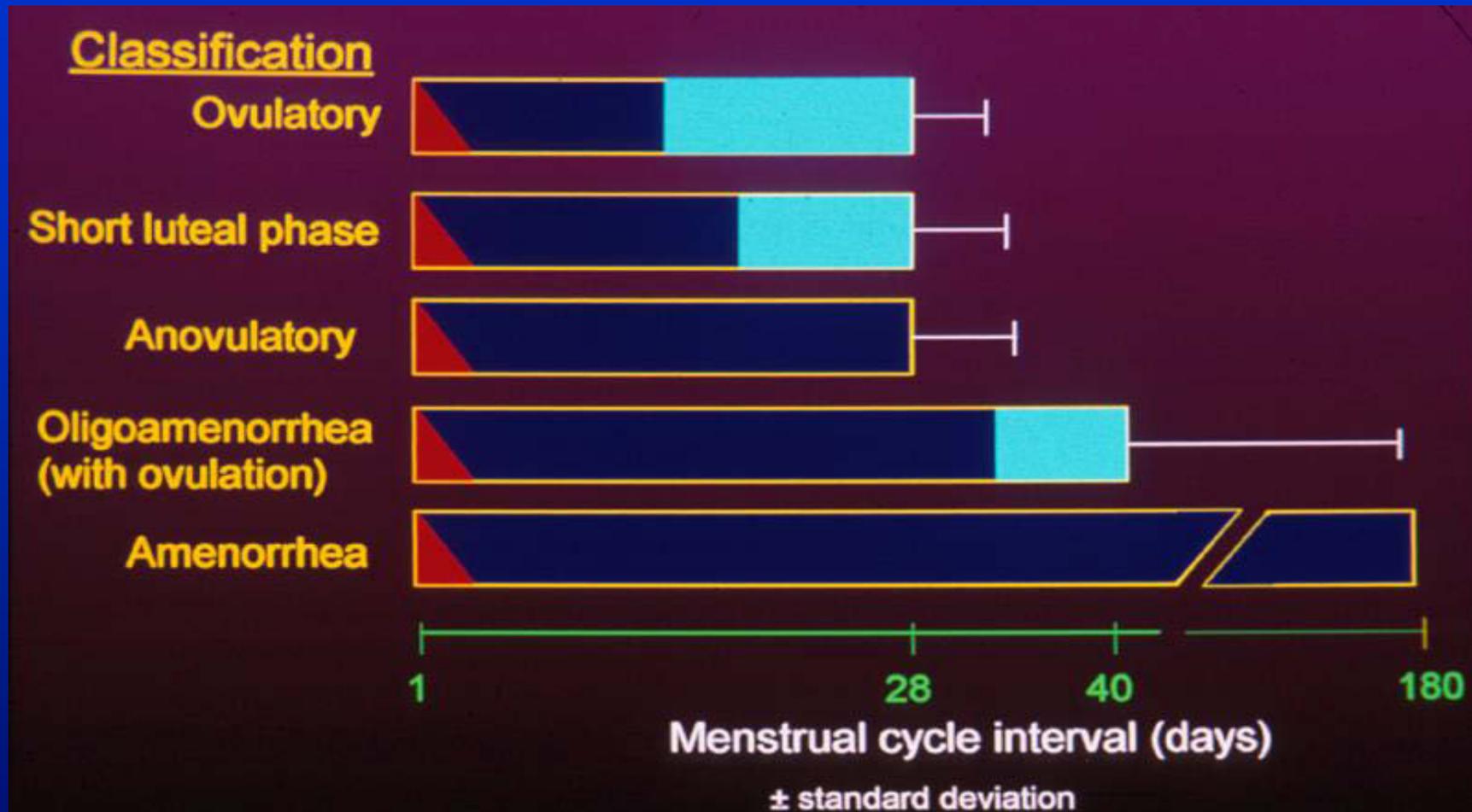
Luteal phase  
length  
= 10-16 days

Flow

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**Classification**





Menstrual cycle disturbances in young adulthood associated with increased later fractures

# Prospective Ovulation Cohort

Prospective observational study in 66 women

All premenopausal, ages 20-42, 18.5-25 BMI

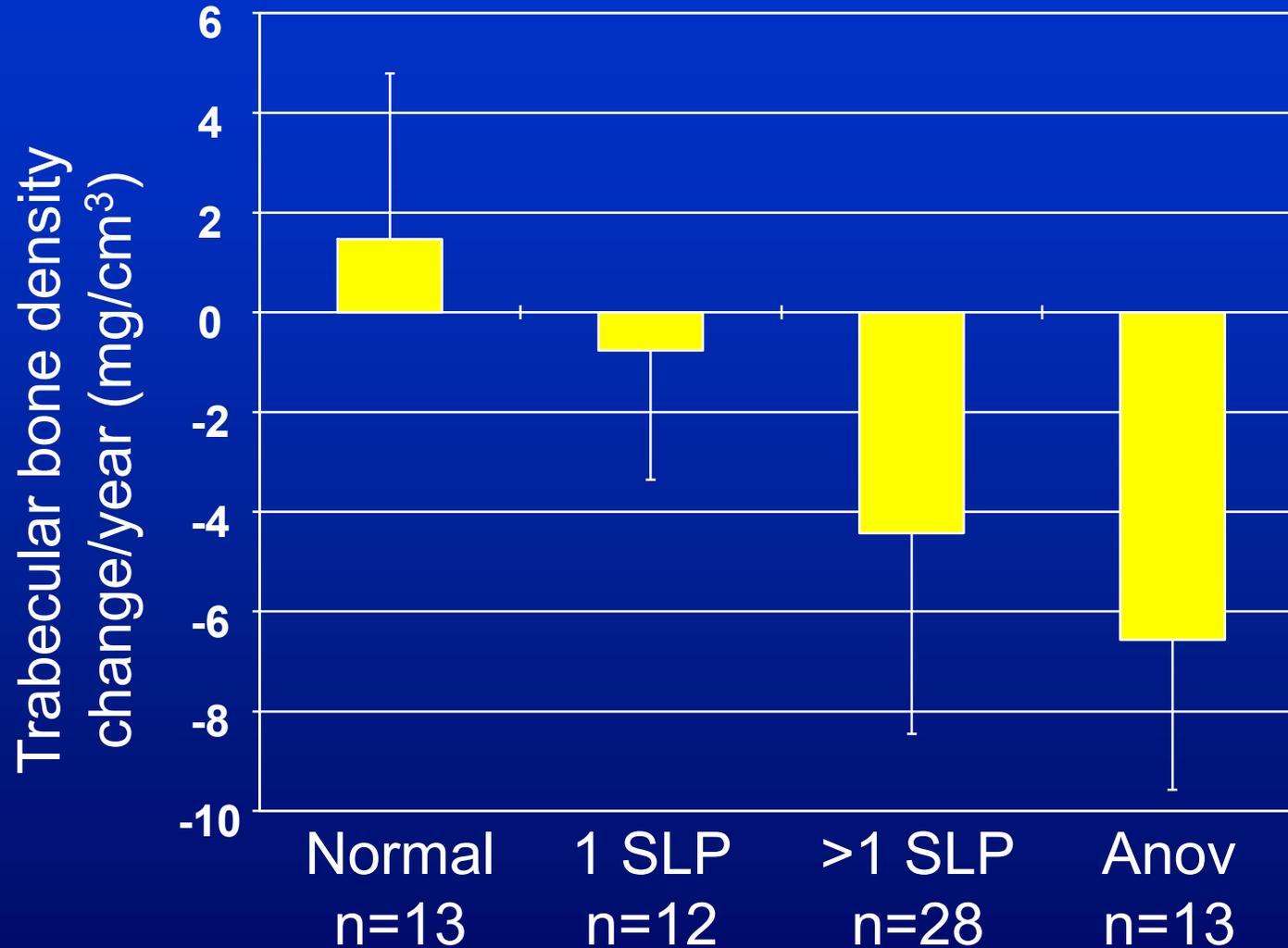
**Varying exercise habits** —normal activity to training for and running a marathon

Required to have regular cycles AND normal length luteal phases on 2 consecutive cycles

QCT bone change—by ovulatory experience

Prior JC *New England J. Med.* 1990; 323:1221

# Prospective Ovulation Cohort



SLP =  
Short luteal  
phase

ANOV =  
anovulation

# Hormones in Bone Renovation

## positives

↓ Bone Loss

**Estrogen**—women  
& also in men

**Testosterone**—men

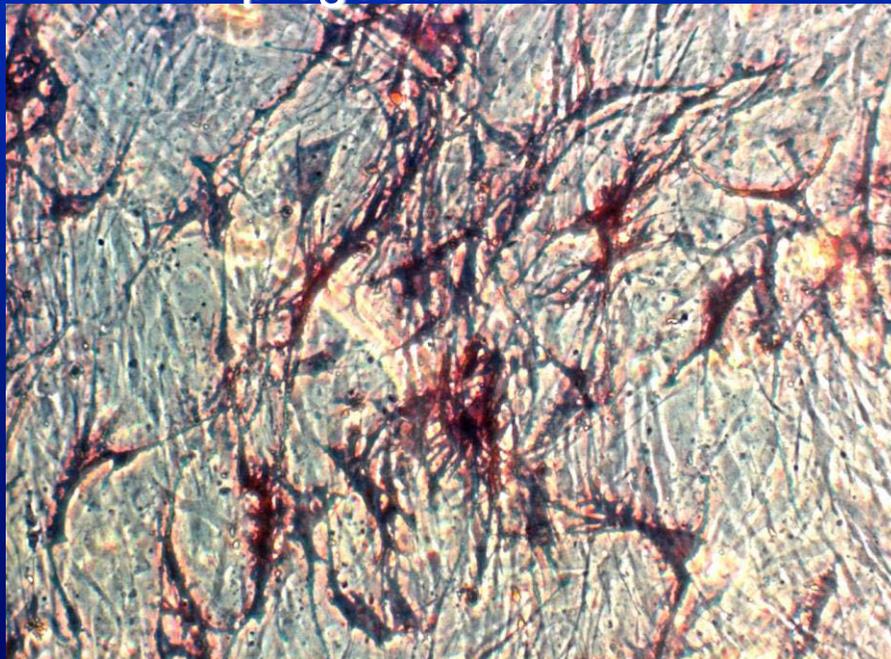
↑ New Bone

**Progesterone**—  
women

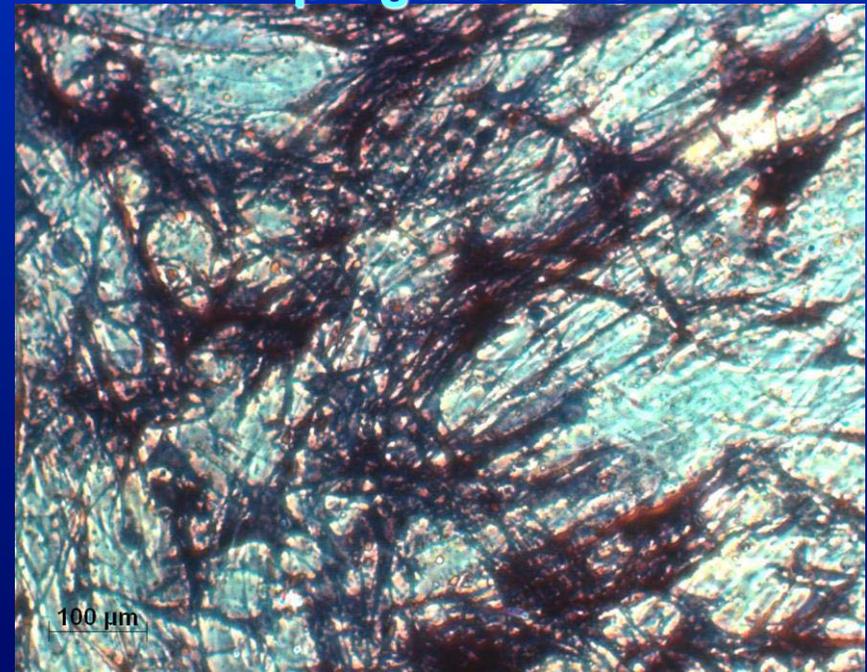
**Testosterone**—men

# Osteoblast cells in culture—bone formation assessed with Alkaline Phosphatase (ALP) *in situ* staining ALP = dark blue/black

28 days of incubation with **estradiol**, no incubation with progesterone ◀



28 days of incubation with **estradiol**, 21 days of incubation with  $10^{-7}M$  **progesterone**



# Premenopausal Bone Remodelling

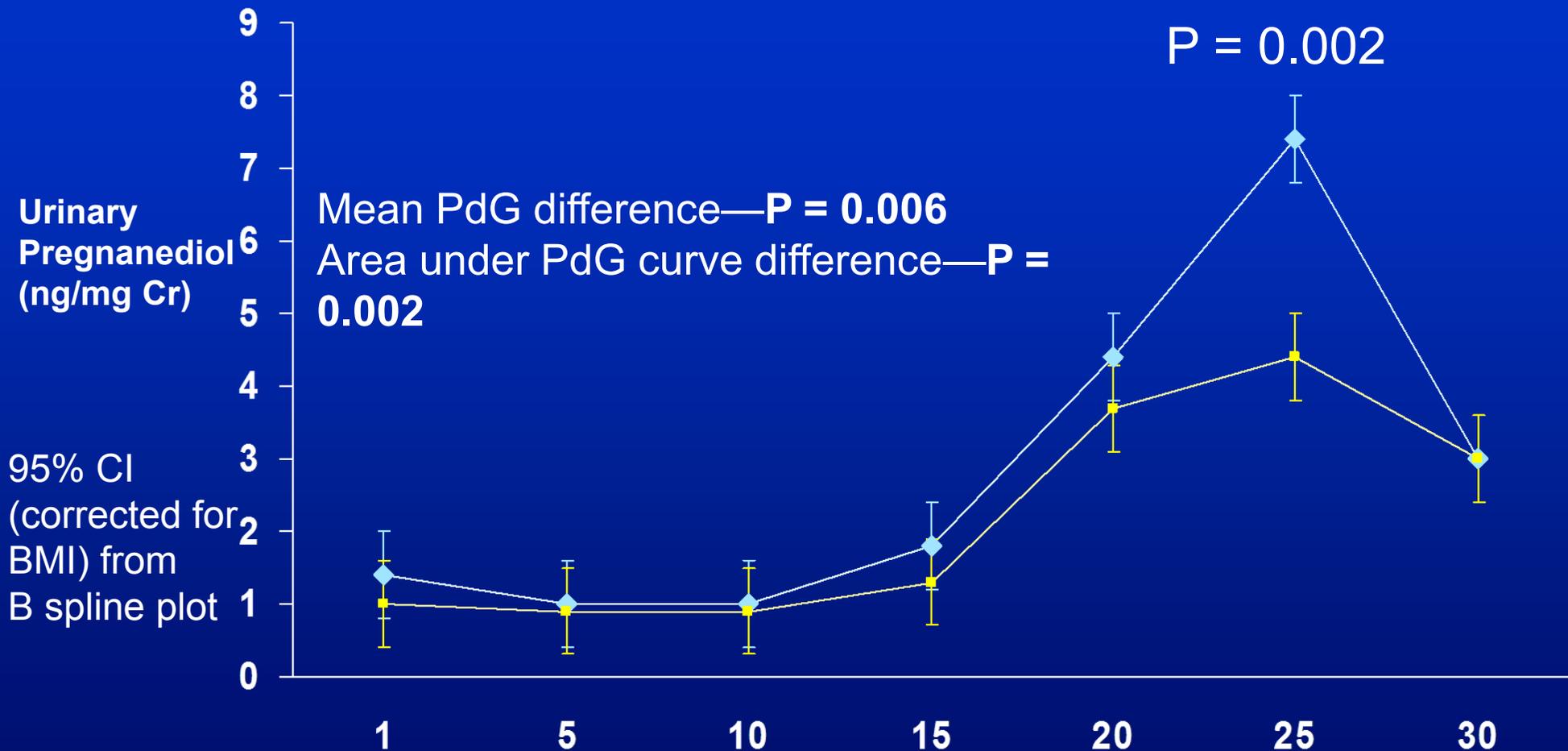
## Epidemiology links low BMD with Ovulatory Disturbances

- ◆ Population-based longitudinal study, women 25-45
- ◆ Nested case-control within the Michigan Bone Health Study, USA
- ◆ **N = 582**; bone mineral density (BMD) in the lowest 10% = **cases** vs. 3<sup>rd</sup> quartile = **controls**
- ◆ Daily urines **E** and **P** X 2 cycles
- ◆ Participation rate = 86%

Sower M-F *J. Bone Min. Res.* 1998;13:1191-1202

# Progesterone Levels in Urine in one cycle

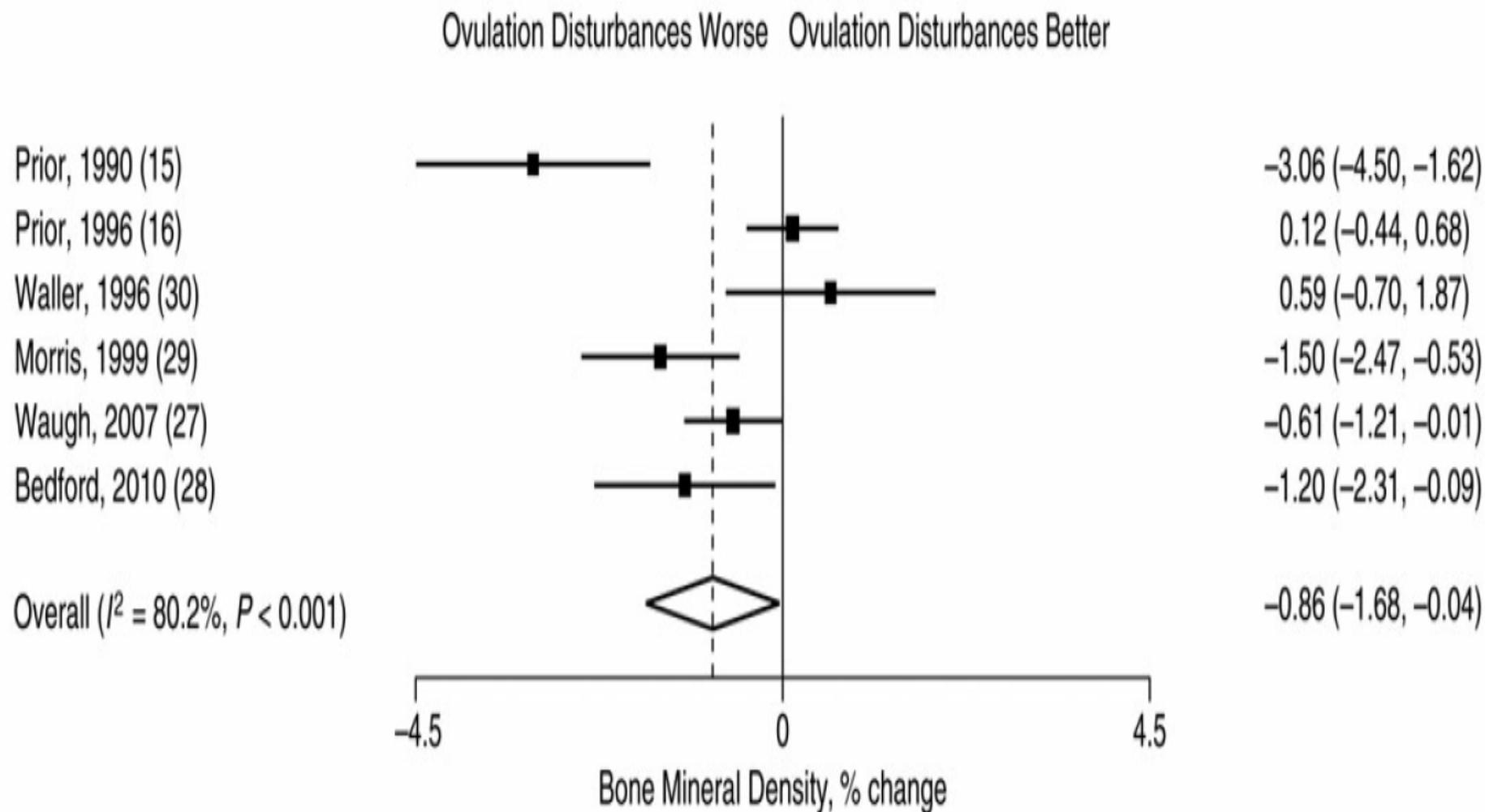
- ◆— Normal BMD n = 34
- Lowest 10th percentile BMD n = 31



Re-drawn from **MF Sowers *J Bone Min Res* 1998;13:1191**

First Author, Year (Reference No.)

Weighted Mean Difference (95% CI)



# Controlled Trial of Cyclic Progestin for Abnormal Cycles/Ovulation

**Purpose**—to prove that **progestin causes increased bone formation**

Normal weight, physically active, ages 20-40

Amenorrhea, oligomenorrhea, regular cycles with short luteal phases, or with anovulation

**61 women** completed a 1-yr randomized double-blind study of **cyclic progestin**/placebo with or without an additional 1000 mg calcium

# Cyclic Progesterone Therapy

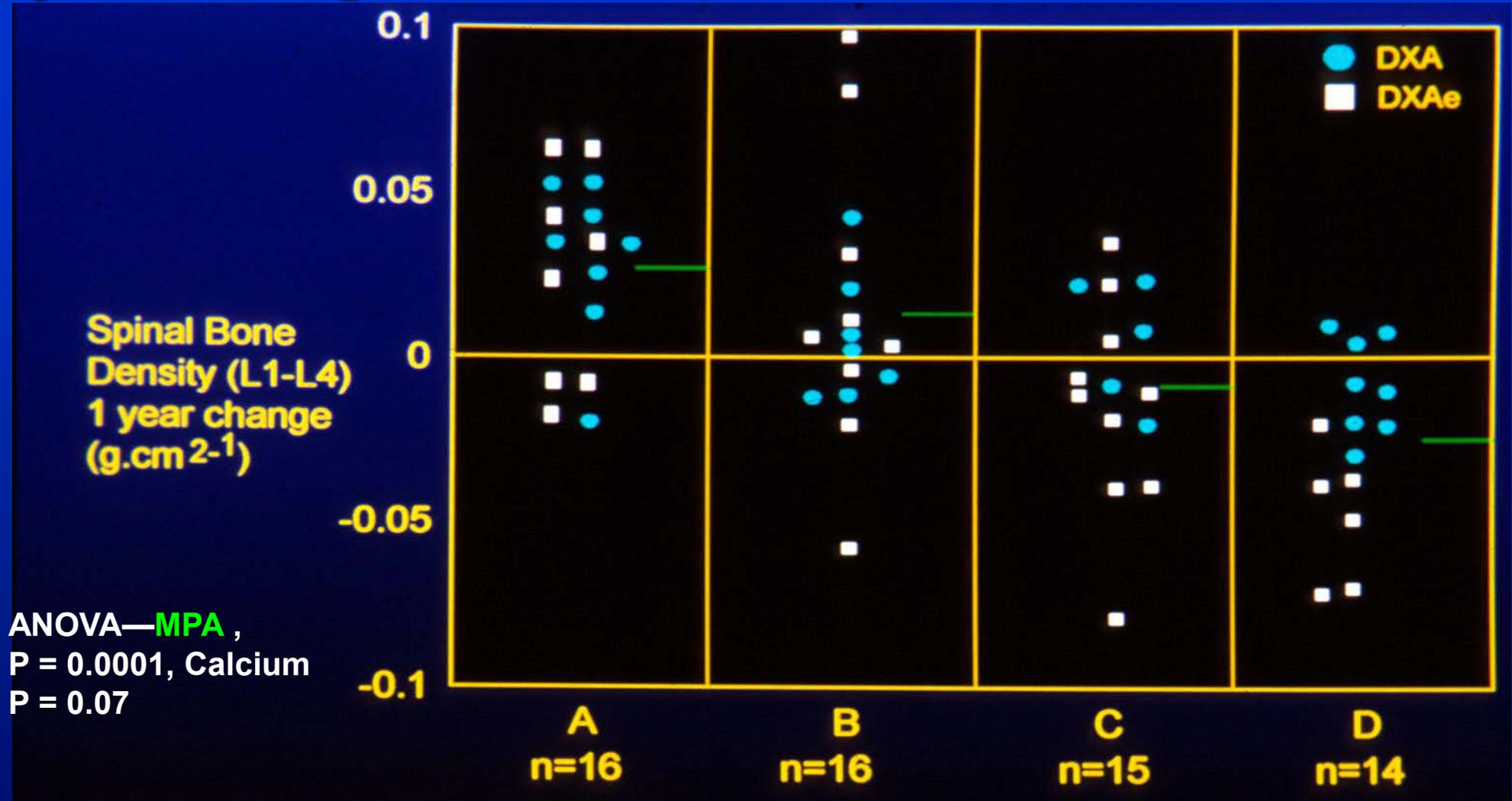


Cyclic Progesterone Therapy-

[www.cemcor.ca](http://www.cemcor.ca)

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# Cyclic Progestin Therapy for Abnormal Cycles



A = Cyclic MPA with 1000 mg calcium; B = MPA/calcium placebo; C = calcium; D = double placebo *J Prior Am J. Med* 1994;96:524

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# Absolute Fracture Risk Reduction

## Current Therapies

Drug	Non-Vertebral	Vertebral
Alendronate	3%	7%
Risedronate	3-5%	5-11%
OHT (E +/- p)	2.2-3.5%*	0.2-0.5%**
Raloxifene	0.2%	0.6-6.5%
Teriparatide	3%	9%
Denosumab	1.5%	5%

\*In women without fracture risks or osteoporosis—from WHI trial

\*\*Clinical rather than X-ray diagnosed vertebral fracture

# Bone Loss Preventing (anti-resorptive) agents

# Absolute Fracture Risk Reduction

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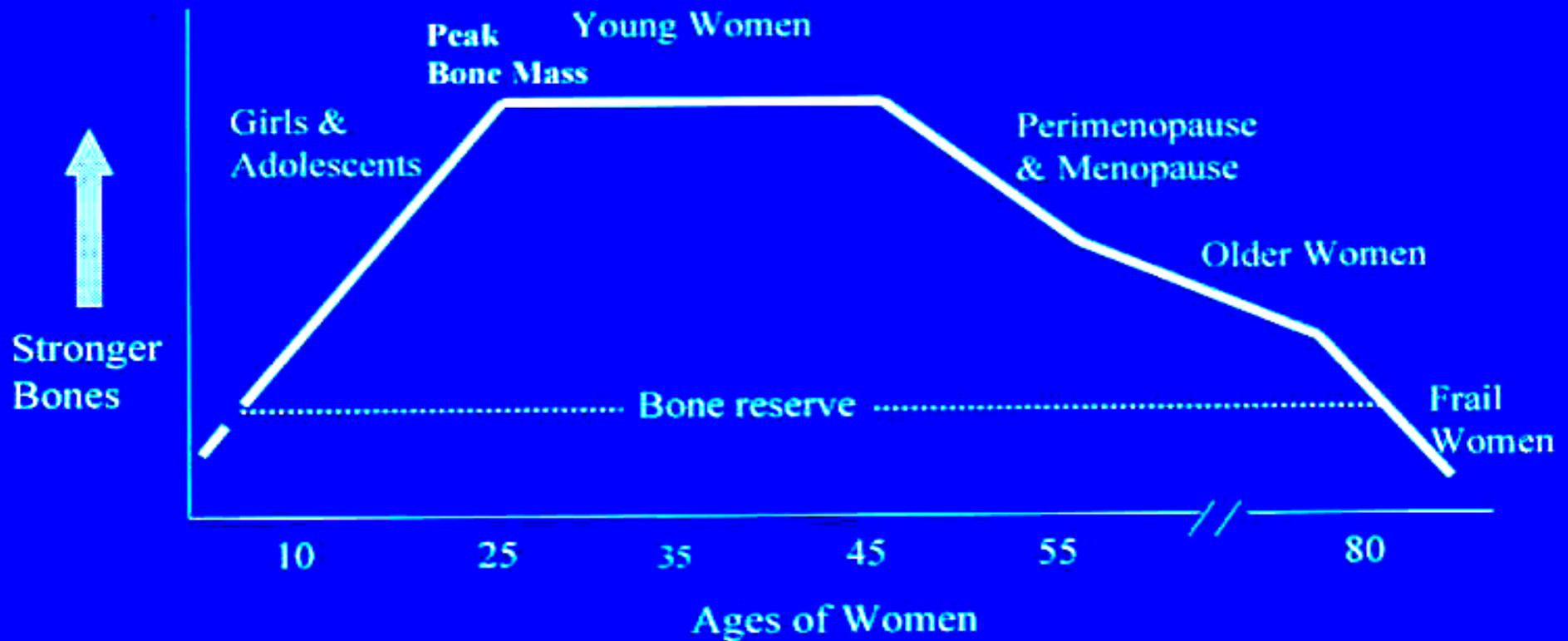
# Anti-resorption Therapies

potentially carry long-term (> 5 yr) risks

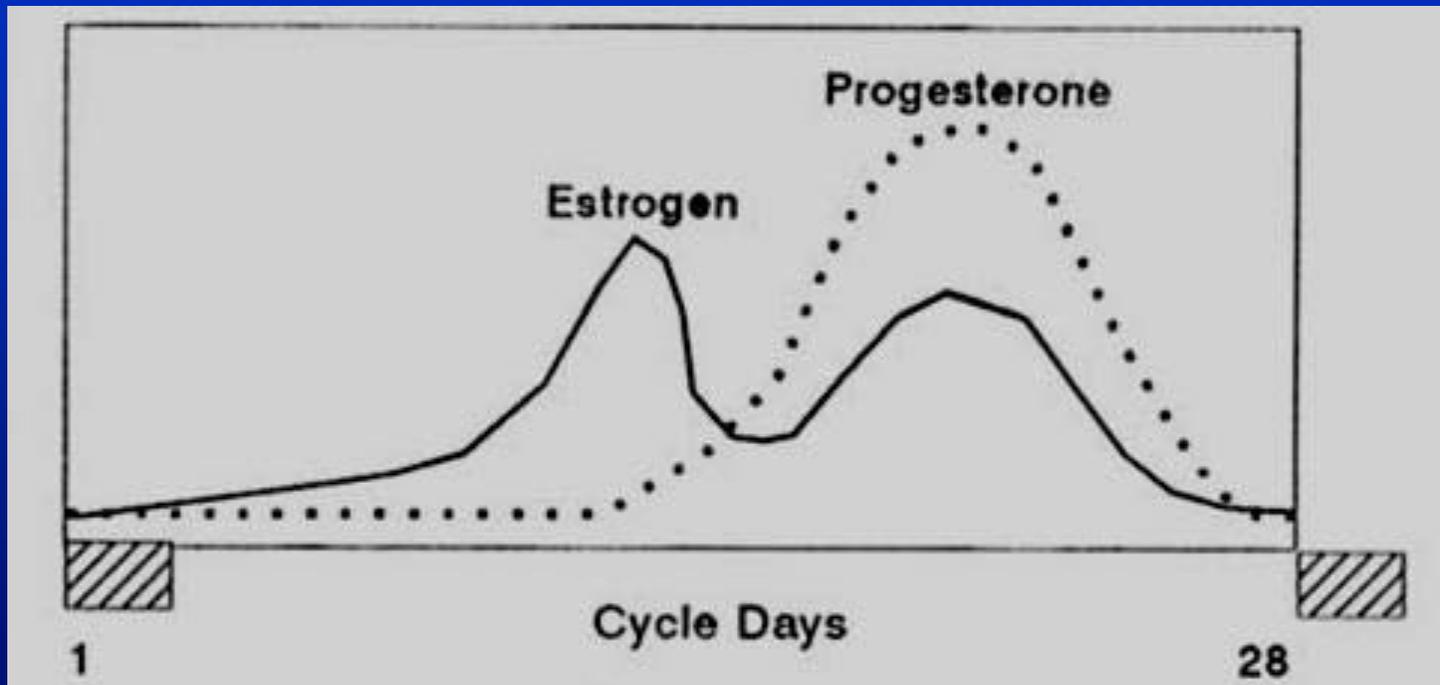
- All therapies that slow bone loss (**Anti-resorptive**) also decrease bone formation.
- With powerful osteoporosis medicines (like **aminobisphosphonates**) there are now new bone problems—*atypical femur fractures*
- With these powerful medicines—also some immune changes like *aseptic jaw necrosis*

Bone Loss Preventing  
(anti-resorptive) agents  
also  
Decrease  
Bone Formation!

# Life Cycle of Bone—Young Women



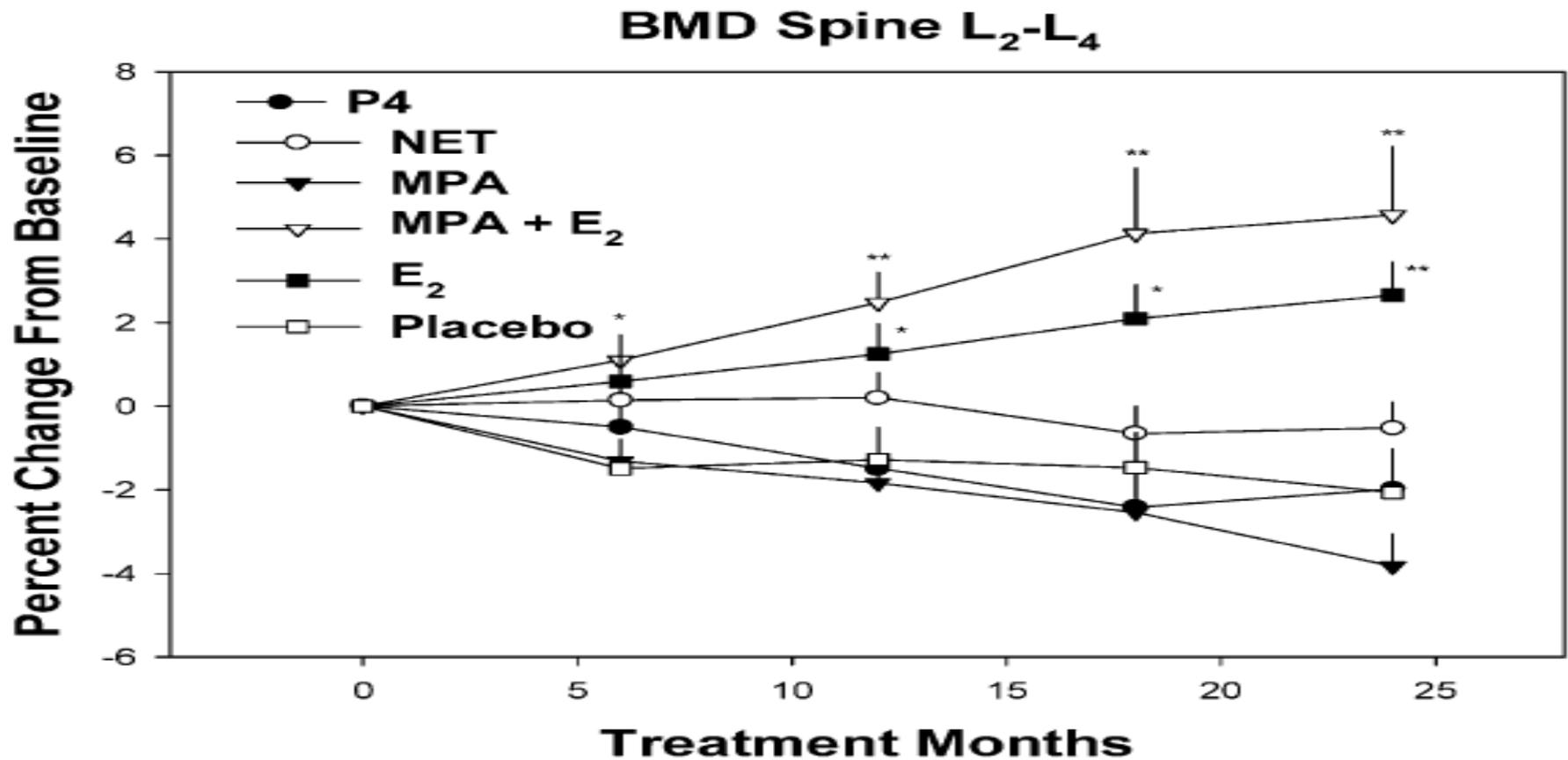
# The Normal Menstrual Cycle—rising and falling Estrogen and Progesterone



Flow

Flow

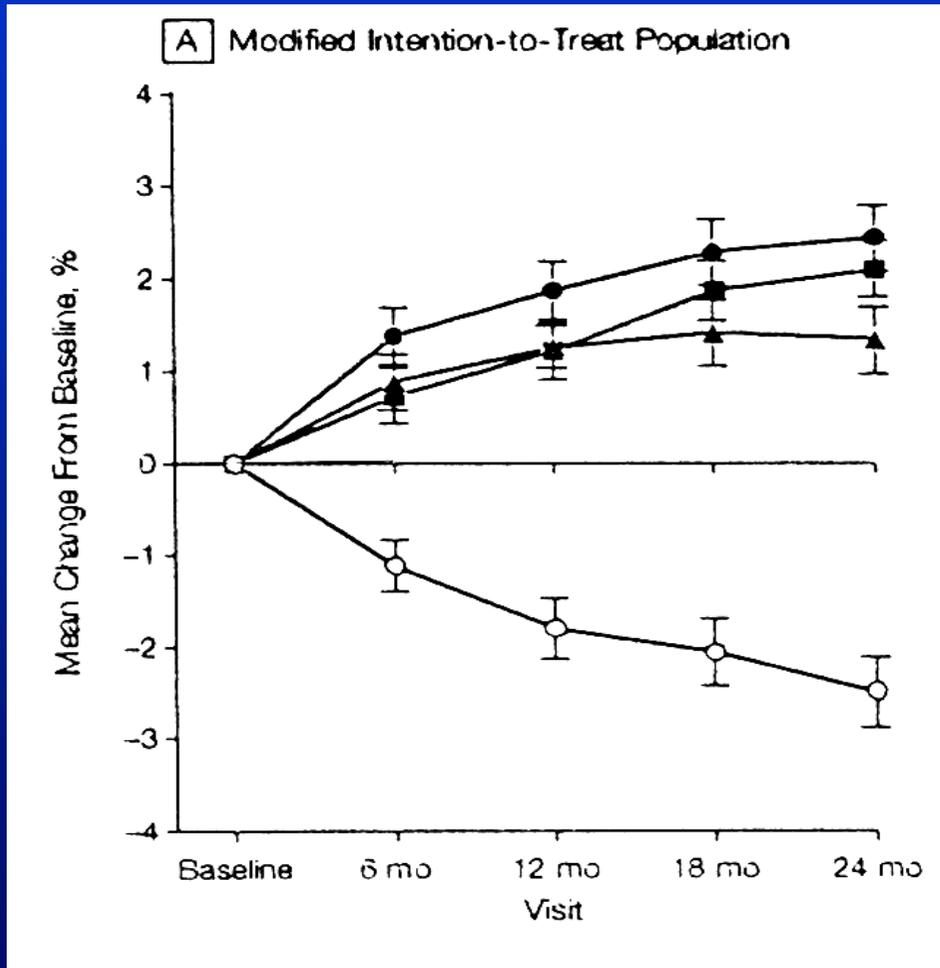
# RCT of Hormones including Progesterone (P4 •) in women early in menopause



Progesterone alone does not  
prevent bone loss if bone  
resorption is ↑

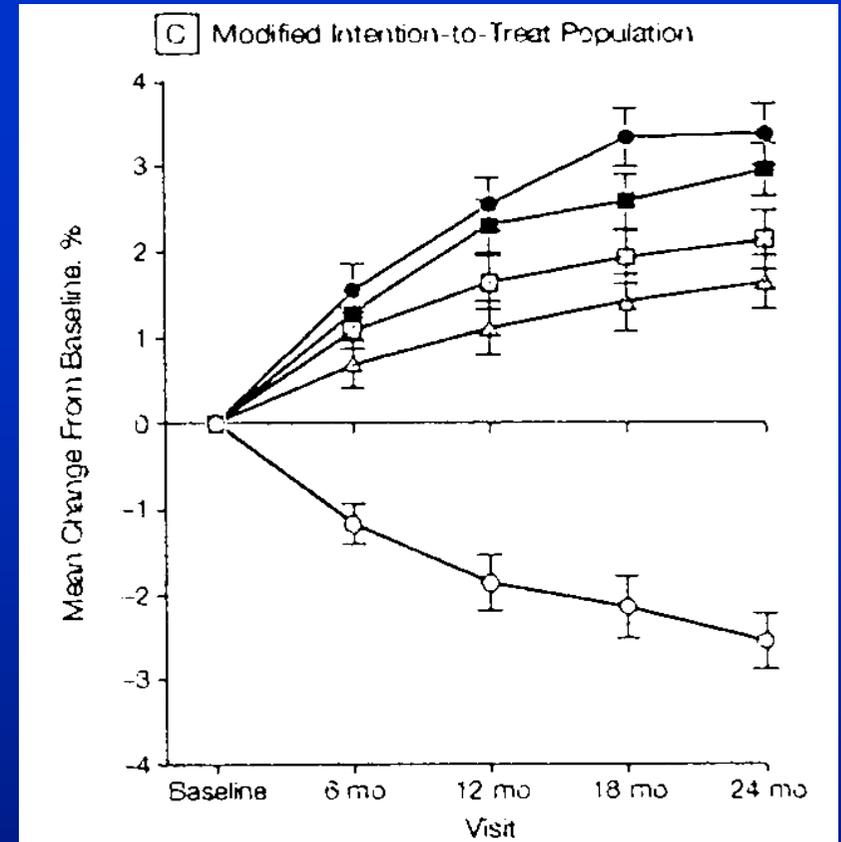
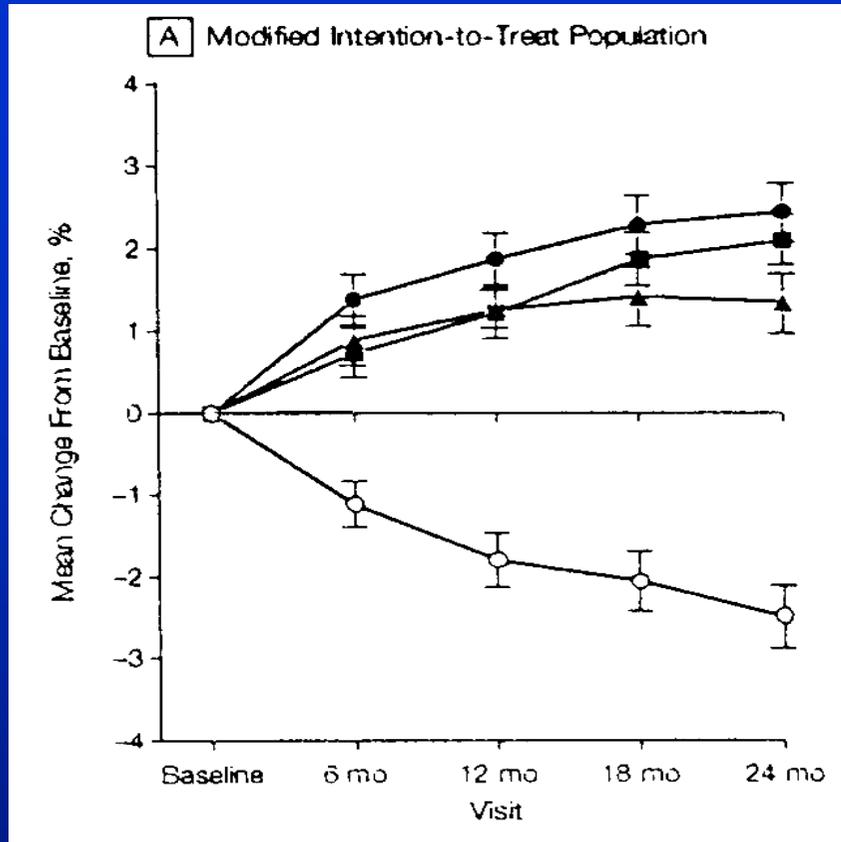
# Women's HOPE trial Estrogen Therapy

Change in Spine DXA on estrogen alone = 2.3%



Estrogen stops  
bone loss and  
allows resorption  
pits to fill

- CEE 0.625 mg/d
- CEE 0.45 mg/d
- ▲ CEE 0.3 mg/d
- Placebo



- CEE 0.625 MPA 2.5 mg/d
- CEE 0.45 MPA 2.5 mg/d
- CEE, 0.45 MPA 1.5 mg/d
- △ CEE 0.3 MPA 1.5 mg/d

# Estrogen-alone

Lindsay R, *JAMA* 2002; 287:2673

# Estrogen & Progestin

# Comparison: Estrogen vs. E + P

Estrogen alone =  $\uparrow$  2.3% over two years

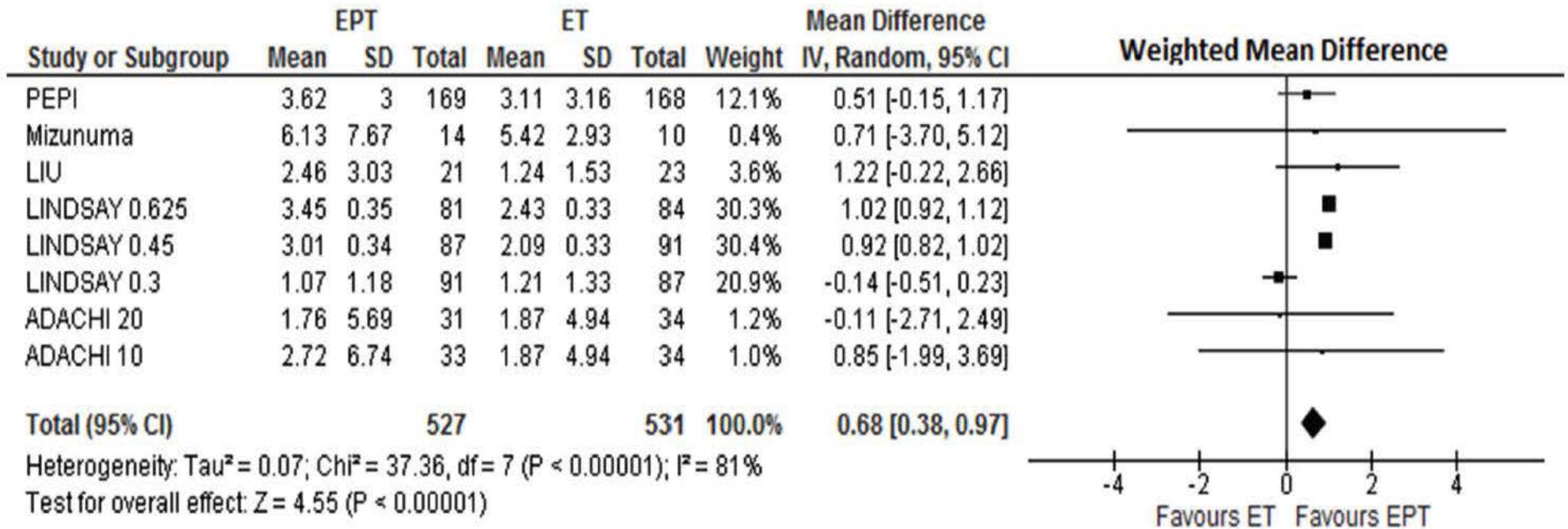
Significantly greater bone gain:

Co-therapy of Estrogen plus low dose daily

Progestin =  $\uparrow$  3.3% over two years

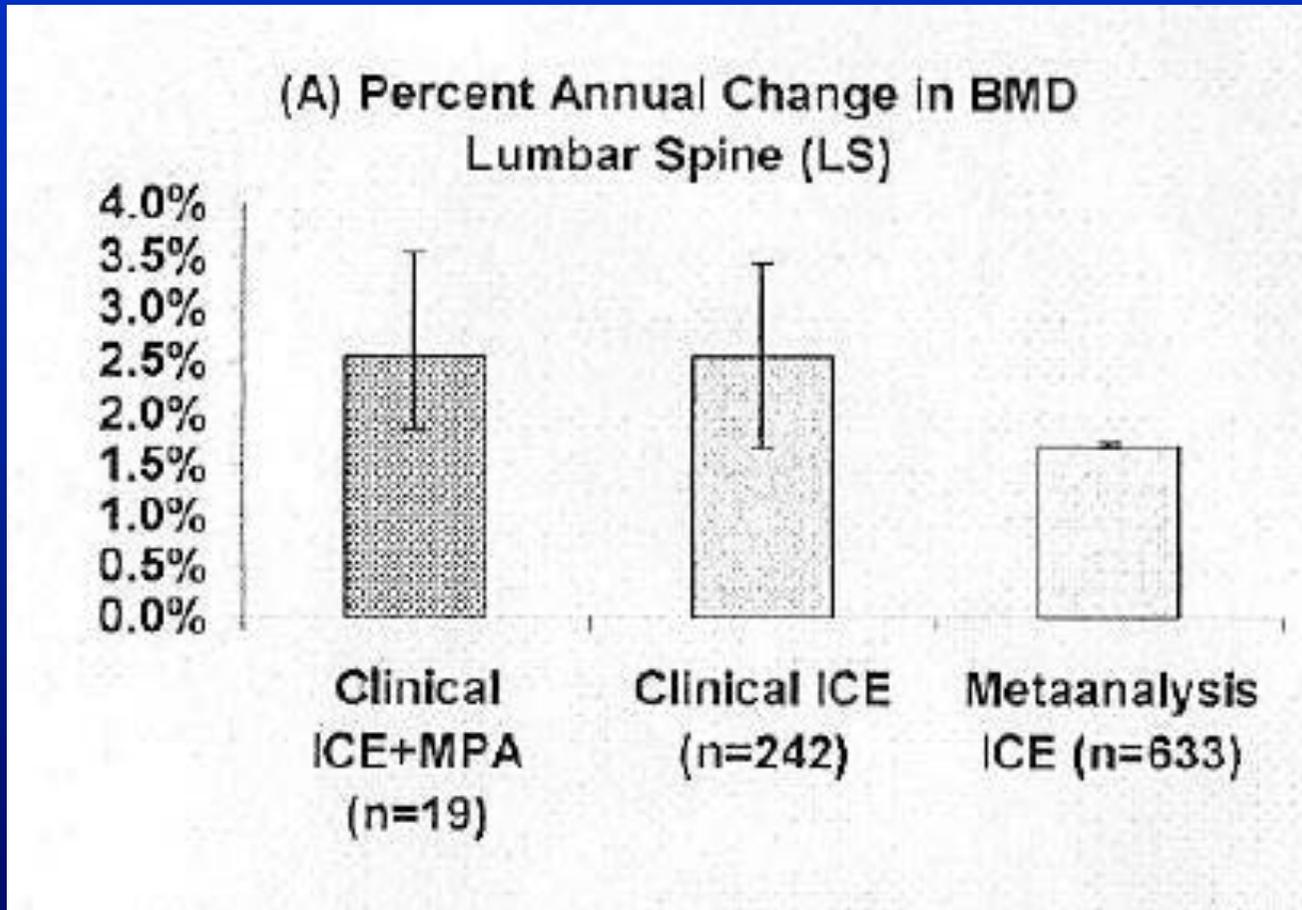
$P < 0.03$

# Meta-analysis—Progestin /P4 adds to E2 bone benefit in menopause



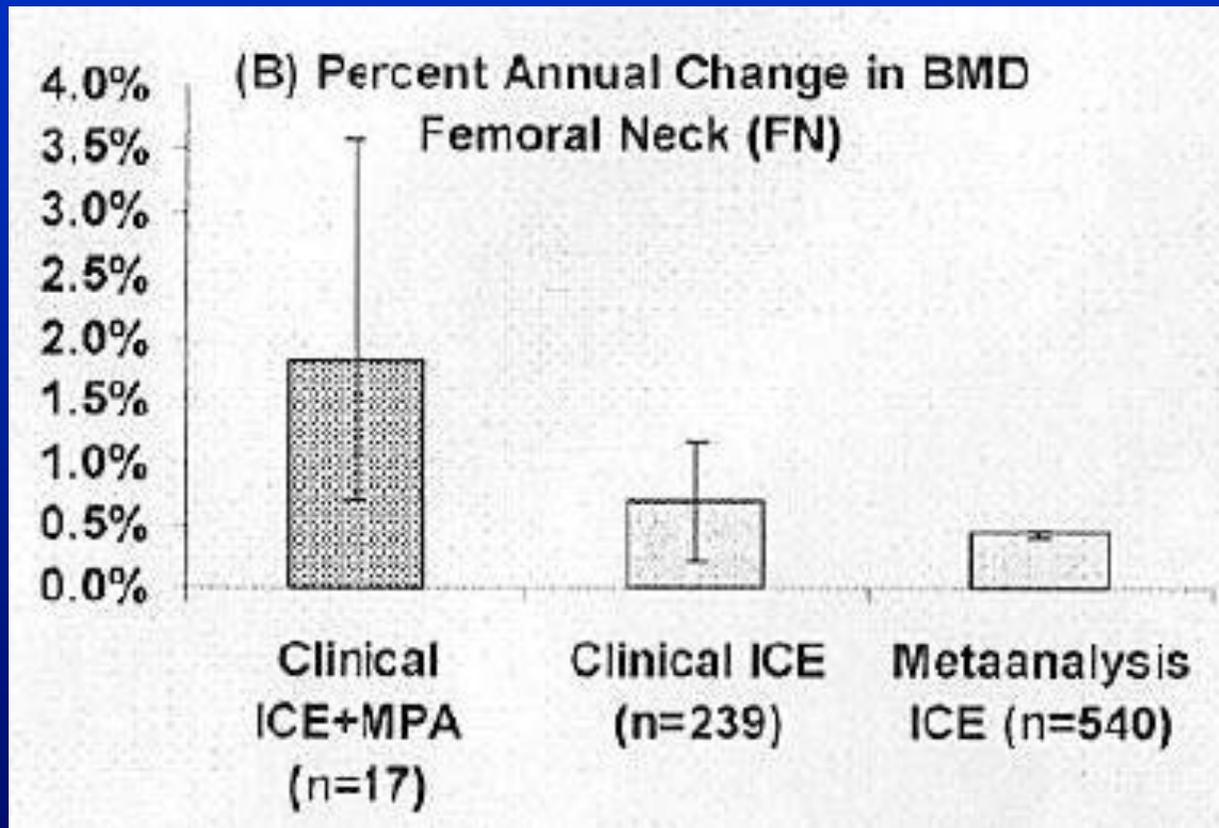
Prior *J Musculoskeletal Neuronal Interact* 2017;17(3):146-154

# Does Co-Therapy of Progesterone with Bisphosphonates Work?



These are a co-therapy data are from a random sample of Prior's clinical charts of menopausal women treated with both progesterone/MPA and **etidronate** = ICE

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# Bone Changes in Older Adulthood



# ABCs of Osteoporosis Prevention

**A** Activity

**E** Easy-going

**B** Brawny

**F** Formation

**C** Calcium

**G** Good Habits

**D** Vitamin D

# Atypical Femoral Shaft Fractures— ? due to >5 y a-bisphosphonates ?





# Questions?



# Progesterone with Antiresorptives

## What we have learned:

- ◆ **Bone resorption-formation imbalance causes fractures**—antiresorptives ↓ bone formation
- ◆ We know little about formation therapies & fracture prevention—except for PTH
- ◆ **Progesterone** ↑ formation but, when bone loss ↑, it works without (*visible*) benefit
- ◆ **Progesterone** added to **estrogen**-benefitted BMD gains—will likely add to fracture prevention. This needs testing. . .

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*The Centre for Menstrual Cycle  
and Ovulation Research*

**Centre for  
Menstrual**



**Cycle &  
Ovulation**

**Research**

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