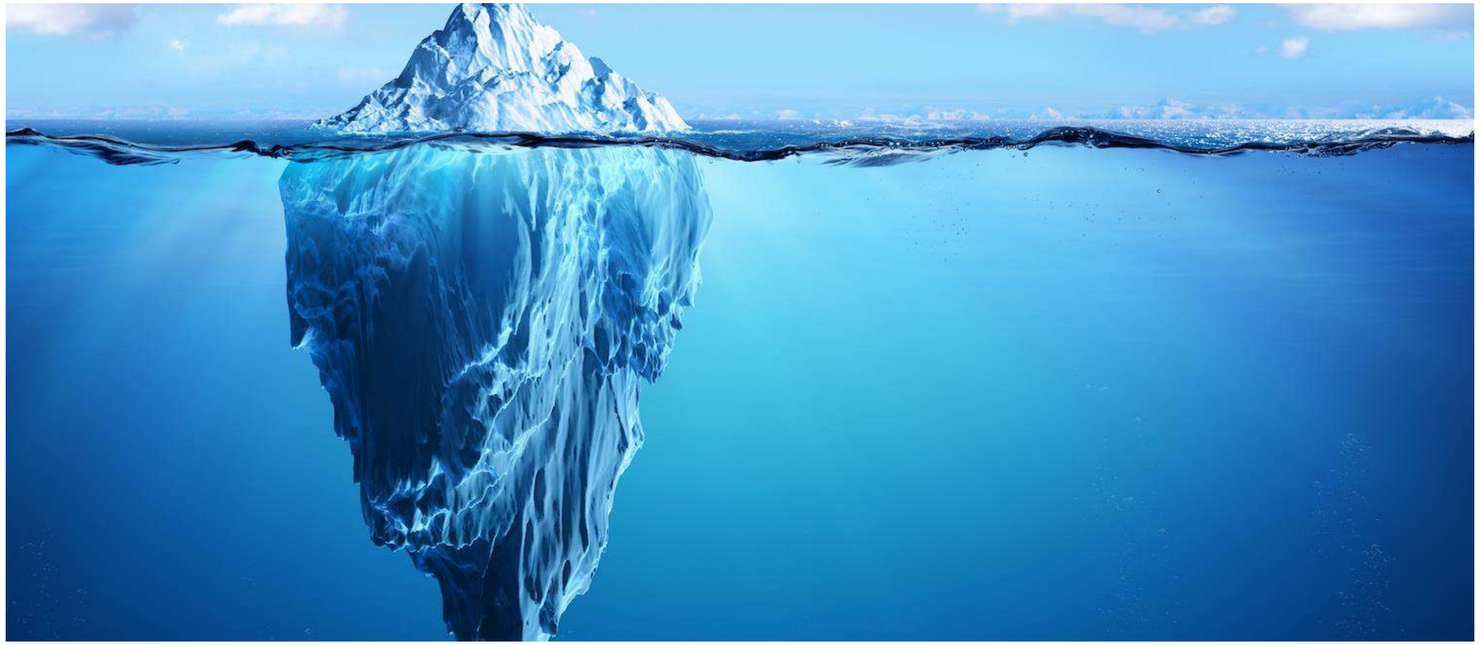


Dr. Jaclyn Smeaton

Autoimmunity & Immune-Mediated Infertility

Autoimmunity

- Up to 23.5 million Americans suffer from AI disease
- Prevalence is rising
- Autoimmunity of the thyroid gland is the most well-known and diagnosed autoimmunity, and prevalence may be underestimated as testing is not always completed
- AI impact on fertility is NOT well-known among patients or providers but evidence demonstrates autoimmunity affecting several reproductive tissues to date
- AI & associated chronic inflammation characterize interactions between nervous, endocrine, and immune systems

National Institutes of Health. www.nih.gov

Autoimmunity

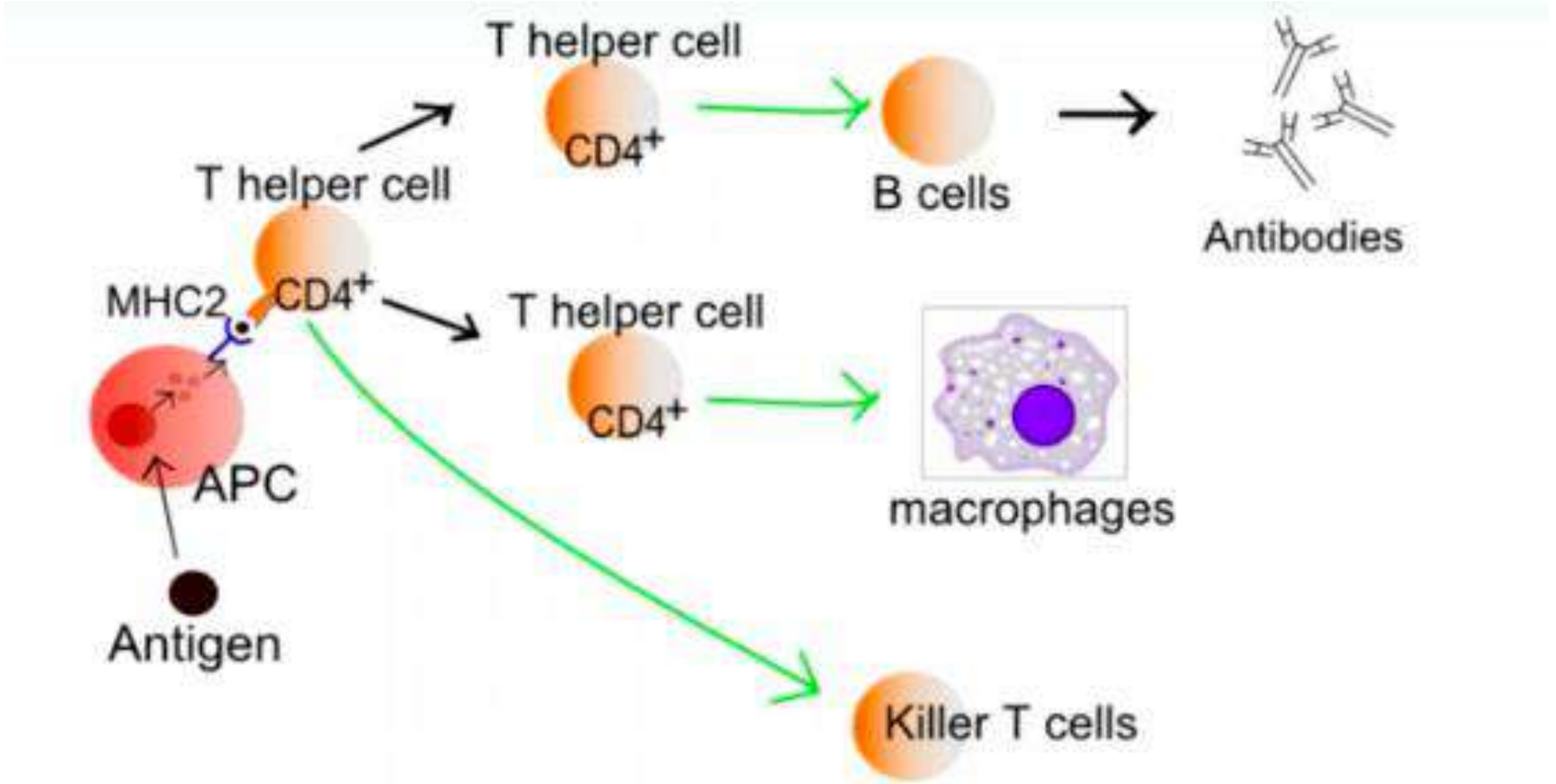
- Endocrine AI is primarily organ specific, but is also often also associated with polyclonal activation and nonendocrine autoimmunity
- Over 80 AI diseases have been identified
- AI can be found in symptomatic patients without specific disease states
- AI can be found in asymptomatic patients too!
- Subclinical AI precedes AI disease diagnosis by months to years and is uniformly associated with decrease fertility and increased miscarriage rates

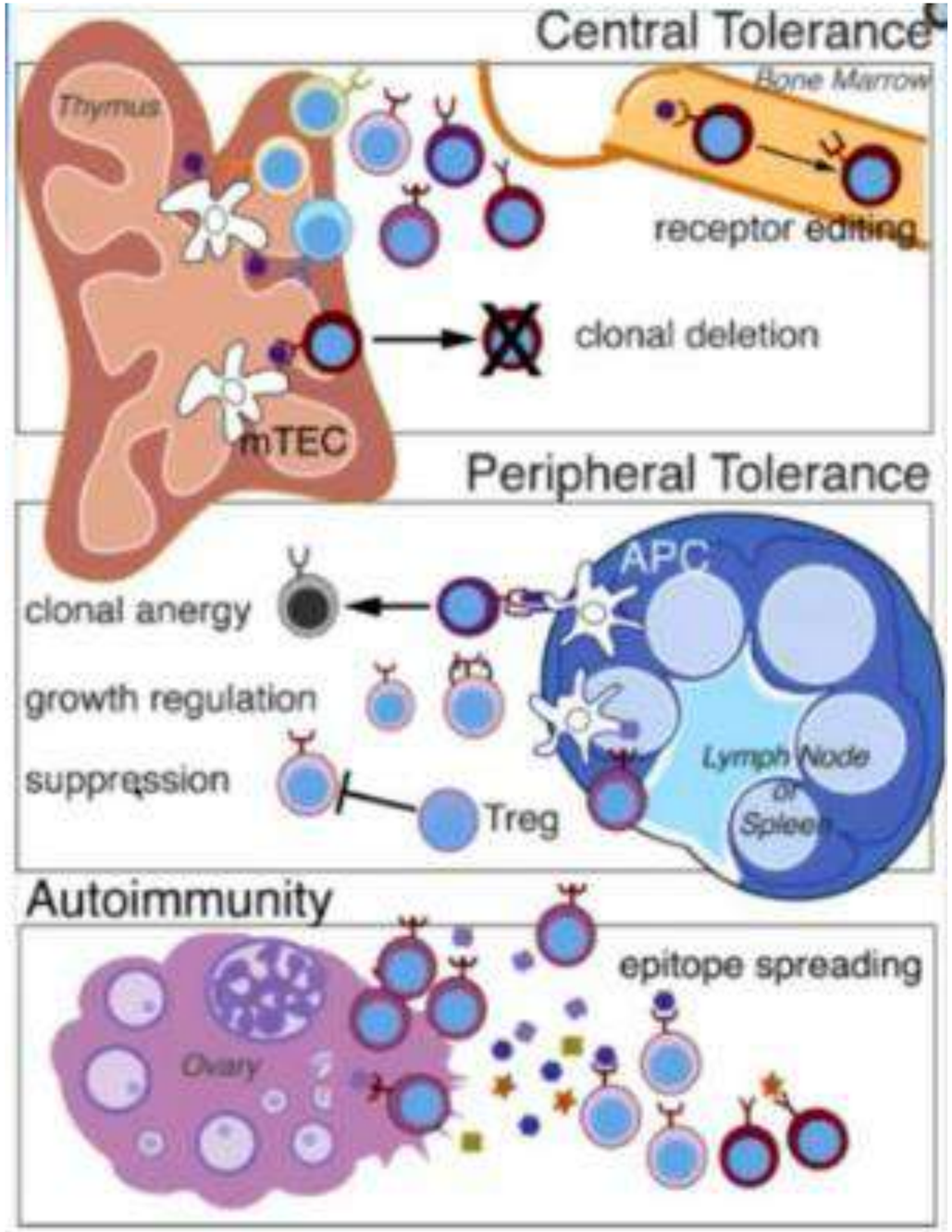
Sen A et al. Nat. Rev. Endocrinol 2014;10:37-50.

Autoimmunity & Fertility

- It is known that autoimmune diseases have effects on fertility
  - Diabetes, autoimmune thyroiditis, systemic lupus erythematosus are linked to decreased fertility
- Other causes of infertility can have autoimmune origins!
  - Premature ovarian failure- a percentage are connected to AI reaction in follicles
  - Endometriosis may have AI components
  - Recurrent pregnancy loss involves autoimmune reactions
  - Unexplained infertility?

The Immune System- A reminder





Immune Checkpoints

Lower Tregs have been implicated in infertility, endo, miscarriage, unexplained infertility, and many AI diseases!

Cheng, Nelson- Seminars in Reproductive Medicine 2011.
McCulough F, NDNR 2014.

How Autoimmunity Happens

- May involve a variety of mechanisms
  - Molecular mimicry
  - Thyroid cell expression of HLA (human leukocyte-associated) molecules (antigens)
  - Bystander activation

Molecular Mimicry

- Similarity between infectious or other exogenous agent and human proteins
- Antibodies and T cells are activated in response to the agent and interact with the human protein (ie thyroid)

Cotran RS, Kumar V, Robins SI. The thyroid. In: Robins SI, editor. Pathological Bases of Disease. 5th edition. Philadelphia, Pa, USA: WB Saunders; 1994.

HLA-II Molecule Expression

- Thyroid epithelial cells from patients with AITD express MHC class II molecules including HLA-DR
  - Infection (or cytokines) induce class II molecule expression on thyroid cells and then these cells act as antigen-presenting cells to initiate an autoimmune response.
  - CMV is one known infection that has this effect
- MHC Class II molecules can present thyroid antigens to autoreactive T cells and activate them

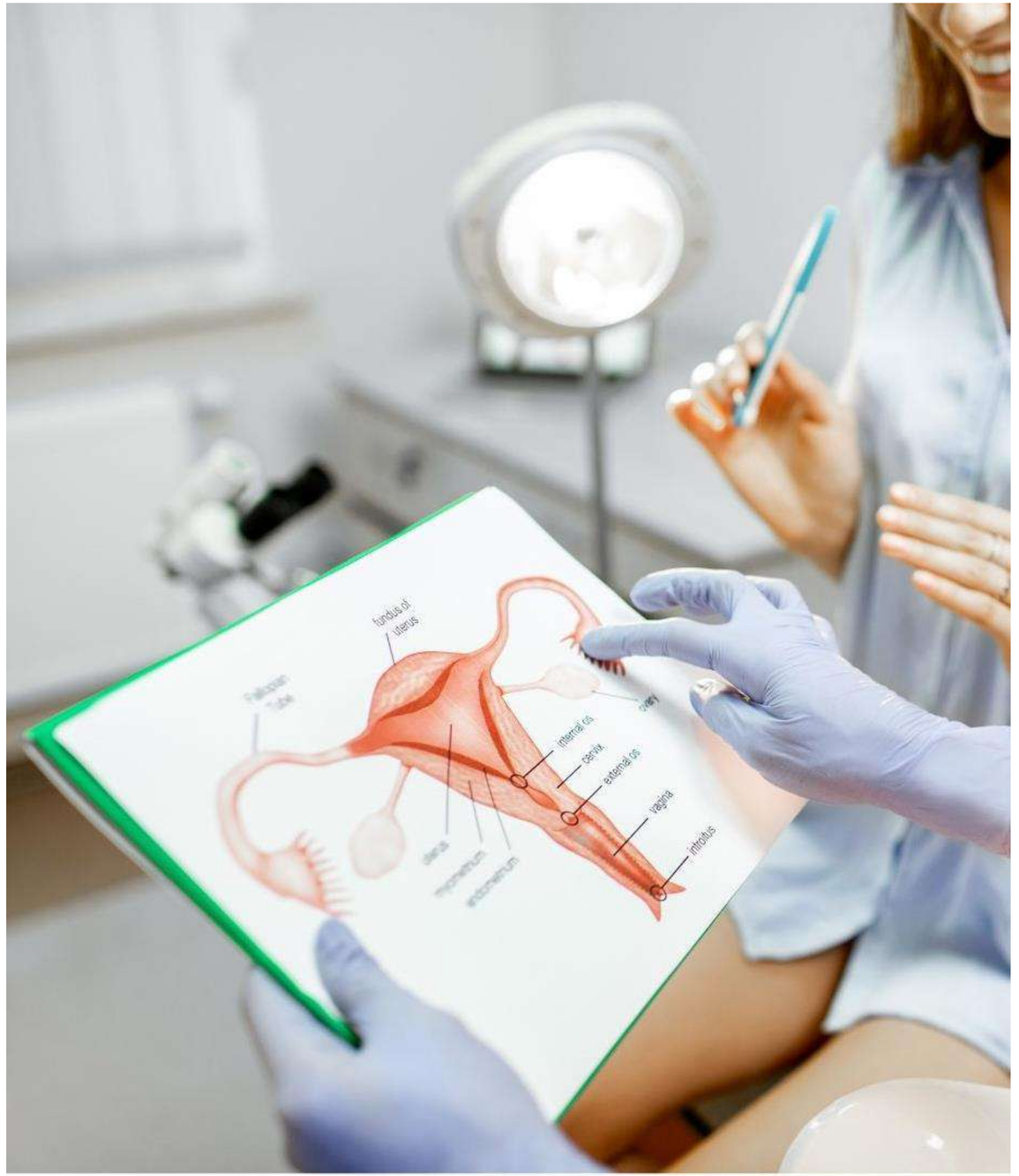
Bottazzo GF, Borrell RP, Hanafusa T, Feldmann M. Role of aberrant HLA-DR expression and antigen presentation in induction of endocrine autoimmunity. *The Lancet*. 1983;2(8359):1115–1118.
Khoury EL, Pereira L, Greenspan FS. Induction of HLA-DR expression on thyroid follicular cells by cytomegalovirus infection in vitro: evidence for a dual mechanism of induction. *The American Journal of Pathology*. 1991;138(5):1209–1223.
Londei M, Lamb JR, Bottazzo GF, Feldmann M. Epithelial cells expressing aberrant MHC class II determinants can present antigen to cloned human T cells. *Nature*. 1984;312(5995):639–641.

Bystander Activation

- Local insult to a tissue initiates a response in the tissue
  - Viral infection of thyroid cells or immune cells
  - Arrival of activated T cells within the thyroid gland
  - Observed with coxsackie virus
- The thyroid's local T-cells are activated, even as innocent "bystanders" via cytokines expressed locally
- This has been observed in animal models, but not explored/observed in humans to date

Cotran RS, Kumar V, Robins SI. The thyroid. In: Robins SI, editor. Pathological Bases of Disease. 5th edition. Philadelphia, Pa, USA: WB Saunders; 1994.

Autoimmune Disorders and Fertility



Autoimmunity & Female Fertility

Box 1 | Endocrine autoimmune diseases and female fertility

Endocrine autoimmune diseases can affect female fertility in various ways:

- Autoimmunity affects hormonal glandular function (for example, thyroiditis leads to hypothyroidism, which in turn leads to hyperprolactinaemia, in turn resulting in anovulation)
- Glandular autoimmunity affects extraglandular targets (for example, suspected cross-reactive epitopes exist between endocrine organs)
- Effects of associated polyclonal events with organ-specific autoimmunity (for example, thyroid, antinuclear and anti-phospholipid antibodies are associated with increased risk of miscarriage)
- By enhancing the speed of follicle or oocyte loss, which might lead to occult primary ovarian insufficiency and premature ovarian insufficiency
- By interfering with normal maternal tolerance induction, which is required for successful implantation of the fetal semi-allograft

Sen A et al. Nat. Rev. Endocrinol 2014;10:37-50.

Autoimmunity & Fertility

- It is known that several autoimmune (AI) diseases affect fertility
  - Diabetes, autoimmune thyroiditis, systemic lupus erythematosus are linked to decreased fertility
  - Women with recurring spontaneous miscarriage & unexplained infertility often demonstrate a diffusely activated immune system. These women often have thyroid autoimmunity or TH2-like AI response
- Even a family history of autoimmunity is connected to pregnancy outcomes (pregnancy loss & rate of live birth)

Connell MT et al. ASRM 2017;108(3).

Diabetes

- Women with T1D tend to have lower AMH levels
- Men & women with T1D have historically reduced fertility, but that has normalized in the last 20 years with greater metabolic control through treatment
  - Elevated glucose can increase risk of miscarriage 30-60%
  - Higher risk of congenital malformations
  - Men have lower semen volume (though still in normal range) and had more DNA fragmentation
- DM1 can lead to hormonal effects, but today, independent of those hormonal effects, diabetes is not known to negatively impact fertility any longer

Autoimmune Thyroiditis

- We have discussed this in our thyroid & adrenal lectures
- Prevalence of isolated thyroid autoimmunity is higher among infertile women, especially with endometriosis or ovulatory dysfunction (18% prevalence in infertile women, versus 8% in controls)
- Some studies demonstrate increased miscarriage risk if TPO is elevated, even in the absence of thyroid dysfunction (4-fold risk)

Poppe K et al. Thyroid 2002;12:997-1001.
Sieiro Netto L. et al. Am J Reprod Immunol 2004;52:312-6.

Systemic Lupus Erythematosus

- Affects women of childbearing age, and thought to impair fertility in a few ways
  - Impairing reproductive capacity specific to fertilization
  - Impairing implantation in uterine wall
  - Difficulties maintaining pregnancy post-implantation
  - Labor complications
- Today, Lupus is not thought to have as much of a negative fertility impact with modern treatment

Hickman R, Gordon C. Rheumatology. Sept 2011;50(9):1555-1558..

Addison’s Disease

- Patients with Addison’s disease have a high association with ovarian antibodies which can lead to premature ovarian failure
- Preclinical stages are LONG with Addison’s
- Sometimes picked up on with 21-hydroxylase enzymes testing, or subtle elevations of ACTH or renin.
- Low androgen levels in women lead to problems with follicular growth and development and can lead to DOR

Multiple Sclerosis

- Most prevalent AI disease that involves the hypothalamus
- Fertility is reduced in patients with MS even before time of diagnosis
- Treatment with mitoxantrone and B-interferon, the most widely used MS drugs, adversely affect fertility, leading to POF and amenorrhea
- MS worsens following treatments with ART, especially if GnRH agonists are used and pregnancy is not established

Sen A et al. Nat. Rev. Endocrinol 2014;10:37-50.

Celiac Disease

- Patients with celiac disease may have multiple nutritional deficiencies that can lead to infertility
- Higher rates of recurrent miscarriage, pregnancy complications, and infertility
- 5-10% of women with history of stillbirth, recurrent miscarriage, IUGR, and infertility tested positive for transglutaminase IgA compared to only 1% of the control group in a 2010 study, suggesting latent Celiac could be a major cause of infertility
- Other studies contradict! CARES trial measured same rates of Celiac in women undergoing IVF compared to general population and showed no impact on fertilization, blastulation, or implantation rates, even when seropositive women ate gluten

Kumar A, Meena M, Begum N, et al. Latent celiac disease in reproductive performance of women Fertility and sterility 24 November 2010.
Juneau CE. PCRS Abstracts 2017;107(3).

Endometriosis

- We have discussed this, but multiple immune components of endometriosis have risen the suggestion that endometriosis (at least for some patients) have some autoimmune etiologies
- Endometriosis can cause mechanical challenges for fertilization and implantation, and can cause inflammation disrupting endometrial receptivity

Nothnick, WB. Treating endometriosis as an autoimmune disease. Fertility and sterility. 2001 Aug;76(2): 223-231.

Hyperprolactinemia

- Associated with several autoimmune diseases including SLE, RA, Celiac disease, T1D, Addison's disease, autoimmune thyroiditis, and antiphospholipid syndrome
- Typically caused by hypersecretory lactotrophic cells in anterior pituitary
- Occurs in 4.1% of women and is associated with menstrual irregularities, anovulation, amenorrhea, and infertility in general
- In autoimmunity, extrapituitary sites can also secrete prolactin
- 15-46% of patients with hyperprolactinemia have associated antiprolactin immunoglobulins or autoantibodies that reduce bioactivity of prl and/or delay clearance from circulation

Sen A et al. Nat. Rev. Endocrinol 2014;10:37-50.

Autoimmunity Summary

Table 1 | Phenotypically defined autoimmune endocrine diseases

Organ and disease	Prevalence per 1,000 of the population	Known effects on fertility	Comments
Hypothalamus			
Multiple sclerosis	0.98[16]–26.4[17]	Yes	–
Diabetes insipidus	Rare	No	–
Pituitary gland			
Lymphocytic hypophysitis	Rare	Yes	Clinical impact depends which cell population in the pituitary is affected and to what degree
Hyperprolactinaemia	0.41–9.55,[46] 1.38[47]	Yes	–
Growth hormone deficiency	Rare	Yes	Case reports in association with antipituitary antibodies[63,64]
Ovaries			
Premature ovarian senescence	~100.0[69]	Yes	–
OPOI	~90.0[69]	Yes	–
POF	~10.0[69]	Yes	–
Lymphocytic (autoimmune) oophoritis	Rare	Yes	Almost exclusively reported in presence of anti-adrenal autoimmunity
The resistant ovary syndrome	Rare	Yes	Aetiology still undetermined
PCOS	15.9–153[107–110]	Yes	Wide range of reported prevalence due to differences in clinical criteria and clinical phenotypes

Sen A et al. Nat. Rev. Endocrinol 2014;10:37-50.

Autoimmunity Summary

Thyroid gland			
Hypothyroidism (Hashimoto thyroiditis)	3.5[15]	Yes	Female prevalence 4.4-times the male prevalence
Hyperthyroidism (Grave disease)	0.8[15]	Unknown	Female prevalence 10-times the male prevalence
Adrenal glands			
Addison disease	0.110–0.144[150]	Yes	Effects on fertility mostly only in association with other autoimmune diseases and APS
Cushing syndrome	0.001–0.004[150]	Unknown	Too rare to determine if affects fertility
Adrenal insufficiency in absence of Addison disease	Unknown	Yes	Associated with hypoandrogenism in turn associated with OPOI, age-associated DOR and POF
Pancreas			
Insulitis and type 1 diabetes mellitus	0.001–0.409[177]	Yes	Highly variable prevalence rates in different populations and different reporting method in view of young age at diagnosis
Other			
Parathyroid gland autoimmunity	Rare	Yes	Only found in association with APS
IgG4-related diseases (pancreatic and thyroid forms)	Rare	Unknown	Newly described diseases
Autoimmune polyglandular syndromes types I–IV	Rare	Yes	–

Abbreviations: APS, autoimmune polyglandular syndromes; DOR, diminished ovarian reserve; OPOI, occult primary ovarian insufficiency; PCOS, polycystic ovary syndrome; POF, premature ovarian failure.

Sen A et al. Nat. Rev. Endocrinol 2014;10:37-50.

Beyond working with patients with diagnosed autoimmune diseases, we should consider the role of “benign autoimmunity” in fertility care

- Overlooked by the medical system in the absence of symptoms
- Little awareness of AI in the gynecological setting
- Lots of pre-clinical & clinical research, but does not catch on clinically
- Serum Ab (anti-phospholipid, anti-thyroid, antinuclear antibodies) can affect fertility even without clinically overt AI disease!

ANAs and Infertility

- 517 infertile female patients undergoing IVF/ICSI and 186 women with a normal reproductive history were evaluated for ANAs
  - 39-45% of infertile women had + ANA versus 16.1% in fertile women
  - High titres (>1:320) was only found in infertile patients
- In another Polish study, + ANA (>1:40) were detected in:
  - 63% of women with endometriosis
  - 70.4% of women with unexplained infertility
  - 3.3% in women with hypothalamic-pituitary dysfunction
  - 5.6% of healthy women

Li Y et al. Taiwan J Obstet Gynecol. 2015 Dec;54(6):742-8.
Malinowski A et al. Ginekol Pol. 1995 Jul;66(7):420-4.

ANAs and Infertility

- In study in women undergoing IVF
  - 66 women (96 cycles) in infertile women with +ANA
  - 233 (285 cycles) in infertile women with – ANA
  - Women with ANAs had lower outcomes with oocytes retrieved, zygotes, cleavage rate, number of available embryos, quality of embryos, pregnancy rate (28.1% v 46.4%), implantation rate (15% v 25.7%)
- Another study had similar results- fewer high-quality embryos, reduced rates of pregnancy, clinical pregnancy rates, and implantation rates

Ying Y et al. Immunol Invest 2012;41(5):458-68.
Ying Y et al. Am J Reprod Immunol. 2013 Sep;70(3):221-9.

Autoimmune Etiologies of Infertility

Autoimmunity & the Reproductive System

Autoimmunity can affect all stages and steps of fertility and conception

- Ovarian function
- Testicular function
- Implantation
- Pregnancy loss

Ovarian Autoimmunity

- Autoimmune reactions have been identified against several ovarian tissues
- Approximately 20% of women with POI have AI contributions
- Theca Cells
  - **Steroidogenic cell autoimmunity (SCA)** causing premature ovarian insufficiency
  - Lymphocytic oophoritis
- Granulosa Cells
  - FSH receptor blocking immunoglobulins create competitive inhibition (seen in patient with myasthenia gravis)
- Oocytes
  - Oocyte antibodies have been detected by ELISA

Spontaneous “Premature Menopause”

Spontaneous POI

- Women <40
- Normal karyotype (46xx)
- Menopausal level FSH
- Oligomenorrhea/amenorrhea
- No iatrogenic cause
- OFTEN in women with Hashimoto’s thyroiditis

Steroidogenic Cell Autoimmunity

- Autoimmunity to steroidogenic enzymes
- About 4% of women with premature ovarian insufficiency/failure will test positive for steroidogenic cell autoimmunity
- AMH may be higher in women with SCA-POI at times. AMH can fluctuate as cycles still happen where more follicles are produced
- Ultrasound can often lead to a false diagnosis of PCOS

Bakalov et al. Fertil Steril, 2005 Oct;84(958-65).
LaMarca et al. J Clin Endocrin Metab 2009;94:3816-23.

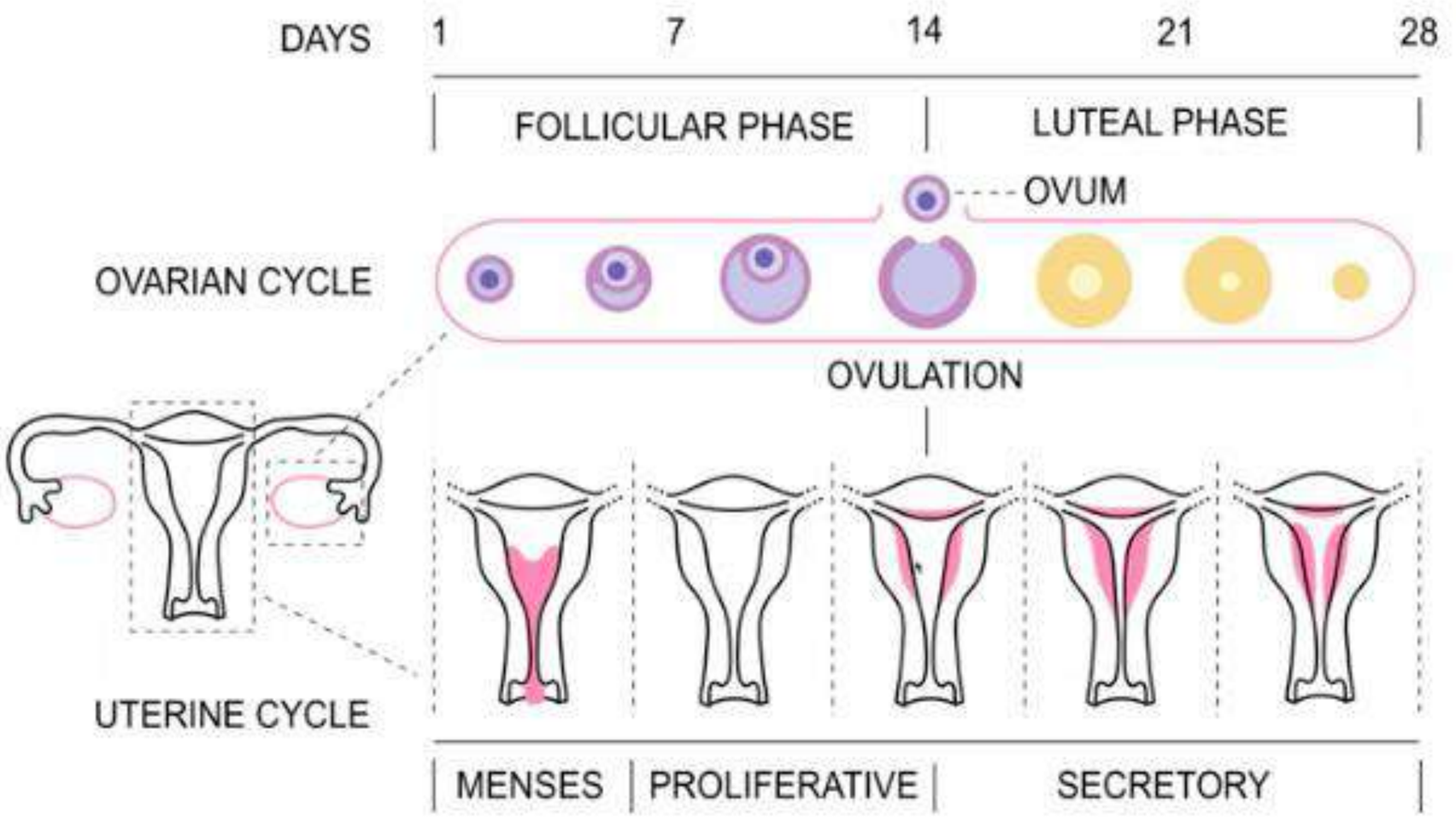
Steroidogenic Cell Autoimmunity

Mechanisms

- Follicle depletion (similar to menopause)
- Follicle dysfunction (FAR more common!)
  - Women have follicles (~75% have detectable follicles)
  - Intermittent and unpredictable function
- Graafian follicle dysfunction
  - Follicle luteinizes too early

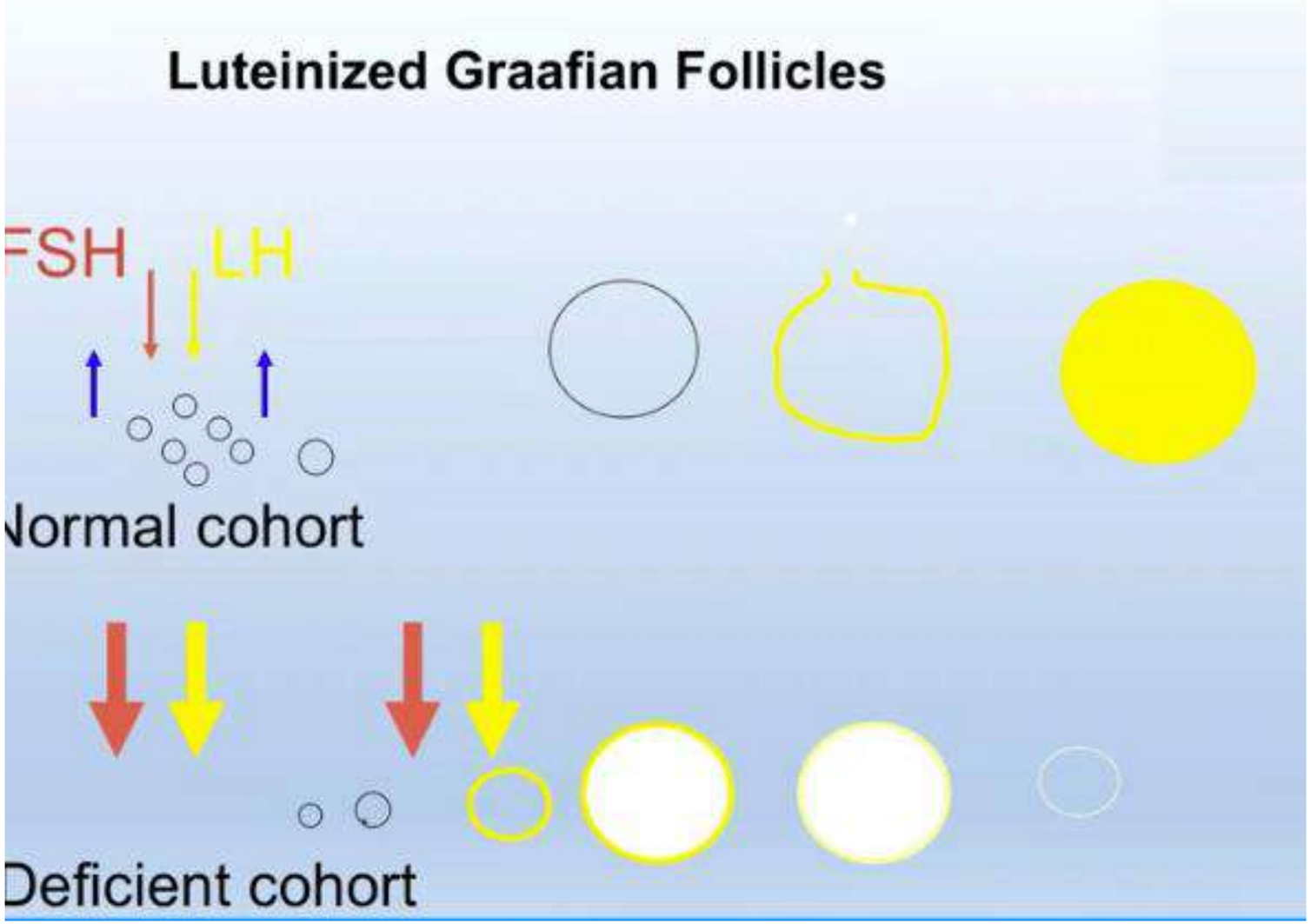
Bakalov et al. Fertil Steril, 2005 Oct;84(958-65).
LaMarca et al. J Clin Endocrin Metab 2009;94:3816-23.

Steroidogenic Cell Autoimmunity



Bakalov et al. Fertil Steril, 2005 Oct;84(958-65).
LaMarca et al. J Clin Endocrin Metab 2009;94:3816-23.

Steroidogenic Cell Autoimmunity



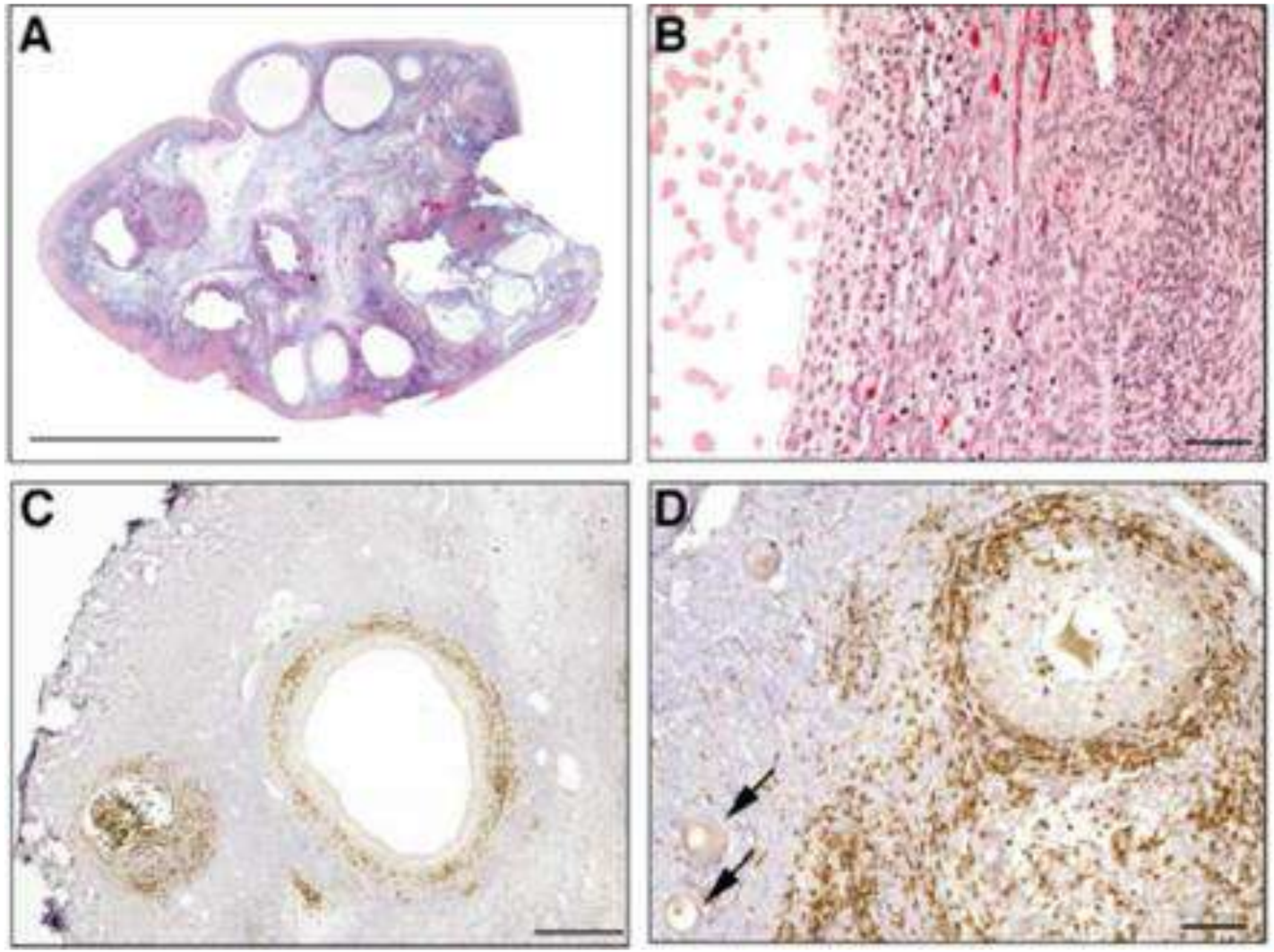
Bakalov et al. Fertil Steril, 2005 Oct;84(958-65).
LaMarca et al. J Clin Endocrin Metab 2009;94:3816-23.

Autoimmune Lymphocytic Oophoritis

- Strong correlation with adrenal antibodies
- Study by Betterle et al:
  - 28/28 cases of autoimmune oophoritis ALSO had adrenal antibodies, not seen in any of 375 controls
- Bakalov study showed that in 90% of women with Addison's disease, POI showed up first!
  - Early marker of Addison's? And if POI is an early marker for severe adrenal dysfunction, could more subtle dysfunction also have an effect?
  - AI oophoritis may mark a long preclinical course towards Addison's
  - Adrenal antibody testing by 21-hydroxylase may be a useful screening test for AI oophoritis and asymptomatic adrenal insufficiency

Betterle 1987
Bakalov et al. Fertil Steril 2005 Oct;84(4):958-65.

Autoimmune Lymphocytic Oophoritis



Betterle 1987
Bakalov et al. Fertil Steril 2005 Oct;84(4):958-65.

Suspicious of autoimmunity with POI?

- Not a lot of great tests!
- Consider testing:
  - 21 hydroxylase (by immunoprecipitation)
    - CPT code 83519
    - Used to diagnose Addison's or AI polyglandular syndrome (APS) type 1
  - Thyroid peroxidase (increased with AI POI)
    - CPT 86376
    - Test for autoimmune thyroiditis
    - antiTPO has high cross-reactivity with anti-zona pellucida Ab
  - Genetic testing
    - Karyotyping should be performed to rule out mosaic Turner's, for example

Conventional Management of AI POI

- Conventionally, donor egg often recommended
- Remember that as disease ebbs & flows, women may have fertile cycles & follicles
- As risk management, consider ACTH-stimulation test every 1-2 years and should be informed of (and watch for) sx of adrenal insufficiency
  - Decreased appetite, weight loss
  - Salt cravings
  - Fatigue
  - Hyperpigmentation of gums & skin creases (ie on knuckles)

Management of AI POI

Need to consider (& manage) impact on

- Endocrine health
- Emotional health
- Reproductive health
- Genetic health

Antisperm Antibodies

- Originally described in 1954 with 2 cases of men exhibiting sperm agglutination
- Prevalence data is limited due to heterogeneity in ASA- antibodies can be located in male or female serum, semen, ovarian follicular fluid, vaginal/cervical secretions, or bound to the outer sperm membrane
- IgA, IgG, and IgM have all been identified

Antisperm Antibodies

- One study showed that in couples with unexplained infertility, 7% of men and 13% of women were ASA positive
- ELISA assay showed ASA was present in sera of
  - 77% of women with unexplained infertility
  - 75% of women with endometriosis
  - 60% of women with tubal infertility
  - 5% of women in control group
- In men, studies show ASA + rates of 10-15%

Antisperm Antibodies

No standardized testing at this point

- IBD- Immunobead assays
  - Semi-quantitative
  - Can determine type and physical location of ASA
  - Good sensitivity/specificity
  - Can conduct test on viable sperm
  - Can be difficult to interpret
- MAR (Mixed Antiglobulin Reaction Test)
  - Similar to IBD, but erythrocytes are used rather than plastic beads
  - Sperm/erythrocyte agglutination can be viewed by light microscopy
  - Rapid assay time, good specificity, can use viable sperm
  - Does not give quantitative info on ASA binding or location

Antisperm Antibodies: Treatment

Conventionally, 3-part treatment regimen

- Decrease ASA production
  - Condom use
  - Systemic corticosteroids (Prednisone 20mg) – limited efficacy
    - Other naturopathic options here??
- Remove ASA already bound to sperm
  - Perform sperm washing, immunodepletion, IgA protease treatment
- Perform ART
  - ASA can significantly decrease success rates
  - Use sperm washing or ICSI may increase pregnancy rates in ASA-positive couples

The Endometrial Inflammosome

- Newer research has identified an “inflammosome” composed of NALP-3 and inflammatory cytokines (capsase-1, IL-1B, IL-18)
- Endometrial samples were collected by hysteroscopy during the implantation window in 10 fertile women and 30 women with RPL. Increased inflammatory activity seen in RPL group
- Autoimmune inflammation of the endometrial tissue, trigger from infection or damage
- A HUGE area for further investigation!

Dippolito et al. Fertil Steril 2016;105(1):111.

Autoimmunity- the Integrative Paradigm

Integrative Approaches to Autoimmunity

Autoimmunity requires 3 factors

- Genetic Predisposition
- Exposure to an antigen (a trigger)
- Intestinal permeability
  - Patients with autoimmunity have higher amounts of zonulin, which reversibly increases intestinal permeability

To Stop the Process

- Reduce triggers & toxins
- Heal the gut
- Provide nutrients to regenerate healthy tissue

Fasano A. Leaky Gut and autoimmune disease. Clin Rev Allergy Immunol. 2012 Feb;42(1):71-8.
Fasano A. Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity, and Cancer. Physiol Rev. Vol 91. Jan 2011. 151-175

Reducing Triggers

- Triggers can be various!
- Let’s use iodine as a trigger example in Hashimoto’s
  - Oxidation of iodide to iodine by TPO produces hydrogen peroxide, usually neutralized by glutathione peroxidase (requires glutathione & selenium)
  - If deficient in glutathione or selenium, oxidative stress can build up & cause tissue damage, triggering inflammation
  - This may be one reason selenium can decrease Ab in hashimoto’s
  - Iodine supplementation should be avoided in patient with Hashimoto’s until TPO Ab < 100 kU/L

Fasano A. Leaky Gut and autoimmune disease. Clin Rev Allergy Immunol. 2012 Feb;42(1):71-8.
Fasano A. Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity, and Cancer. Physiol Rev. Vol 91. Jan 2011. 151-175

Environmental Triggers

- Many environmental toxins can cause tissue damage and may contribute to autoimmunity
- Halogens (fluoride, bromide (ie PBDEs in flame retardants), chlorine (in PCBS), etc)
- Xenoestrogens (BPA, phthalates, parabens)
- Heavy metals, pesticides, and more!

Patrick L. Understanding Endocrine Disruption: Focus on Thyroid Disease. MM XVII April 18-19. Presentation

Infectious Triggers

- Several infectious agents have been studied as triggers for AI disease in susceptible individuals
  - Rubella
  - Hep C (when treated with interferon)
  - Coxsackie virus
  - CMV/EBV/Herpes viruses
  - Yersinia enterocolitica
  - Retroviruses
  - H. pylori
  - Borrelia burgdorferi
  - Mycoplasma
  - Candida
  - Chlamydia

Tomer Y, Davies TF. Infection, thyroid disease, and autoimmunity. *Endocrine Reviews*. 1993;14(1):107–120.

Address Intestinal Permeability

Support Gut Integrity

- Glutamine 5-10g daily
- Zinc carnosine, 20-30 mg daily
- NAC (1.8g daily)/Glutathione 200 mg daily
- Probiotics
- Quercetin (1000 mg daily)
- N-acetyl Glucosamine (NAG)

Fasano A. Leaky Gut and autoimmune disease. Clin Rev Allergy Immunol. 2012 Feb;42(1):71-8.
Fasano A. Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity, and Cancer. Physiol Rev. Vol 91. Jan 2011. 151-175

Address Intestinal Permeability

Elimination diet

SCD/GAPS diets

Lacto-fermented foods

Diet-

- Nutrient-dense, paleo/anti-inflammatory/Mediterranean
- Reduce/remove grains, especially gluten, which can increase expression of zonulin
- High omega 3s, healthy fats

Fasano A. Leaky Gut and autoimmune disease. Clin Rev Allergy Immunol. 2012 Feb;42(1):71-8.
Fasano A. Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity, and Cancer. Physiol Rev. Vol 91. Jan 2011. 151-175

Nutrition & Autoimmunity

There is a clear association with Celiac disease & Hashimoto's

Some clinicians encourage a gluten free diet for all patients with autoimmunity

Food allergy testing can be an appropriate means to tailor the patient's diet to one that minimally stimulates the immune system

Nutrition & Autoimmunity

Remember that proper nutrition is dependent upon good digestion & absorption/assimilation

Common nutrient deficiencies seen in autoimmunity include

- B12
- Selenium
- Vitamin E
- Glutathione
- Zinc
- Iron/ferritin

Rostami R, Aghasi MR, et al. Enhanced oxidative stress in Hashimoto's thyroiditis: inter-relationships to biomarkers of thyroid cuntion. Clin Biochem. 2013 Mar;46(4-5):308-12.
Ness-Abramof R, Nabriski DA, et al. Prevalance and evaluation of B12 deficienct in patients with autoimmune thyroid disease. Am J Med Sci. 2006 Sep;332(3):119-22.

Low Grade Inflammation & Infertility

Low-Grade Inflammation & Infertility

- Outside of autoimmunity, low-grade inflammation should also be considered with patient struggling to conceive!
- Inflammation is critical for ovulation and implantation
- Peripheral pro-inflammatory cytokines and endometrial inflammation have been shown to be higher in women with IVF failure
- Inflammation is involved in pathophysiology for PCOS and endometriosis
- Increased inflammation can contribute to subfertility among women even without a frank reproductive disorder

Radin RG, Sjaarda LA, Silver RM, et al. C-Reactive protein in relation to fecundability and anovulation among eumenorrheic women. *Fertil Steril*. 2018;109(2):232-239.e1. doi:10.1016/j.fertnstert.2017.10.025

Low-Grade Inflammation & Infertility

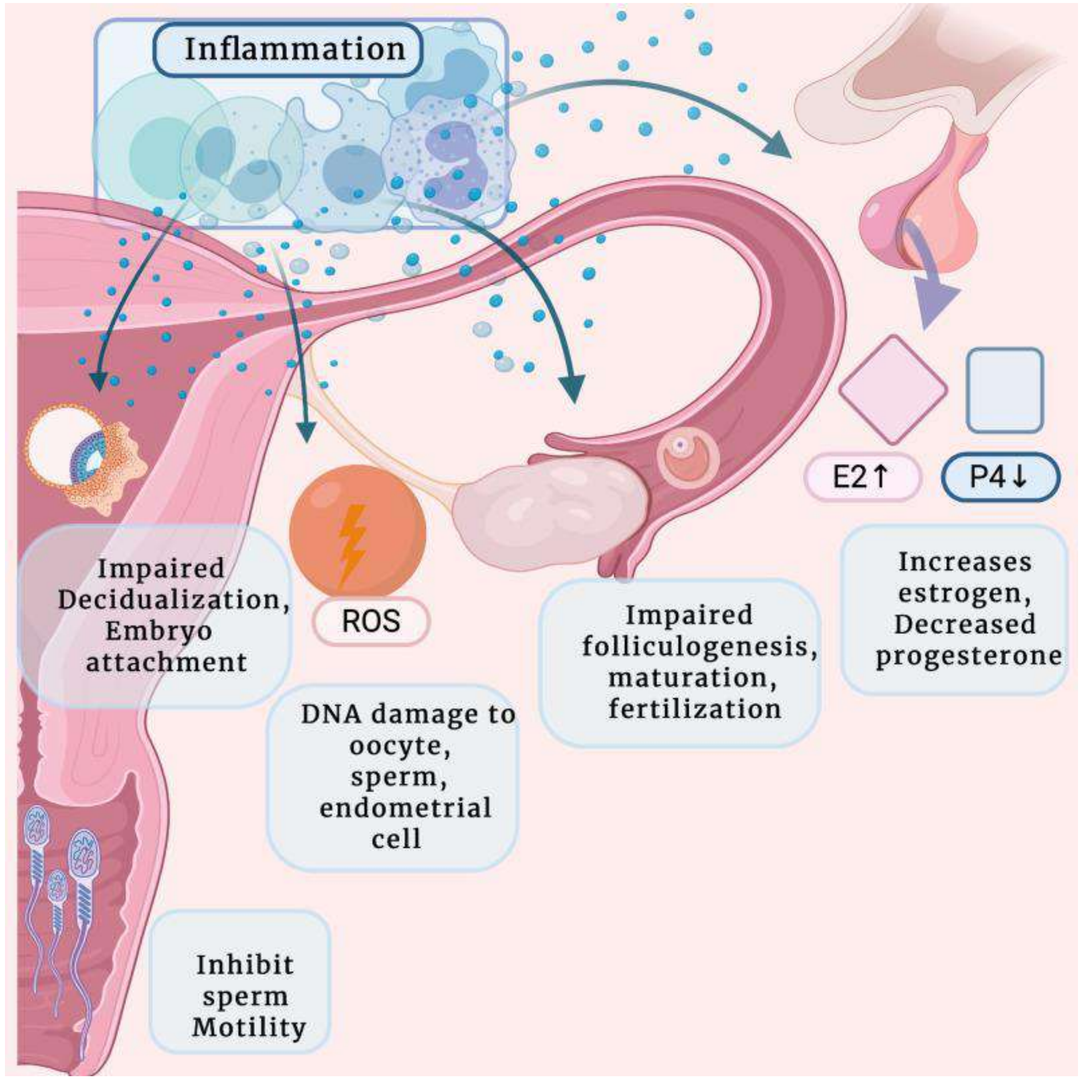
Inflammation can impact fertility in a number of ways:

- Causing hormonal imbalance (generally increased E and decreased P)
- Impairing follicular maturation
- Impairing fertilization
- Damaging DNA, lipids and proteins of oocyte, sperm, and other cells
- Inhibit implantation
- Inhibit sperm motility

Mohammed Rasheed HA, Hamid P. Inflammation to Infertility: Panoramic View on Endometriosis. *Cureus*. 2020;12(11):e11516. Published 2020 Nov 16. doi:10.7759/cureus.11516

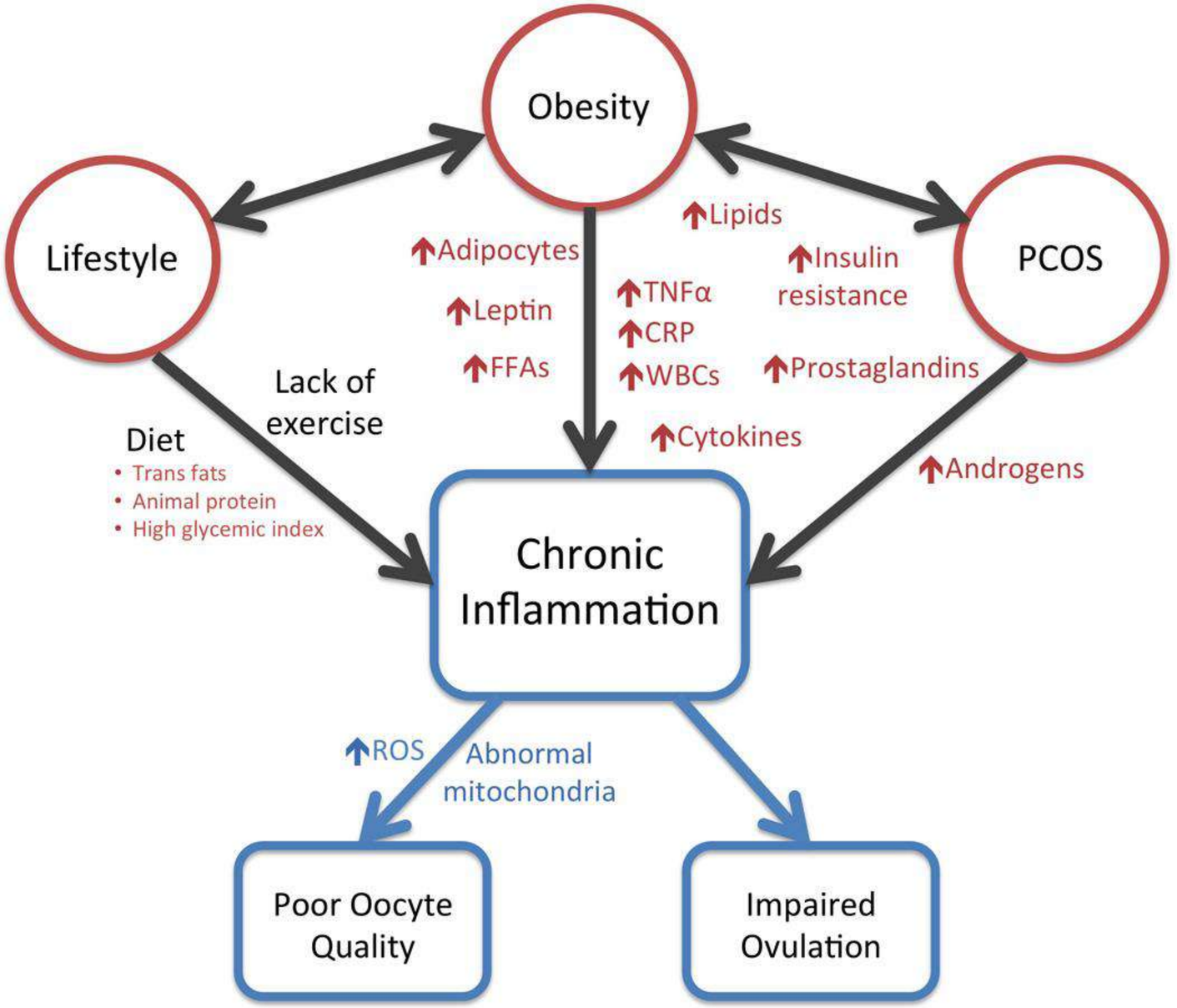
Radin RG, Sjaarda LA, Silver RM, et al. C-Reactive protein in relation to fecundability and anovulation among eumenorrheic women. *Fertil Steril*. 2018;109(2):232-239.e1. doi:10.1016/j.fertnstert.2017.10.025

Inflammation & the path to Infertility



Mohammed Rasheed HA, Hamid P. Inflammation to Infertility: Panoramic View on Endometriosis. *Cureus*. 2020;12(11):e11516. Published 2020 Nov 16. doi:10.7759/cureus.11516

Inflammation & the path to Infertility



Boots CE, Jungheim ES. Inflammation and Human Ovarian Follicular Dynamics. *Semin Reprod Med*. 2015;33(4):270-275. doi:10.1055/s-0035-1554928

EAGeR trial

- Effects of Aspirin in Gestation and Reproduction Trial
- Low dose aspirin taken daily while ttc restored pregnancy & live birth rates to levels found in women with lower pre-treatment inflammation levels (based on hsCRP)
- Effect was more profound in women with BMI <25 versus >25 and lower waist to hip ratio, suggesting complex relationship between adiposity-associated versus non-adiposity-associated inflammation
- INTERESTINGLY, inhibition of COX-2 can prevent follicle rupture and studies show that giving NSAIDs in the first 80% of ovulatory process can inhibit ovulation. Avoid drugs that inhibit prostaglandin.

Radin RG, Sjaarda LA, Silver RM, et al. C-Reactive protein in relation to fecundability and anovulation among eumenorrheic women. *Fertil Steril*. 2018;109(2):232-239.e1. doi:10.1016/j.fertnstert.2017.10.025
Sjaarda LA, Radin RG, Silver RM, et al. Preconception Low-Dose Aspirin Restores Diminished Pregnancy and Live Birth Rates in Women With Low-Grade Inflammation: A Secondary Analysis of a Randomized Trial. *J Clin Endocrinol Metab*. 2017;102(5):1495-1504. doi:10.1210/jc.2016-2917

Immunity & Inflammation

Consider screening for inflammation through measurement of:

- ANA
  - Negative, or in the range of 1:40-1:60 (may be normal)
- Sedimentation rate
  - 0-29 mm/hr for women (0-22 mm/hr for men)
- hs-CRP
  - <2 mg/L (optimal) <3 mg/L (“normal”)

Be careful, as all of these markers are controversial and have mixed data!!

hsCRP, Inflammation, & Infertility

- hsCRP seems to be our best inflammatory marker to understand a patients' inflammatory state and implications on fertility
- CRP fluctuates in the menstrual cycle, with peak levels near ovulation
- Higher hsCRP is associated with reduced fecundability (adjusted Fecundability odds ratio FOR = 0.74), particularly with obesity
- Optimal is <2.0 mg/L
- 20-40% of women of reproductive age are >2.0 mg/L

Sjaarda LA, Radin RG, Swanson C, et al. Prevalence and Contributors to Low-grade Inflammation in Three U.S. Populations of Reproductive Age Women. *Paediatr Perinat Epidemiol*. 2018;32(1):55-67. doi:10.1111/ppe.12409

Support Immune Balance & Lower Inflammation

- Omega 3s 2-4g day EPA +DHA
- Botanicals for TH1/TH2 balance
- Acupuncture
- Curcumin
  - Downregulates TNF-A, IL-2, 6, 8, 12
  - Antiinflammatory effects in TH-1 and TH-2 mediated conditions (ie Crohn's & UC)
- Vitamin D (supplement to 60-80 ng/L)

Wetz I, Nowosadzka M. Hashumoto's Thyroiditis.
Filardi et al. Nutrients. 2020 Oct; 12(10): 3179.

- If you need to balance immune system, here are some sample therapeutics

Stimulate Th-1 cell production	Stimulate Th-2 cell production
Ashwaganda	Alcohol
Astragalus	Anatabine
Beta-glucan mushrooms and other immune boosting mushrooms	Candida
	Cortisol
Chlorella and other algae products*	Curcumin from turmeric
Echinacea	DHEA
Estrogen	Genistein
Glutathione	Green tea extract
Gram-negative bacteria (endotoxin)	Lycopene
Licorice root	Parasites
Melissa officinalis (lemon balm)	Pine bark extract
Panax ginseng	Pycnogenol (natural ingredient in apples)
Polypodium leucotomos fern extract (Difur)	Quercetin
Selenium	Resveratrol
Viruses	Soluble fiber
Yoga, restorative exercise	Vigorous exercise
	White willow bark

*Algae may contain high amounts of iodine

Kharrazian, D. “Why am I still Having Thyroid Symptoms When My Lab Tests Are Normal?”

Increase Regulatory T Cells

- Probiotics
  - Strains studied include L casei, L salivarius, L rhamnosis, B lactis, L reuterii
  - Bifidobacterium infantis is also anti-inflammatory
  - Strain-specific data is mixed
- EGCG
- Weightlifting/UV light
- Vitamin A/D
- Butyrate
- Glutathione/SOD

Wetz I, Nowosadzka M. Hashumoto's Thyroiditis.

Thank you!