Changes of Immune Cells during Menstrual Cycle

건양의대
산부인과
이성기

Neuroendocrine and Immune System

- Interactions between two systems?
  - Sex steroids
  - Prolactin
  - ACTH

Sex steroids may influence immune cells

- Menopause
  - ↓Total lymphocytes
    - Especially ↓ B cells, and CD4+ T cells
- POF
  - ↓ CD4+ T cells
  - ↑ CD8+ T cells, NK cells, and B cells

Life Sci 1994;54:1305-12

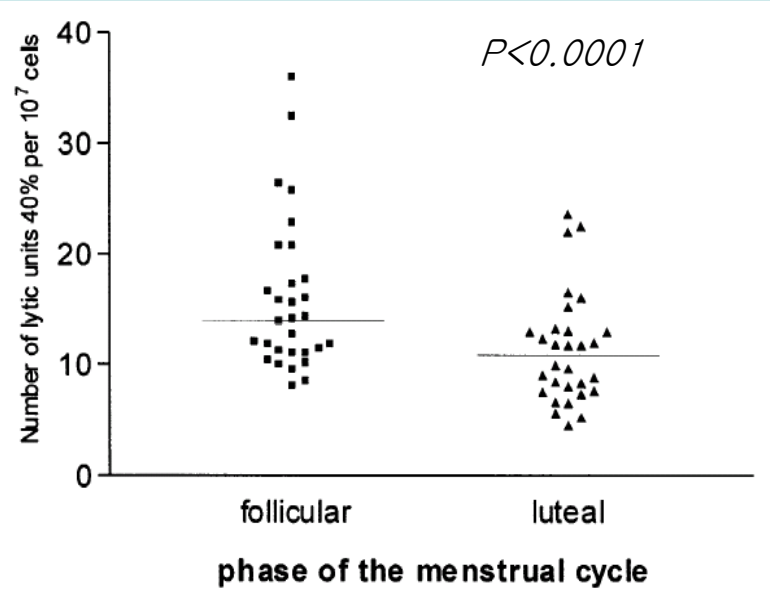
- Sheehan syndrome
  - ↑ T cells, CD4+, CD8+, CD19+ lymphocytes

Rev Invest Clin, 1993;45:247

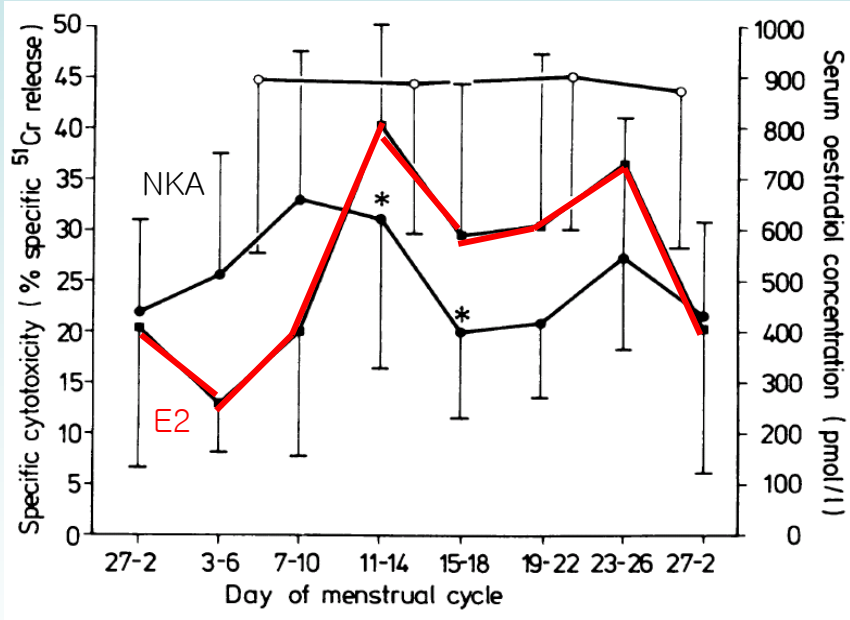
Controversy in menstrual impacts on immune system

- It does change.
  - ↓ CD8+ T cells at preov. period *(Clin Exp Obstet Gynecol, 1983;10:115)*
  - ↑ No. of *NK in early luteal phase (Gynecol Oncol, 2001, 81:254)*
  - ↓ NKA in luteal phase *(JRI, 2001;50:151, Br Med J, 1985;290:884)*
- No changes in T and/or B cell subsets
  - *Lopez-Karpovitchs et al. Rev Invest Clin, 1993;45:247*
  - *Coulam et al. AJRI, 1983;4:88*

NK Activity during Menstrual Cycle



JRI 2001, 50:151



•Significant variation seen during ovulation (unpaired t test, p=0.008)

Br Med J 1985, 290:884

Expansion of Treg during follicluar phase ?

Table I. *Comparative frequencies of $CD4^+CD25^+$, $CD4^+CD25^{high}$, and $FOXP3^+$ cells and sex hormone levels during the menstrual cycle*

	Day 3[a]	Day 9	Day 12[a]	Day 19	Day 24
First menstrual cycle					
Absolute number $CD4^+/\mu l$[b]	900.0	974.0	1150.0	1102.0	957.0
$CD4^+CD25^+$ frequency, %[c]	13.0	22.0	26.0	15.0	11.0
$CD4^+CD25^{high}$ frequency, %[d]	0.97	1.3	1.4	1.0	0.89
FOXP3 expression, %[e]	3.8	8.3	9.6	7.3	4.1
Estradiol level, pg/ml	30.0	146.0	219.0	106.0	31.0
Progesterone level, ng/ml	0.25	0.20	0.89	11.70	0.43
Second menstrual cycle					
Absolute number $CD4^+/\mu l$[b]	953.0	870.0	910.0	890.0	960.0
$CD4^+CD25^+$ frequency, %[c]	9.9	11.0	17.0	10.0	18.0
$CD4^+CD25^{high}$ frequency, %[d]	0.78	0.86	1.12	0.95	1.27
FOXP3 expression, %[e]	2.7	4.3	8.2	4.0	5.0
Estradiol level, pg/ml	31.0	74.0	173.0	82.0	118.0
Progesterone level, ng/ml	0.20	0.20	0.22	12.3	13.90

[a] Days of the menstrual cycle.
[b] Absolute count of $CD4^+$ cells acquired from complete blood.
[c] Frequency of peripheral blood $CD4^+CD25^+$ T lymphocytes expressed as percentage of $CD4^+$ T lymphocytes.
[d] Frequency of peripheral blood $CD4^+CD25^{high}$ T cell subset expressed as percentage of $CD4^+$ T lymphocytes.
[e] Frequency of FOXP3 expression in peripheral blood $CD4^+$ T lymphocytes.

J Immunol, 2007;178: 2572

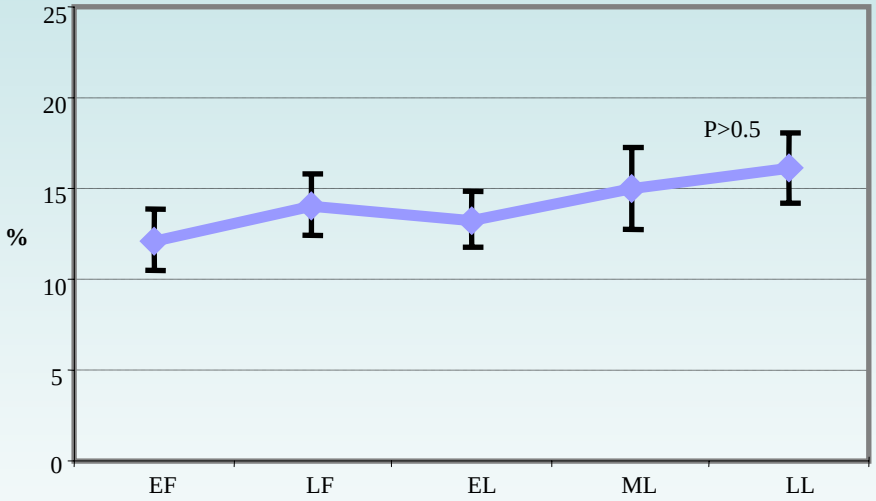
Importance to know whether the immune cells fluctuate during menstrual cycle

- Basic question of effects of sex steroid onto immune cells
- To determine the best period for immunologic tests

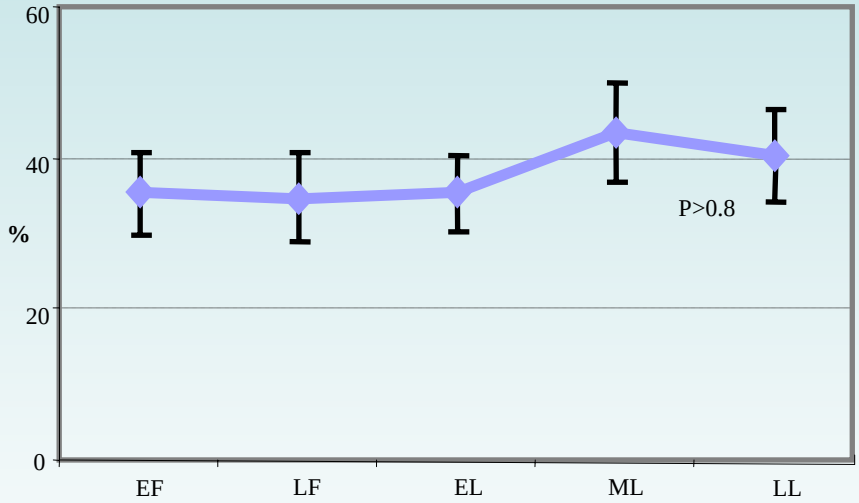
Study design

- Healthy women in reproductive ages
  - Nineteen women with regular menstrual cycles (mean age 30.5 years, range 24 - 42 years)
    - Six parous women and 13 nulliparous women
    - No history of abortions, active diseases or a history of autoimmune diseases
    - No one had taken any immunomodulatory agents
- Serial peripheral blood sampling
  - MCD#2-4, #11-13, #16-18, #20-22, and #26-27
- Immune markers
  - T, B, NK cells, and NK cytotoxicity
  - TNF-α, IFN-γ, IL-10, and Th1/Th2 cytokine ratio in CD3+CD8- ce lls
  - Treg, and Th17 cells

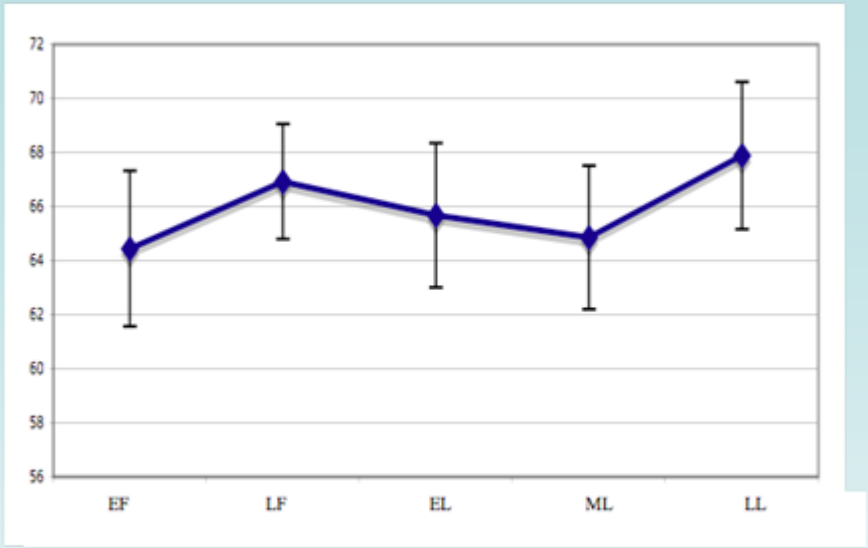
NK Levels



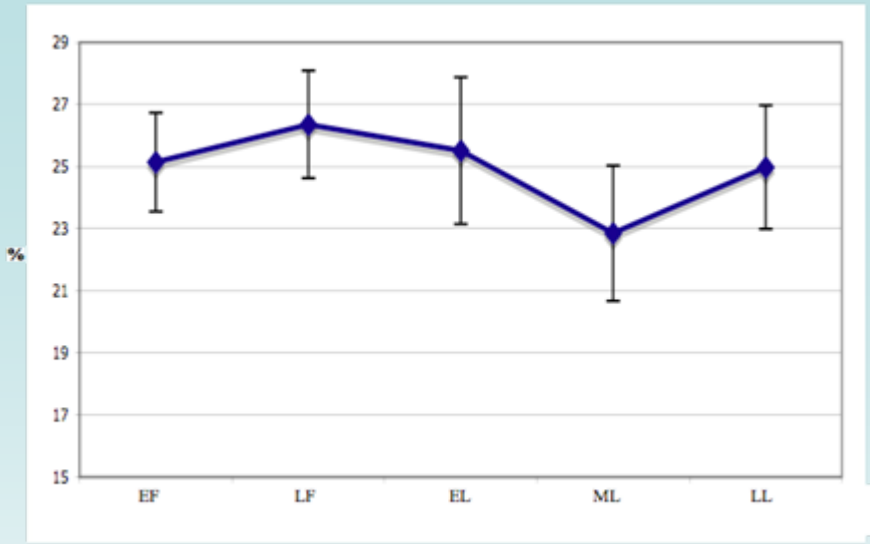
NK Cytotoxicity



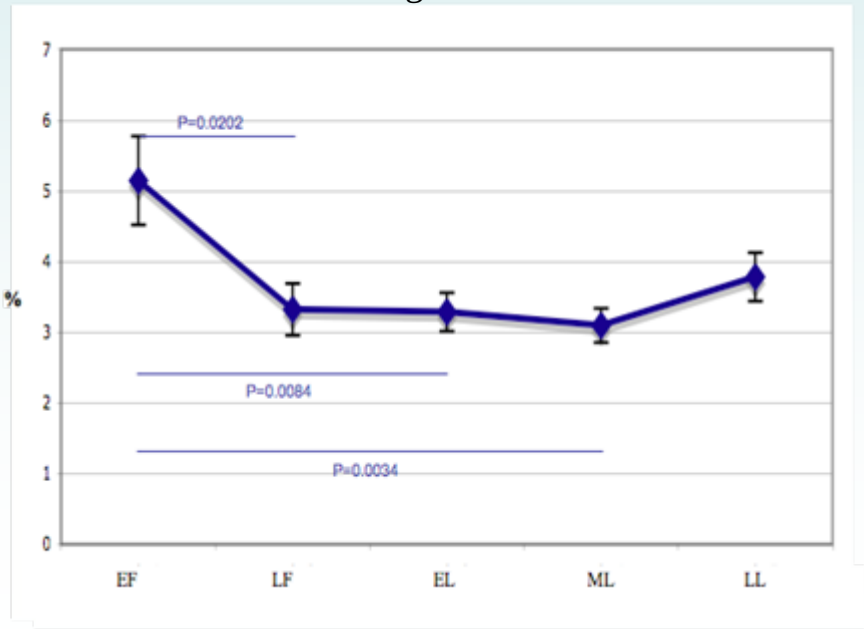
TNF-α secreting CD3+CD8- Cells



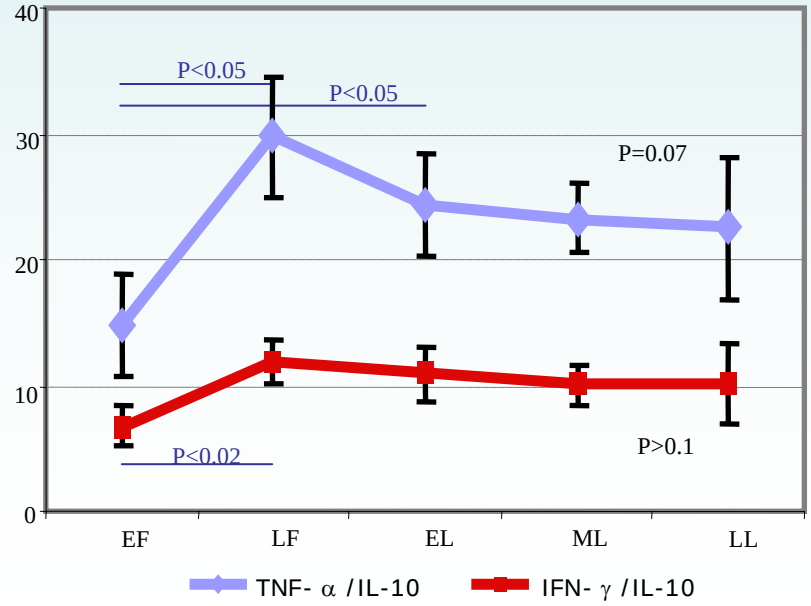
IFN-γ secreting CD3+CD8- Cells



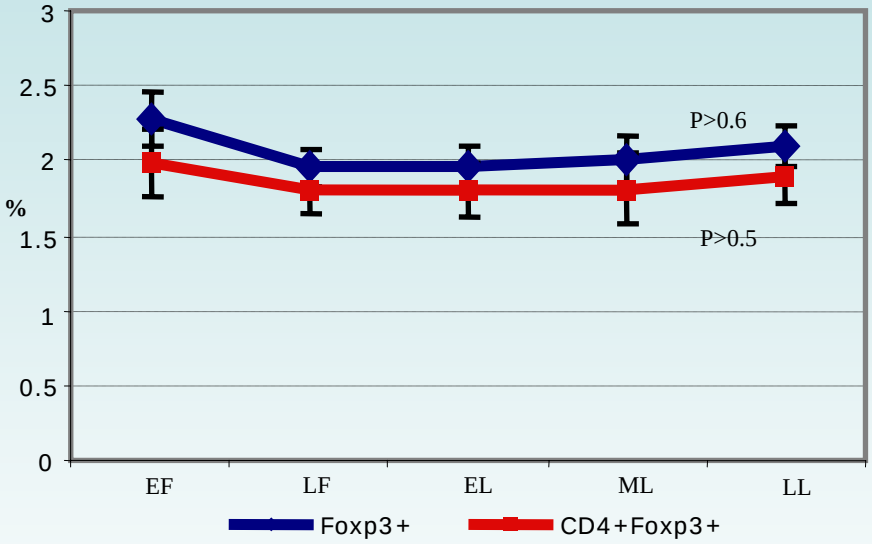
IL-10 secreting CD3+CD8- Cells



The ratio of Th1/Th2 cytokine producing CD3+CD8-T cells



Foxp3+ Treg Cells



Levels of IL-17 Producing Th17 cell