

**RUTGERS**

Robert Wood Johnson  
Medical School

# Hemostasis During the Menstrual Cycle

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Uterine Hemostasis Colloquium  
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FOUNDATION FOR  
**Women & Girls**  
with Blood Disorders

# References

- Trigg



# Case

- 30 year-old female with history of heavy menstrual bleeding, postpartum hemorrhage, and bleeding after wisdom tooth extraction
- A comprehensive hemostatic evaluation was non-diagnostic
- Is there a role for repeat, menstrual cycle specific testing in this woman?



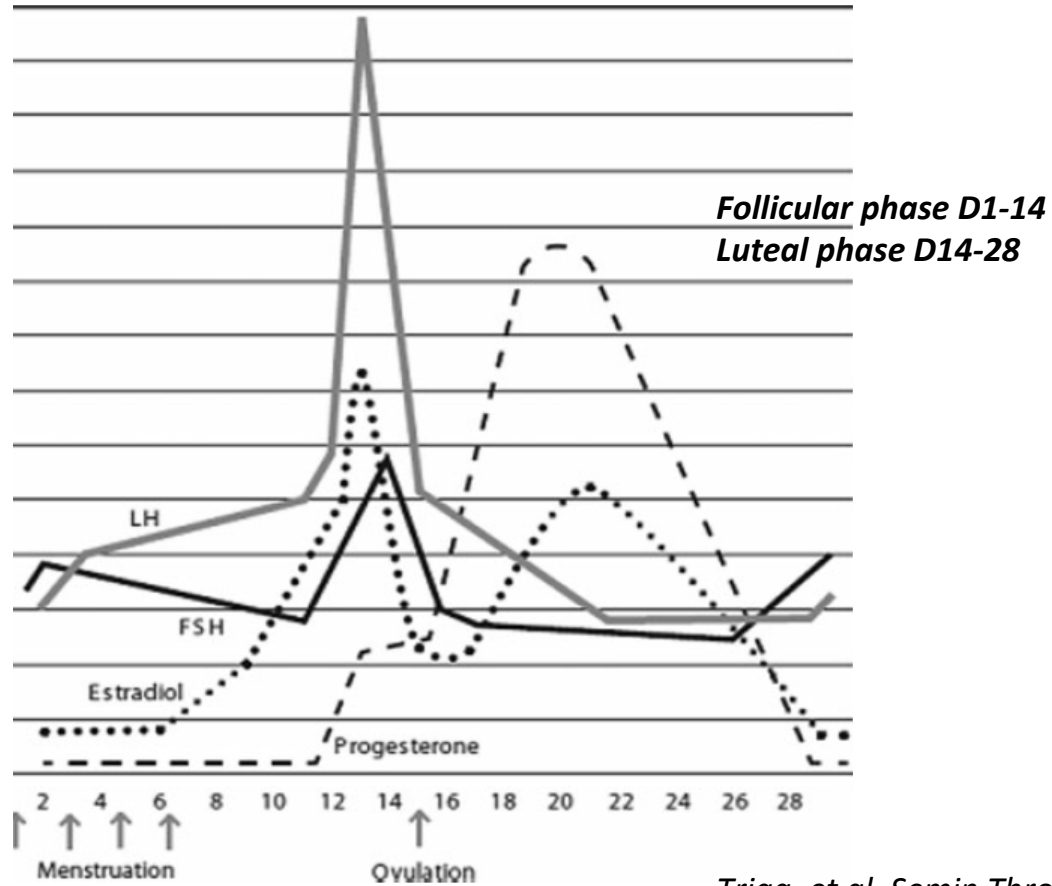
- Hormonal Changes During Menstrual Cycle
- Hemostatic Changes During Menstrual Cycle
  - VWF
  - Platelet function
  - Coagulation factors
  - Fibrinogen
  - Fibrinolytic
- What are the implications?
  - Testing
  - ? Increase or decrease in thromboembolic or bleeding risks



# **HORMONAL CHANGES**



# Hormonal Changes During Menstrual Cycle





# Hormones During Follicular and Luteal Phases

*Giardina, et al. J Clin Endocrinol Metab. 2004; 89:6179-6184*

Hormone	Follicular	Luteal	p
Estradiol (pg/ml)	59.1 ± 30.2	87.6 ± 36.7	<0.01
FSH (mIU/ml)	4.5 ± 1.5	3.7 ± 2.2	<0.05
Progesterone (ng/ml)	0.8 ± 0.7	7.1 ± 2.9	<0.001
LH (mIU/ml)	3.5 ± 1.9	5.7 ± 9.7	NS

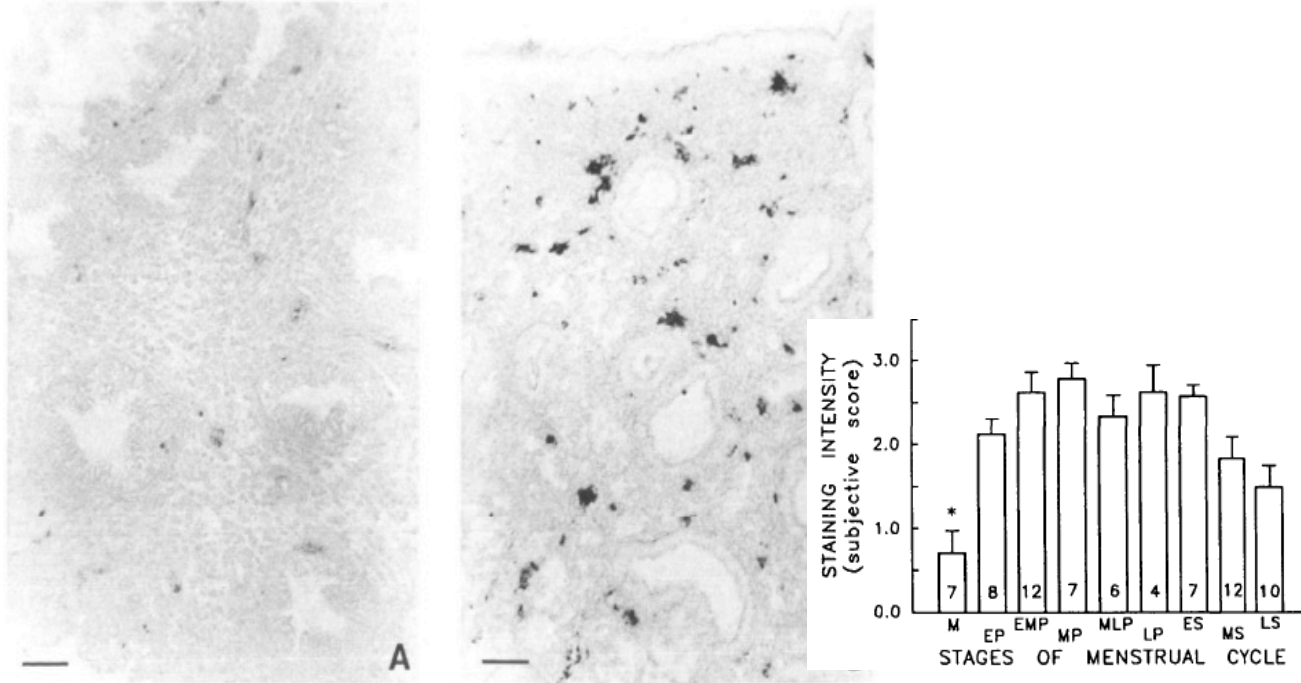


**VON WILLEBRAND FACTOR**





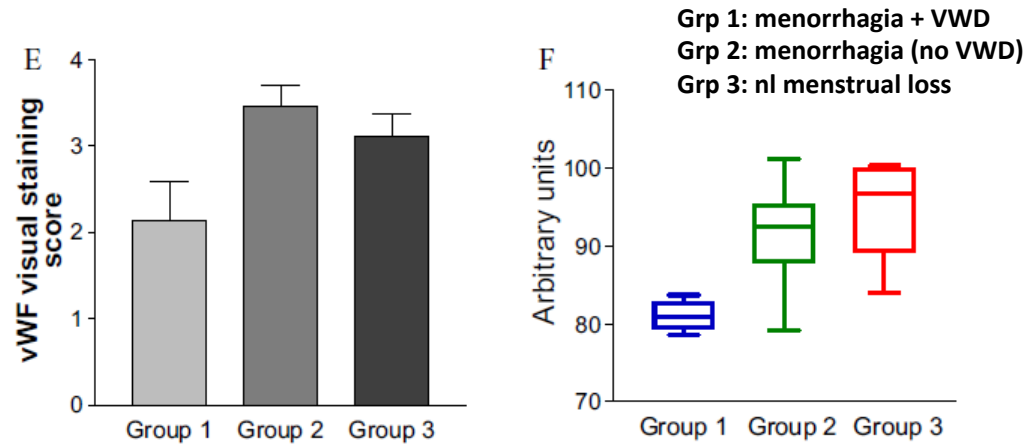
## Changes in Endometrial VWF with Menstrual Cycle



Comparison of vWF staining in menstrual (A) and late proliferative (B) phase human endometrium ( $\times 200$ ). (Bar = 50  $\mu\text{m}$ ).



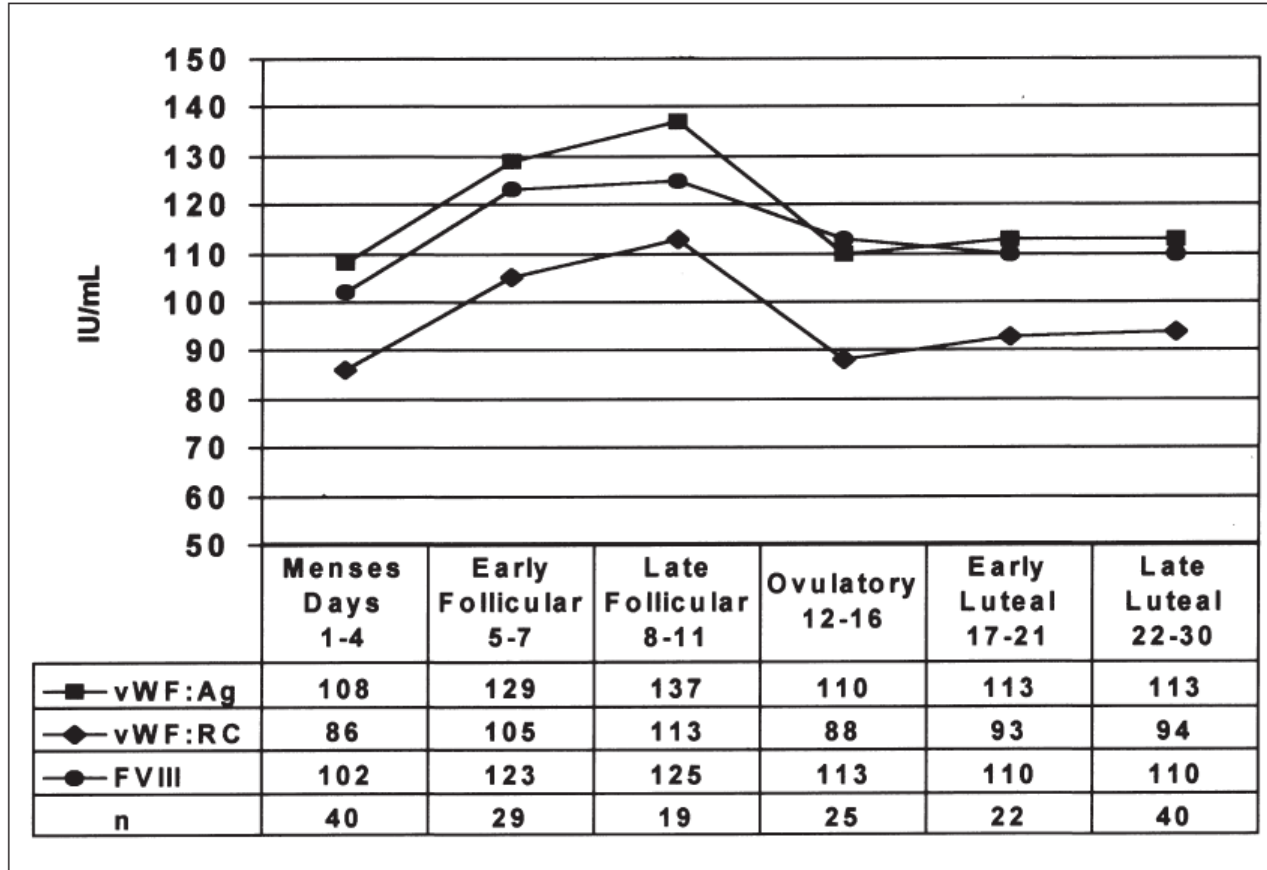
# Changes in Endometrial VWF with Menorrhagia



Agarwal, El Sheikh, Kulkarni, Baff, Kadir. *Fertil Steril.* 2010; 94:2335-7



## Changes in Plasma VWF and Factor VIII (n=175)





# VWF Cyclical Variation vs No Cyclical Variation

*Knol HM, et al. Thromb Haemost. 2012; 107:22-29*

## **Cyclical Variation**

- Miller et al, 2002
- Kadir et al, 1999
- Blomback et al, 1997
- Roell et al, 2007
- Jern et al, 1991

## **No cyclical variation**

- Onundarson et al, 2001
- Koh et al, 2005
- Feuring et al, 2002
- Giardina et al, 2005
- He et al, 1999

***VWF levels approximately 10% (range 2-24%) lower in menstrual/early follicular phase compared to luteal phase***



# **PLATELET COUNT AND FUNCTION**



# Platelet Counts ( $n=30$ )

*Koh, et al. Clin Appl Thrombosis/Hemostasis. 2005; 11(3):295-301*

Cycle	Day 1-3	Day 5-9	Day 10-14	Day 21-26	p
Plt ct	299 ± 61.4	301.2 ± 66	318.9 ± 61.9	305.5 ± 63.2	0.62

No statistically significant variation with menstrual cycle



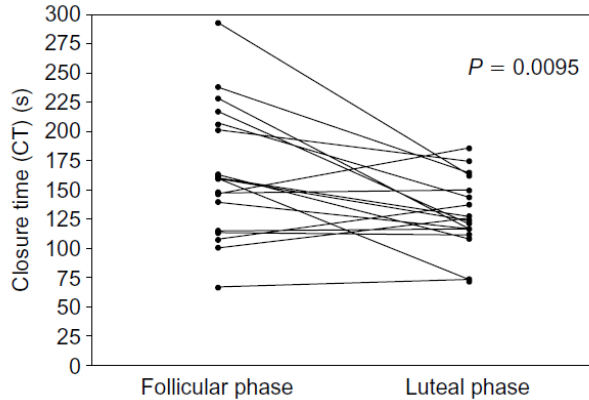
## Platelet Function:

### PFA100 in Premenopausal Women—No OC ( $n=18$ )

Collagen/Epi Cartridge:

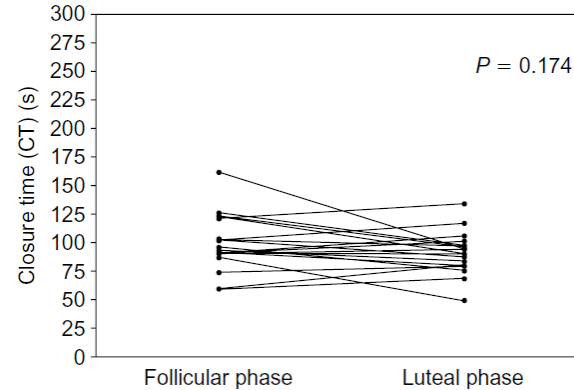
Shorter CT in Luteal Phase  $\rightarrow$   $\uparrow$  Plt Fn

( $\Delta = -34.6 \pm 50.1$  sec;  $p=0.0095$ )



Collagen/ADP Cartridge:

NS  $\Delta$  CT





# COAGULATION FACTORS





# Changes in Endometrial Tissue Factor Expression During Menstrual Cycle

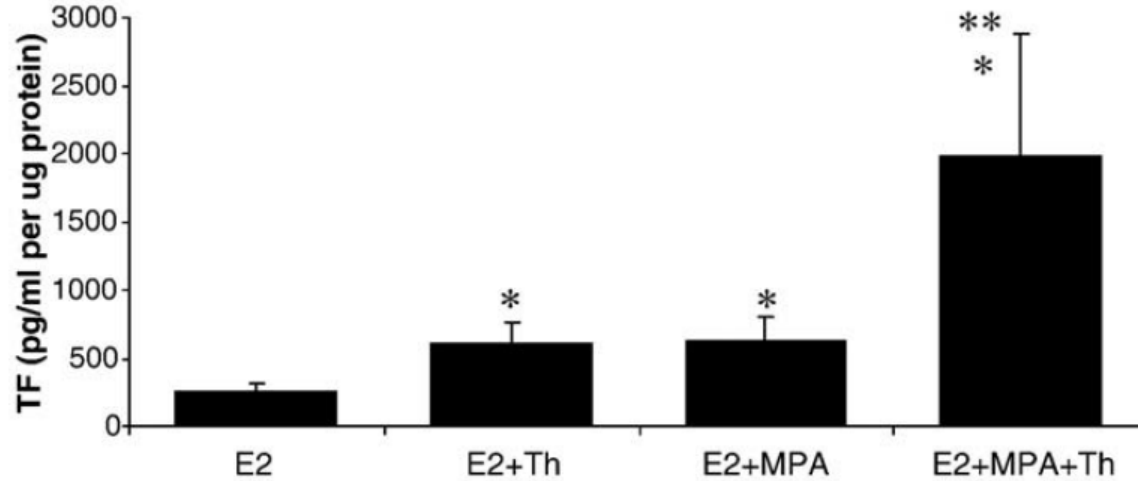
- TF is primary initiator of hemostasis in endometrium
- Progesterone initiates decidualization of endometrial stromal cells during mid-luteal phase
- TF expression increased by progesterone in decidualized stromal cells late luteal phase

*Lockwood, et al. Thrombosis Research. 2009; 124:516-520.*



# Effects of Progesterone and Thrombin on TF Expression in Decidual Cells

*Lockwood, et al. Thrombosis Res. 2009; 124:516-520*

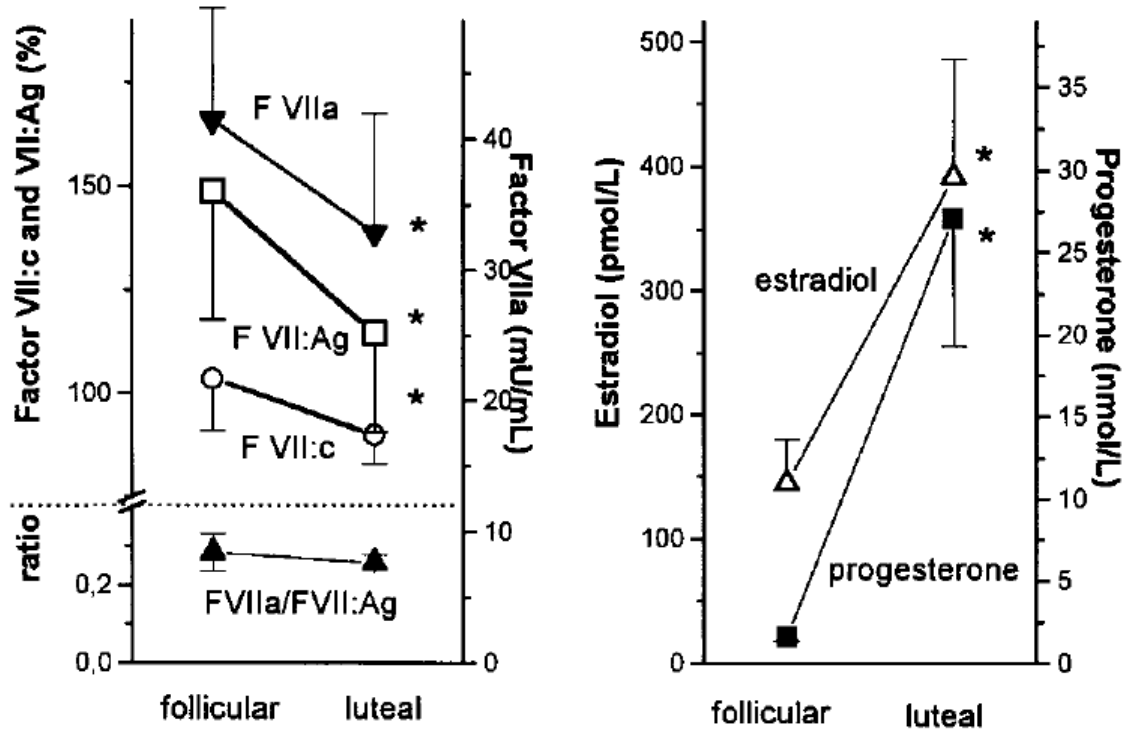


**P<0.05 \*vs E2; \*\*vs E2 +MPA, \*\* vs E2 +Th**



# Plasma Factor VII

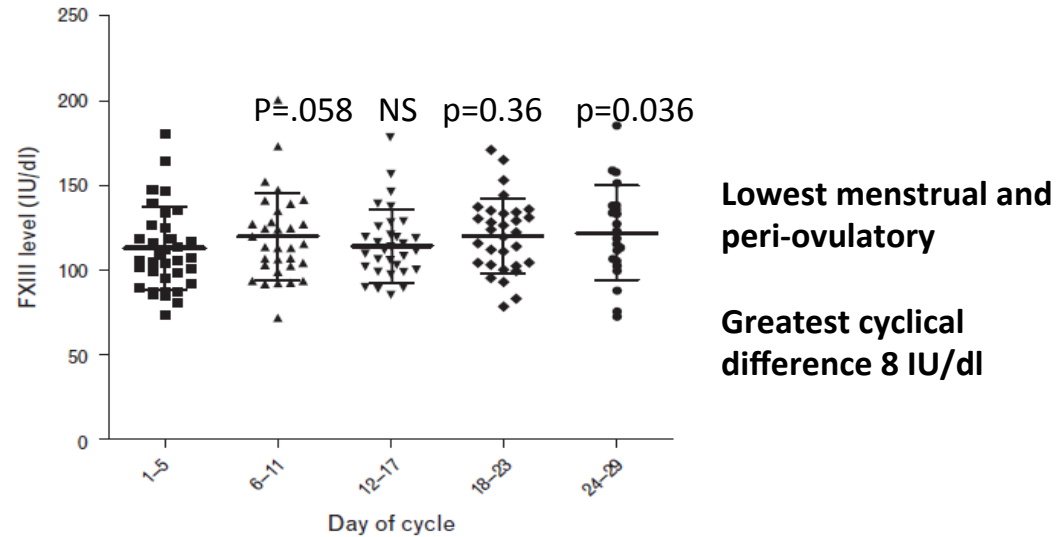
Kapiotis, et al. *Thromb Haemost.* 1998; 80:588-91



Factor VIIa: 20% lower FVIIa luteal phase (-18% midcycle) vs follicular  
men 46% higher than women ( follicular) phase



# Factor XIII



*Sharief et al, Blood Coag Fib 2016;27:786-790*



# Coagulation Factors

- XI- no menstrual cycle variation
  - *Kadir et al, Thromb Haemost 1999;82:1456-61*
- VII-lowest mid-cycle and luteal phase
  - *Kapiotis et al, Thromb Haemost 1998;80:588-91*
  - *Larsen et al, Scand J Clin Lab Invest 1996;56(3):241-9*
- II, X- no significant menstrual cycle variation
  - *Blomback et al, JTH 2007;5:855-858*
- XIII-lowest menstrual (d1-5) and peri-ovulatory (d13-15)
  - *Bolis et al, Clin Exp Obstet Gynecol 1982;9:22-25*
  - *Sharief et al, Blood Coag Fib 2016;27:786-790*

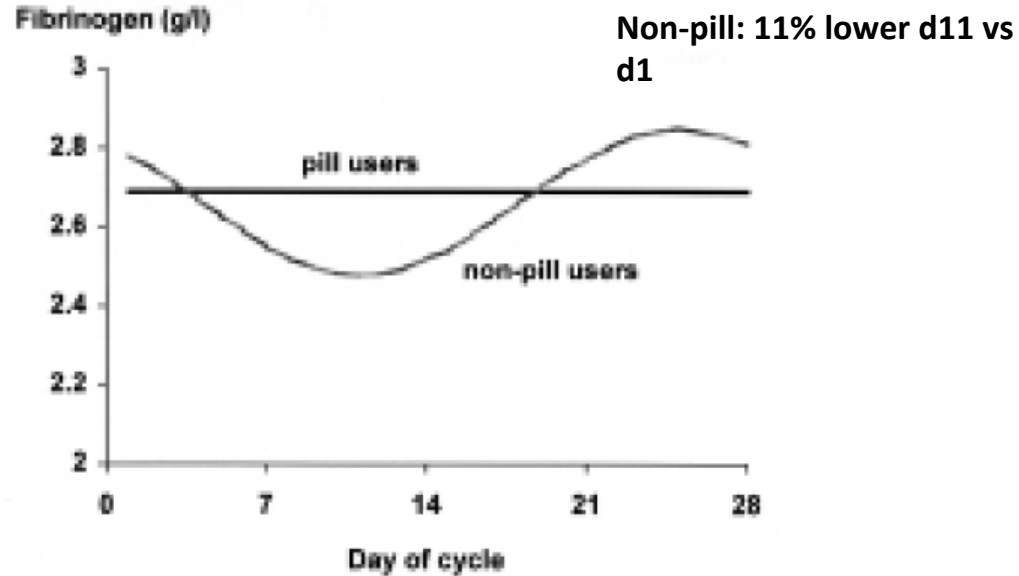


**FIBRINOGEN**



# Fibrinogen: Cycle variation (No OC)

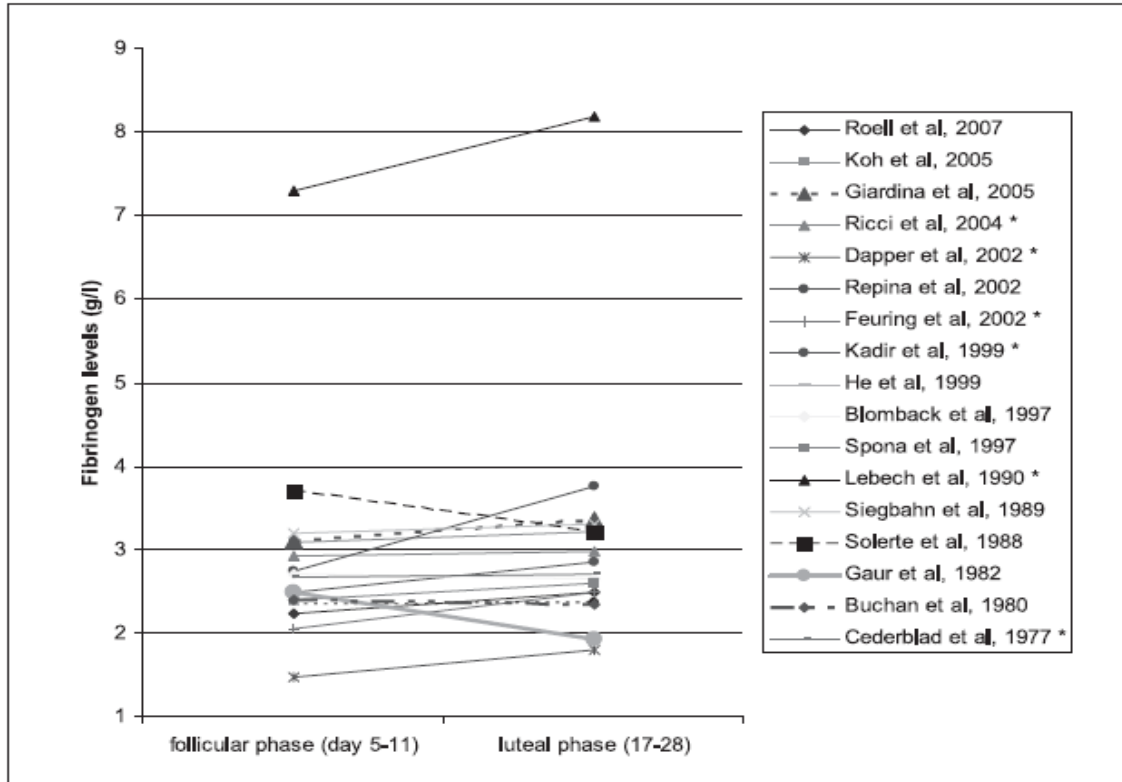
## Lowest Day 11



*Kadir, et al. Thromb Haemost. 1999; 82:1456-61*



# Fibrinogen



**6/20 lowest follicular phase; 2/20 lowest luteal phase**

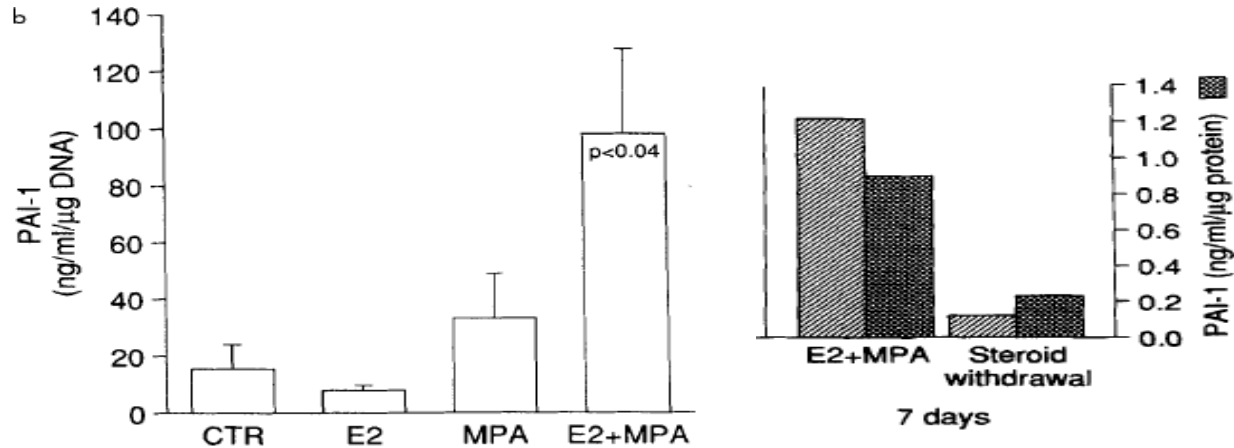




# **FIBRINOLYTIC PARAMETERS**



# PAI-1 in Decidual Cell Cultures Treated with Progesterone

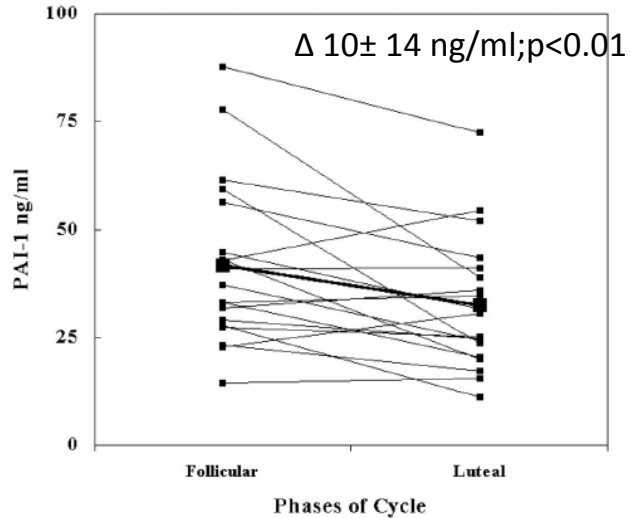


*Lockwood, et al. Ann NY Acad Sci. 1994; 734:57-59*

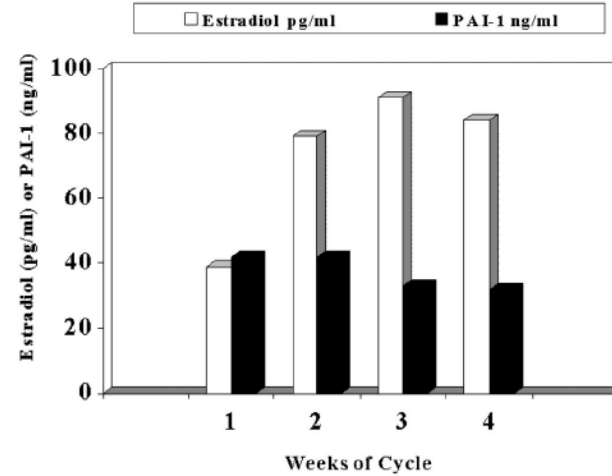


# PAI-1

## Difference follicular/luteal phase



## Inverse relationship estradiol and PAI-1 over 4 week cycle





# Fibrinolytic Parameters in Plasma

## Cyclical Variation

- **PAI-1 2/11 studies**
  - **Lowest luteal phase** (*Giardina, et al. J Clin Endocrin Metab. 2004; 89:6179-6184*)
  - **Lowest follicular phase** (*Chung, et al. Breast Cancer Res Treat. 1998; 49:41-50*)
- **tPA 1/10 studies**
  - **Lowest luteal phase** (*Ricci, et al. Hum Reprod. 2004; 19:838-848*)
- **uPA 2/3 studies**
  - **Lowest ovulatory phase** (*Chung, et al, Breast Cancer Res Treat. 1998; 49:41-50*)
  - **Lowest luteal phase** (*Dorr, et al. Thromb Haemost. 1993; 70:873-875*)
- **D-dimer 2/5 studies**
  - **Lowest luteal phase** (*Giardina, et al. J Clin Endocrin Metab. 2004; 89:6179-6184*)
  - **Lowest late follicular** (*Koh, et al. Clin Appl Thromb Hemost. 2005; 11(3):295-301*)



# Thrombin Generation:

*NI Menstrual Cycle (n=102)*

- Higher during luteal phase than follicular phase ( $1524 \pm 283$  vs.  $1609 \pm 343$ ;  $p=0.027$ )
- *No strong correlation between TG and hemostatic parameters*
- *Progesterone highest in luteal phase*

*Chaireti R, et al. Hum Rep. 2013; 28(7):1846-1852*



## Summary: Cyclical Variation Hemostatic Parameters

- **VWF**-lowest menstrual/early follicular phase
- **Platelet function**—longer CT follicular phase
- **Coagulation factors**
  - **VII**-lowest mid-cycle and luteal
  - **XIII**- lowest menstrual and peri-ovulatory
  - **XI, II, X**- no cyclic variation
- **Fibrinogen**
  - Lowest follicular phase
- **Fibrinolytic** parameters
  - Conflicting data
- **Thrombin generation**
  - Highest luteal phase
  - Poor correlation with hemostatic parameters



# Implications

- Testing—potential implications borderline results
- ? variation in bleeding or thrombotic risks

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