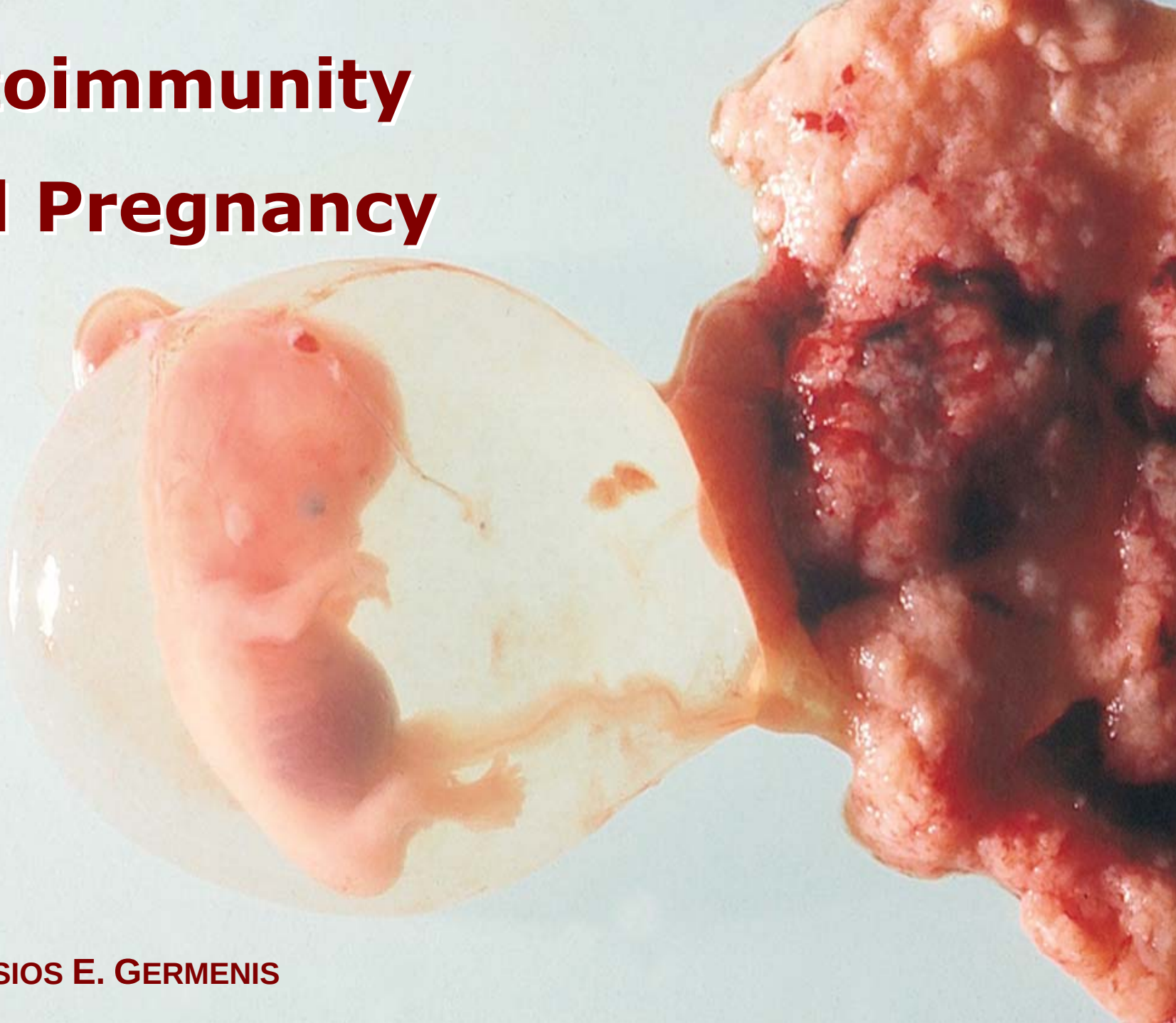
# Autoimmunity and Pregnancy



ANASTASIOS E. GERMENIS

# Immune homeostasis

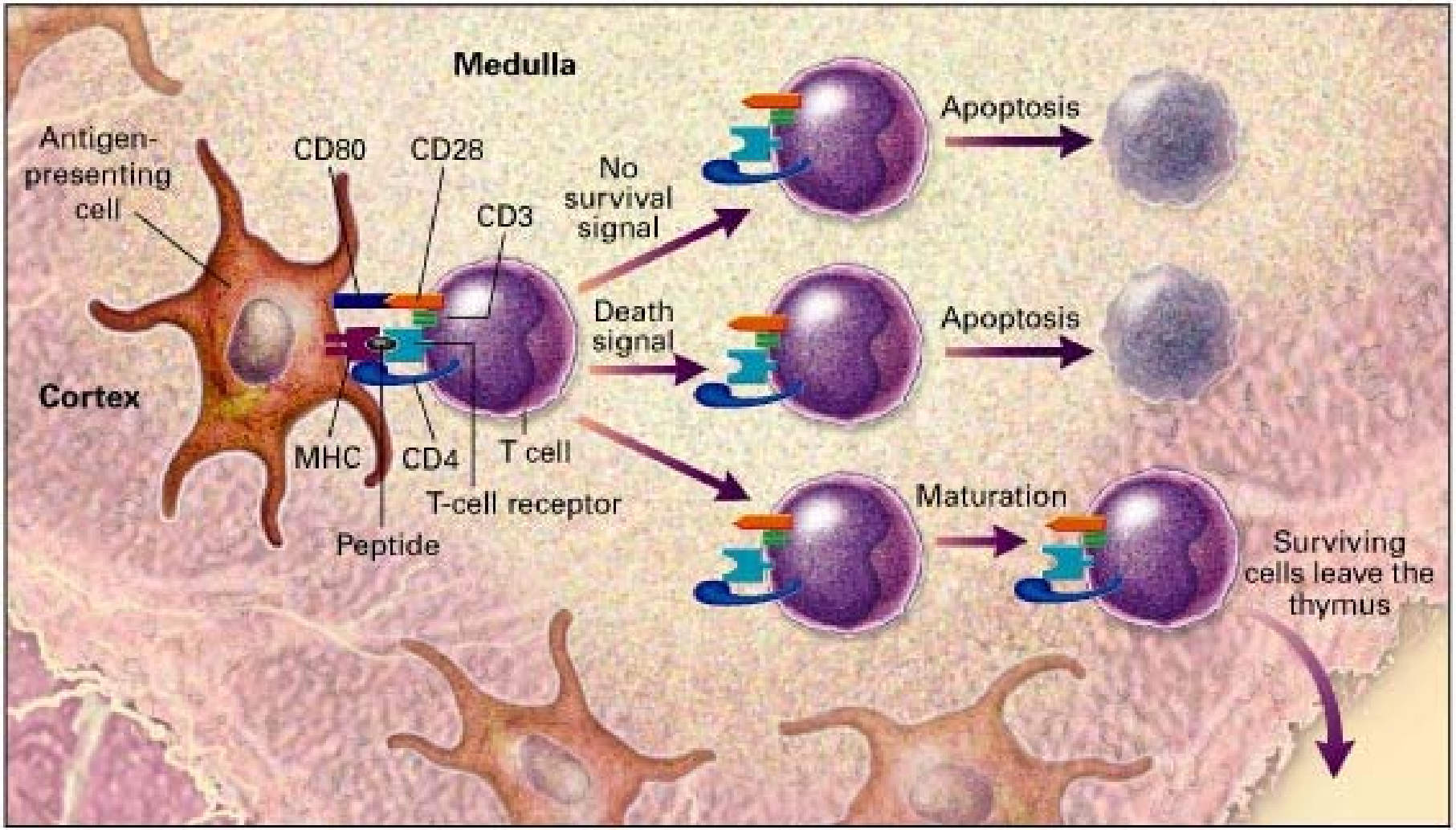
Immunity against pathogens

Autoreactivity

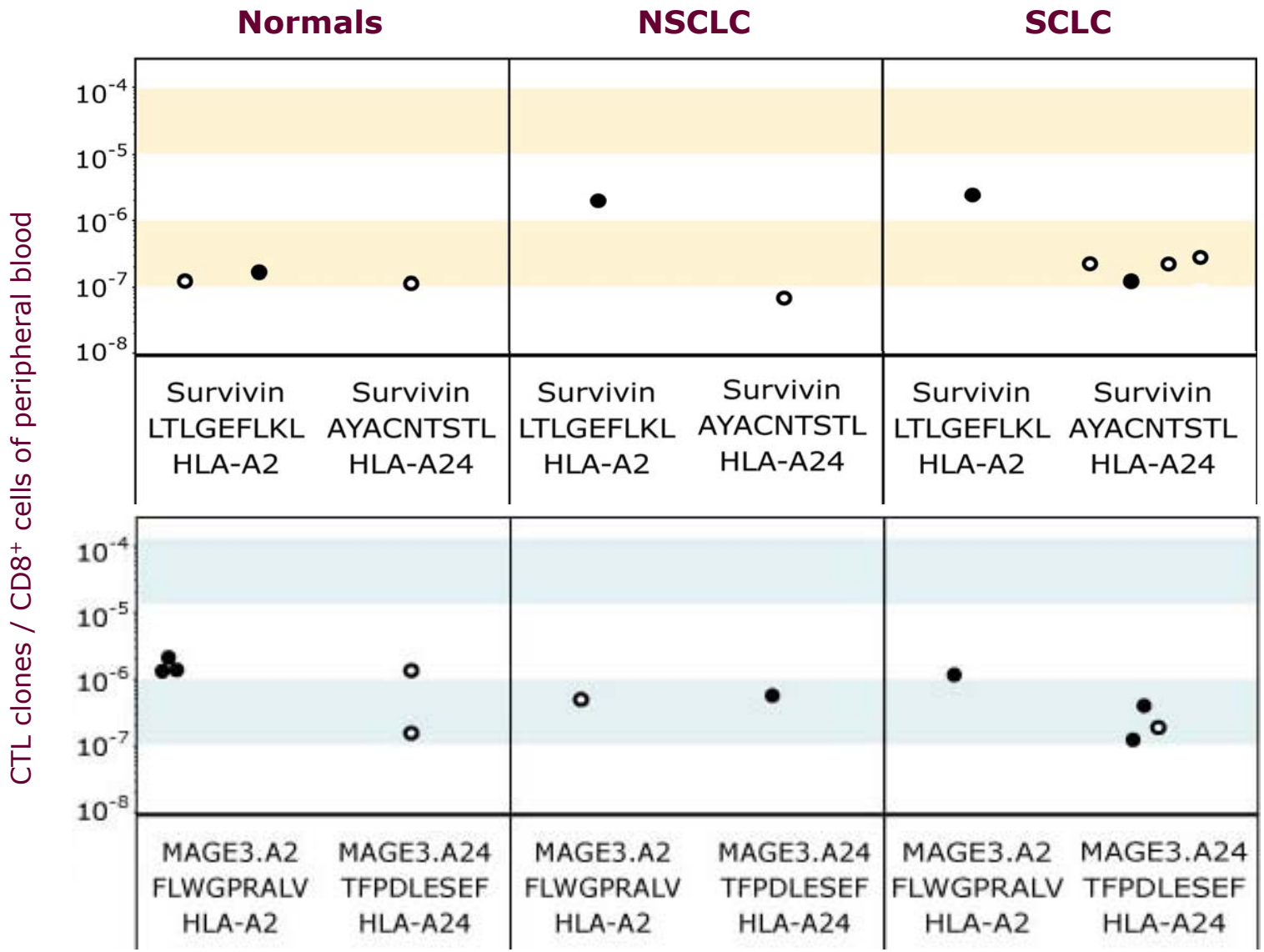
"Collateral damage"

# The Clonal Selection Theory

## Central tolerance

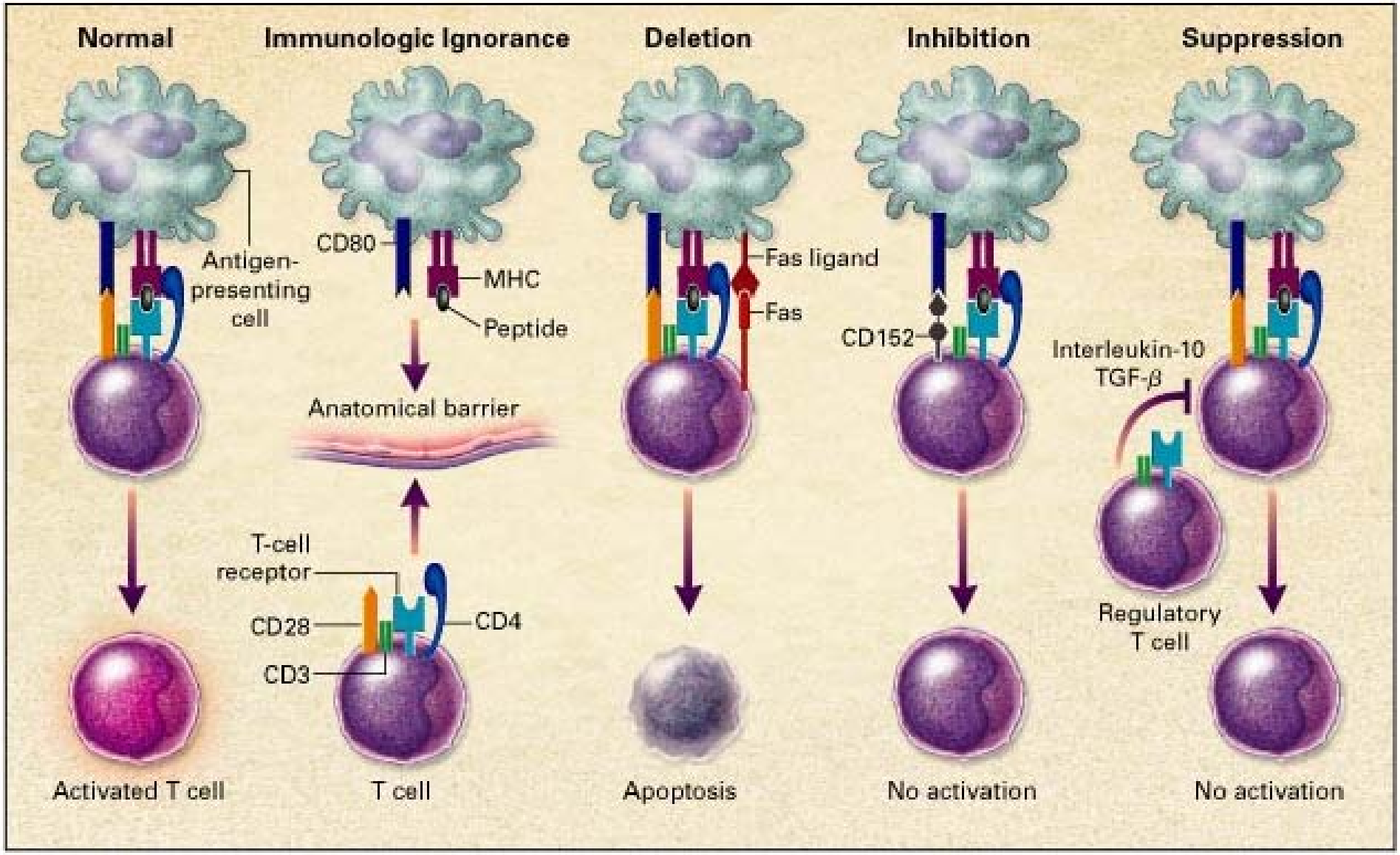


# Anti-self CTL clones in the periphery




Karanikas et al (unpublished results)

# Peripheral tolerance



# Autoimmunity

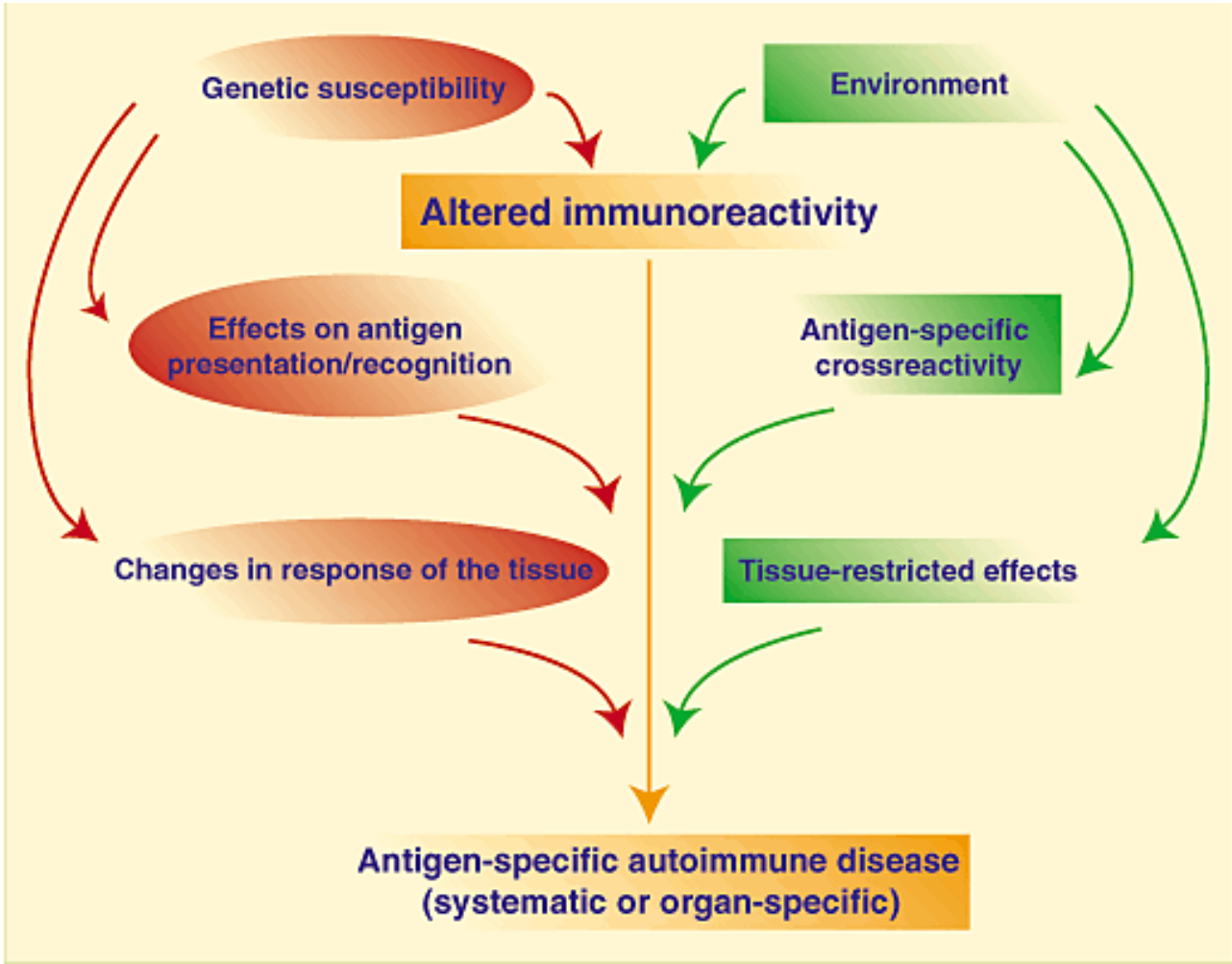
A state wherein the host mounts an immune response to self

**A low level of autoreactivity is *physiologic* and *crucial to normal immune function***, e.g.

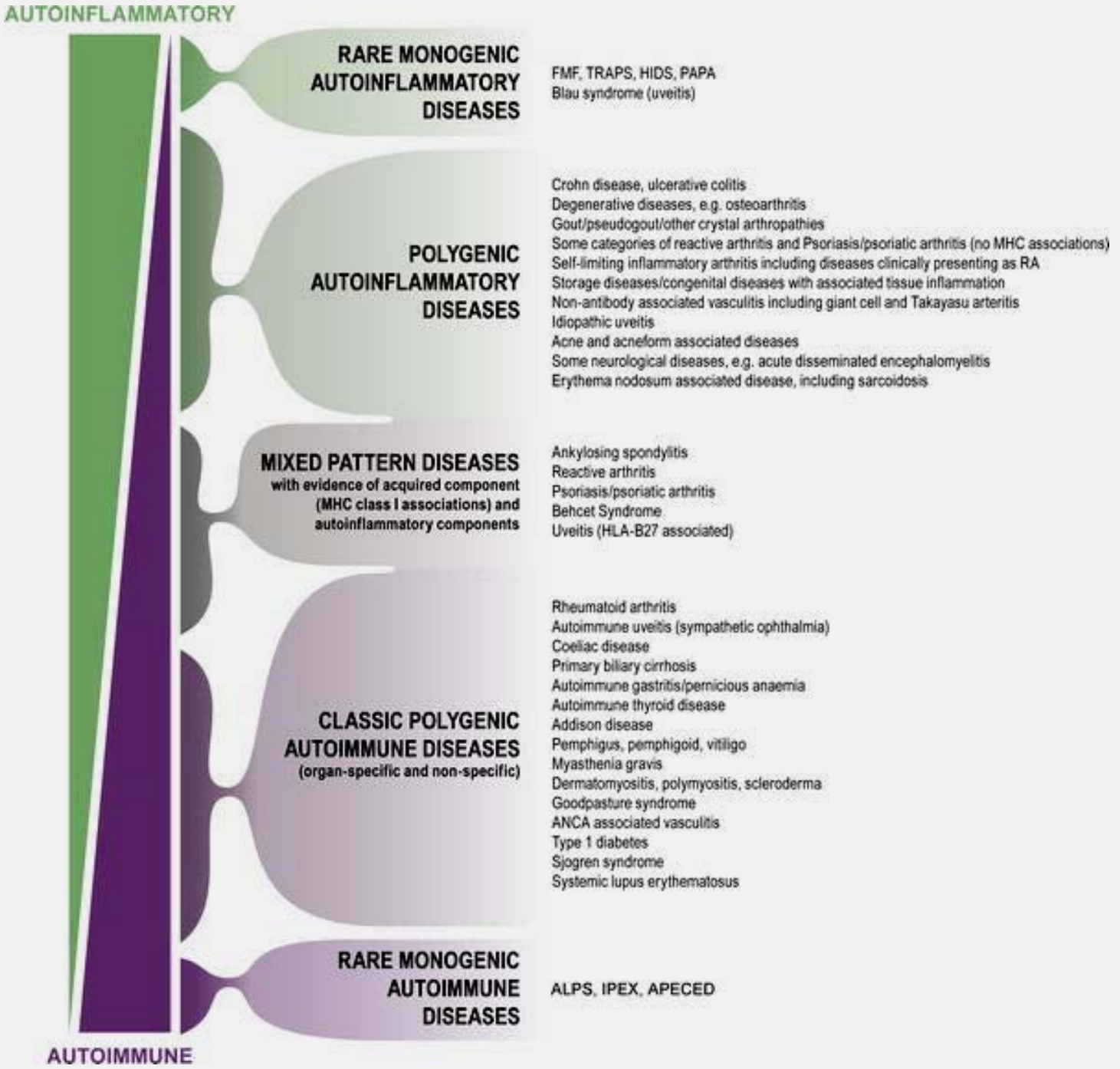
- Modulation of normal antibody responses following acute infections by anti-idiotypic responses of the normal host
- Cancer immunosurveillance
- Natural autoantibodies facilitate the clearance of senescent cells and autoantigens, and therefore, prevent the activation of cognate autoimmune responses

# Autoimmune diseases

The *clinicopathologic state* wherein the host mount
a *detrimental* immune response
to self-antigens of normal cells and organs



# The immunological disease continuum

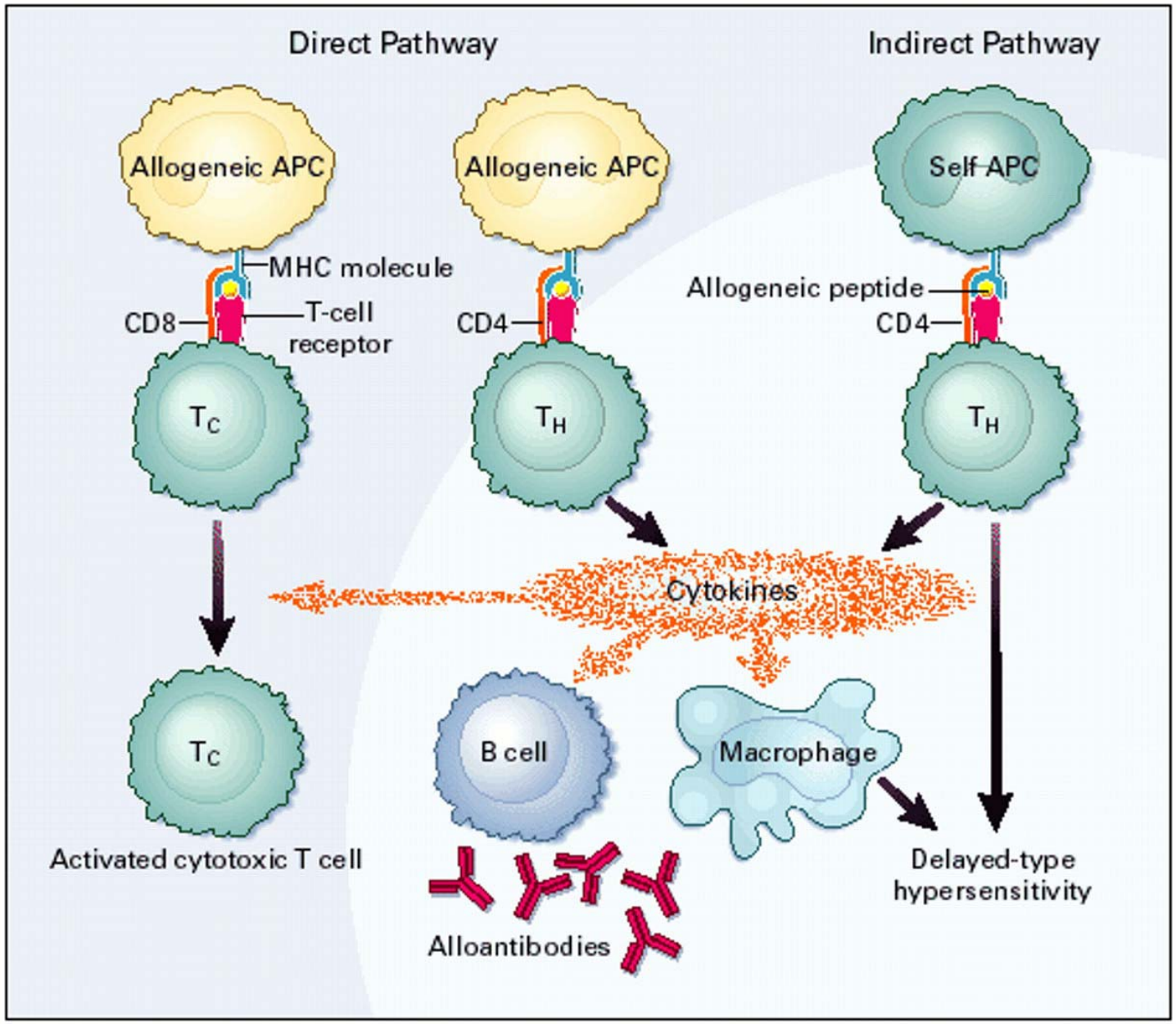


# Microchimerism

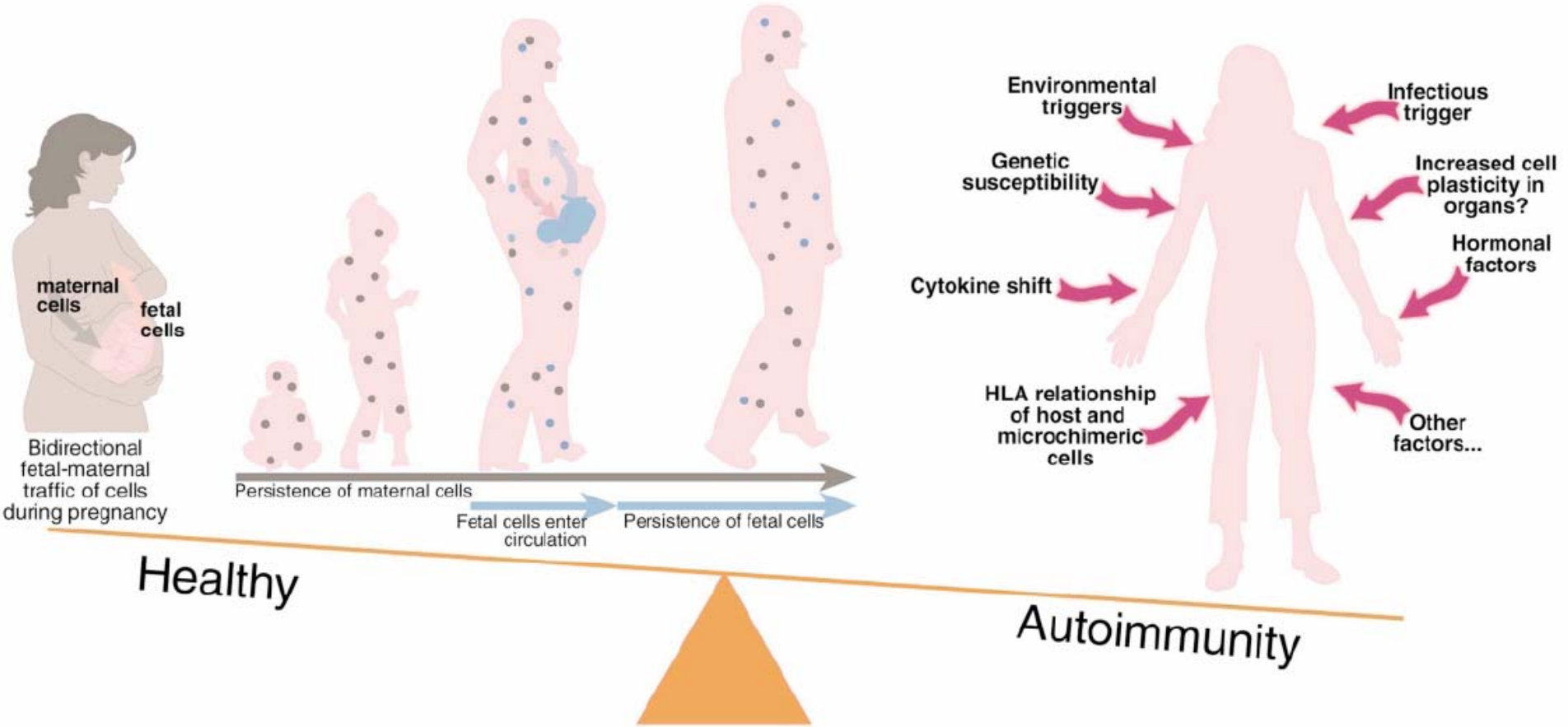
a small number of cells or DNA from one individual harbored in another individual

- ADs have higher prevalence in women
- Increased incidence after childbearing age
- Similarities between AD and the cGvHD
- Other sources of microchimerism, including from a twin, the mother or a blood transfusion
- Long-term persistence of microchimerism

# Are ADs auto-alloimmune or allo-autoimmune?



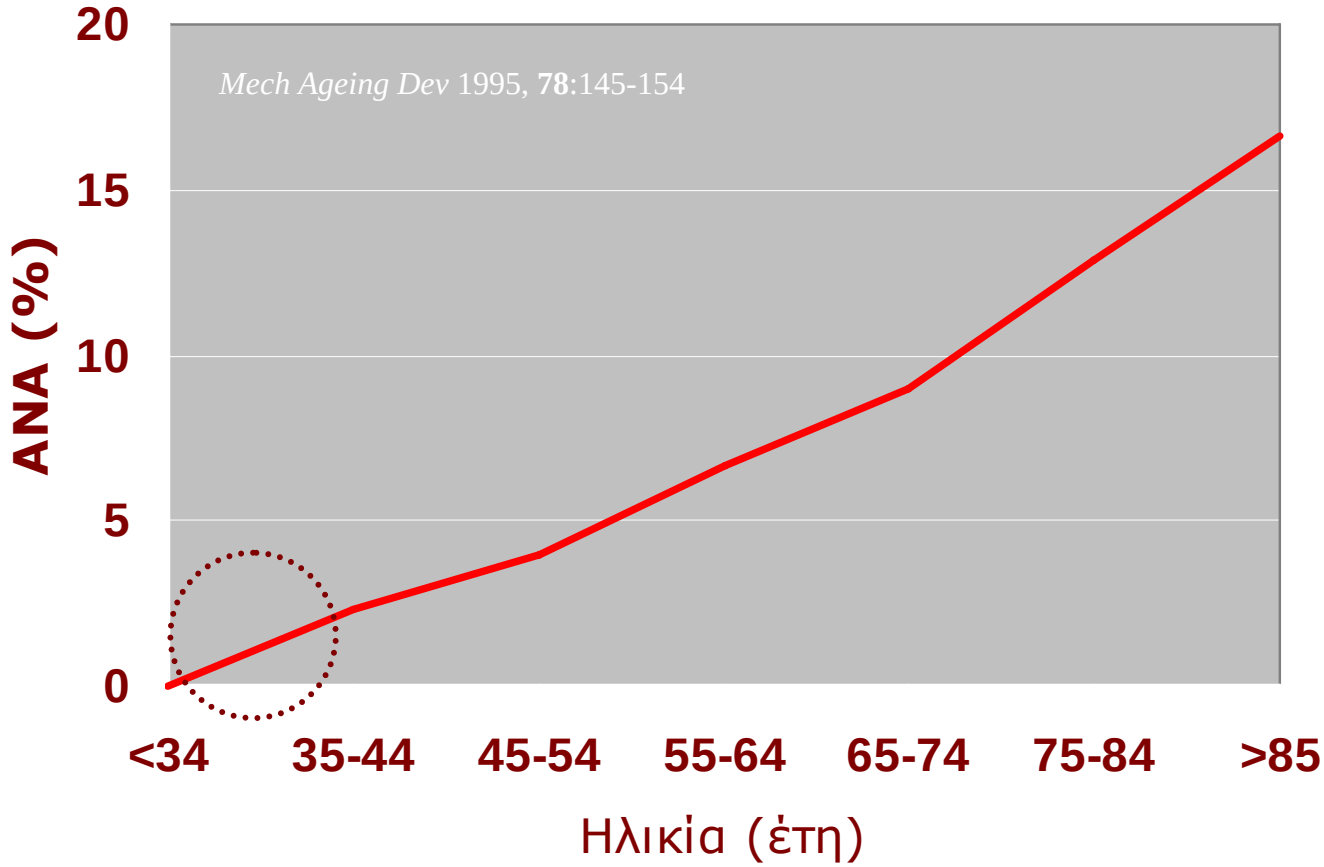
# Bystander and potential pathogenic microchimerism



***What is the clinical significance for the gynecologist of autoantibody positivity in the absence of overt AID?***

***What is the clinical significance of uncovering autoantibody positivity after an obstetric complication?***

# AIDs are preceded by a long preclinical phase in which individuals can be identified by the presence of autoantibodies



1. Are autoantibodies predictors of mother's disease?

2. Does autoimmunity cause infertility?

3. Does autoimmunity cause recurrent pregnancy loss?

4. Do mother autoantibodies represent a risk of AIDs for the fetus?

# Are autoantibodies in pregnancy predictors of future mother's disease?

**RA in healthy pregnant women followed up for a year:**

- 0/401 RF(–)
- 2/9 RF(+)

Iijima T et al. *Ann Rheum Dis* 1998; **57:** 460–63

**HLA, GAD, IC autoantibodies at delivery, 5-yrs follow-up:**

- 43/184 pos for at least one T1D-associated autoantibody
- 24/43 developed T1D

Ferber KM et al. *J Clin Endocrinol Metab* 1999; **84:** 2342–48

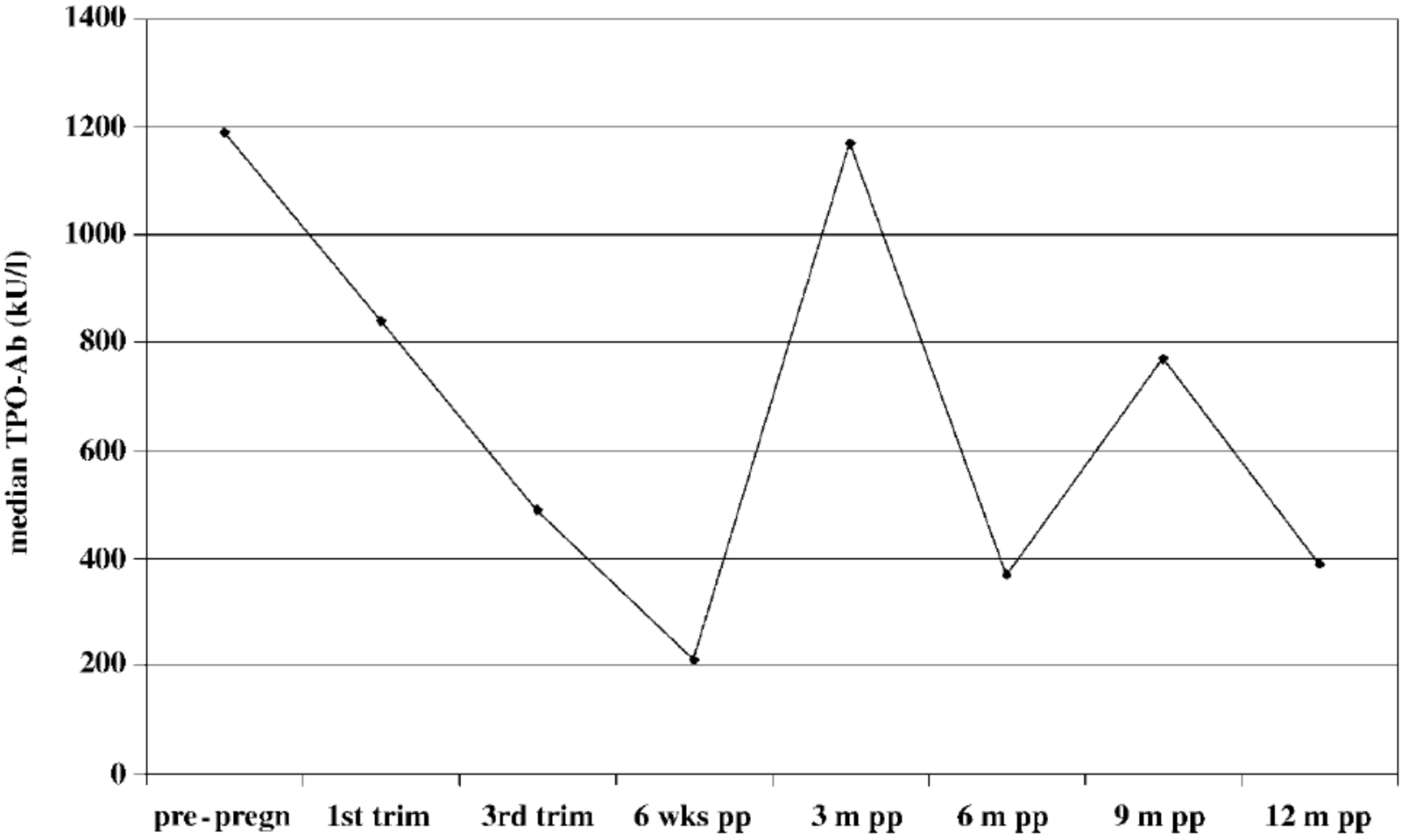
**Mothers who have babies with NLE and anti-Ro/La in their serum subsequently commonly develop symptoms consistent with RDs**

McCune AB et al. *Ann Intern Med* 1987; **106:** 518–23

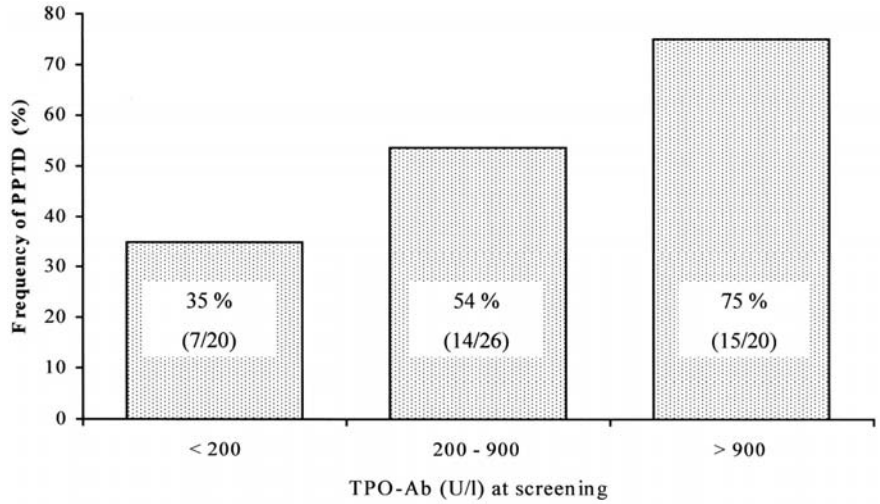
Julkunen H, Eronen M. *Arthritis Rheum* 2001; **44:** 647–52

Waltuck J, Buyon JP. *Ann Intern Med* 1994; **120:** 544–51

# TPO decrease during pregnancy, rise shortly after pregnancy and then decrease towards the end of the first postpartum year



- Women who express elevated TPO or TG in the 1st trimester of pregnancy have a 33–52% chance of developing PPTD
- Prevalence 1.1 to 16.7% (mean 7.5%)
- PPTD may also occur after loss of pregnancy at 5–20 wk gestation
- **Despite an initial recovery, about 25% have overt hypothyroidism ≥4 yrs later**
- PP hyperthyroidism is 20-fold more frequent than Graves' disease
- Absence of TSH-R Abs in thyrotoxic phase, except pre-existing Graves' disease




Nøhr SB et al. *J Clin Endocrinol Metab* 2000; **85**:3191-3198

# Does autoimmunity cause infertility?

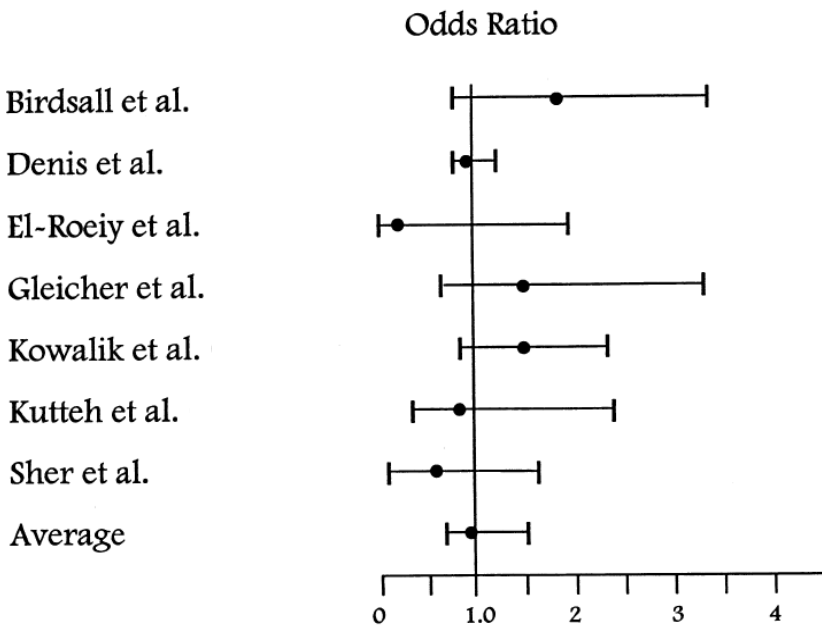
## Autoantibodies in general infertility population

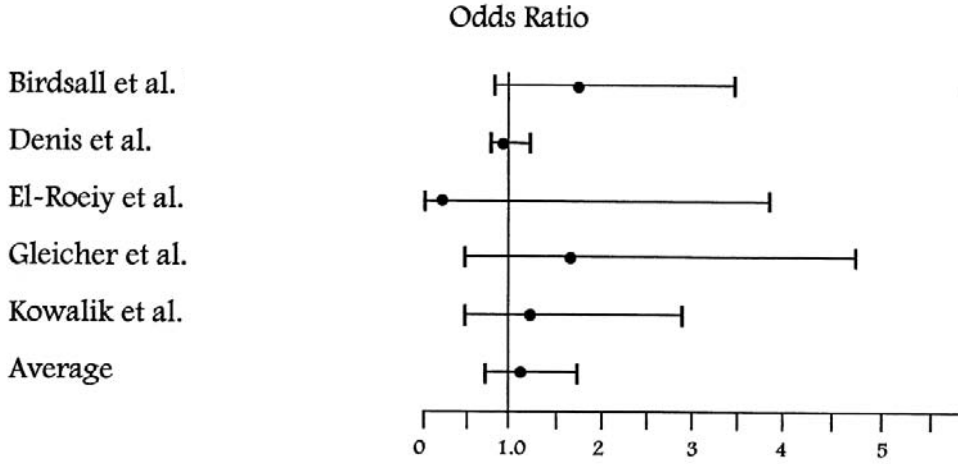
| Study | Population | Smooth Muscle | Thyroid Antigens | Nuclear Antigens | Phospholipids |
|---|---|---|---|---|---|
| Wilson | ovulatory dysfunction n = 77 | 35%* | 10% | 20%* | — |
| | fertile controls n = 77 | 3% | 14% | 3% | — |
| Taylor | unexplained infertility n = 41 | 49%* | — | 10% | 17%* |
| | pregnancy women n = 351 | 17% | — | 3% | 6% |
| Roussev | unexplained infertility n = 45 | — | 9%* | — | 42%* |
| | "normal" controls n = 15 | — | 0% | — | 7% |

* $p < 0.05$

Stovall DW et al. *Clin Obstet Gynecol* 1999; **42**:979

# The relative likelihood of clinical pregnancy and live birth pregnancy in women undergoing IVF who have aPL compared with women lacking aPL




*Hornstein. In vitro fertilization success. Fertil Steril 2000.*

**aPL testing is of no clinical benefit**

**to women undergoing IVF-ET**

# Does autoimmunity cause infertility?

**There is *no* strong evidence that**

**autoimmunity is a likely cause of primary infertility**

Carson SA, Branch DW. Management of recurrent early pregnancy loss. ACOG Practice Bulletin. *Clinical management guidelines for obstetrician-gynecologists* 2001; 24: 1–12

Royal College of Obstetricians and Gynaecologists. Scientific Advisory Committee Opinion Paper 5. *Immunological testing and interventions for reproductive failure*. 2003; 1–8

# Does autoimmunity cause infertility?

| | Patients (%) | Controls (%) | OR (95% CI) |
|---|---|---|---|
| Anti-prothrombin | 22/69 (31.9) | 10/120 (8.3) | 5.15 (2.12–12.74) |
| aPL | 8/69 (11.6) | 3/120 (2.5) | 5.11 (1.18–25.35) |
| Group 1 (ASCA, aPL or anti-prothrombin) | 35/69 (53.7) | 15/120 (18.3) | 4.59 (2.25–9.39) |

Shoenfeld Y et al. *Am J Reprod Immunol* 2006; **56**:337–344

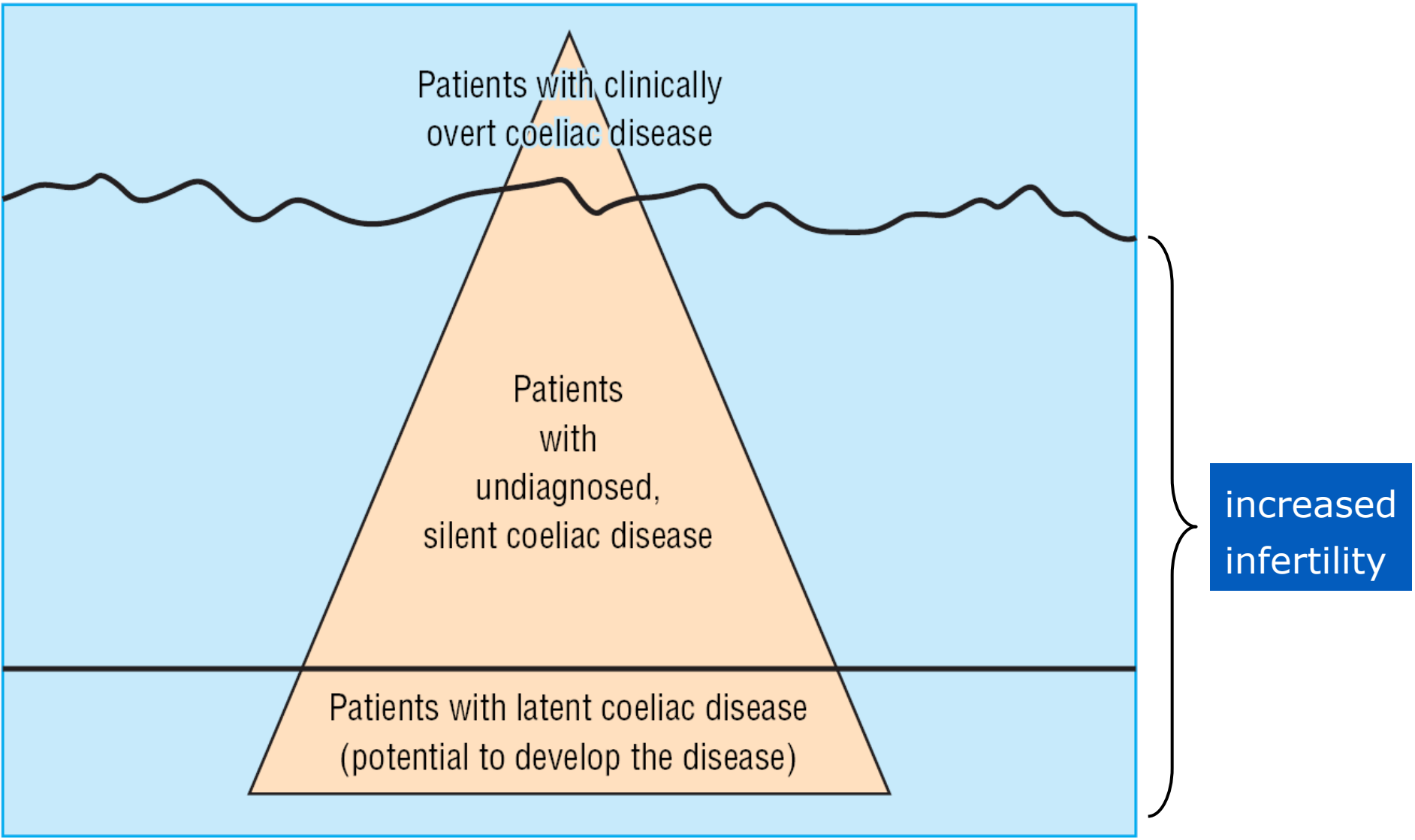
# Risk of infertility associated with thyroid autoimmunity

| Reference (country) | Year | Subjects | Thyroid Abs | RR (95% CI) | *P* |
|---|---|---|---|---|---|
| Wilson *et al.* (GB) | 1975 | Infertile | 8/77 | 0.73 | 0.52 (NS) |
| | | Controls | 11/77 | (0.28–1.92) | |
| Roussev *et al.* (USA) | 1996 | Infertile | 5/63 | 1.19 | 0.80 (NS) |
| | | Controls | 0/15 | (0.13–11.00) | |
| Geva *et al.* (Israel) | 1997 | Infertile | 15/80 | 3.75 | 0.09 (NS) |
| | | Controls | 2/40 | (0.81–17.30) | |
| Kutteh *et al.* (USA) | 1999 | Infertile | 132/688 | 1.32 | 0.20 (NS) |
| | | Controls | 29/200 | (0.85–2.05) | |
| Kaider *et al.* (USA) | 1999 | Infertile | 51/167 | 2.08 | 0.02 |
| | | Controls | 16/109 | (1.11–3.88) | |
| Reimand *et al.* (Estonia) | 2001 | Infertile | 2/108 | 0.48 | 0.34 (NS) |
| | | Controls | 15/392 | (0.11–2.15) | |
| Poppe *et al.* (Belgium) | 2002 | Infertile | 61/438 | 1.68 | 0.80 (NS) |
| | | Controls | 8/100 | (0.78–3.65) | |
| [a]Poppe *et al.* (Belgium) | 2002 | Infertile | 35/197 | 2.28 | 0.05 |
| | | Controls | 8/100 | (1.02–5.12) | |
| All studies pooled | – | Infertile | 274/1621 | 1.95 | < 0.0001 |
| | | Controls | 81/933 | (1.50–2.53) | |

[a]Pertaining to the identifiable female causes of infertility.

Prummed MF, Wiersinga WM. *Eur J Endocrinol* 2004; **150**:751–755

# The celiac disease iceberg



# Does autoimmunity cause infertility?



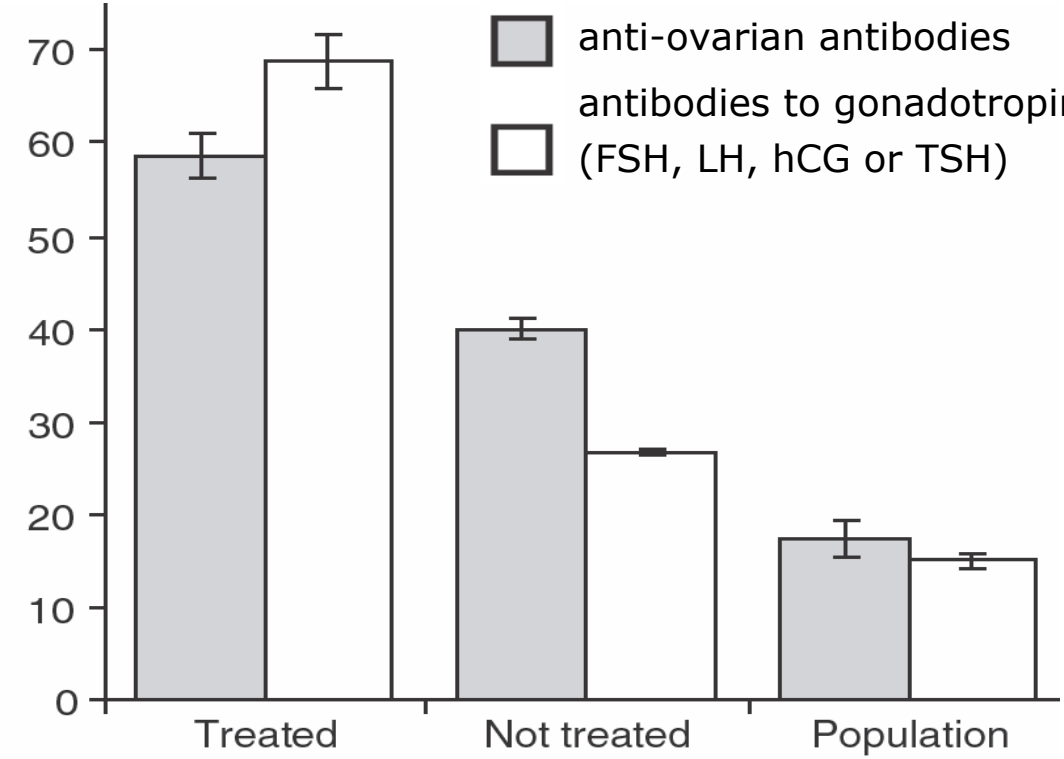
- Autoantibodies to endometrium refluxed into the peritoneal cavity may be a possible cause of infertility among patients with endometriosis
- Lack of consistency and reproducibility
- Endometriosis may be associated with an increased prevalence of autoantibodies in general
- The only evidence available merely points to a possible association between autoantibodies and endometriosis and in no way implies a cause-and-effect relationship with infertility or any other aspect of the disease

# Does autoimmunity cause infertility?

## Zona pellucida antibodies

- Initial investigators using nonspecific assays and few control women reported a very high prevalence of zona pellucida antibodies among infertile women.
- With refinement of the assay, the prevalence of these antibodies seems to be much lower than initially reported.
- Whether or not this prevalence is higher in infertile women than in fertile women remains controversial, and certainly a cause-and-effect relationship between zona pellucida antibodies and infertility has yet to be established.

# GAB and OVAB in patients with unexplained infertility




58 patients with unexplained infertility

- 38 received exogenous gonadotropins within the last 2 years
- 15 never never received exogenous gonadotropin

Shatavi SV et al. *Am J Reprod Immunol* 2006; **56**:286–291

# Are patients with autoimmune diseases infertile?

- Except for drug-induced (e.g., cyclophosphamide) ovarian failure, primary infertility is not prominent among patients with the RAD (RR≤1.5)
- Autoimmune thyroid, ovary and adrenal failure do cause infertility by interfering with endocrine function.
- Sublinical celiac disease and infertility (?)

# Does autoimmunity cause recurrent pregnancy loss?

**No other current topic in Gynecology**

**better illustrates the concept of controversy**

**than the role of autoantibodies**

**in recurrent pregnancy loss**

# aPL as a cause of RSA

- aPL are detected in ~10% of patients with RSA
- In ~85% of them viable pregnancies are obtained with appropriate thromboprophylaxis
- 7–25% of RSA have APS as the main risk factor, association not being synonymous with cause

# Revised classification criteria for APS

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met

## Clinical criteria

1. Vascular thrombosis

One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity

(a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

(b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia defined according to standard definitions [11], or (ii) recognized features of placental insufficiency or

(c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

## Laboratory criteria

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on LAs/phospholipid-dependent antibodies)
2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. > 40 GPL or MPL, or > the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA
3. Anti-$\beta_2$ glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer > the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures

Miyakis S et al. *J Thromb Haemost* 2006; **4**:295–306

# Obstetric APS

Women with repeatedly positive tests for aPL…

1. without a poor obstetric history, SLE or a thrombotic history.
2. with recurrent early pregnancy loss or (at least) one fetal loss in absence of SLE or a thrombotic history.
3. with high frequencies of fetal loss, SLE, a thrombotic history, or combinations of these.

Women with repeatedly positive tests for aPL…

1. without a poor obstetric history, SLE or a thrombotic history.

**Routine screening is not recommended,**

**because the pregnancy outcome is similar**

**for those treated with aspirin**

**and those receiving standard care**

# aPL as a cause of RSA

| | Patients (%) | Controls (%) | OR (95% CI) |
|---|---|---|---|
| ASCA | 21/108 (19.4) | 7/120 (5.8) | 3.9 (1.5–10.6) |
| Prothrombin | 36/109 (33) | 10/120 (8.3) | 5.42 (2.4–12.5) |
| aPL | 12/109 (11) | 3/120 (2.5) | 4.82 (1.2–22.2) |
| Group 1 (ASCA, aPL or anti-prothrombin) | 57/109 (52.3) | 22/120 (18.3) | 5.23 (2.8–2.9) |

Shoenfeld Y et al. *Am J Reprod Immunol* 2006; **56**:337–344

# Miscarriages in women with positive thyroid antibodies

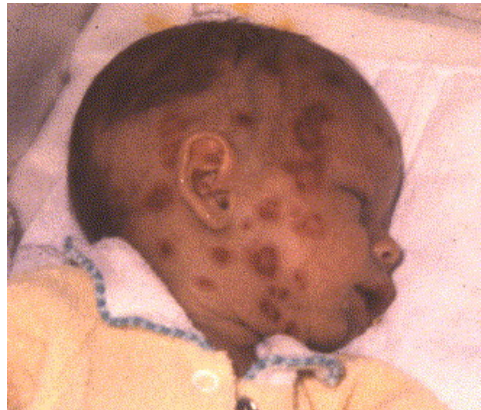
| Reference | Country | No. of subjects | Positive thyroid Ab (%) | Miscarriage rate in | | | *P* |
|---|---|---|---|---|---|---|---|
| | | | | Ab positive (%) | | Ab negative (%) | |
| Stagnaro-Green *et al.* (1990) | USA | 552 | 19.6 | 17.0 | vs | 8.4 | 0.011 |
| Glinoer *et al.* (1991) | Belgium | 726 | 6.2 | 13.3 | vs | 3.3 | < 0.005 |
| Lejeune *et al.* (1993) | Belgium | 363 | 6.3 | 22.0 | vs | 5.0 | < 0.005 |
| Pratt *et al.* (1993) | USA | 42 | 31.0 | 67.0 | vs | 33.0 | NA |
| Singh *et al.* (1995) | USA | 487 | 22.0 | 32.0 | vs | 16.0 | 0.002 |
| Bussen and Steck (1995) | Germany | 66 | 17.0 | 36.0 | vs | 7.0 | < 0.03 |
| Iijima *et al.* (1997) | Japan | 1179 | 10.6 | 10.4 | vs | 5.5 | < 0.05 |
| Esplin ety al. (1998) | USA | 149 | 33.0 | 29.0 | vs | 37.0 | > 0.05 |
| Kutteh *et al.* (1999) | USA | 900 | 20.8 | 22.5 | vs | 14.5 | 0.01 |
| Muller *et al.* (1999) | Netherlands | 173 | 14.0 | 33.0 | vs | 19.0 | 0.29 |
| Bussen *et al.* (2000) | Germany | 48 | 30.6 | 54.2 | vs | 8.3 | 0.002 |
| Dendrinos *et al.* (2000) | Greece | 45 | 32.5 | 37.0 | vs | 13.0 | < 0.05 |
| Bagis *et al.* (2001) | Turkey | 876 | 12.3 | 50.0 | vs | 14.1 | < 0.0001 |

Prummed MF, Wiersinga WM. *Eur J Endocrinol* 2004; **150**:751–755

# Autoantibodies and the risk of transmitting ADs from mother to fetus

## Neonatal lupus erythematosus

- US Research Registry for Neonatal Lupus (Hospital for Joint Disease, NY): 304 mothers and their 360 affected children
- Anti-SSA/Ro-SSB/La associated CHB/myocarditis affects 2% of neonates born to mothers with these autoantibodies
- These antibodies are present in >85% of mothers whose fetuses are identified with conduction abnormalities in a structurally normal heart
- 1st and 2nd degree AV blocks can been detected by fetal echocardiography progressing postnatally despite the clearance of maternal antibodies: **a window of treatment opportunity**
- **35% of the mothers are asymptomatic**



Buyon JP, Clancy RM. *Autoimmunity* 2003; **36**:41–50

***Thank you***

***for your attention***