Clinical Immunologic Tests

Lee, Sung-Ki
Dept. OBGYN
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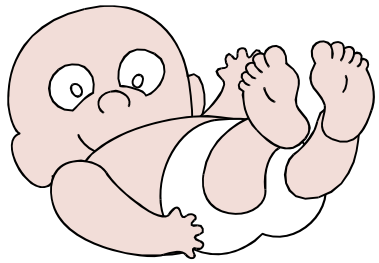
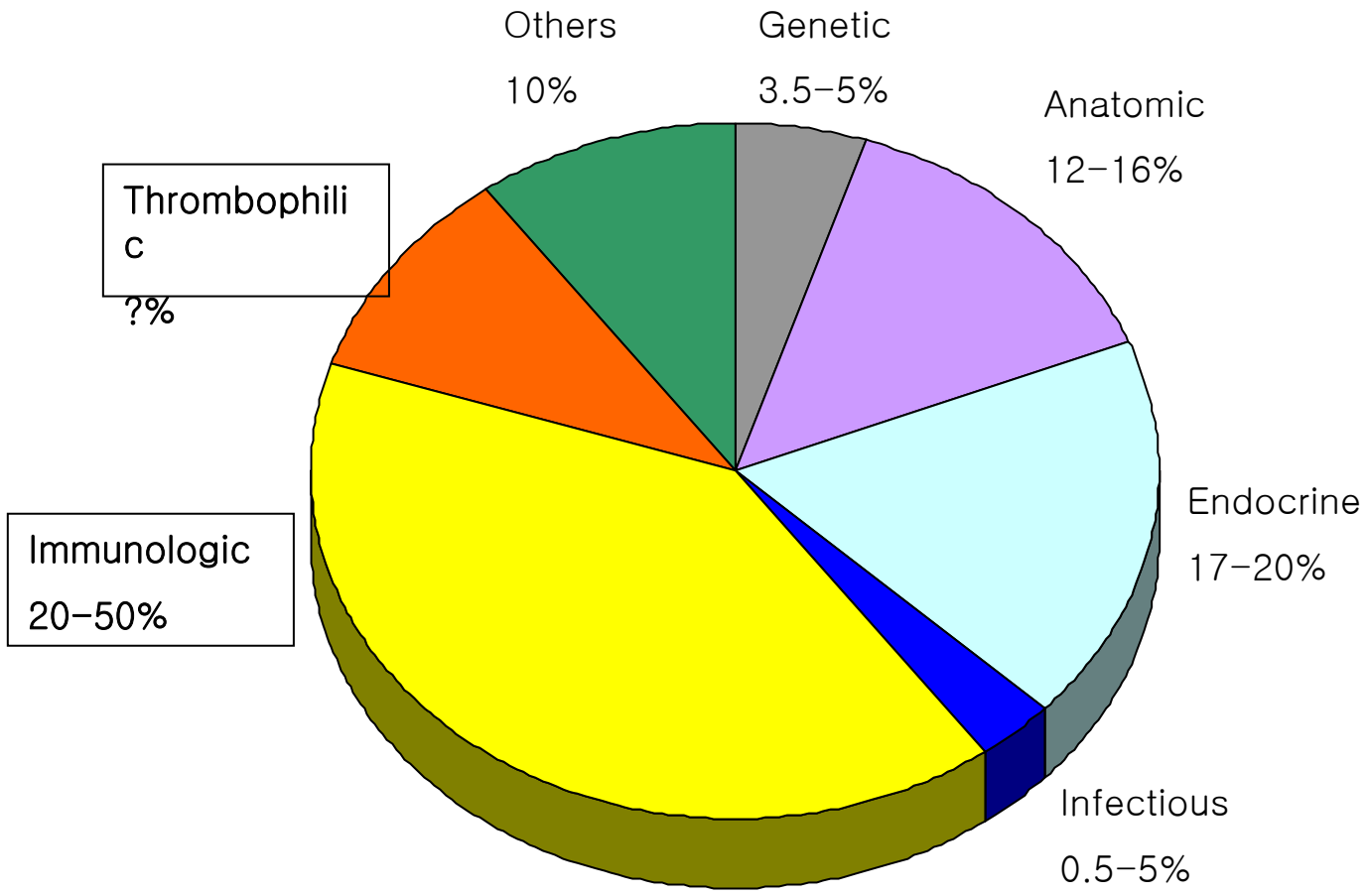


Etiologies of Recurrent Abortion



Berek and Novak's Gynecology, 14th ed.

Maternal Immune Reaction in Normal and Abnormal Pregnancy

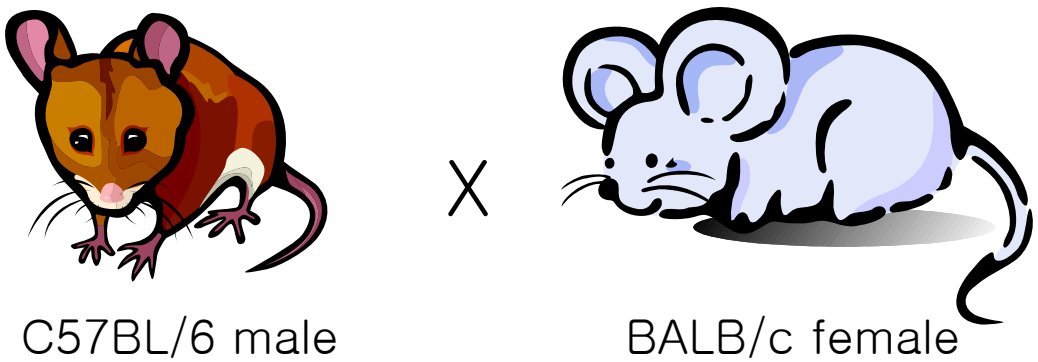
- Systemic
  - T cells
    - ↓ Th1/Th2 cytokine production
    - ↓ Cell-mediated immunity
  - NK cells
    - ↓ No. Peripheral NK
  - Monocytes and granulocytes
    - Functionally activated
    - ↑ Innate immunity
  - Dendritic cells
    - Controversial

- Local
  - T cells
    - ↓ No.
    - ↓ Th1/Th2 cytokine production
    - ↑γδ T
  - uNK cells
    - ↑ In first trimester
    - ↑ Innate immunity
  - Monocytes and macrophages
    - ↑ No.
    - ↑ Innate immunity
    - Role in placentation

preg prepreg

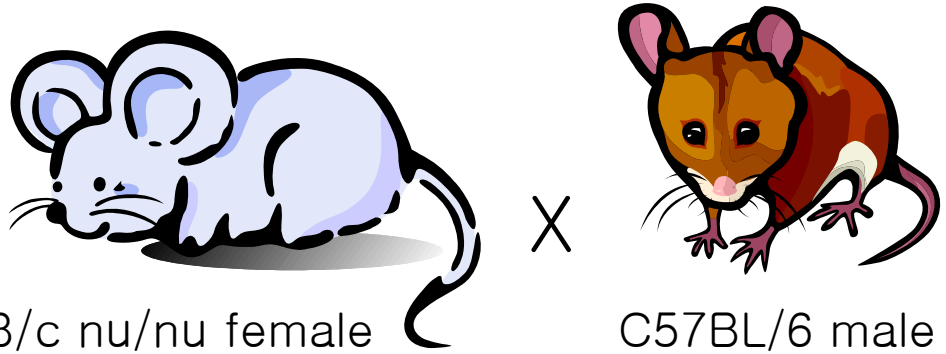
Hum Reprod Update 2003,9:347-357

Adoptive transfer of whole lymphocytes



C57BL/6 male X BALB/c female

Whole lymphocytes



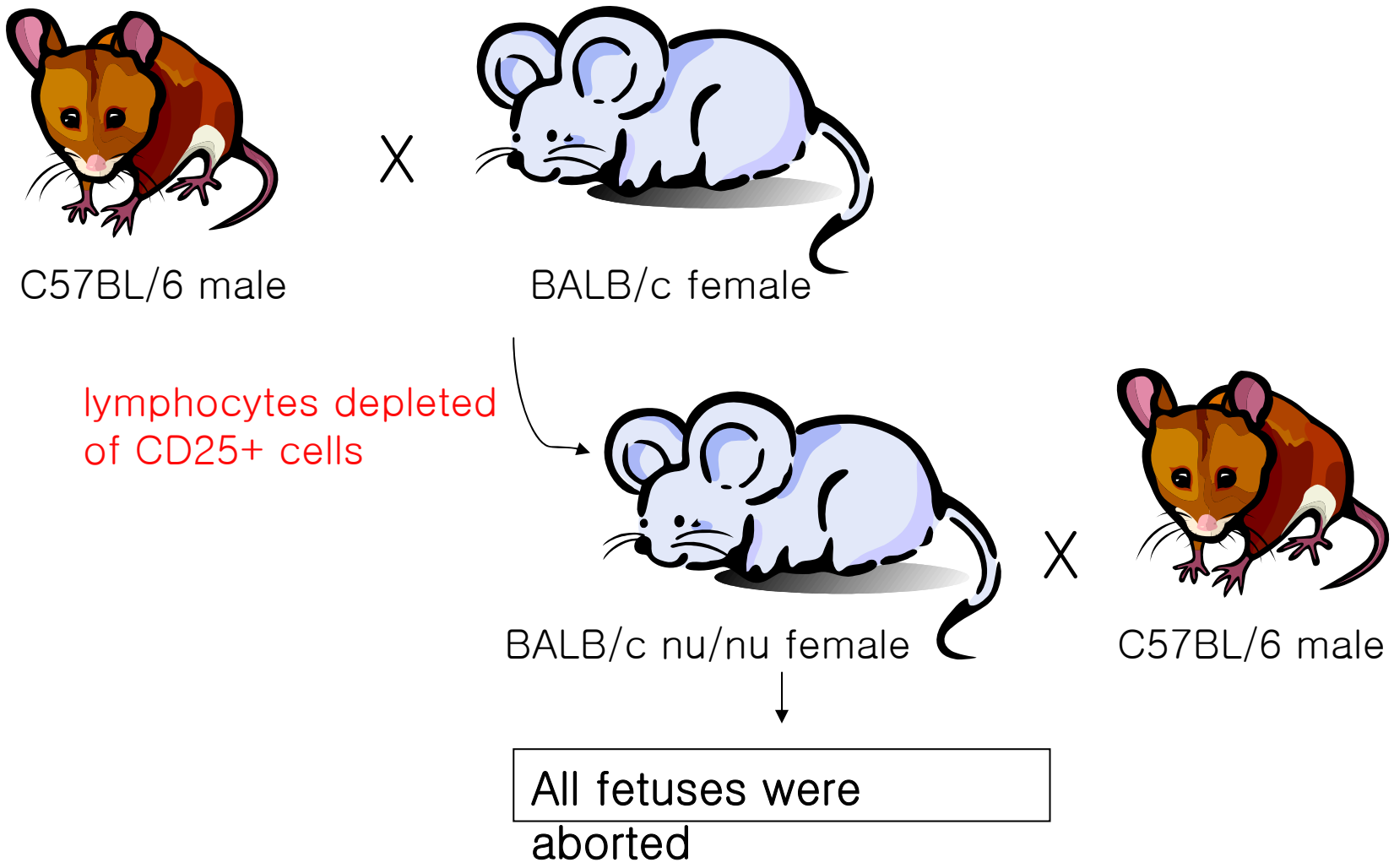
BALB/c nu/nu female X C57BL/6 male

Breeding efficiency of nude mice: 50%

60% of mice became pregnant

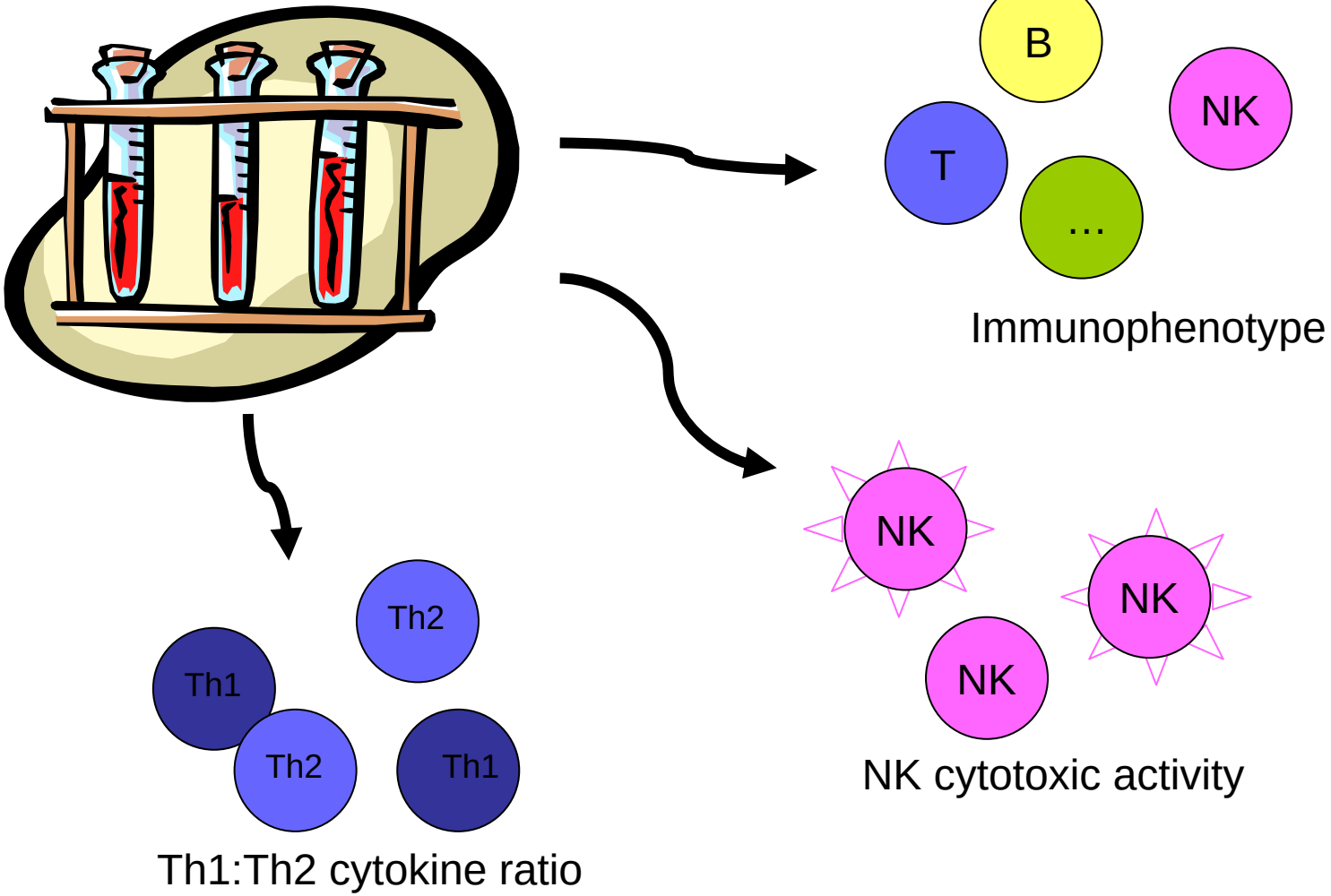
Aluvihare VR et al., Nat Immunol 2004;5:266-271

Adoptive transfer of CD4+CD25- cells



Aluvihare VR et al., Nat Immunol 2004;5:266-271

Immunologic Laboratory for Alloimmunity



Immunomorphology and NK Level and Cytotoxicity

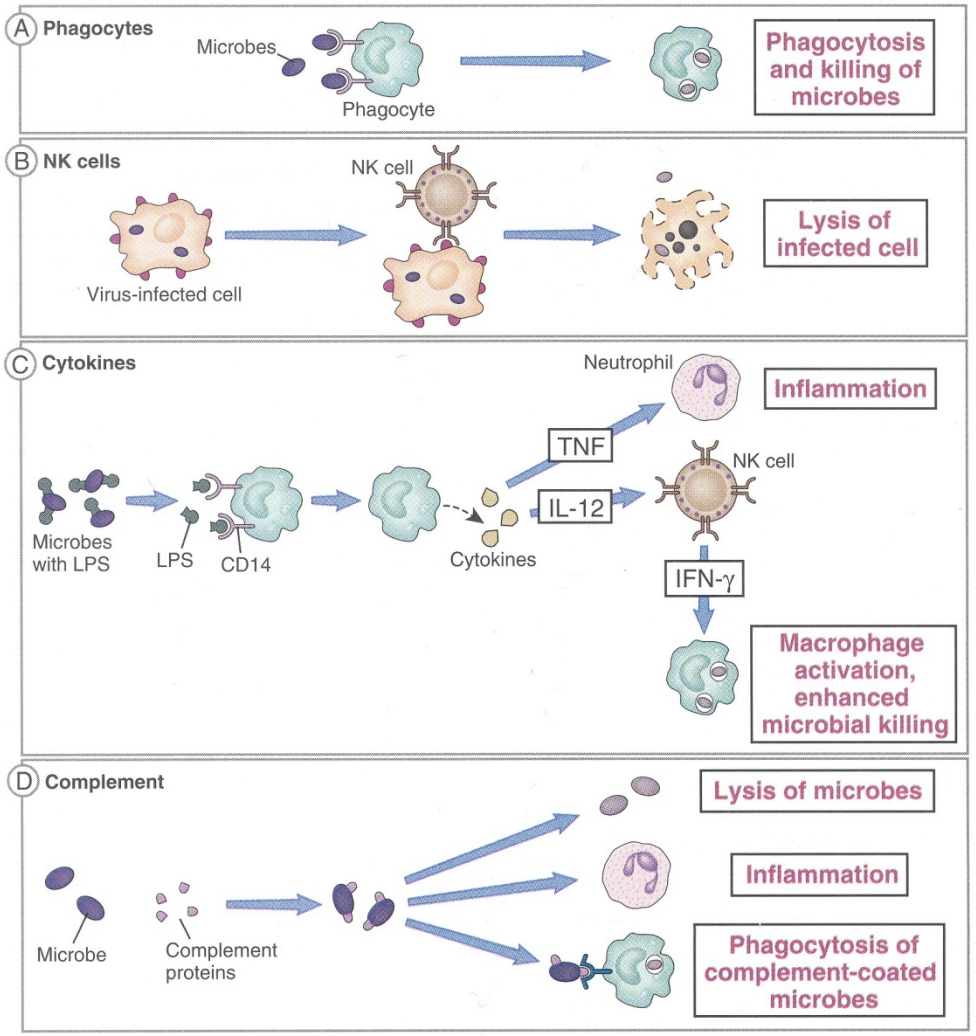
Innate Immunity

Components	Principal Functions
Barriers	
Epithelial layers	Prevent microbial entry
Defensins	Microbial killing
Intraepithelial lymphocytes	Microbial killing
Circulating Effector Cells	
Neutrophils	Early phagocytosis and killing of microbes
Macrophages	Efficient phagocytosis and killing of microbes, secretion of cytokines that stimulate inflammation
NK cells	Lysis of infected cells, activation of macrophages
Circulating Effector Proteins	
Complement	Killing of microbes, opsonization of microbes, activation of leukocytes
Mannose-binding lectin (collectin)	Opsonization of microbes, activation of complement (lectin pathway)
C-reactive protein (pentraxin)	Opsonization of microbes, activation of complement
Coagulation factors	Walling off of infected tissues
Cytokines	
TNF, IL-1, chemokines	Inflammation
IFN-α, -β	Resistance to viral infection
INF-γ*	Macrophage activation
IL-12	IFN-γ production by NK cells and T cells
IL-15	Proliferation of NK cells
IL-10, TGF-β	Control of inflammation

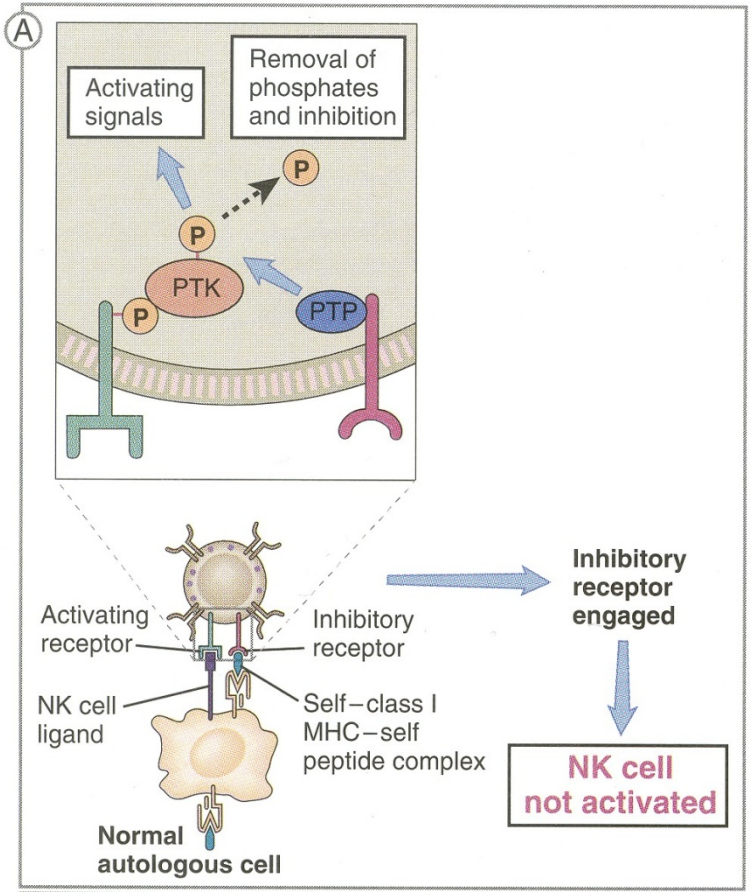
*IFN-γ is also produced during adaptive immune responses and is discussed in Chapter 11 as a cytokine of adaptive immunity.

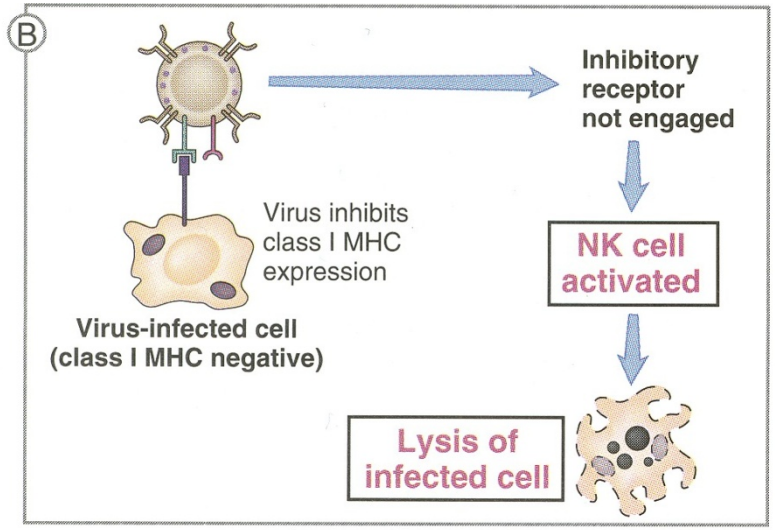
Abbreviations: IFN-α, interferon-α; IL-1, interleukin-1; NK, natural killer; TGF-β, transforming growth factor-β, TNF, tumor necrosis factor.

Components of Innate Immunity



Activating and Inhibiting Receptors of NK cells





Effector Functions of NK cells

- Targets
  - Virus infected cells and tumor cells
- Two main functions
  - Cytolysis
    - Secretion of perforin, granzymes, and granuloysin
  - Activation of macrophage by IFN-γ
    - To Increase phagocytosis

PB-NK

- 10-15% of lymphocytes in PB
- Phenotypes
  - $CD56^{dim}CD16^{+}$, ~90%
  - $CD56^{bright}CD16^{-}$, ~10%

  - CD56: homotypic adhesion
  - CD16: low affinity Fcγ receptor

CD56 as a Prognostic factor

Human Reproduction vol.15 no.5 pp.1163–1169, 2000

Peripheral natural killer cytotoxicity and $CD56^{pos}CD16^{pos}$ cells increase during early pregnancy in women with a history of recurrent spontaneous abortion

Table III. Retrospective analysis of putative risk factors for subsequent miscarriage within recurrent spontaneous abortion (RSA) women

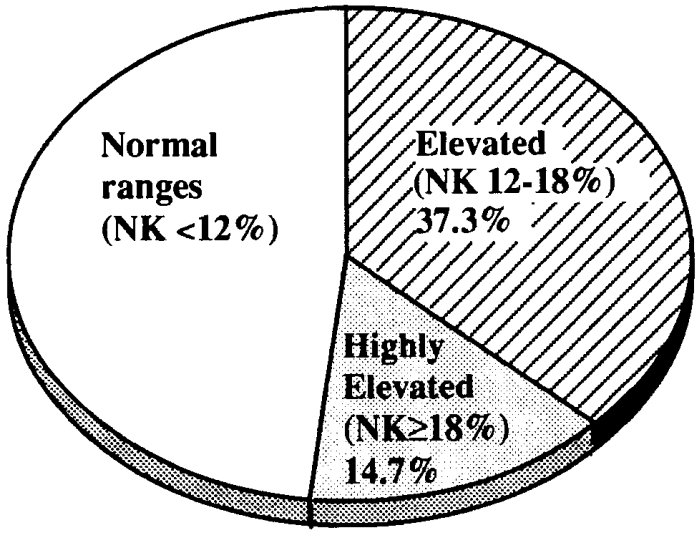
Parameter	Threshold value	Successful pregnancy[a]	Miscarriage[a]	*P* value
Lytic units	<322	4 (3)	3 (3)	
	⩾322	12 (7)	5 (3)	NS
% $CD56^{pos}CD3^{neg}$	<12.0	8 (5)	0 (0)	
	⩾12.0	7 (4)	7 (5)	⩽0.01 (0.05 to <0.10)
% $CD56^{pos}CD16^{pos}CD3^{neg}$	<20.7	12 (8)	7 (6)	
	⩾20.7	4 (2)	2 (1)	NS
% $CD56^{pos}CD16^{neg}CD3^{neg}$	<4.0	14 (8)	5 (3)	
	⩾4.0	1 (1)	2 (3)	NS
% $CD56^{pos}CD16^{neg}/CD56^{pos}$ $CD16^{pos}$	<0.08	5 (3)	2 (1)	
	⩾0.08	10 (6)	5 (5)	NS

NS = not significant.

[a]Number of RSA women with successful pregnancy or subsequent miscarriage after dichitomizing using the specific threshold values. Values in parentheses are the numbers of RSA women with three or more subsequent miscarriages.

Threshold of NK number

- 12%
  - Coulam et al,, 1995, AJRI
  - Beer et al., 1996, AJRI



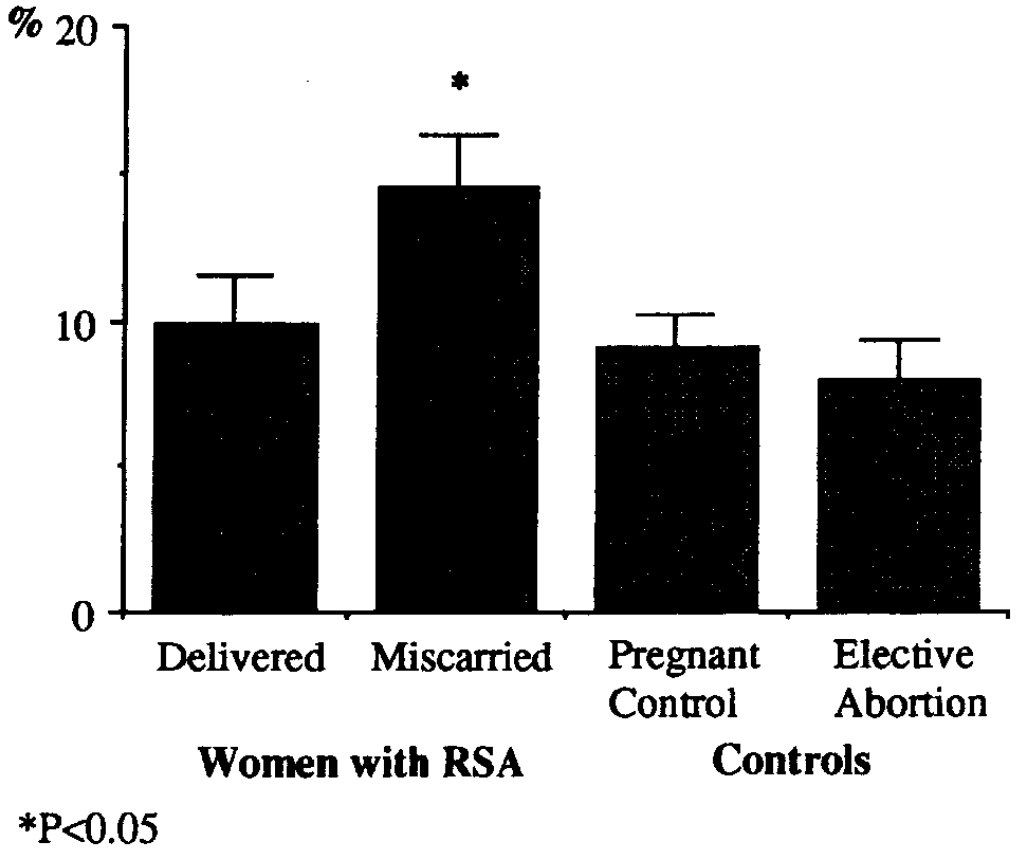
Elevated peripheral blood CD56+ cells in non-pregnant RSA women

Immunophenotype in RSA and Implantation Failure

- Higher $CD56^+$ level in nonpregnant RSA women
- Higher $CD19^+$, $CD56^+$, and $CD56^+CD16^+$ levels in pregnant RSA women
- Higher $CD19^+CD5^+$ cells in women with autoAb+ to nuclear component
- Higher $CD56^+$, and $CD56^+CD16^+$ in women with APA+
- Higher $CD56^+$ cells in IF patients
- $CD56^+ \geq 18\%$: all women aborted

Beer et al., AJRI, 1996,35:376

NK Levels and OB Outcomes in Pregnant RSA Women with LIT



AJRI 1996,35:376–382

The immunophenotype of patients with recurrent pregnancy loss

Dorota Darmochwal-Kolarz[a,*], Bozena Leszczynska-Gorzelak[b], Jacek Rolinski[a], Jan Oleszczuk[b]

	RSA (n=14) Median (%)	Control (n=18) Median (%)	P value
CD3+	77.6	68.45	NS
CD4+	48.5	43.0	<0.05
CD8+	23.5	26.2	NS
CD4:CD8	2.2	1.42	<0.05
CD3-CD16/CD56+	14.35	9.9	<0.05
CD19+	8.5	14.45	<0.005
CD19CD5+	2.0	0.9	<0.05

Eur J Obstet Gynecol Reprod Biol 2002;103:53

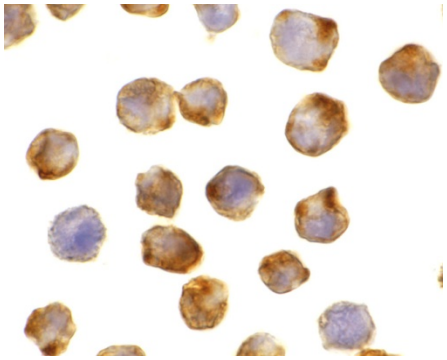
Immunophenotype in Normal Healthy Women with Hx of Successful Pregnancies

	Normal healthy Control, n=18 (%)
CD3+	51-79
CD4+	30-52
CD8+	16-40
CD3-CD16/CD56+	3-12
CD19+	5-17
CD19CD5+	0-1.5

Eur J Obstet Gynecol Reprod Biol 2002;103:53

K562 cells

- The K562 cell line derived from a CML patient in blast crisis
- Target cells for NK cells
  - No expression of MHC class I molecules
  - No inhibition of NK activity by MHC class I-KIR interaction.



NK Cytotoxicity

Preconceptional natural-killer-cell activity as a predictor of miscarriage

Koji Aoki, Shoji Kajiura, Yujin Matsumoto, Mayumi Ogasawara, Setsuo Okada, Yoshiaki Yagami, Norbert Gleicher

There is no immunological test for the prospective identification of alloimmune causes of miscarriage. We investigated whether activity of natural killer cells was predictive of subsequent abortion in women who had had unexplained recurrent abortions and had received no treatment. 24 women with high preconceptional NK activity, defined as mean plus 1 SD of NK activity of 47 controls, had a significantly higher abortion rate in the next pregnancy than 44 women with normal levels of NK activity (71 vs 20%; relative risk 3·5; 95% CI 1·8–6·5). The preconceptional evaluation of NK activity in women with recurrent miscarriages may thus be predictive of the risk of pregnancy loss at the next conception.

Lancet 1995; **345**: 1340–42

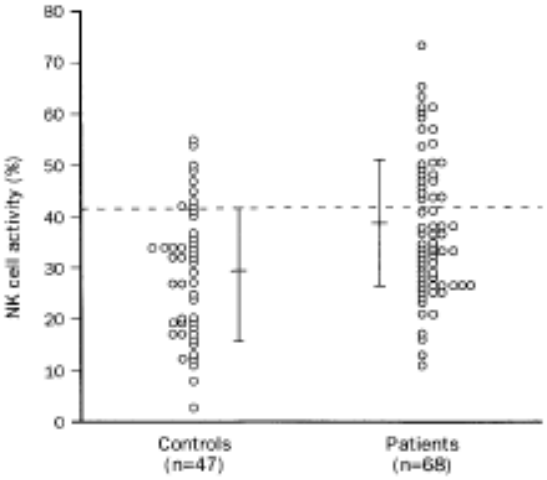


Figure: **Preconceptional NK activity**
Dotted line indicates value taken as a high level of NK activity.

Measurement of NK activity

- Chromium-51 release cytotoxicity assay
  - 3.7×10^3 Bq ^{51}Cr-labelled K562 cells
  - 2×10^5 PBMCs
  - Calculation: ([test cpm-spontaneous cpm]/[max. cpm-spontaneous cpm])x100
  - *Aoki et al., Lancet, 1995*
- Flow cytometric assay
  - 1×10^4 K562 cells
  - 5×10^5, 2.5×10^5, or 1.25×10^5 PBMCs
  - Calculation: % dead K562 cells-% spontaneous K562 cell death
  - *Gilman-Sachs et al., AJRI, 1999*

AJRI 1999; 41:99–105
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American Journal of Reproductive Immunology
ISSN 8755-8920

Natural Killer (NK) Cell Subsets and NK Cell Cytotoxicity in Women with Histories of Recurrent Spontaneous Abortions

ALICE GILMAN-SACHS, BRIAN K. DUCHATEAU, CHERYL J. ASLAKSON, GHISLAINE P. WOHLGEMUTH, JOANNE Y. KWAK, ALAN E. BEER, AND KENNETH D. BEAMAN

TABLE I. Summary of Data Obtained from the Flow Cytometric NK Cell Cytotoxicity Assay[a]

	Range		Mean		SD	
	High Responder[b]	Low Responder[b]	High Responder[b]	Low Responder[b]	High Responder[b]	Low Responder[b]
Cytotoxicity at E:T ratio of 50:1	20.1–38.3	5.8–19.9	26.3	13.7	4.7	3.9
Cytotoxicity at E:T ratio of 25:1	15.0–27.0	3.1–14.8	19.7	9.1	3.2	2.9

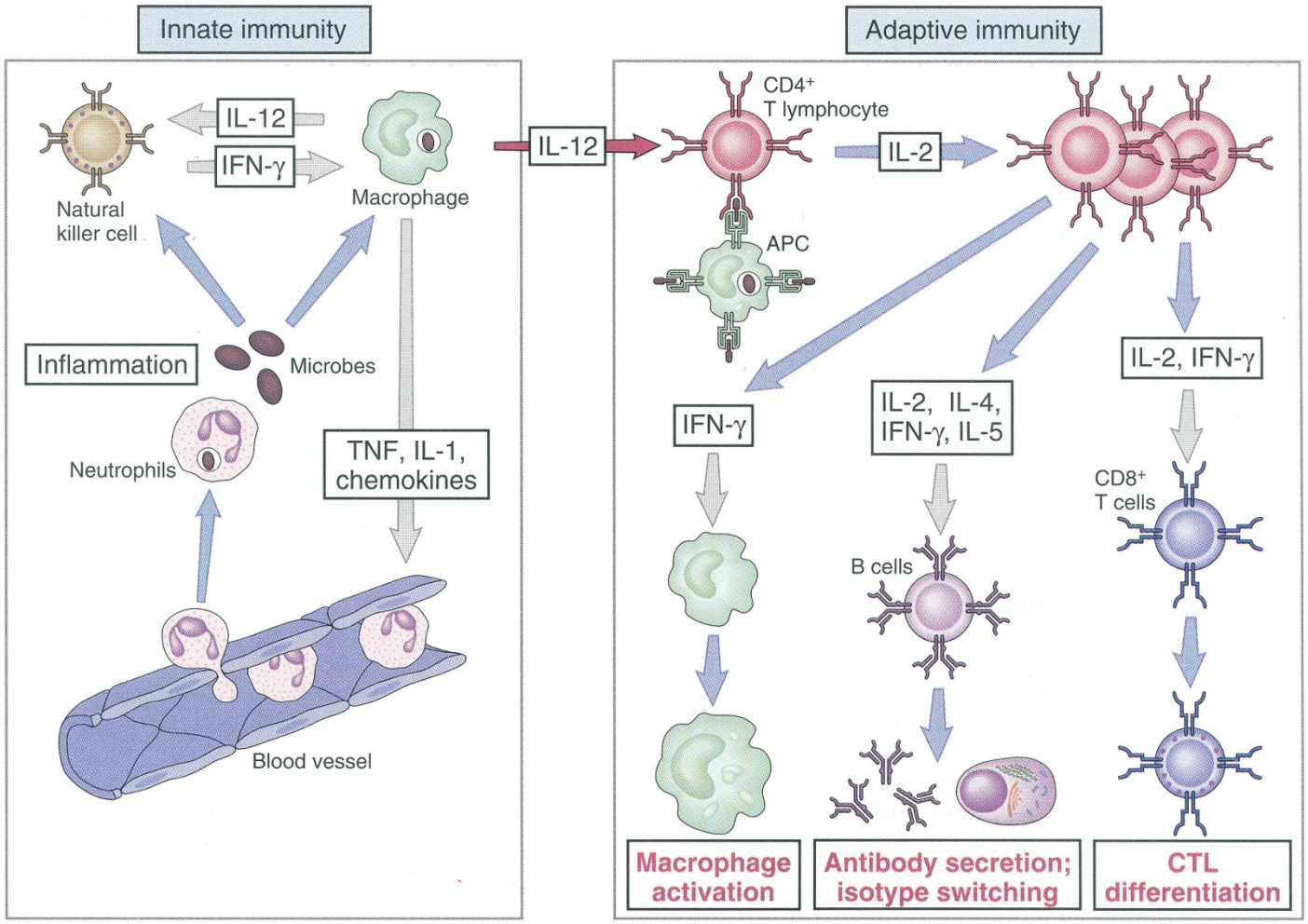
SD, standard deviation.

[a] *Values listed are percentages of cytotoxicity detected using the flow cytometric NK cell cytotoxicity assay.*

[b] *At an E:T ratio of 50:1, a high responder was defined as an individual with a cytotoxicity of 20% or greater. A low responder was defined as an individual with a cytotoxicity less that 20%. At an E:T ratio of 25:1, a high responder was defined as an individual with a cytotoxicity of 15% or greater. A low responder was defined as an individual with a cytotoxicity less than 15%.*

Cytokine Assay

Cytokines in Host Defense



Th1 and Th2 subsets of $CD4^+$ T cells

Property	T_H1 Subset	T_H2 Subset
Cytokines produced		
IFN-γ, IL-2, TNF	+++	−
IL-4, IL-5, IL-13	−	+++
IL-10	±	++
IL-3, GM-CSF	++	++
Cytokine receptor expression		
IFN-γ receptor β chain	−	++
IL-12 receptor (signaling, or β2, chain)	++	−
Chemokine receptor expression		
CCR3 (eotaxin receptor)	±	++
CCR4	±	++
CXCR3	++	±
Ligands for E- and P-selectins	++	±
Antibody isotypes stimulated (mouse)	IgG2a	IgE, IgG1 (IgE, IgG4 in humans)
Macrophage activation	+++	−

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; TFN, tumor necrosis factor.

Human Reproduction Vol.18, No.4 pp. 767–773, 2003 DOI: 10.1093/humrep/deg156

Increased T helper 1 cytokine responses by circulating T cells are present in women with recurrent pregnancy losses and in infertile women with multiple implantation failures after IVF

J.Y.H.Kwak-Kim[1,2,3], H.S.Chung-Bang[1], S.C.Ng[2], E.I.Ntrivalas[2], C.P.Mangubat[1], K.D.Beaman[2], A.E.Beer[1,2] and A.Gilman-Sachs[2]

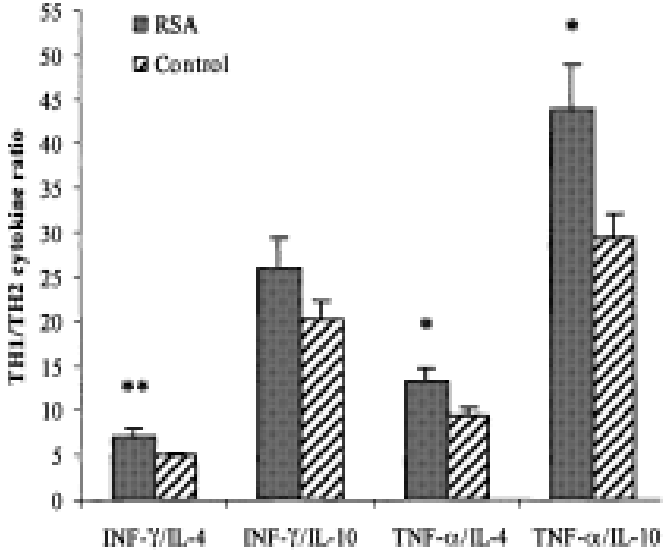
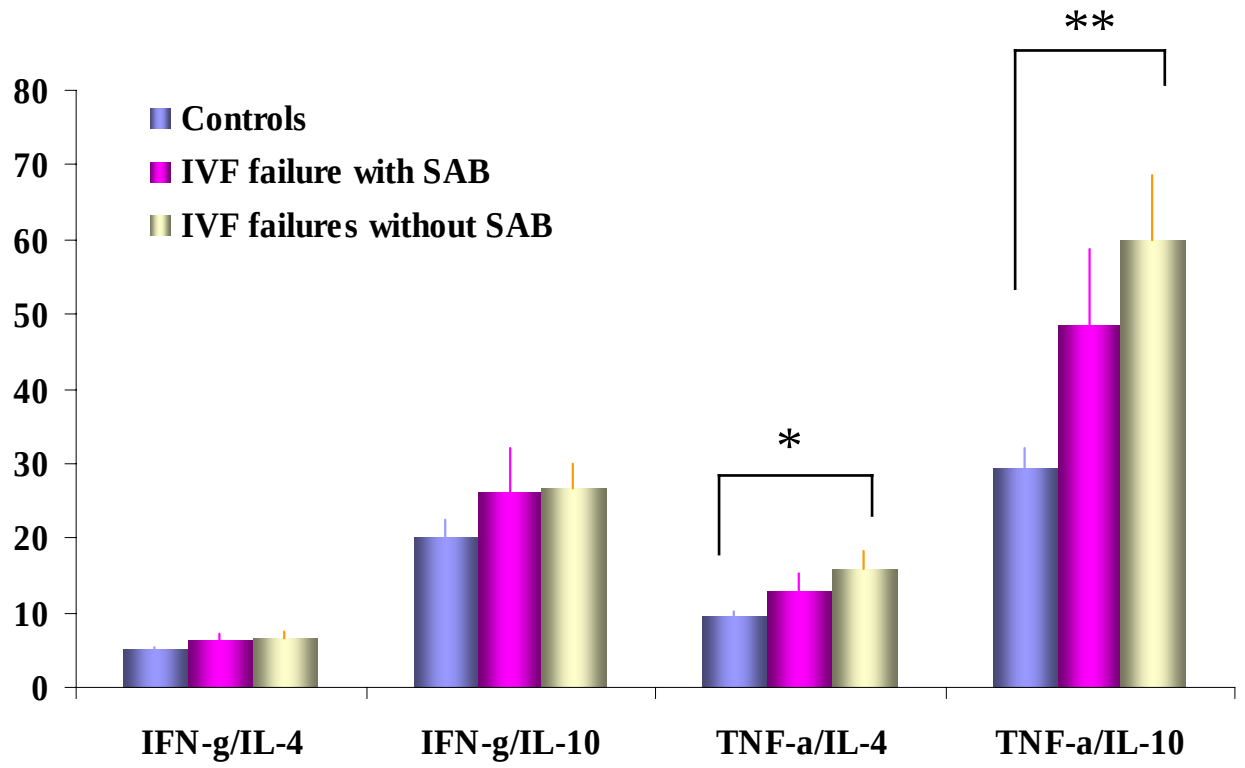


Figure 3. Comparison of Th1/Th2 cytokine producing CD3+/CD8– cell ratios in women with three or more recurrent spontaneous abortions ($n = 26$) and normal fertile controls ($n = 21$). Values present the mean ± SEM. *$P < 0.05$; **$P < 0.01$. IL = interleukin; for other abbreviations, see Table III.

Th1/Th2 Ratios in CD3+CD4+ Cells of Women with Multiple IVF Failures



*P<0.05
**P<0.005

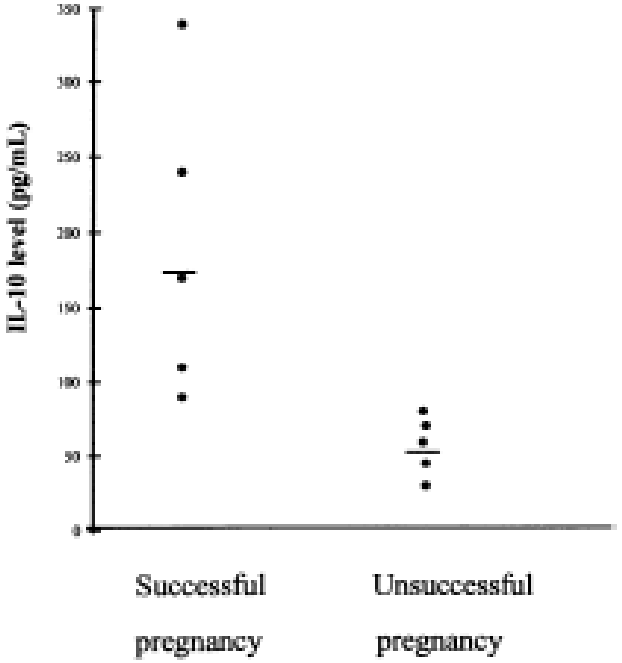
Human Reprod 2003;18:767

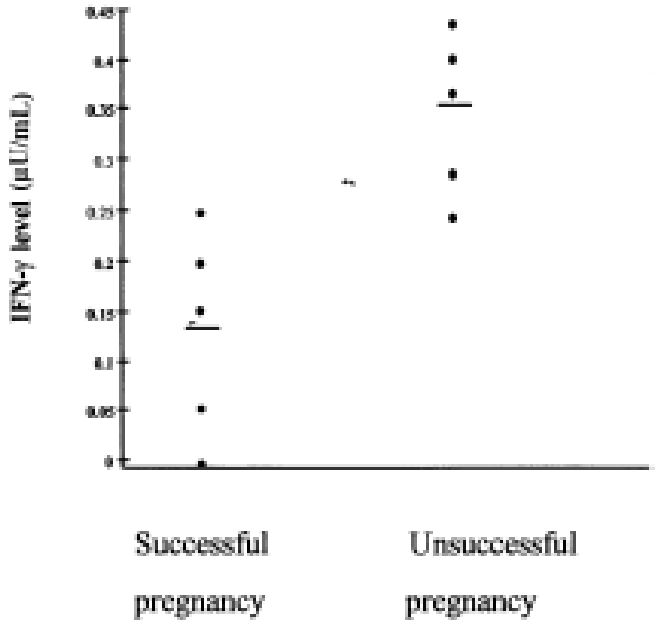
FERTILITY AND STERILITY®
VOL. 73, NO. 6, JUNE 2000

Evidence of a T_H 1 type response associated with recurrent miscarriage

Carol Jenkins, M.Sc.,[a] Judith Roberts, M.R.C.O.G.,[a] Rhoda Wilson, Ph.D.,[a] Marjorie A. MacLean, M.D.,[a] Jane Shillito, M.R.C.O.G.,[a] and James J. Walker, M.D.[b]

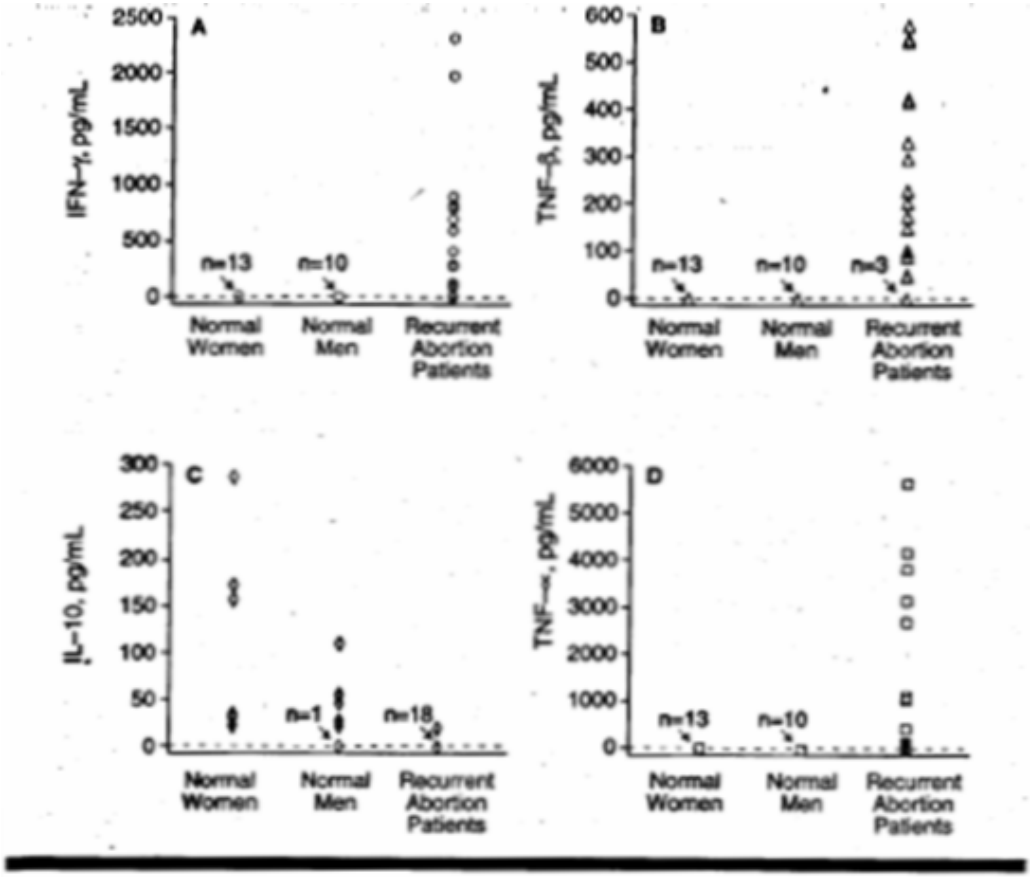
Glasgow Royal Infirmary, Glasgow, Scotland and St. James Hospital, Leeds, West Yorkshire, United Kingdom





T-Helper 1–Type Immunity to Trophoblast in Women With Recurrent Spontaneous Abortion

Joseph A. Hill, MD; Katalin Polgar, PhD; Deborah J. Anderson, PhD



Levels of interferon gamma (IFN-γ) (A), tumor necrosis factor-β (TNF-β) (B), interleukin-10 (IL-10) (C), and TNF-α (D) in trophoblast-activated peripheral blood mononuclear cell culture supernatants among reproductively normal women (n=13), normal men (n=10), and patients with recurrent spontaneous abortion (n=20).

Analysis of Immunologic Tests

IMK-Lymphocyte Assay

Collecting blood 1ml into heparin tube.

First staining Whole blood samples

A. BD Leucogate (CD45-FITC / CD14-PE)

B. Isotype Control (IgG1-FITC / IgG2a-PE)

C. CD3-FITC / CD19-PE

D. CD3-FITC / CD4-PE

E. CD3-FITC / CD8-PE

F. CD3-FITC / CD16+CD56-PE

RBC lysis by lysing solution.

The stained samples were evaluated on flow cytometer.

a. T (CD3+) lymphocytes

b. B (CD19 +) lymphocytes

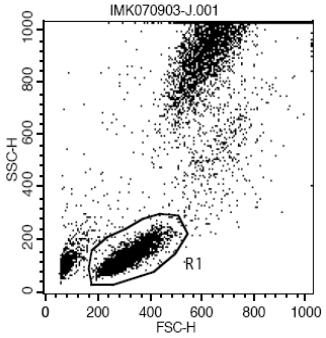
c. helper/inducer T (CD3+CD4) lymphocytes

d. suppressor/cytotoxic T (CD3+CD8+) lymphocytes

e. natural killer (NK) (CD3-CD16+and/or CD56+) lymphocytes

f. helper/suppressor T-lymphocyte ratio (CD3+CD4+/CD3+CD8+)

Immunomorphology Assay

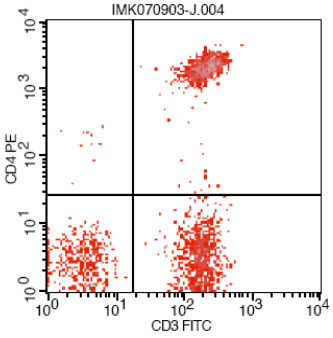


Gate Statistics

File: IMK070903-J.001
Sample ID: JY Kim
Tube: Leucogate
Acquisition Date: 03-Sep-07
Gated Events: 10000
X Parameter: FSC-H (Linear)

Log Data Units: Linear Values
Patient ID:
Panel: IMK Lymph
Gate: No Gate
Total Events: 10000
Y Parameter: SSC-H (Linear)

Gate	Events	% Gated	% Total
G1	2966	29.66	29.66

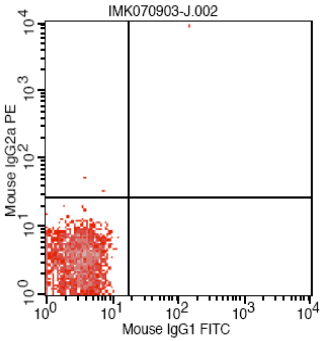


Quadrant Statistics

File: IMK070903-J.004
Sample ID: JY Kim
Acquisition Date: 03-Sep-07
Gated Events: 2629
Quad Location: 18, 26

Log Data Units: Linear Values
Tube: CD3/CD4
Gate: G1
Total Events: 10000

Quad	Events	% Gated	% Total	X Mean	Y Mean
UL	10	0.38	0.10	3.98	180.27
UR	971	36.93	9.71	215.08	2081.60
LL	503	19.13	5.03	3.59	3.21
LR	1145	43.55	11.45	183.52	3.93

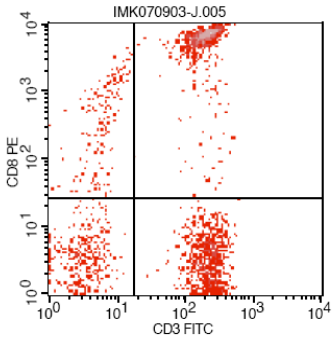


Quadrant Statistics

File: IMK070903-J.002
Sample ID: JY Kim
Tube: Mouse IgG1/Mouse IgG2a
Acquisition Date: 03-Sep-07
Gated Events: 2951
Quad Location: 18, 26

Log Data Units: Linear Values
Patient ID:
Panel: IMK Lymph
Gate: G1
Total Events: 10000

Quad	Events	% Gated	% Total	X Mean	Y Mean
UL	3	0.10	0.03	4.96	38.37
UR	1	0.03	0.01	137.00	9139.82
LL	2947	99.86	29.47	3.49	3.70
LR	0	0.00	0.00	***	***

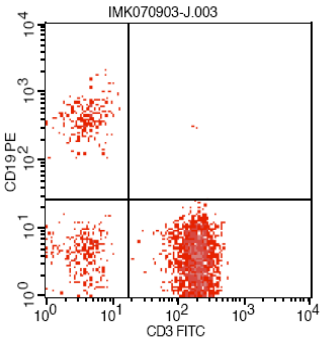


Quadrant Statistics

File: IMK070903-J.005
Sample ID: JY Kim
Acquisition Date: 03-Sep-07
Gated Events: 2602
Quad Location: 18, 26

Log Data Units: Linear Values
Tube: CD3/CD8
Gate: G1
Total Events: 10000

Quad	Events	% Gated	% Total	X Mean	Y Mean
UL	155	5.96	1.55	6.79	799.60
UR	1055	40.55	10.55	194.12	6245.75
LL	390	14.99	3.90	3.55	4.21
LR	1002	38.51	10.02	220.63	3.91

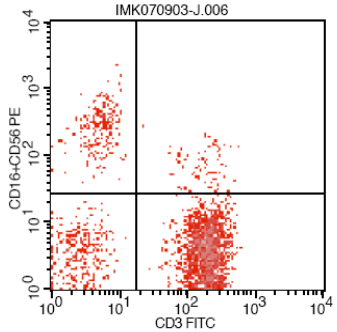


Quadrant Statistics

File: IMK070903-J.003
Sample ID: JY Kim
Tube: CD3/CD19
Acquisition Date: 03-Sep-07
Gated Events: 2858
Quad Location: 18, 26

Log Data Units: Linear Values
Patient ID:
Panel: IMK Lymph
Gate: G1
Total Events: 10000

Quad	Events	% Gated	% Total	X Mean	Y Mean
UL	227	7.94	2.27	4.46	480.41
UR	3	0.10	0.03	201.51	213.60
LL	292	10.22	2.92	4.03	4.91
LR	2336	81.74	23.36	192.96	4.19



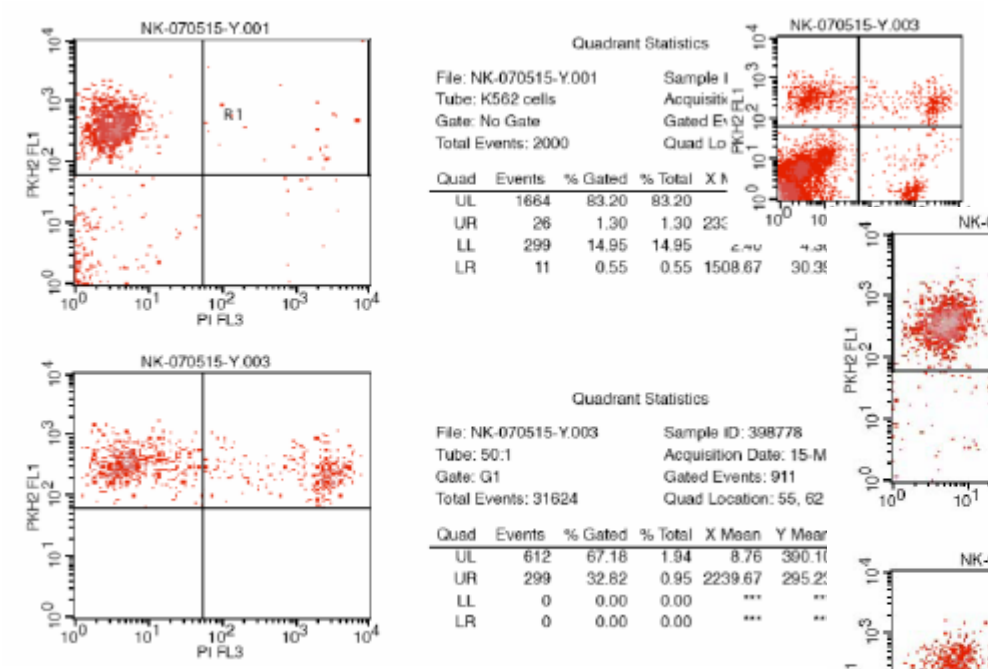
Quadrant Statistics

File: IMK070903-J.006
Sample ID: JY Kim
Acquisition Date: 03-Sep-07
Gated Events: 2952
Quad Location: 18, 26

Log Data Units: Linear Values
Tube: CD3/CD16+CD56
Gate: G1
Total Events: 10000

Quad	Events	% Gated	% Total	X Mean	Y Mean
UL	224	7.59	2.24	5.33	337.63
UR	78	2.64	0.78	183.69	83.67
LL	348	11.79	3.48	3.03	4.24
LR	2302	77.98	23.02	194.49	4.29

NK Cytotoxicity Assay



Quadrant Statistics

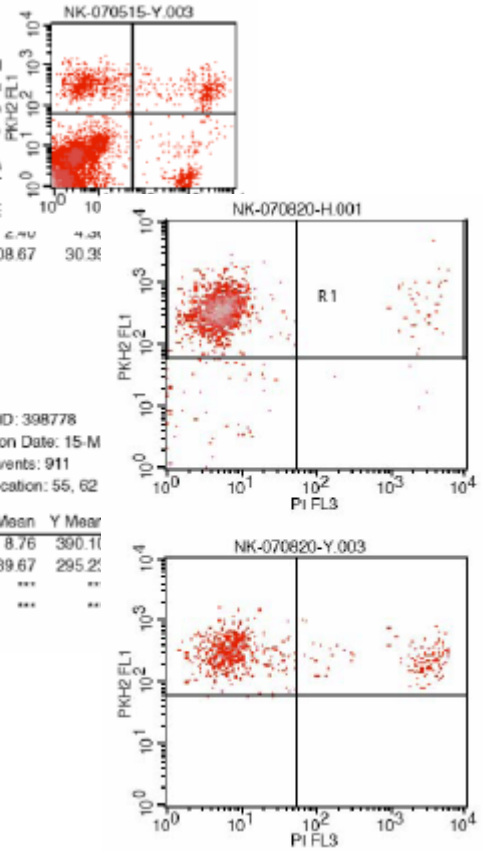
File: NK-070515-Y.001
Tube: K562 cells
Gate: No Gate
Total Events: 2000

Quad	Events	% Gated	% Total	X M
UL	1664	83.20	83.20	
UR	26	1.30	1.30	23
LL	299	14.95	14.95	
LR	11	0.55	0.55	1508.67

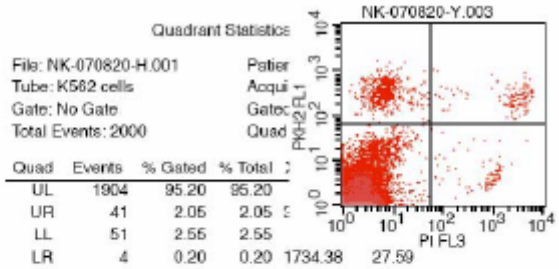
Quadrant Statistics

File: NK-070515-Y.003
Tube: 50:1
Gate: G1
Total Events: 31624
Sample ID: 398778
Acquisition Date: 15-M
Gated Events: 911
Quad Location: 55, 62

Quad	Events	% Gated	% Total	X Mean	Y Mean
UL	612	67.18	1.94	8.76	390.1
UR	299	32.82	0.95	2239.67	295.2
LL	0	0.00	0.00	***	**
LR	0	0.00	0.00	***	**



Initial test



Quadrant Statistics

File: NK-070820-H.001
Tube: K562 cells
Gate: No Gate
Total Events: 2000

Quad	Events	% Gated	% Total	
UL	1904	95.20	95.20	
UR	41	2.05	2.05	
LL	51	2.55	2.55	
LR	4	0.20	0.20	1734.38 27.59

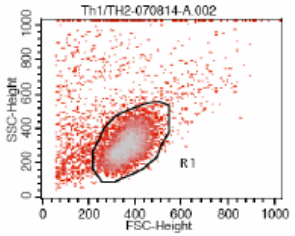
Quadrant Statistics

File: NK-070820-Y.003
Tube: 50:1
Gate: G1
Total Events: 171150
Patient ID: 398778
Acquisition Date: 20-Aug-07
Gated Events: 721
Quad Location: 55, 62

Quad	Events	% Gated	% Total	X Mean	Y Mean
UL	600	83.22	0.35	8.77	360.60
UR	121	16.78	0.07	2696.93	278.89
LL	0	0.00	0.00	***	***
LR	0	0.00	0.00	***	***

1 week after IVIG Tx

TH1/TH2 Intracellular Cytokine Ratio

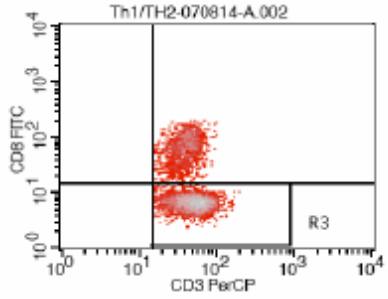


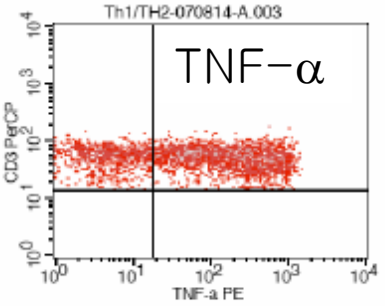
Gate Statistics

File: Th1/TH2-070814-A.002
Tube: mouse isotype control
Gate: No Gate
Total Events: 10000

Sample ID: 303272
Acquisition Date: 14-Aug-07
Gated Events: 10000

Gate	Events	% Gated	% Total
G1	8711	87.11	87.11
G2	5570	55.70	55.70
G3	4045	40.45	40.45



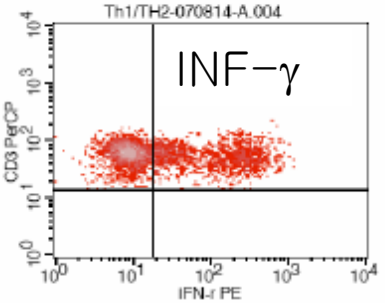


Quadrant Statistics

File: Th1/TH2-070814-A.003
Tube: TNF-a
Gate: G3
Quad Location: 17, 13

Sample ID: 303272
Acquisition Date: 14-Aug-07
Gated Events: 3428

Quad	Events	% Gated	% Total	X Mean	Y Mean
UL	968	28.24	9.68	6.34	58.23
UR	2460	71.76	24.60	278.94	55.41
LL	0	0.00	0.00	***	***
LR	0	0.00	0.00	***	***

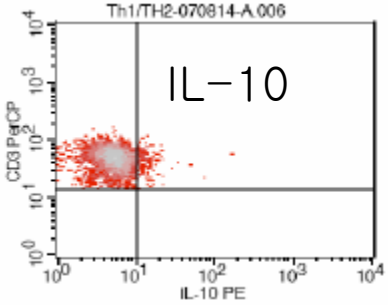


Quadrant Statistics

File: Th1/TH2-070814-A.004
Tube: IFN-r
Gate: G3
Quad Location: 17, 13

Sample ID: 303272
Acquisition Date: 14-Aug-07
Gated Events: 4165

Quad	Events	% Gated	% Total	X Mean	Y Mean
UL	2514	60.36	25.14	8.99	63.90
UR	1651	39.64	16.51	159.75	58.90
LL	0	0.00	0.00	***	***
LR	0	0.00	0.00	***	***



Quadrant Statistics

File: Th1/TH2-070814-A.006
Tube: IL-10-2.5
Gate: G3
Quad Location: 10, 13

Sample ID: 303272
Acquisition Date: 14-Aug-07
Gated Events: 4005

Quad	Events	% Gated	% Total	X Mean	Y Mean
UL	3812	95.18	38.12	5.19	51.06
UR	193	4.82	1.93	14.15	48.10
LL	0	0.00	0.00	***	***
LR	0	0.00	0.00	***	***

Reference Range at RFUMS/CMS

Immunomorphology	
%$CD3^+$	60-85
%$CD19^+$	2-12
%$CD56^+$	2-12
% $CD19^+CD5^+$	5-10
NK cytotoxicity assay (Effector:Target)	
50:1	10-40*
25:1	5-30
12.5:1	3-20
TH1/TH2 intracellular cytokine ratio	
TNF-α/IL-10 (CD3+CD4+)	13.2-30.6
INF-γ/IL-10 (CD3+CD4+)	5.8-20.5

Time to test and Sampling

- In the morning
  - Follicular phase
  - 1 week after IVIG
- Sampling
  - 5 to 7 ml per test
  - in heparinized tube (green-top)
  - should be arrived at the lab within 24 hrs

Reproductive Immunology Laboratory, Konyang University Hospital

Printed on
2007.09.06

Patient		Unit No	Physician
Sample #	Draw Date	Entered on	Refering Hospital
1	07.09.03	07.09.05	
Reference #			
1			

IMK test

Name	Result	Units	Limits
Total T cell	72.56	%	59 ~ 85
Total B cell	13.21	%	6.4 ~ 23.0
Th cell	44.1	%	31-61
Tc cell	26.43	%	11 ~ 38
Th/Tc ratio	1.6685585	ratio	0.9 ~ 3.6
NK cell	13.17	%	5.6 ~ 31

NK Assay (% Killed) Follow up

Name	Result	Units	Limits
50:1	36.37	%	10 ~ 40
25:1	24.42	%	5 ~ 30
12.5:1	15.1	%	3 ~ 20

Th1:Th2 intracellular cytokine ratios

Name	Result	Units	Limits
TNF-α	70.47	%	
IFN-γ	47.33	%	
IL-10	5.49	%	
TNF-α:IL-10	12.836066	Ratio	13.2 ~ 30.6
IFN-γ:IL-10	8.6211293	Ratio	5.8 ~ 20.5

End of Patient Report

Comments

정상범위에 있습니다.
경계부위에 있습니다.
비정상적인 소견을 보입니다. 면역치료의 대상으로 사료됩니다.

Laboratory Tests for RSA

Causes	Valuable	Unproven	Worthless
Genetic	Karyotype		HLA
Anatomic	HSG, hysteroscopy		
Endocrine	TSH, PRL	FSH, CCCT, LH, A, Noyes criteria	
Infectious		Mycoplasma, Ureaplasma,Chlamydia	
Thrombophilia*	*FVL, Factor II,* **Antithrombin m. Prot.C & S, Homocysteine,**		
Immunologic	ACL, LAC	**NK, Th1/Th2 ratio, ATA, other autoAbs**	ANA, antipaternal cytotoxic Ab, MLR, suppressor factors, cytokines, oncogene, growth factors, embryotoxic factor

Berek and Novak's Gynecology, 14th ed.

Japanese Guideline to Evaluate RSA

Basal tests	CBC, CRP, VDRL, Chlamydia Ag, Vaginal culture for bacterial infection,
1st screening	TVUS, HSG, PRL, LH, FSH, TSH, fT4, glucose, P4, BBT, parental chromosome study, ANA, APA, antiβ2g, LAC, ACL IgG/M, anti-PS IgG/M aPTT, PT, Factor XII activity
2nd screening	Hysteroscopy, SonoHSG, MRI 75OGTT, HbA1C Protein C activity and level Protein S activity and level + AT III when pregnancy loss in 2nd trimester or later Anti-DNA, anti-SS-A/RO, NK activity, Th1/Th2 ratio, blocking Ab activity, anti-HLA

Acta Obstet et Gynecol Japonica 2004;56(6):859-862

의료보험 적용여부

- Immunomorphology
  - 심평원에 보험적용여부 질의함
  - 급여 적응대상으로 보기 어렵다고
- NK cytotoxicity assay
  - 심평원에 신의료기술 신청함
  - 아직 답신 없음
- Th1/Th2 cytokine assay
  - 심평원에 신의료기술 신청함
  - 아직 답신 없음

미국: FDA 미승인, 일부 보험회사 인정, 일부 대학 CPT code에 준해 검사 시행

일본: 비급여, 합법적, 학회인정
NK activity,
Th1/Th2 ratio,
blocking Ab activity,
anti-HLA

Conclusions

- Systemic immune is important in pregnancy as well.
- Useful 3 immunologic tests
  - Immunophenotype test
  - NK cytotoxicity assay
  - Th1/Th2 cytokine assay
- To assess prognosis and define indications of Tx.
- To monitor Tx. response