

RUTGERS

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Hemostasis During the Menstrual Cycle

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Uterine Hemostasis Colloquium

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FOUNDATION FOR
Women & Girls
with Blood Disorders



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?



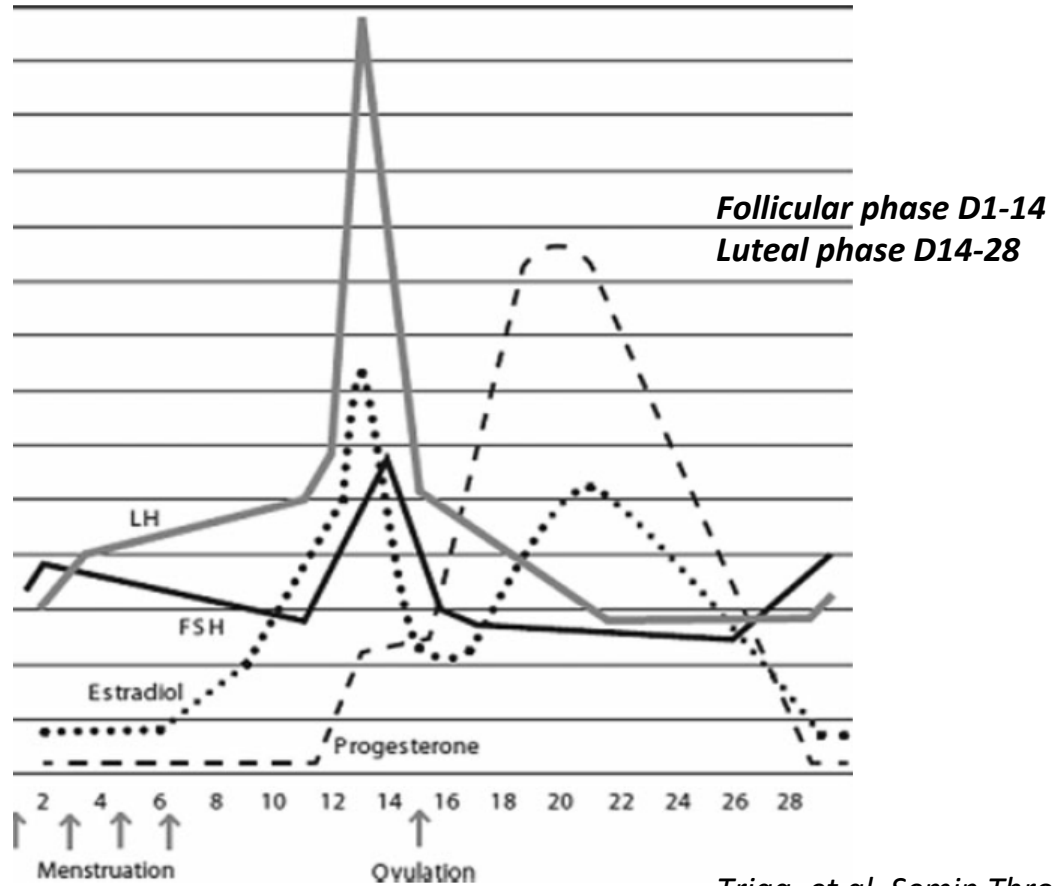
- Hormonal Changes During Menstrual Cycle
- Hemostatic Changes During Menstrual Cycle
 - VWF
 - Platelet function
 - Coagulation factors
 - Fibrinogen
 - Fibrinolytic
- What are the implications?
 - Testing
 - ? Increase or decrease in thromboembolic or bleeding risks



HORMONAL CHANGES



Hormonal Changes During Menstrual Cycle



Trigg, et al. *Semin Thromb Hemost*
2011; 37:77-86



Hormones During Follicular and Luteal Phases

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

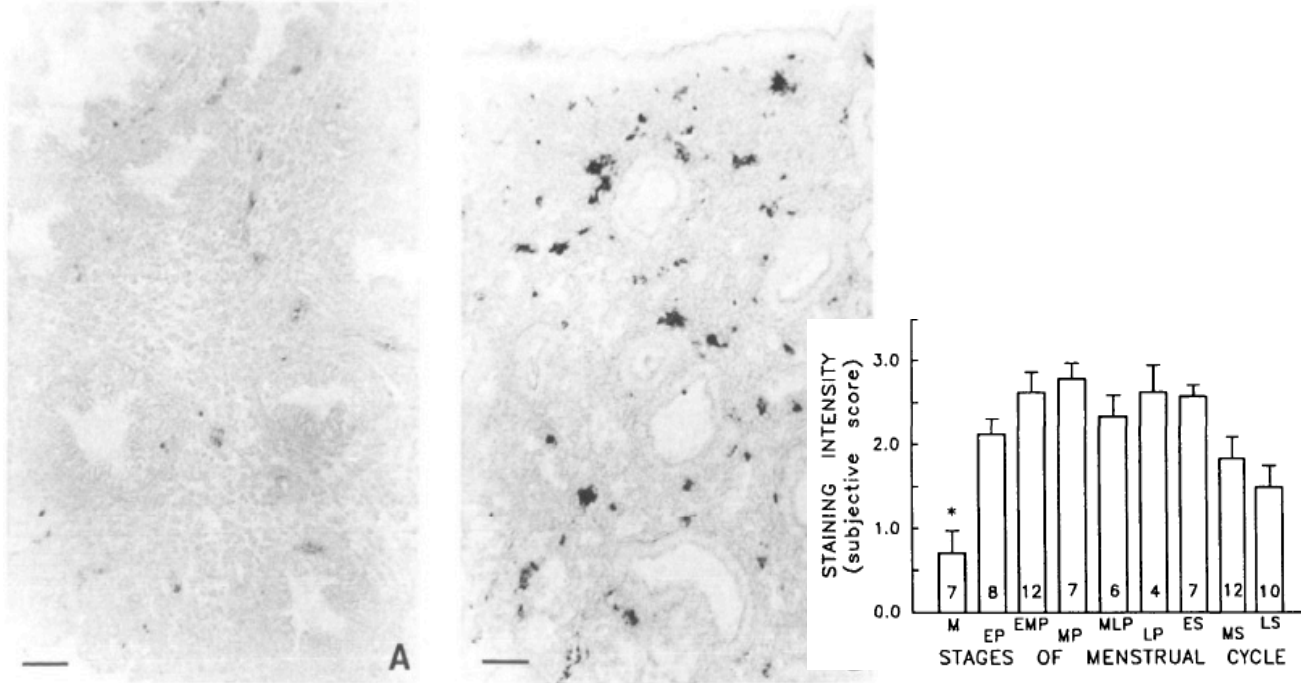
Hormone	Follicular	Luteal	p
Estradiol (pg/ml)	59.1 ± 30.2	87.6 ± 36.7	<0.01
FSH (mIU/ml)	4.5 ± 1.5	3.7 ± 2.2	<0.05
Progesterone (ng/ml)	0.8 ± 0.7	7.1 ± 2.9	<0.001
LH (mIU/ml)	3.5 ± 1.9	5.7 ± 9.7	NS



VON WILLEBRAND FACTOR



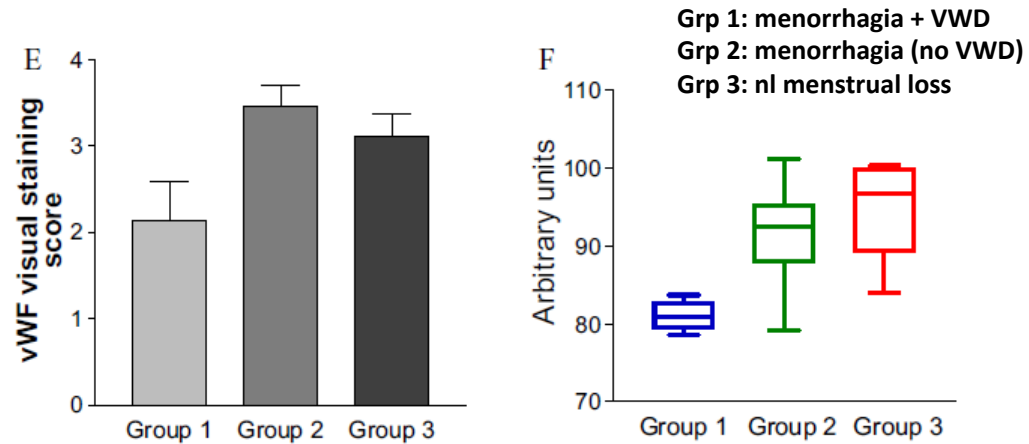
Changes in Endometrial VWF with Menstrual Cycle



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



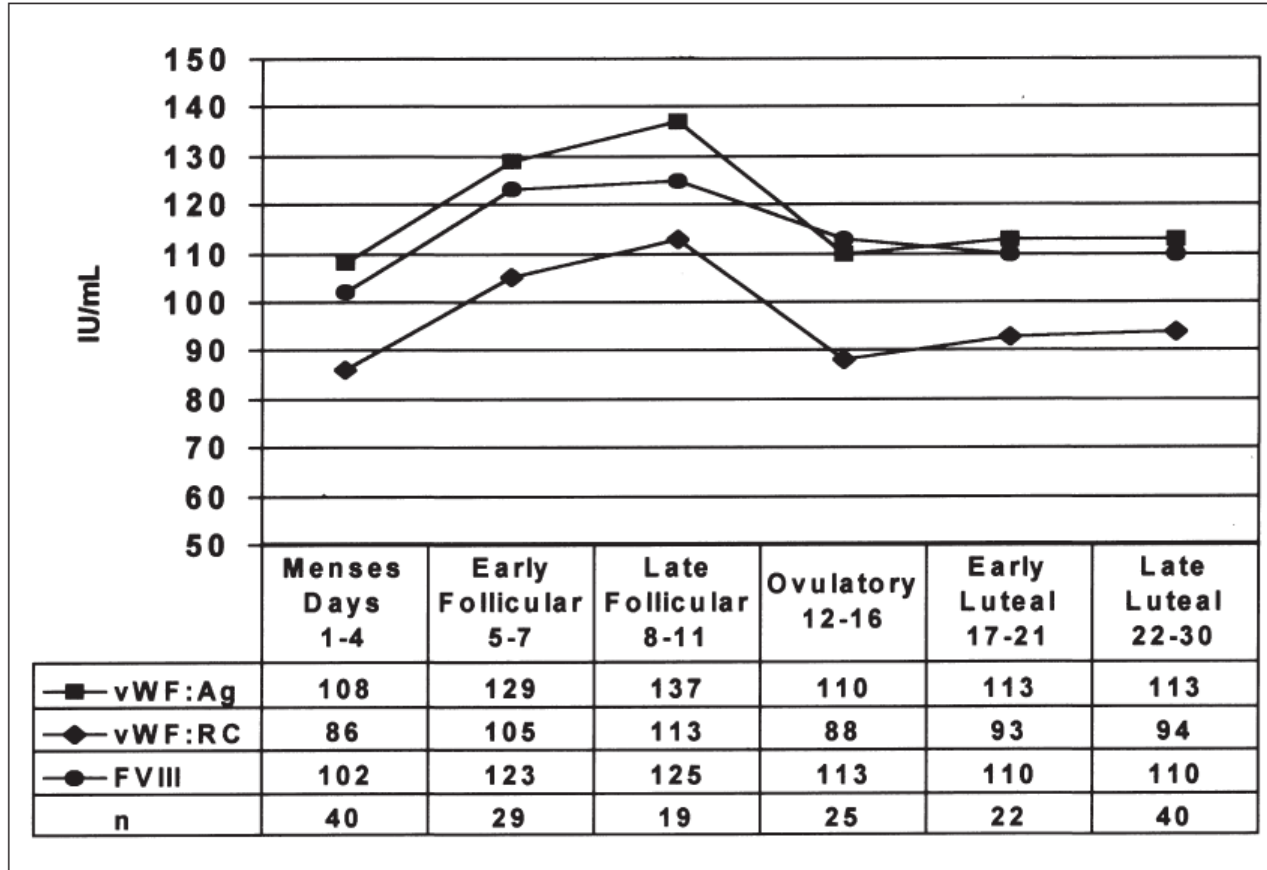
Changes in Endometrial VWF with Menorrhagia



Agarwal, 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



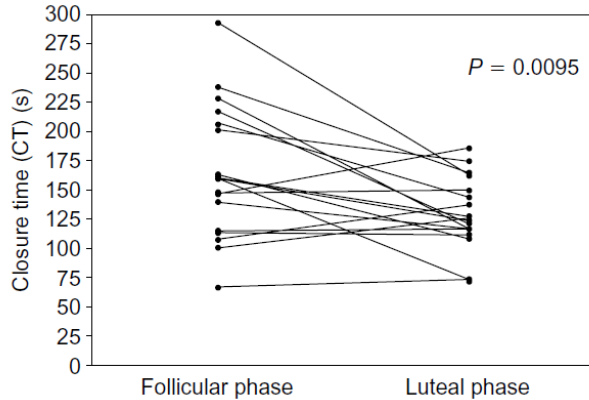
Platelet Function:

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

Collagen/Epi Cartridge:

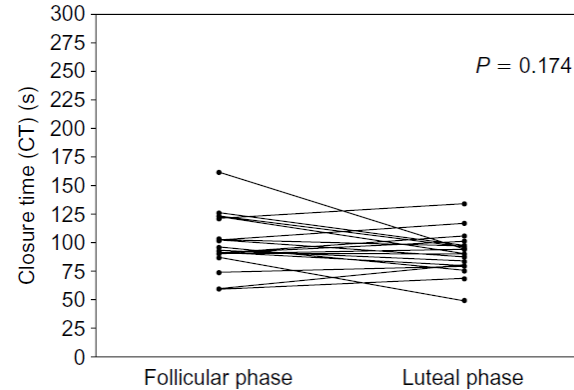
Shorter CT in Luteal Phase \rightarrow \uparrow Plt Fn

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



Collagen/ADP Cartridge:

NS Δ CT





COAGULATION FACTORS



Changes in Endometrial Tissue Factor Expression During Menstrual Cycle

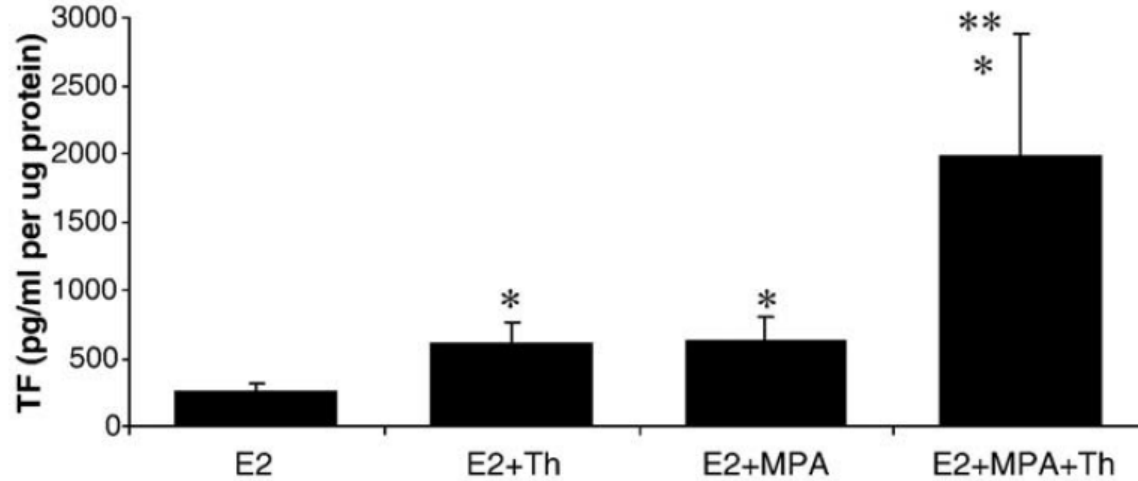
- TF is primary initiator of hemostasis in endometrium
- Progesterone initiates decidualization of endometrial stromal cells during mid-luteal phase
- TF expression increased by progesterone in decidualized stromal cells late luteal phase

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

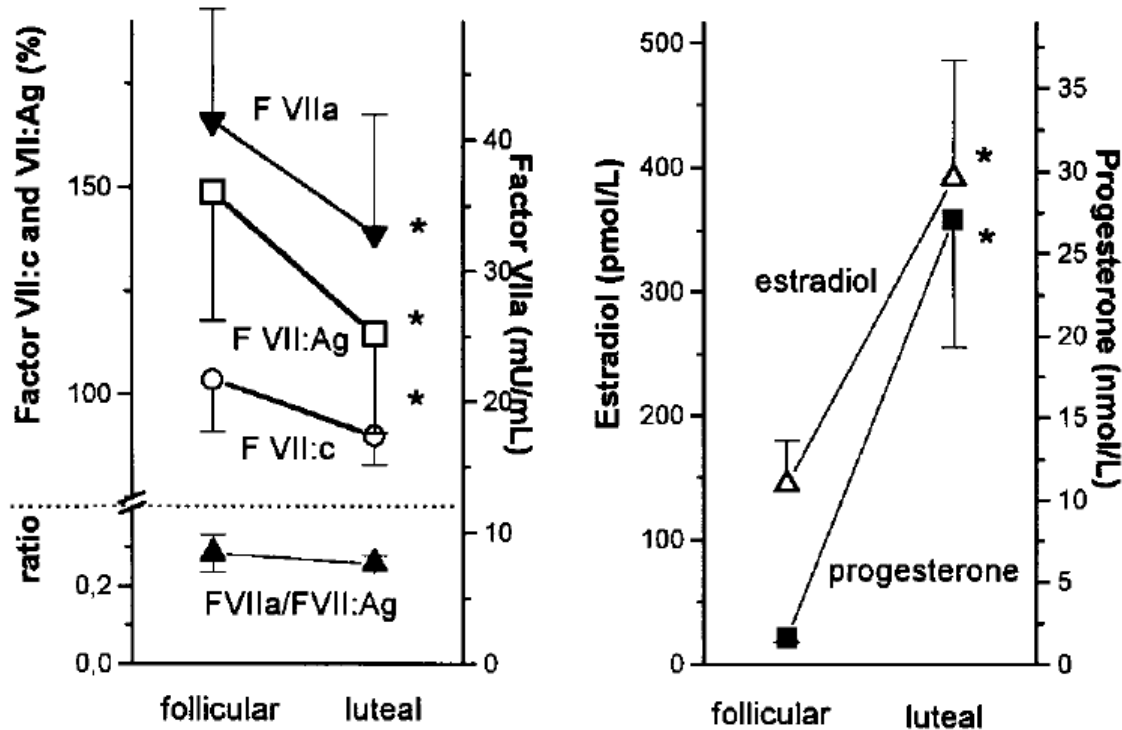


P<0.05 *vs E2; **vs E2 +MPA, ** vs E2 +Th



Plasma Factor VII

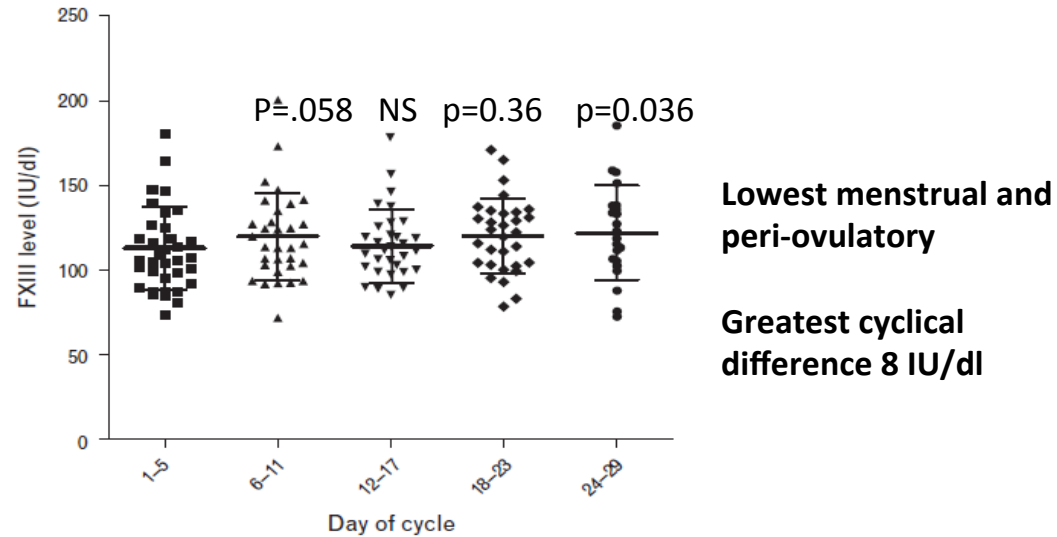
Kapoitis, et al. *Thromb Haemost.* 1998; 80:588-91



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
 - *Kapoitis 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*

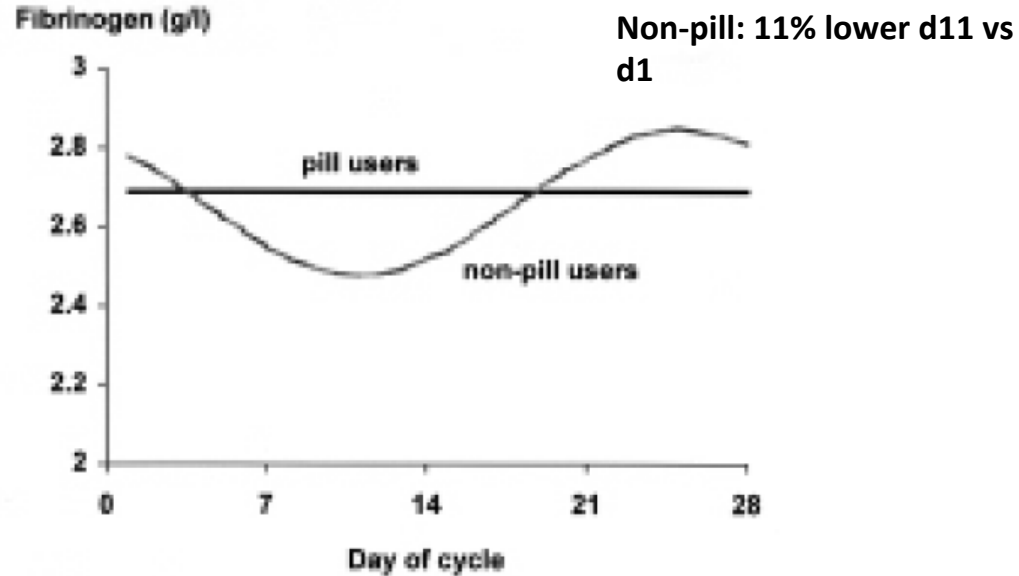


FIBRINOGEN



Fibrinogen: Cycle variation (No OC)

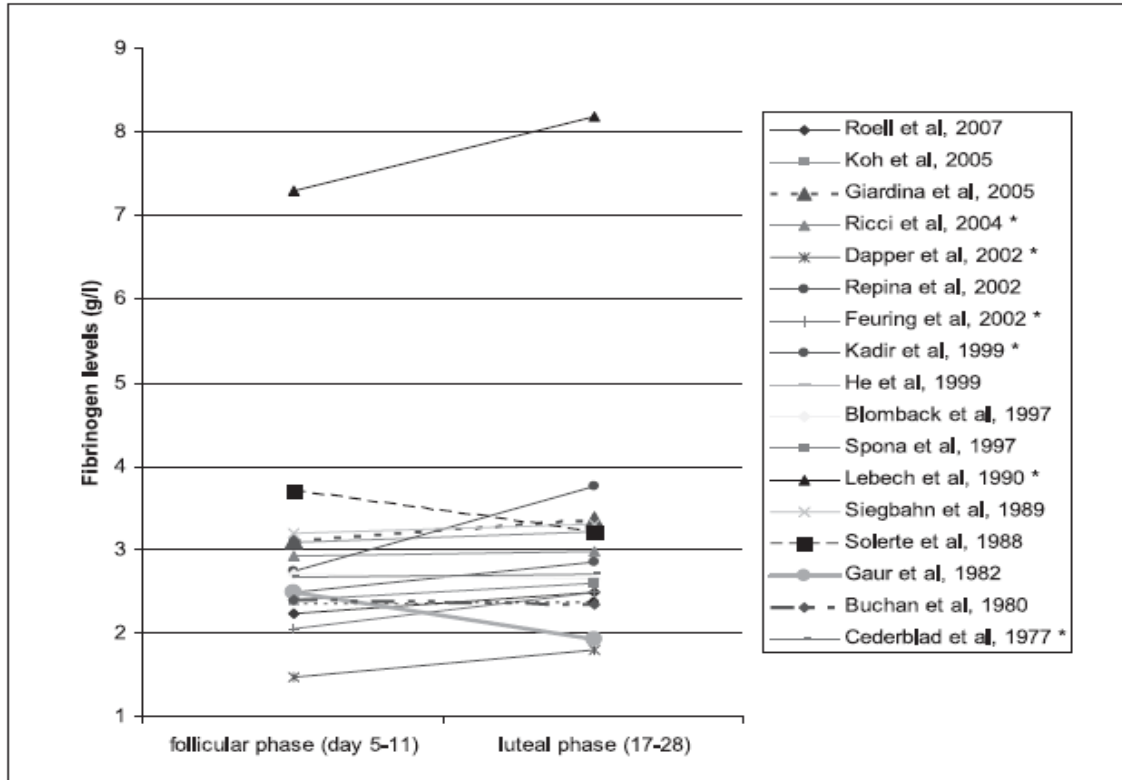
Lowest Day 11



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



Fibrinogen



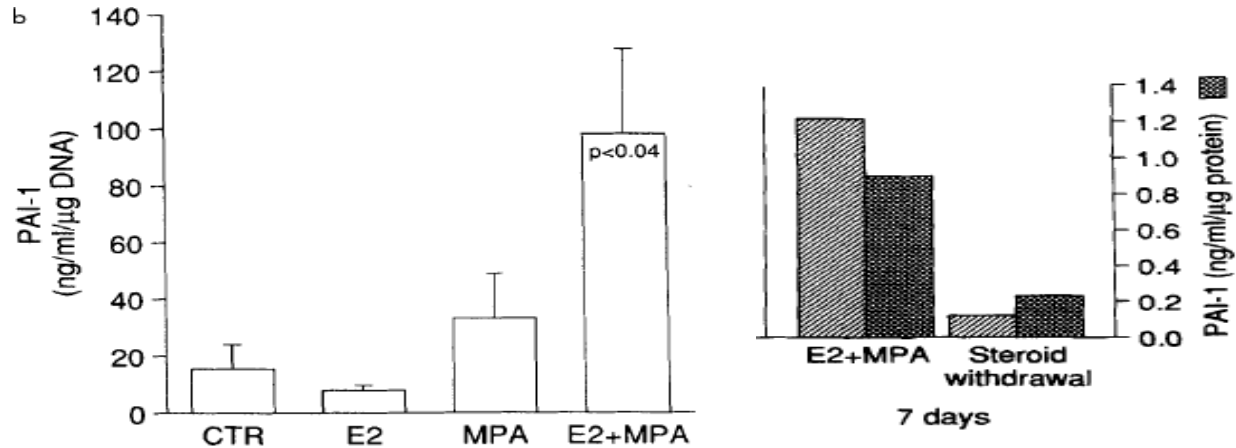
6/20 lowest follicular phase; 2/20 lowest luteal phase



FIBRINOLYTIC PARAMETERS



PAI-1 in Decidual Cell Cultures Treated with Progesterone

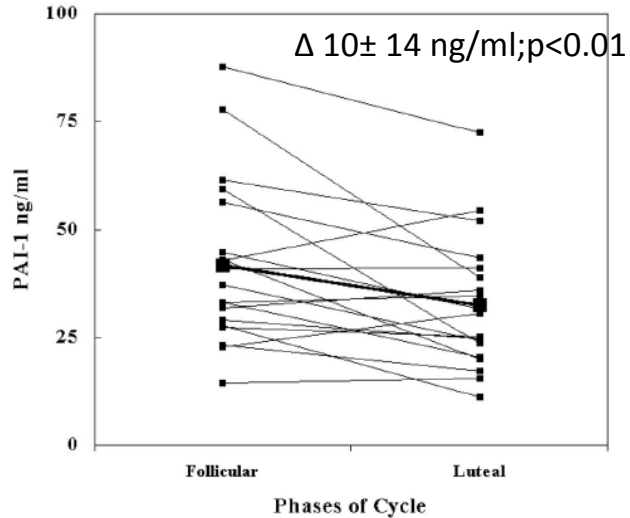


Lockwood, et al. Ann NY Acad Sci. 1994; 734:57-59

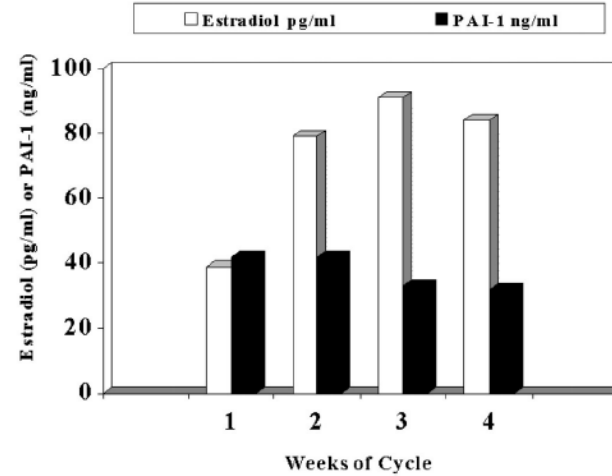


PAI-1

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 ± 283 vs. 1609 ± 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