WHY AM I NOT PREGNANT NOW?

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Disclosures

- Relevant Financial Relationships:
  - Employed at Oak Point University and Keiser University as Assistant Professor / Instructor respectively
  - Employed at Serenity Family Wellness as Clinical Director
- Relevant Nonfinancial Relationships
  - Past President of the ACA Acupuncture Council
  - Former member of the IDFPR Acupuncture Board
- The information within this presentation will be given fairly and without major bias

WHY THIS LECTURE SHOULD NOT BE CALLED OPTIMIZING FERTILITY

Course Goals & Objectives

Goals

- Provide an understanding of the barriers to health in women trying to get pregnant.
- Discuss basic lab values, advanced testing and genetics to best support women's and men's fertility potential.
- Empower and engage patients with skills and knowledge in their fertility and pregnancy journey.

Objectives

- Review recent statistics and morbidity / mortality in perinatal women.
- Discuss current medical treatment considerations for barriers to fertility.
- Define normal values in basic and advanced lab studies coupled with improved patient history taking techniques and coordination of care what the best possible customized care plan for a patient looking to achieve a healthy pregnancy.
- Review treatment possibilities and methodology using full scope care for a chiropractic physician.


Statistics
organization
scientific
descriptive
analysis
samples
collection
data
interpretation
statistical
Inference
theory
mathematical
experiments
science
prediction
probability
population
statistic
total
mean
parameters
mathematics
provides
inferential
consider
concerned
also
wide
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pertaining
discipline
branch
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well
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referring
Statisticians
sampling
particular
disciplines
hypothesis
observations
inductive
grouped
provide
theoretical
prove
confused
survey
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wrong
larger
roots
given
collecting
since
deduce
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problems
considered
social
working
useful
ways
improve
process
soundness
terms
empirical
summarize
successful
element
logically
companies
usually
vital
draw
necessary
using
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expertise
sciences
comprise
applications
aspects
art
gained
people
thinking
planning
models direct
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statistician
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consultants
focus
probabilities
misleading
academic
new
way
opposite
uncertainty
communicating
together
calculated
quality
plural
rather
fields
method
patterns
true
results
government
direction
number
deals
singular
distinct
closely
seems
research
subject
explanation
predictions
basis
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whose
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surveys
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a.k.a
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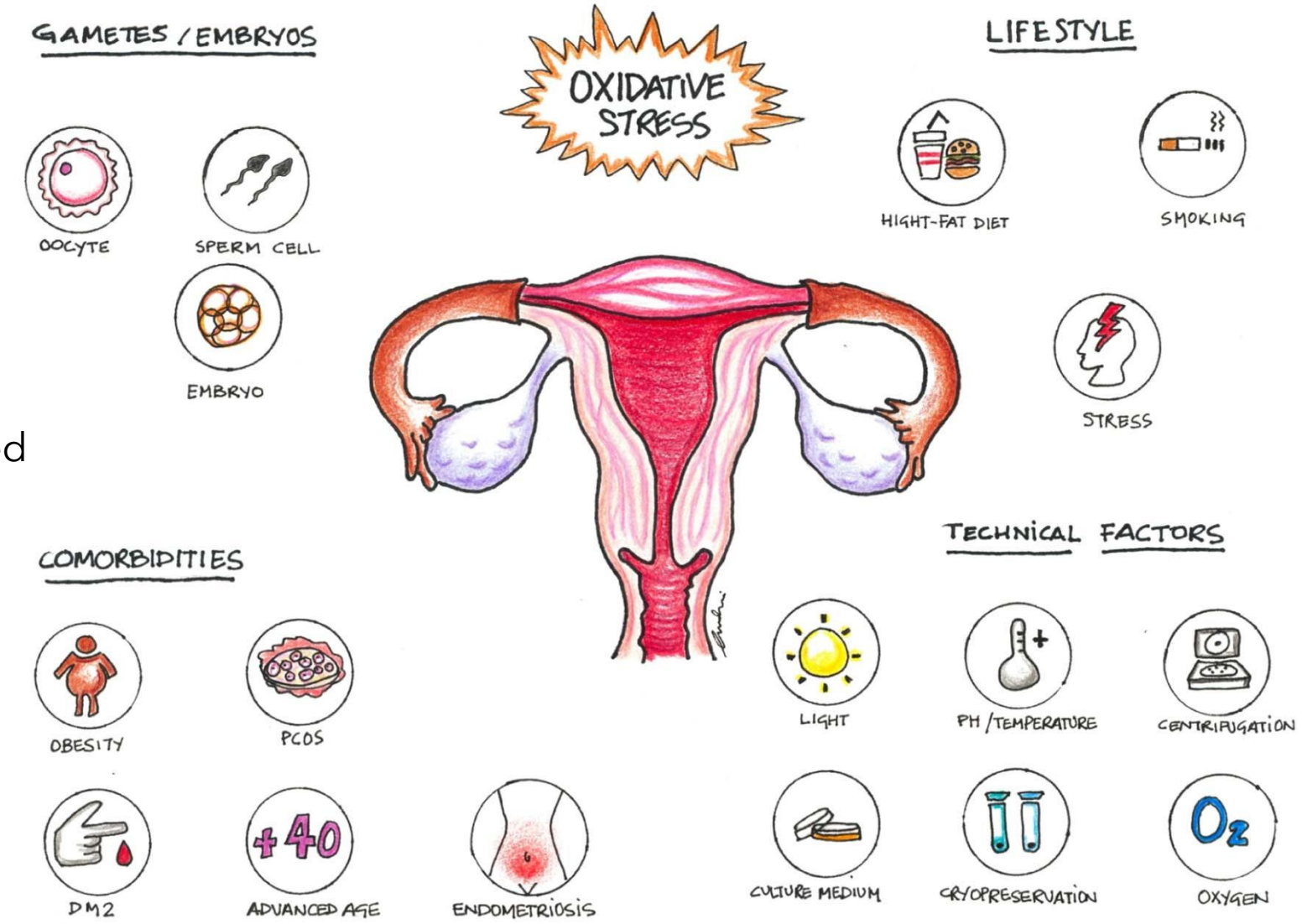
What is Infertility?

- Inability for a couple of reproductive age to establish a pregnancy in $\geq$ 1 year of unprotected sex
- Over 35 yoa then $\geq$ 6 months
- 1 in every 4 couples in developed nations struggles to get pregnant
- For a healthy woman in her 20s or early 30s, the chances of conceiving each month is 25–30%
  - 40 years old, the chances are 10% or less
- Male fertility rates change with age as well
  - 30% drop in sperm production after 45 yoa

Co-Morbidity Factors Affecting Fertility

"The role of mitochondrial activity in female fertility and assisted reproductive technologies: overview and current insights"



REPRODUCTIVE BIOMEDICINE ONLINE 36 (2018) 686–697

PRAMS
PREGNANCY RISK ASSESSMENT MONITORING SYSTEM

Prevalence of Selected Maternal and Child Health Indicators for Illinois, Pregnancy Risk Assessment Monitoring System (PRAMS), 2016–2019

Health Indicator	2016		2017		2018		2019		Overall 2019[§]
	N[#]	% (95% CI)[¶]	N[#]	% (95% CI)[¶]	N[#]	% (95% CI)[¶]	N[#]	% (95% CI)[¶]	% (95% CI)[¶]
Nutrition									
• Multivitamin use ≥4 times a week during the month before pregnancy	1378	44.6 (41.7-47.5)	1220	43.1 (40.1-46.2)	1304	43.7 (40.8-46.7)	1232	41.4 (38.4-44.5)	41.8 (41.0-42.5)
Pre-pregnancy Weight									
• Underweight (Body Mass Index [BMI]<18.5 kg/m^2)	1329	4.0 (3.0-5.4)	1162	2.7 (1.9-3.9)	1263	2.9 (2.1-4.1)	1198	3.1 (2.2-4.3)	3.3 (3.0-3.6)
• Overweight (BMI 25-29.9 kg/m^2)	1329	26.6 (24.1-29.4)	1162	26.4 (23.7-29.3)	1263	26.6 (24.0-29.4)	1198	24.3 (21.7-27.1)	26.2 (25.5-26.9)
• Obese (BMI≥30 kg/m^2)	1329	21.9 (19.5-24.5)	1162	26.1 (23.4-29.0)	1263	25.6 (23.1-28.3)	1198	27.2 (24.4-30.1)	27.1 (26.4-27.8)
Substance Use									
• Any cigarette smoking									
◦ During the 3 months before pregnancy	1302	16.7 (14.6-19.1)	1201	16.1 (13.9-18.6)	1288	14.7 (12.7-17.0)	1214	15.4 (13.2-17.8)	15.1 (14.6-15.7)
◦ During the last 3 months of pregnancy	1304	7.6 (6.1-9.4)	1202	6.8 (5.3-8.6)	1288	6.9 (5.5-8.5)	1214	6.7 (5.3-8.4)	6.8 (6.5-7.2)
◦ Postpartum	1302	10.0 (8.3-12.0)	1202	11.0 (9.2-13.2)	1287	9.6 (7.9-11.5)	1213	9.4 (7.7-11.4)	9.7 (9.2-10.1)
• Any e-cigarette use									
◦ During the 3 months before pregnancy	1365	2.0 (1.3-2.9)	1213	3.1 (2.2-4.5)	1296	3.5 (2.5-4.8)	1220	4.3 (3.2-5.8)	4.3 (4.0-4.6)
◦ During the last 3 months of pregnancy	1362	0.3 (0.1-0.9)	1212	1.3 (0.7-2.3)	1297	1.3 (0.8-2.2)	1217	1.1 (0.6-1.9)	1.3 (1.1-1.4)
• Hookah use in the last 2 years	1358	4.3 (3.2-5.7)	1206	3.5 (2.5-4.8)	1289	4.2 (3.2-5.6)	1210	2.9 (2.0-4.2)	4.7 (4.4-5.1)
• Heavy drinking (≥8 drinks a week) during the 3 months before pregnancy	1369	3.5 (2.6-4.8)	1213	2.4 (1.6-3.5)	1304	2.4 (1.7-3.5)	1219	3.3 (2.3-4.6)	2.9 (2.6-3.2)
Intimate Partner Violence (IPV)[‡]									
• Experienced IPV during the 12 months before pregnancy by a husband or partner and/or an ex-husband or partner	1359	2.2 (1.5-3.3)	1206	2.7 (1.8-3.9)	1288	1.8 (1.1-2.8)	1204	1.8 (1.1-2.8)	3.0 (2.8-3.3)
• Experienced IPV during pregnancy by a husband or partner and/or an ex-husband or partner	1355	1.3 (0.8-2.3)	1206	1.3 (0.8-2.3)	1289	1.4 (0.8-2.3)	1205	1.5 (0.9-2.6)	2.0 (1.8-2.2)
Depression									
• Self-reported depression in the 3 months before pregnancy	1378	7.8 (6.3-9.5)	1221	9.7 (8.0-11.8)	1306	12.3 (10.5-14.4)	1233	11.9 (10.0-14.1)	15.1 (14.5-15.7)
• Self-reported depression during pregnancy	1366	8.6 (7.1-10.4)	1210	9.9 (8.2-12.0)	1294	11.1 (9.3-13.1)	1217	13.8 (11.8-16.1)	14.8 (14.2-15.4)
• Self-reported postpartum depressive symptoms**	1365	9.6 (7.9-11.4)	1206	9.3 (7.7-11.3)	1298	9.7 (8.1-11.5)	1216	10.8 (9.0-12.9)	13.4 (12.9-14.0)
Health Care Services									
• Health care visit in the 12 months before pregnancy	1353	70.2 (67.4-72.9)	1207	70.3 (67.3-73.1)	1298	72.8 (70.0-75.4)	1222	72.6 (69.7-75.3)	68.0 (67.2-68.7)
• Began prenatal care in 1st trimester	1354	88.3 (86.1-90.1)	1205	88.4 (86.2-90.3)	1294	88.5 (86.4-90.3)	1215	89.1 (86.9-91.0)	87.7 (87.2-88.3)
• Had a flu shot in the 12 months before birth	1371	57.4 (54.4-60.2)	1213	58.3 (55.2-61.4)	1292	61.1 (58.2-64.0)	1221	64.0 (60.9-66.9)	60.8 (60.1-61.6)
• Had maternal postpartum checkup	1365	92.6 (90.8-94.1)	1209	92.4 (90.5-94.0)	1301	93.0 (91.3-94.4)	1218	93.9 (92.2-95.3)	90.7 (90.3-91.2)
Pregnancy Intention									
• Mistimed	1373	21.2 (18.8-23.7)	1216	18.7 (16.3-21.3)	1298	17.6 (15.5-20.1)	1228	19.9 (17.5-22.5)	19.3 (18.7-19.9)
• Unwanted pregnancy	1373	6.4 (5.1-8.0)	1216	8.4 (6.8-10.4)	1298	8.1 (6.6-9.9)	1228	6.8 (5.4-8.5)	6.5 (6.2-6.9)
• Unsure whether wanted pregnancy	1373	14.4 (12.4-16.6)	1216	15.7 (13.6-18.2)	1298	16.3 (14.2-18.7)	1228	15.5 (13.3-17.9)	15.7 (15.1-16.2)
• Intended pregnancy	1373	58.1 (55.1-61.0)	1216	57.2 (54.1-60.3)	1298	57.9 (54.9-60.8)	1228	57.9 (54.8-60.9)	58.5 (57.7-59.3)

Health Indicator	2016		2017		2018		2019		Overall 2019[§]
	N[#]	% (95% CI)[¶]	N[#]	% (95% CI)[¶]	N[#]	% (95% CI)[¶]	N[#]	% (95% CI)[¶]	% (95% CI)[¶]
Postpartum[††] Family Planning									
• Use of any postpartum contraception[††‡‡]	1333	79.9 (77.5-82.2)	1203	78.5 (75.8-81.0)	1284	77.3 (74.7-79.7)	1209	74.8 (72.0-77.4)	76.4 (75.7-77.0)
• Highly effective contraceptive methods									
• Male or female sterilization	1333	9.8 (8.2-11.8)	1203	9.3 (7.6-11.3)	1284	9.6 (8.0-11.5)	1209	9.6 (7.9-11.6)	11.5 (11.0-12.0)
• Long acting reversible contraceptive method[§§]	1333	16.5 (14.4-18.9)	1203	14.9 (12.8-17.3)	1284	16.1 (14.0-18.4)	1209	17.1 (14.9-19.6)	17.3 (16.7-17.9)
• Moderately effective contraceptive methods[§§]	1333	25.8 (23.3-28.5)	1203	25.0 (22.4-27.9)	1284	26.9 (24.3-29.6)	1209	24.6 (21.9-27.4)	24.6 (23.9-25.3)
• Least effective contraceptive methods[§§]	1333	27.8 (25.3-30.5)	1203	29.3 (26.5-32.2)	1284	24.7 (22.2-27.4)	1209	23.5 (21.0-26.2)	23.0 (22.4-23.7)
Oral Health									
• Teeth cleaned during pregnancy by a dentist or dental hygienist	1373	44.3 (41.4-47.2)	1216	44.5 (41.4-47.6)	1298	42.8 (39.9-45.8)	1223	48.1 (45.0-51.2)	45.9 (45.1-46.7)
Health Insurance Status One Month Before Pregnancy[¶¶]									
• Private insurance	1318	61.9 (58.9-64.8)	1186	59.7 (56.5-62.8)	1274	62.8 (59.8-65.6)	1216	60.6 (57.5-63.7)	62.7 (62.0-63.5)
• Medicaid	1318	24.8 (22.2-27.5)	1186	25.7 (23.0-28.7)	1274	25.2 (22.7-27.9)	1216	25.0 (22.3-27.8)	22.6 (22.0-23.3)
• No insurance	1318	11.9 (10.0-14.1)	1186	13.8 (11.7-16.2)	1274	11.1 (9.3-13.3)	1216	13.5 (11.4-15.8)	13.8 (13.2-14.4)
Health Insurance Status for Prenatal Care[¶¶]									
• Private insurance	1279	60.8 (57.8-63.8)	1175	57.9 (54.7-61.1)	1261	61.4 (58.4-64.3)	1194	59.7 (56.6-62.8)	59.8 (59.1-60.6)
• Medicaid	1279	34.8 (32.0-37.8)	1175	38.6 (35.6-41.8)	1261	34.9 (32.0-37.8)	1194	35.3 (32.3-38.4)	36.2 (35.5-37.0)
• No insurance	1279	1.0 (0.5-1.8)	1175	0.8 (0.4-1.5)	1261	1.0 (0.5-1.9)	1194	1.1 (0.6-2.1)	2.8 (2.5-3.1)
Health Insurance Status Postpartum[††¶¶]									
• Private insurance	1333	57.7 (54.7-60.6)	1192	55.1 (51.9-58.2)	1281	58.3 (55.3-61.2)	1212	56.8 (53.7-59.9)	57.7 (56.9-58.4)
• Medicaid	1333	31.7 (29.0-34.6)	1192	34.4 (31.4-37.5)	1281	30.6 (27.9-33.5)	1212	30.3 (27.5-33.3)	29.9 (29.2-30.6)
• No insurance	1333	8.2 (6.6-10.0)	1192	9.4 (7.6-11.5)	1281	8.8 (7.2-10.7)	1212	10.6 (8.8-12.7)	11.5 (11.0-12.0)
Infant Sleep Practices									
• Baby most often laid on back to sleep	1323	79.9 (77.4-82.2)	1175	81.5 (78.9-83.8)	1271	84.2 (81.8-86.2)	1203	82.6 (80.0-84.8)	79.6 (78.9-80.2)
Breastfeeding Practices									
• Ever breastfed	1336	88.6 (86.5-90.4)	1188	88.2 (86.0-90.1)	1273	87.0 (84.8-88.8)	1204	90.8 (88.8-92.5)	87.9 (87.4-88.4)
• Any breastfeeding at 8 weeks	1320	67.1 (64.2-69.9)	1173	68.3 (65.2-71.2)	1264	65.8 (62.9-68.6)	1191	69.0 (66.0-71.9)	67.7 (67.0-68.4)

[§]PRAMS site aggregate for 2019: Alabama, Alaska, Arkansas, Colorado, Connecticut, Delaware, District of Columbia, Florida, Georgia, Hawaii, Illinois, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, New Hampshire, New Jersey, New Mexico, New York City, New York State, North Carolina, North Dakota, Oregon, Pennsylvania, Puerto Rico, Rhode Island, South Dakota, Tennessee, Utah, Vermont, Virginia, Washington, Wisconsin, and Wyoming met the required 50% response rate threshold for inclusion.

[#]Unweighted sample size

[¶]Weighted percent (95% Confidence Interval)

[‡]Defined as being pushed, hit, slapped, kicked, choked, or physically hurt in any way by a husband/partner and/or an ex-husband/ex-partner. In 2016 (Phase 8), the question response options were expanded to include "my ex-husband or ex-partner" in addition to "my husband or partner"

[**]Defined as "always" or "often" feeling down, depressed, or hopeless or having little interest or little pleasure in doing things she usually enjoyed since delivery.

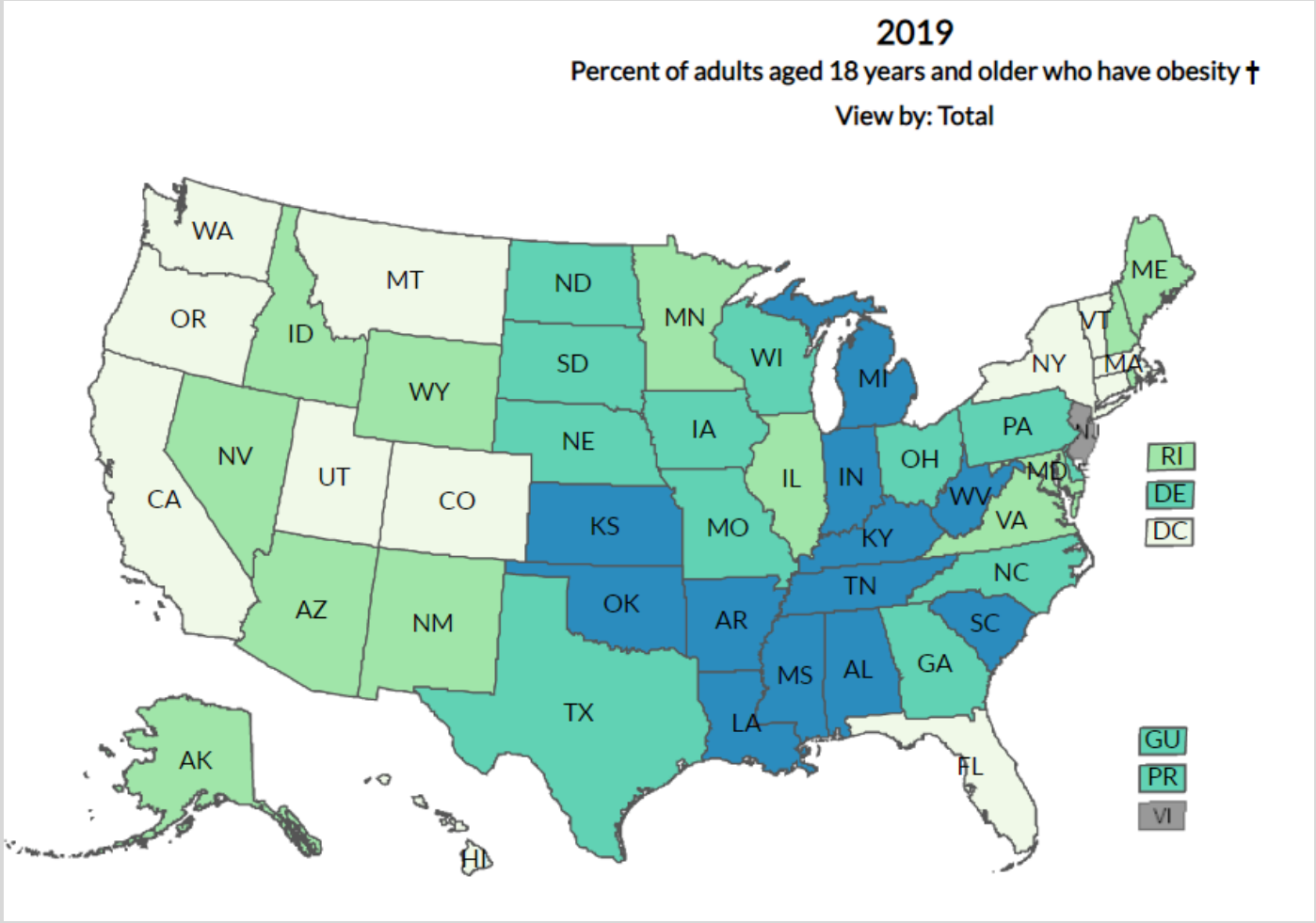
[††]Postpartum is defined as the time the PRAMS survey was completed

[‡‡]Defined as using any kind of birth control postpartum (female or male sterilization; intrauterine device (IUD); contraceptive implant; birth control pills; shots or injections; contraceptive patch; vaginal ring; condoms; rhythm method/natural family planning; withdrawal).

[§§]Long-acting reversible contraception (LARC) methods include Intrauterine Device (IUD) or contraceptive implant. Moderately effective methods include birth control pills, shots or injections (e.g., Depo–Provera), contraceptive patch, and vaginal ring. Least effective methods include condom, rhythm method/natural family planning, and withdrawal. Women who selected the "other" write-in option were excluded from the analysis.

[¶¶]Insurance is coded as Medicaid (Medicaid or state-named Medicaid program); Private (Private only, any other insurance in combination with private, TRICARE or other military insurance); No insurance (no insurance or Indian Health Service (IHS) only; in Alaska this also includes Alaska Tribal Health System that are part of the IHS response option); other state-specific government plans or programs such as SCHIP/CHIP are excluded from estimates.

2019 CDC Statistics for Obesity



This is all based off BMI – which we know should be correlated to Waist Hip Ratios

Country/Ethnic Group	Gender	Gender	
Ethnic South/Central American	Male	>90 cm	>35.5 inches
	Female	>80 cm	>31.5 inches
Chinese, Japanese	Male	>90 cm	>35.5 inches
	Female	>80 cm	>31.5 inches
Europids, Sub-Saharan African, Eastern Mediterranean, Middle East (Arab) populations	Male	>94 cm	>37 inches
	Female	>80 cm	>31.5 inches
USA (mixed ethnicity)	Male	>102 cm	>40 inches
	Female	>88 cm	>35 inches

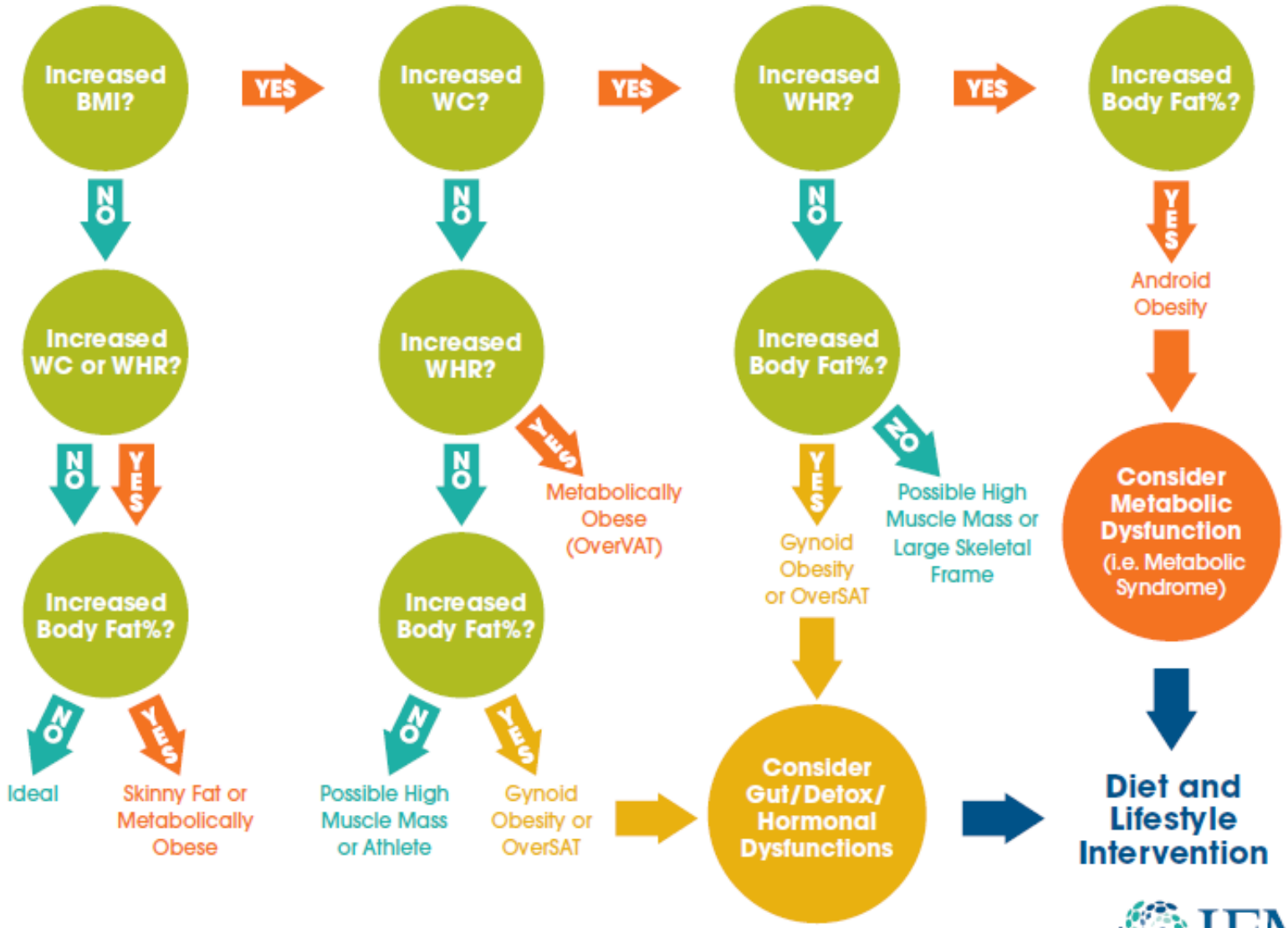
From IFM: Waist Circumference (WC) by Gender and Ethnicity for Increased Health Risk

Body Composition Assessment – Measurements for Working Through the Flow Diagram

Measurement	Male	Female
BMI normal	>18 <25	>18 <25
BMI overweight	>25	>25
BMI obese	>30	>30
Waist circumference (WC) (US, non-ethnic)	>40 inches (102 cm)	>35 inches (88 cm)
Waist-to-Hip Ratio (WHR) (US, non-ethnic)	>0.9	>0.8
Fat mass %		
Age 20–39	8–13	17–21
Age 40–59	11–16	19–23
Age 60–79	13–18	24–31

Functional Nutrition Evaluation

Anthropometrics: Body Composition Flow Diagram



IFM

Version 3

Flow Chart to Augment BMI Calculations

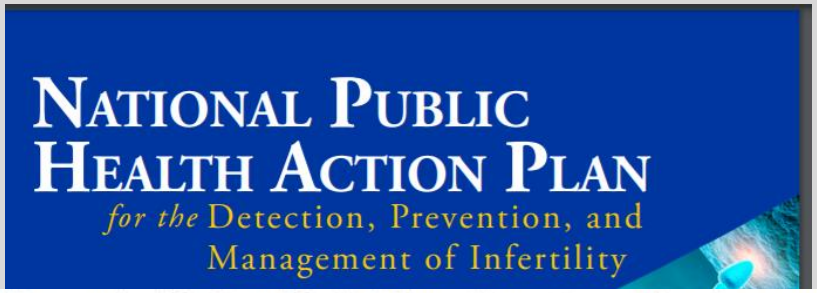
Coupled with BIA or other body density measurement tools, will help explain to patients the need to

eat better

balance gut

support detox

balance hormones etc…



New methods for measuring infertility and for identifying and improving conditions that are precursors to infertility are needed. Improving our understanding about the causes of infertility will enhance preventive and therapeutic options for both women and men and reduce our reliance on the use of more invasive methods to treat infertility at later stages.

Research is needed to better understand many known and potential causes of infertility, including but not limited to the following:

- Reproductive aging—that is, establishing biomarkers, determining the predictors and correlates of early depletion of the ovarian reserve, and the effects of age on semen quality and reproductive function.
- Important developmental periods—that is, identifying factors that affect fertility during certain developmental periods (e.g., preconception, *in utero*, puberty, transgeneration) to identify the best time for intervention.
- Infectious diseases—that is, the proportion of cases of tubal factor infertility attributable to infectious diseases and the role of specific infections, such as chlamydia, gonorrhea, mycoplasmas, trichomoniasis, bacterial vaginosis, tuberculosis of the reproductive tract, microbial organisms associated with reproductive tract infections, epididymoorchitis, prostatitis, and mumps.
- Chronic conditions and diseases—including endocrine and metabolic diseases such as primary ovarian insufficiency, polycystic ovary syndrome, hypothalamic amenorrhea, menstrual cycle defects, endometriosis, uterine leiomyomata, thyroid disorders, metabolic syndrome, diabetes, autoimmune disorders, meiotic aneuploidy, cystic fibrosis, varicocele, testicular disorders, multiple sclerosis, general urologic health, and immune-mediated disorders.
- Behavioral factors—such as diet, exercise, sleep, psychological and physiological stress, caffeine consumption, tobacco and alcohol use, weight gain or loss, nutritional disorders, illicit or prescription drug use, and illicit use of anabolic steroids and growth hormones.
- Iatrogenic causes—such as chemotherapy or associated medications for testicular or ovarian cancer and antiretroviral therapy for HIV/AIDS.
- Occupational and environmental hazards—such as radiation, repetitive motion or posture, injury (e.g., reproductive or urinary tract trauma such as that experienced during military duty), or natural or synthetic chemicals and compounds with hormonal activities (e.g., endocrine disruptors).
- Genetic influences—such as male karyotype abnormalities, Y chromosome microdeletions, or androgen receptor gene abnormalities.

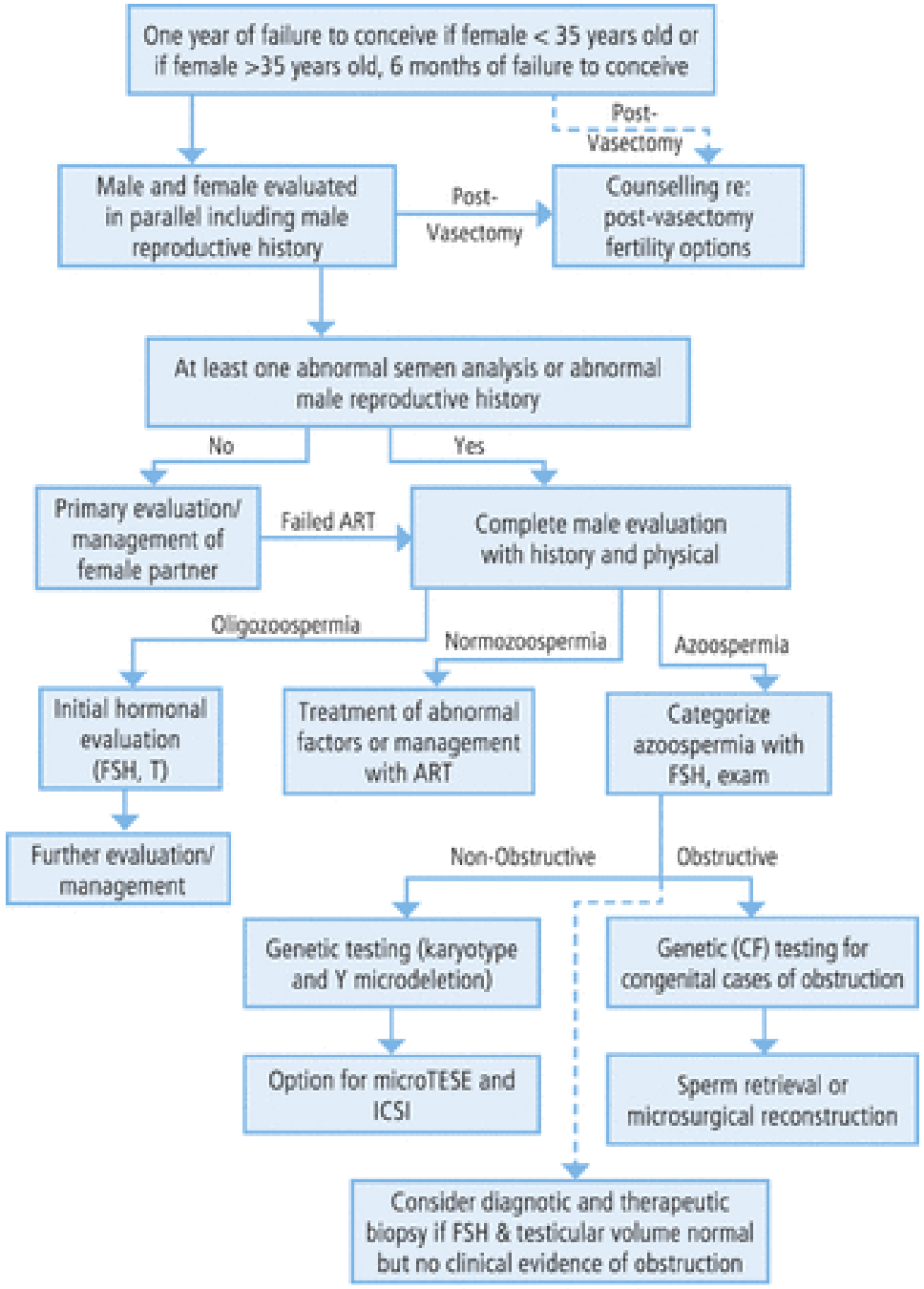
CDC Has A Plan

- 26-page document identifying the issues (not bad)
  - Monitor and evaluate the short- and long-term safety of infertility interventions
  - Eliminate disparities in access to high-quality infertility services, including diagnosis, referral, and treatment
  - Promote further development, adoption, evaluation, and implementation of evidence-based guidelines and recommendations that address the prevention, diagnosis, and management of infertility
  - Develop educational programs to increase awareness of the safety and effectiveness of treatments for infertility and other options for managing infertility.

And They Know What Can Make It Worse…

What increases a man's risk of infertility?

- Age. Although advanced age plays a much more important role in predicting female infertility, couples in which the male partner is 40 years old or older are more likely to report difficulty conceiving.
- Being overweight or obese.
- Smoking.
- Excessive alcohol use.
- Use of marijuana.
- Exposure to testosterone. This may occur when a doctor prescribes testosterone injections, implants, or topical gel for low testosterone, or when a man takes testosterone or similar medications illicitly for the purposes of increasing their muscle mass.
- Exposure to radiation.
- Frequent exposure of the testes to high temperatures, such as that which may occur in men confined to a wheelchair, or through frequent sauna or hot tub use.
- Exposure to certain medications such as flutamide, cyproterone, bicalutamide, spironolactone, ketoconazole, or cimetidine.
- Exposure to environmental toxins including exposure to pesticides, lead, cadmium, or mercury.



YET WHERE IS DIET & LIFESTYLE?

Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline PART II

American Urological Association Journal on Urology

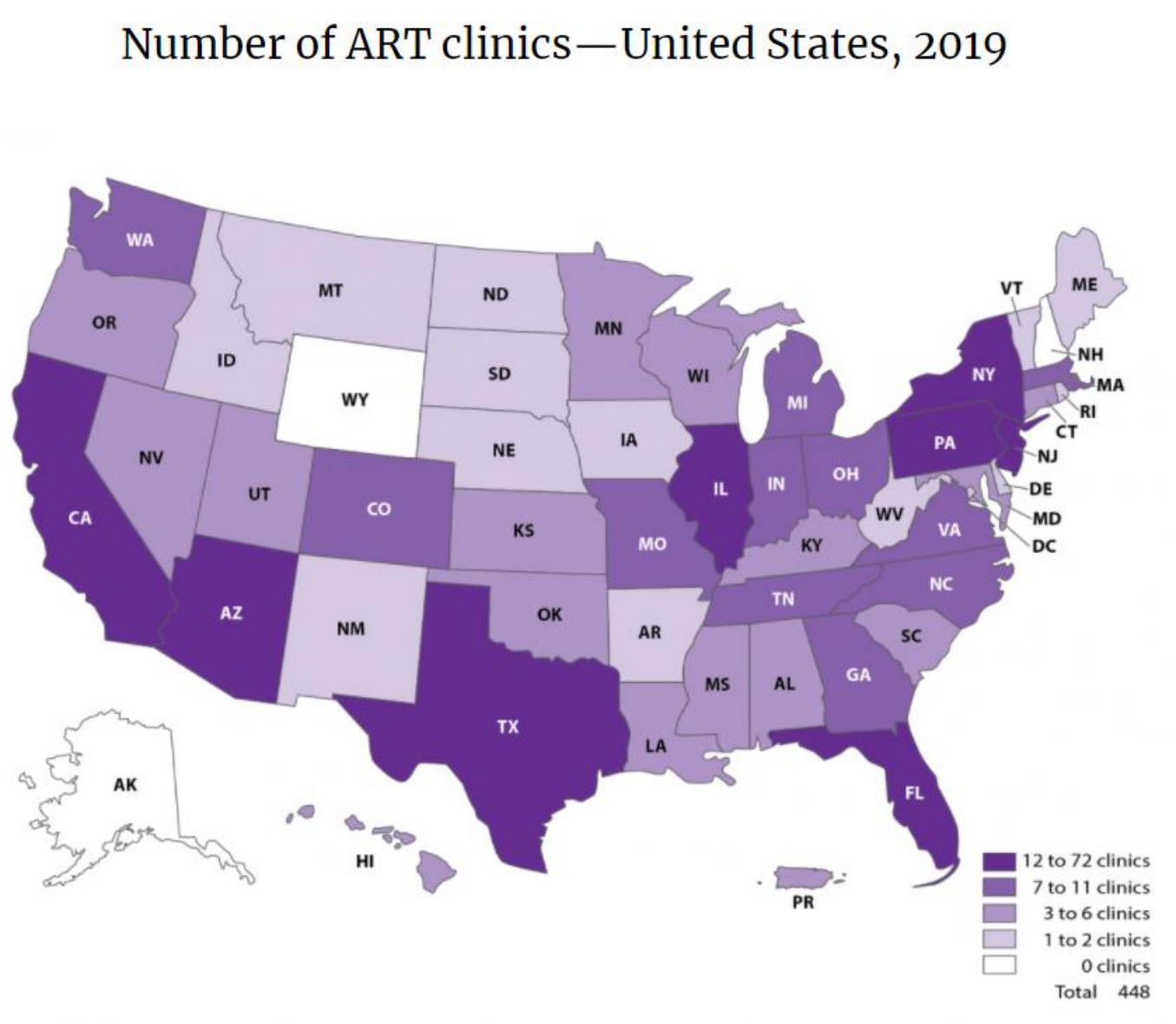
But Here They Have Missed The Mark!

What increases a woman's risk of infertility?

Female fertility is known to decline with

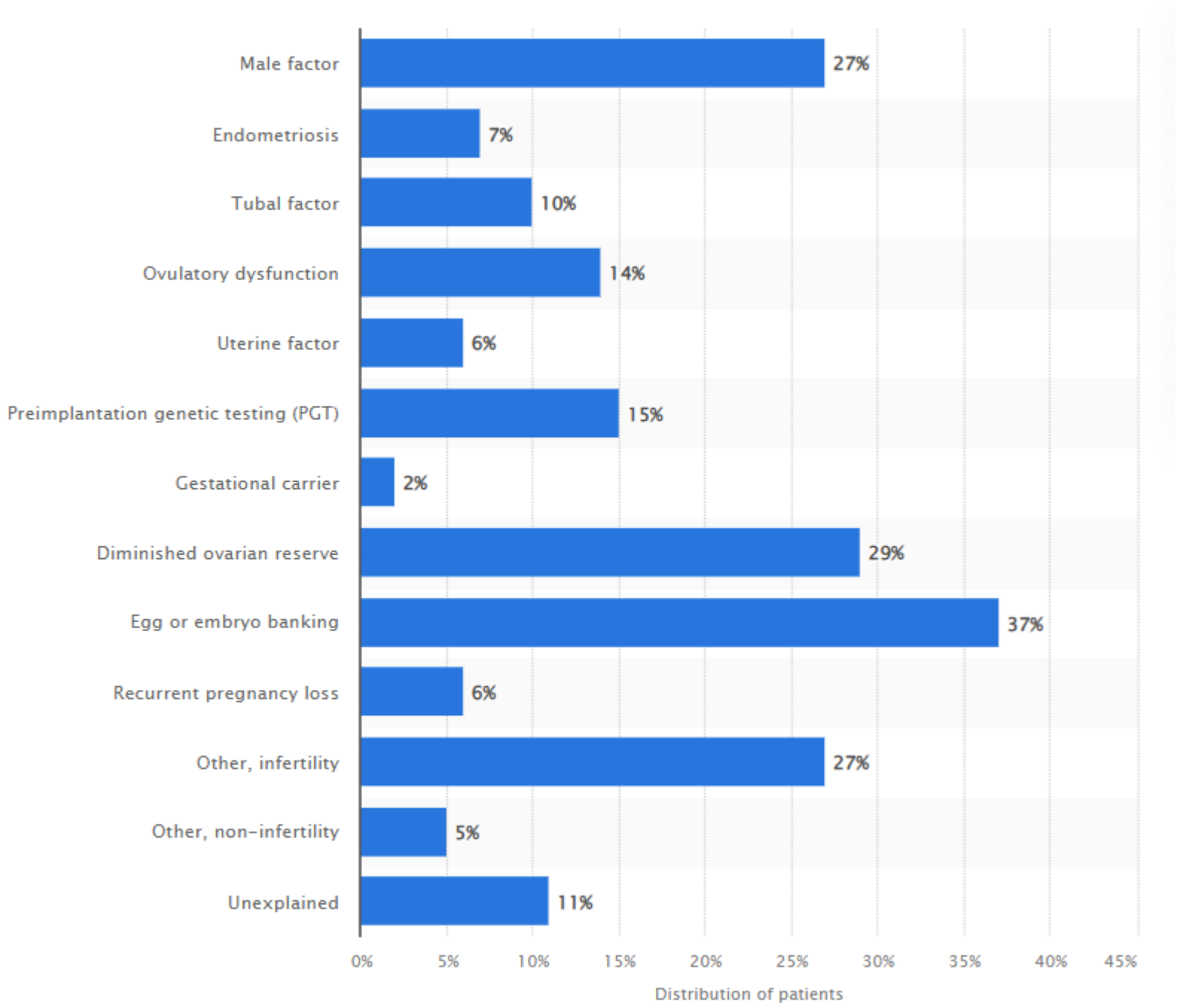
- Age. About 1 in 6 couples in which the woman is 35 and older have fertility problems. Aging decreases fertility because older women have fewer eggs left, the eggs are less healthy, and the woman is more likely to have health conditions that can cause fertility problems. Aging also increases a woman's chances of miscarriage and of having a child with a genetic abnormality.
- Smoking.
- Excessive alcohol use.
- Extreme weight gain or loss.
- Excessive physical or emotional stress that results in amenorrhea (absent periods).


WHAT
WHERE
WHEN
WHY



- 2019 = 489 U.S fertility clinics
  - 448 give data
  - California (72), Texas (42), and New York (43) have the most clinics
- National rate of ART = 3,226 procedures / 1 million women of reproductive age (15-44 yoa)
- Higher than National rates of use in California, Connecticut, Delaware, DC, Hawaii, Illinois, Maryland, New Hampshire, New York, Pennsylvania, Rhode Island, Utah, Vermont, and Virginia
  - Massachusetts and DC = >twice the national level
- 19 states have insurance mandates for coverage of ART cycles at least 2 cycles

https://www.ncsl.org/research/health/insurance-coverage-for-infertility-laws.aspx



PATIENTS USING ART FOR INFERTILITY 2019

Fertility rates have changed

- Conception choices delayed
  - Average age of first pregnancy
    - Large cities VS smaller towns
    - Education
    - Male VS Female age
  - History of contraception
    - Duration and type
  - Nutrition / lifestyle / access to medical care
  - Society of “NOW” not later
  - Toxic World
    - Pollutants
    - EMF

Fertility Industry

- Average cost of testing: $70-$5,000
- Average cost of IUI: $400-$1,000
- Average cost of IVF (medication included)
  - Own eggs: $11,500-15,000
  - Donor eggs: add $9,000-12,000
  - PGS (pre-implantation genetic screening): add $3,200-$5,000
  - ICSI (intra-cytoplasmic sperm injection): add $1,500
  - Without meds included: $12,500

- All cheaper in the UK / Europe (1/3 the price)
  - Medical tourism is very popular

Fertility

To treat couples undergoing treatment for infertility, one needs to understand the following things for women and men

- Normal hormone flux, physiology & preconception care
  - I'm taking into consideration you remember all of this
- Terminology for medical procedures & medications
- Testing – Lab and Functional
- Psychological, financial and psychological impact

nothing says "romantic evening" like charting cervical mucus

No, MY mommy loves ME more. She endured years of testing, surgeries, monitoring, fertility drugs and procedures to make me. What did YOUR mom

I feel much better now that I know it is God's will for me to be depressed, broke, and physically screwed up. I think I'll "just adopt!"

You thought IVF would work on the first try?

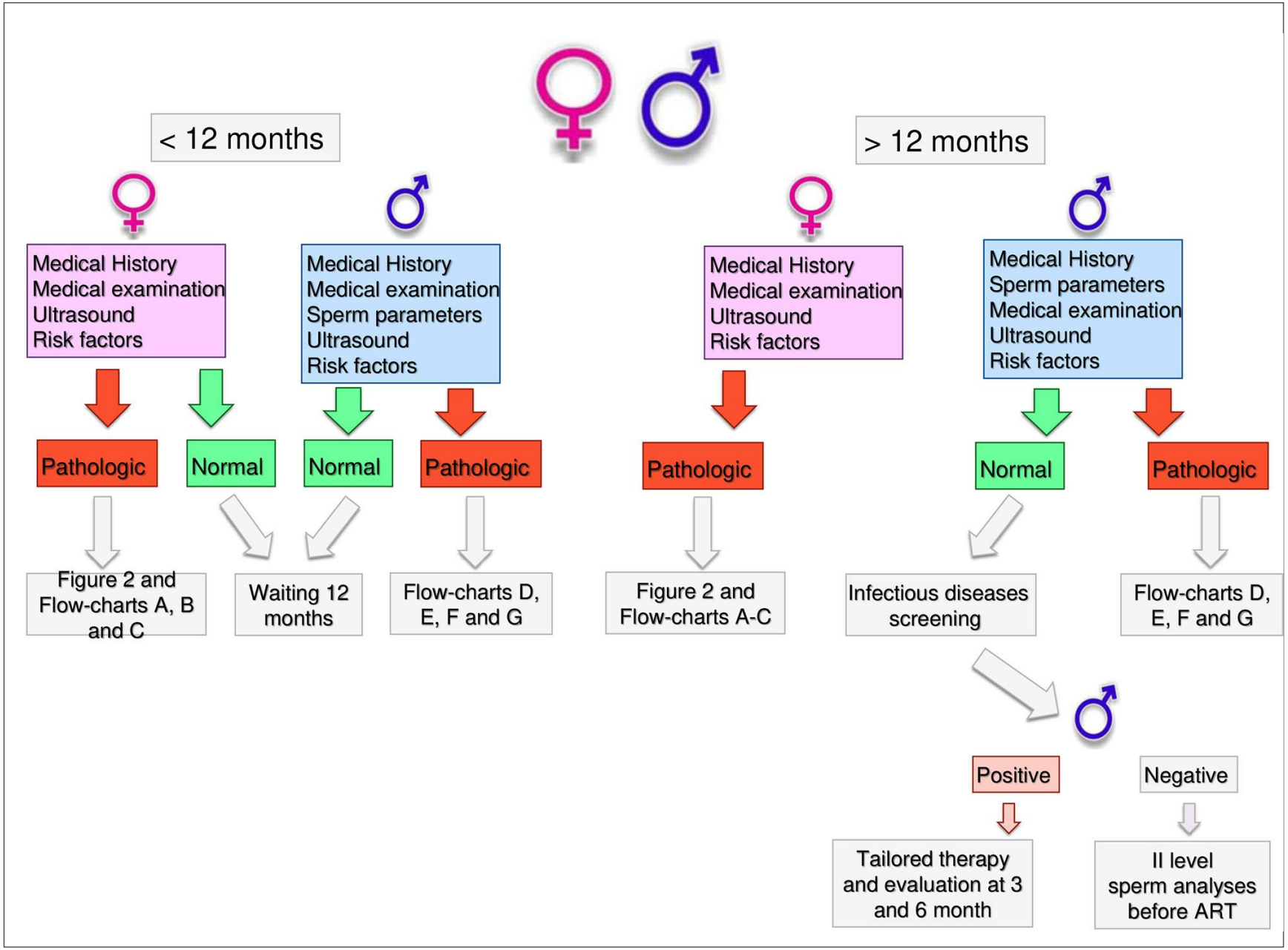
That's funny.

Diagnostic Flow Chart

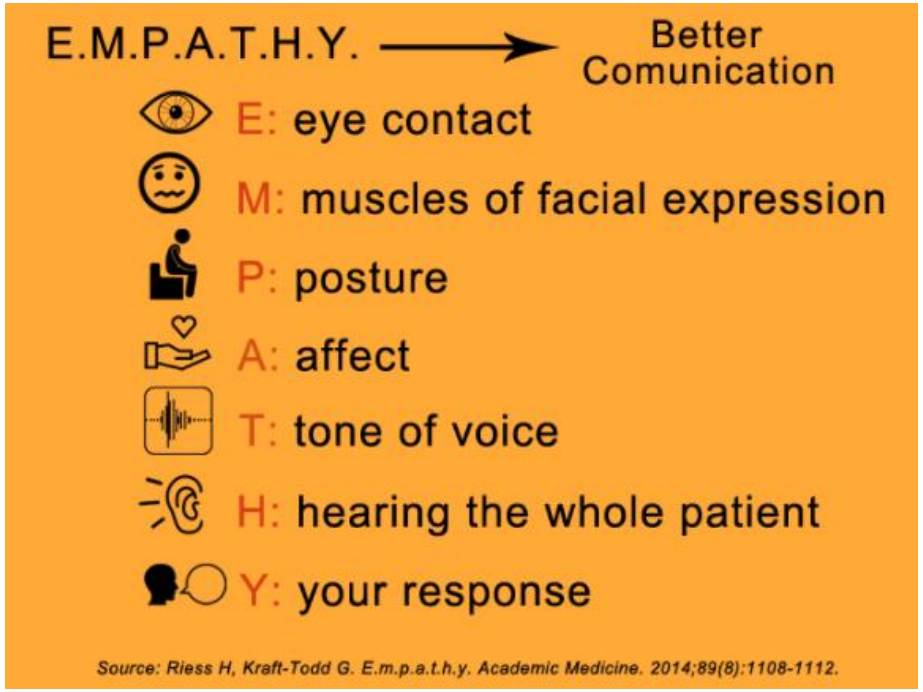
Specific to conditions as well as men and women

Problem: for women - just all leads to IVF / IUI

Front. Endocrinol., 19 January 2021 | https://doi.org/10.3389/fendo.2020.591837



HOW TO HELP SUPPORT



Meet People Where They Are NOW

- Emotionally
- Financially
- Time Commitment (both)
- Be supportive, yet honest
- Have tissues
- Be present and grounded yourself

Test + History =
Balance the Biggest Items First

Balance	Balance the GI tract / microbiome
Support	Support hepatic biotransformation
Clear	Clear micronutrient deficiencies
Get	Get autoimmunity under control
Remove	Remove toxic elements in lifestyle
Help	Help with stress reduction / adrenal tone

Mechanisms that Cause Infertility

- Body Mass Index (BMI) and Infertility
- Male Andropause Factors
- Psychological Stress and Infertility
- Dietary Causes of Infertility
- Lifestyle Factors and Infertility
- Dysglycemia Causes of Infertility
- Female Reproductive Cells, Tissues, and Fluid Factors
- Environmental Causes of Infertility
- Medications Impacting Fertility
- Medical Conditions that Increase Oxidative Stress
- Male Sperm Health Factors
- Underlying Autoimmunity
- Female Pelvic Anatomical Factors
- Male Pelvic Anatomical Factors
- Ovulation and Menstrual Cycle Factors

ACCORDING TO DR. DATIS KHARRAZIAN

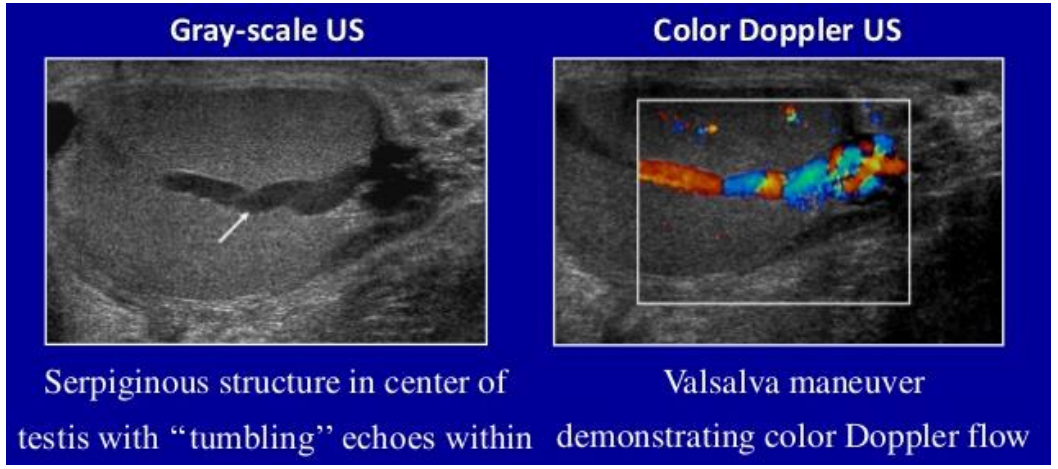
Rule Out Anatomical Issues 1^{st} and Always!

Normal Uterine Cavity

ABOVE: *A normal uterine cavity will be free from obstructions.*

Obstructed Uterine Cavity

ABOVE: *This ultrasound shows obstructions in the uterine cavity.*



Serpiginous structure in center of testis with "tumbling" echoes within

Valsalva maneuver demonstrating color Doppler flow

Steps to Get and Stay Pregnant

- **1. Normalize a woman's cycle**
- **2. Normalize gametes, anatomy and function – both male and female**
- 3. Optimize pregnancy maintenance / reduce possible complications
- 4. Optimize fetal health and development
- 5. Reduce risk of development of childhood development disorders
- 6. Support postpartum recovery and optimize maternal postpartum health

CHINESE PARABLE

"Cultivate the soil before you plant the seed"

Generically Taking a Better Fertility History

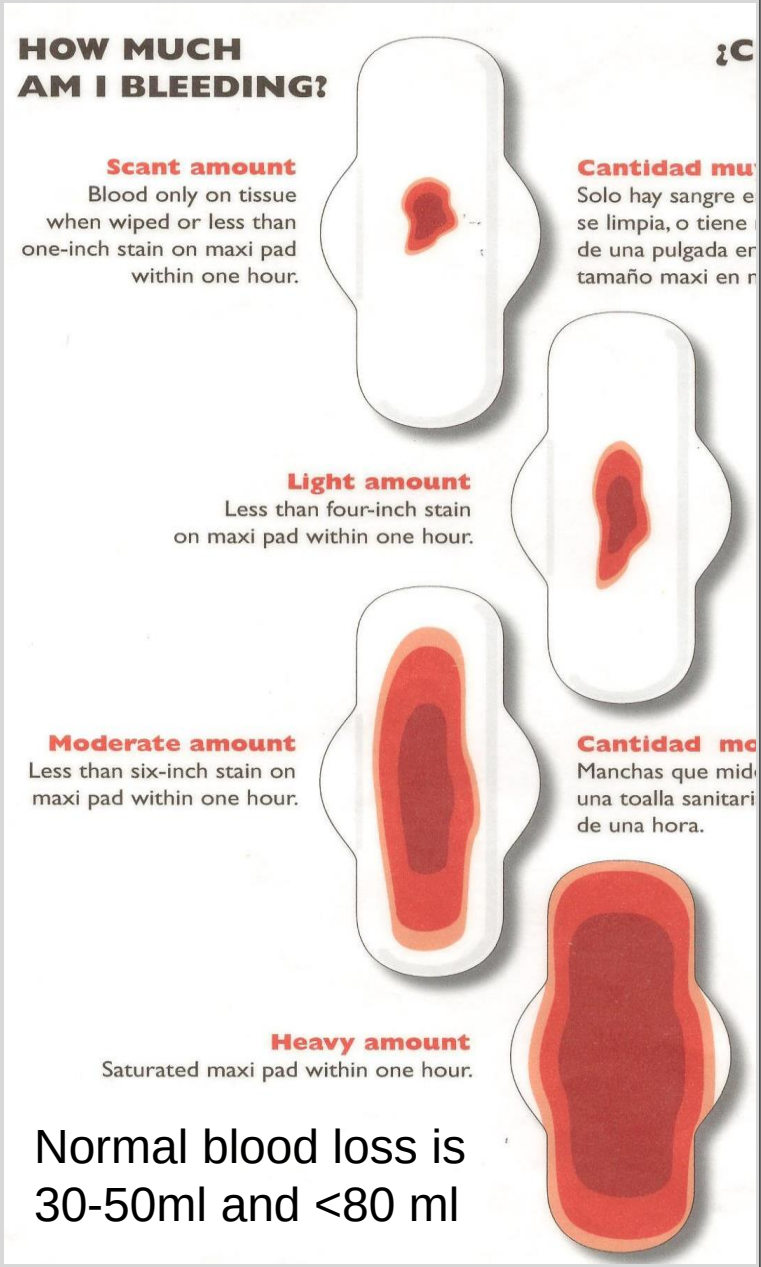
- Blood sugar / dysglycemia
- Gastrointestinal
- Thyroid (hyper / hypo)
- Anemia
- Autoimmune disease
  - Family history of Autoimmune
- BMI with Waist / Hip; BIA
- Exercise
- STI history
- Chemical exposure
  - Includes chemo / rad / toxic chemicals / jobs
- Ever been / gotten anyone pregnant
  - Termination / carry / miscarry
- Previous abdominal surgeries
- Smoke/ Vape
  - Cigarettes or marijuana
  - Take other drugs
- Alcohol and caffeine intake
- 24-hour dietary intake
- Stress rating / mental health check
  - Coping
- Medications may impact fertility

Taking a Better History for Fertility: Women

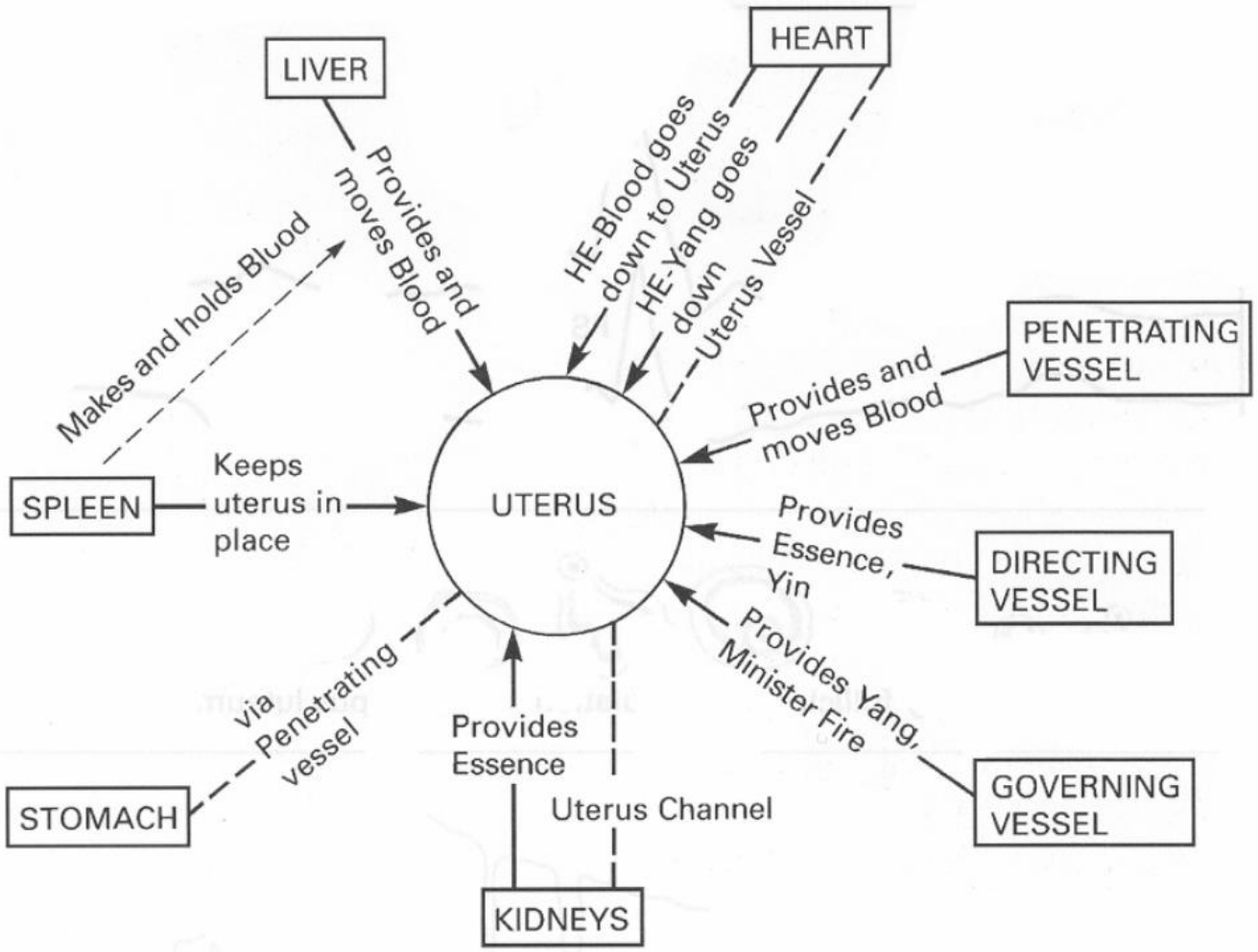
- Menstrual cycle history
  - When did you start and what is it like
  - When did mom reach menopause
- Contraceptive / HRT history
  - What, when and how long
- PCOS
- Endometriosis
- Fibroids / Polyps / Cysts / Growths
- Fallopian tube blockage
- Hyperprolactinemia
  - Nipple discharge
  - Vaginal dryness / pain with intercourse
  - Decreased sex drive
- Hypothyroid
  - Reduced muscle and brain endurance
  - Fatigue
  - Hair loss / thinning
  - Trouble regulated temperature

Normal Menstruation

- Approximate onset at age 10-14; lasts until 50's
- Cycle at day 24-36 with period lasting 3-7 days – best at 28-29 days for cycle
  - Lunar cycle really 29.5 days
- Color: deep red, light in the beginning, deep in the middle, pinkish at the end
- No cramps, PMS or brown blood
  - Mybeautifulcervix.com
- What are women using for their menses?
  - Cups
  - Pads
  - Tampons



Normal blood loss is 30-50ml and <80 ml



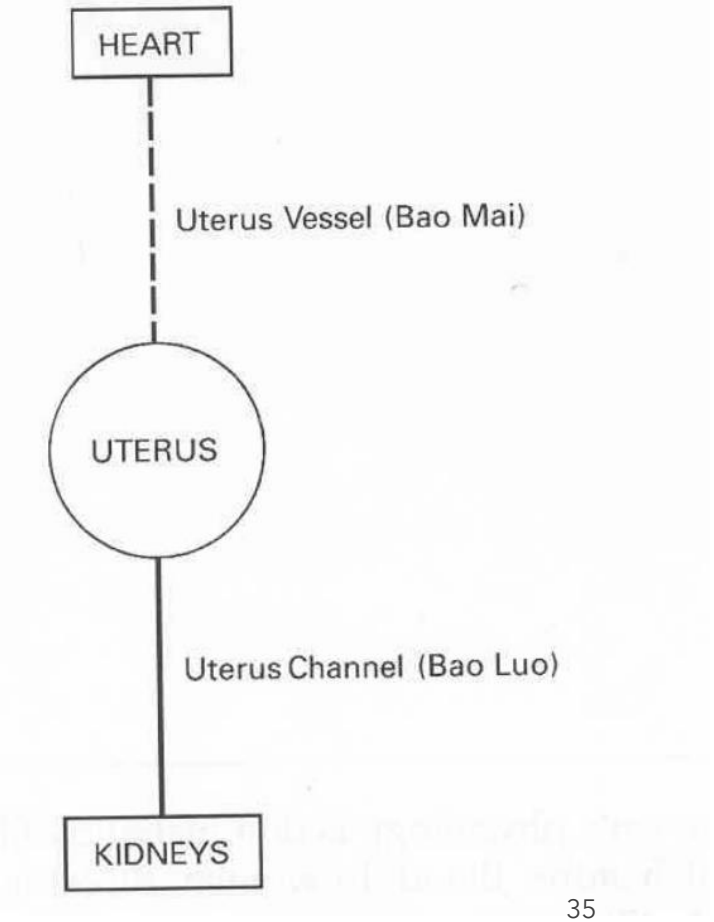
The Uterus and Internal Organs.

TCM View

- Uterus (Zi Bao) is most important extraordinary organ
  - Yin functions: stores blood and fetus
  - Yang functions: discharge blood / baby
- Organ functions
  - Regulates menses and houses fetus in pregnancy
- Closely related to
  - CV (Ren / Directing vessel) – qi, yin and essence
  - Chong Mai (Penetrating) – blood to uterus
    - Both originate in KD, flow through the uterus, regulate menses, conception and pregnancy
  - Kidney – essence
  - GV – yang essence for ovulation; Room for Sperm

TCM View: Uterus & Menses

- In men, Bao=Room for Essence (Dan Tian)
  - Prostate similar but not as important as uterus
- Connect to KD via Bao Luo (channel)
  - KD is origin of menstrual blood (Tian Gui), mother of the LV, provides blood to uterus via Chong and Ren
- Connect to HT via Bao Mai (vessel)
  - Explains emotional influence on menses
  - Heart qi and blood descend to uterus
    - Control onset of both menses and ovulation
  - Helps from Tian Gui with KD essence



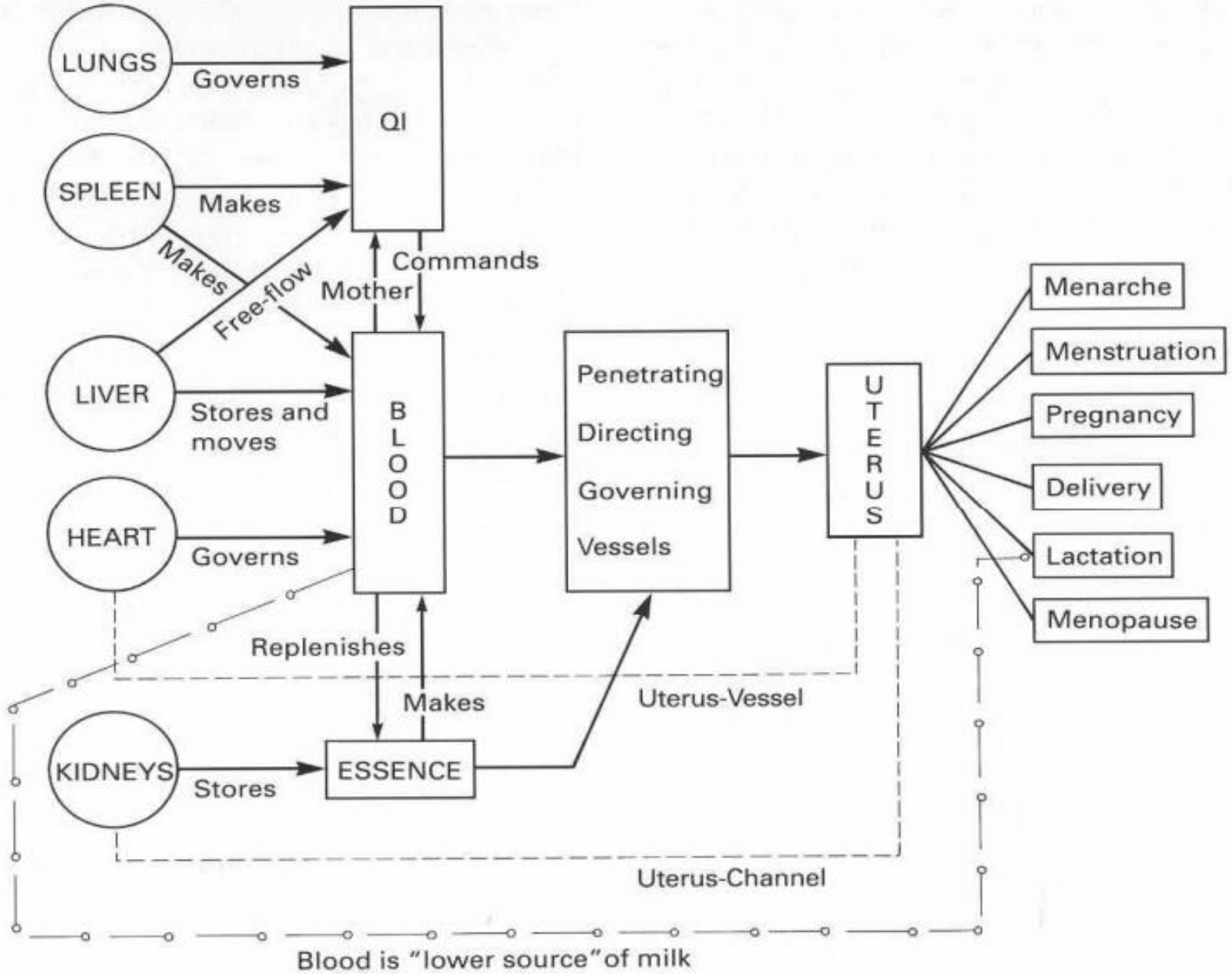


Fig. 2.15 Interrelationships of the Internal Organs, the Vital Substances, the Uterus and the Extraordinary Vessels.

TCM View: Uterus & Menses

- Normal menstruation and fertility depends on the state of KD essence and HT blood
  - HT blood deficient, HT qi does not descend to the uterus
  - KD essence deficient, menstruation does not occur
  - TCM views the period length as 4-6 days
  - In TCM: menses is not blood; it is essence
- Kidney is responsible for all functions in Western Medicine related to uterus, fallopian tubes and ovaries, and the hypothalamus-pituitary-ovarian axis

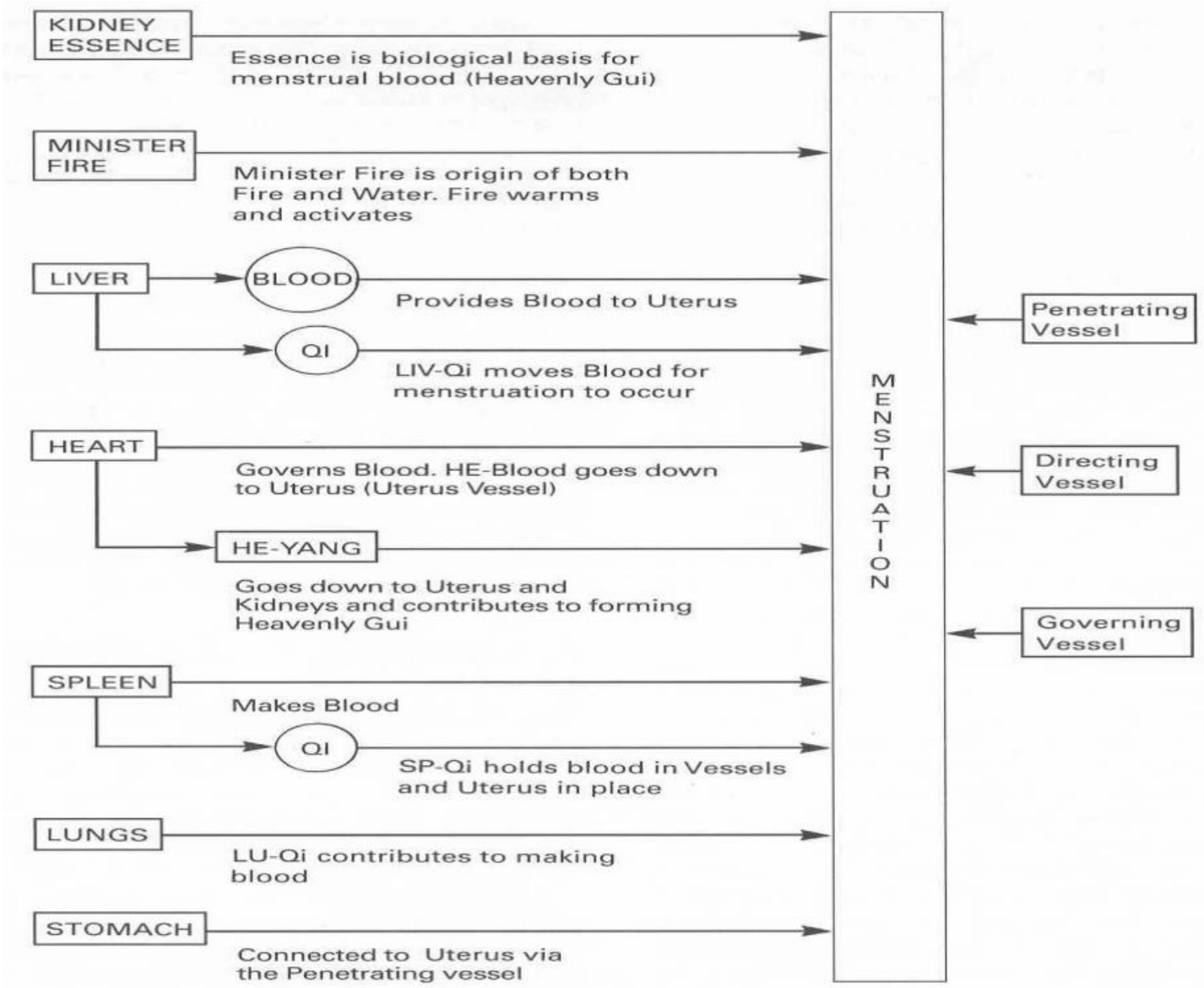
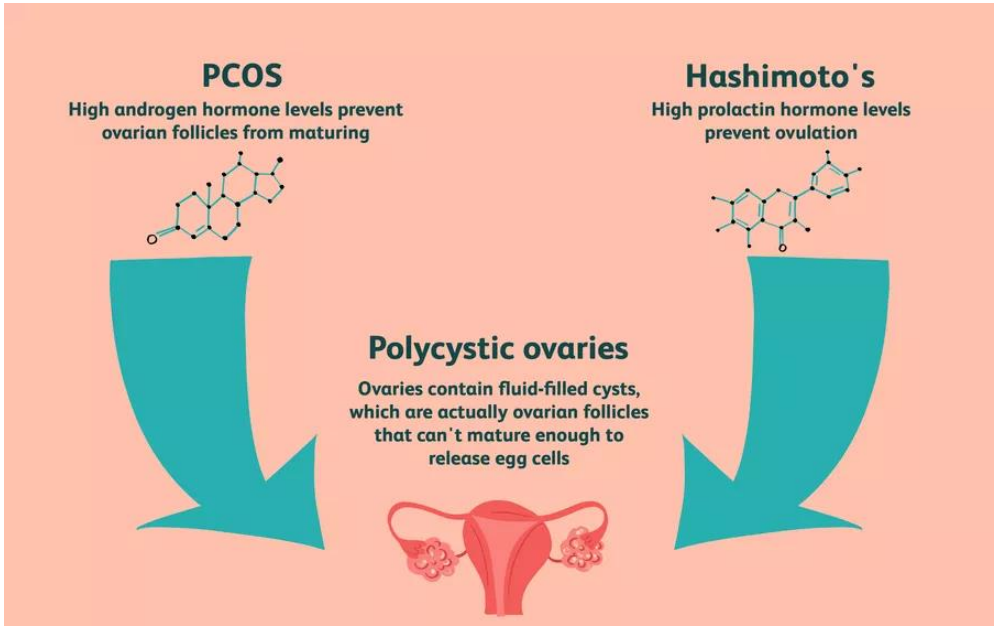
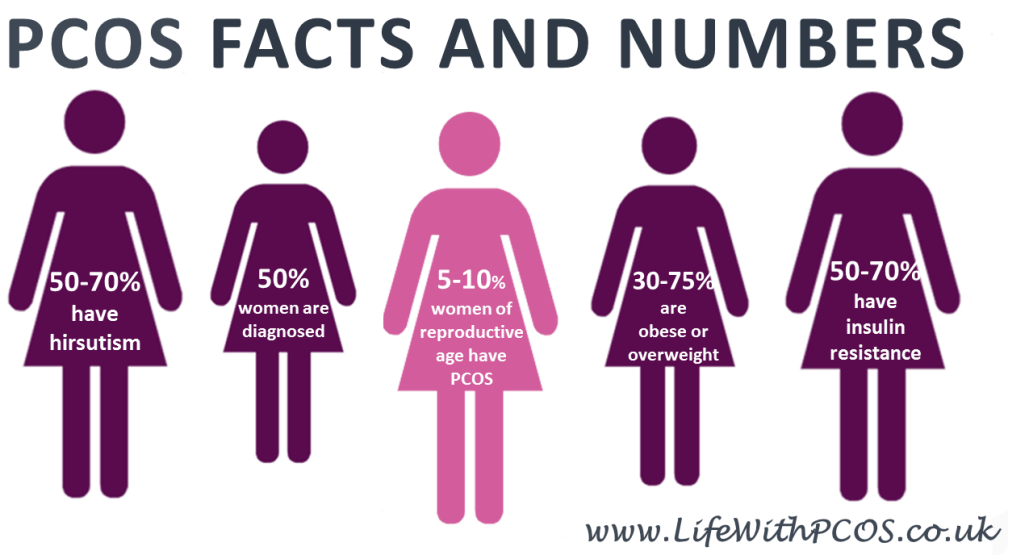


Fig. 2.6 Internal Organs and menstruation.





Female Condition: PCOS

Unwanted hair (face or body)'; Hair thinning
Acne
Irregular or infrequent menses
Fatigue / sugar cravings post meals
Energy drops in the afternoon
Weight gain / difficulty losing weight

Mine are not always this picture

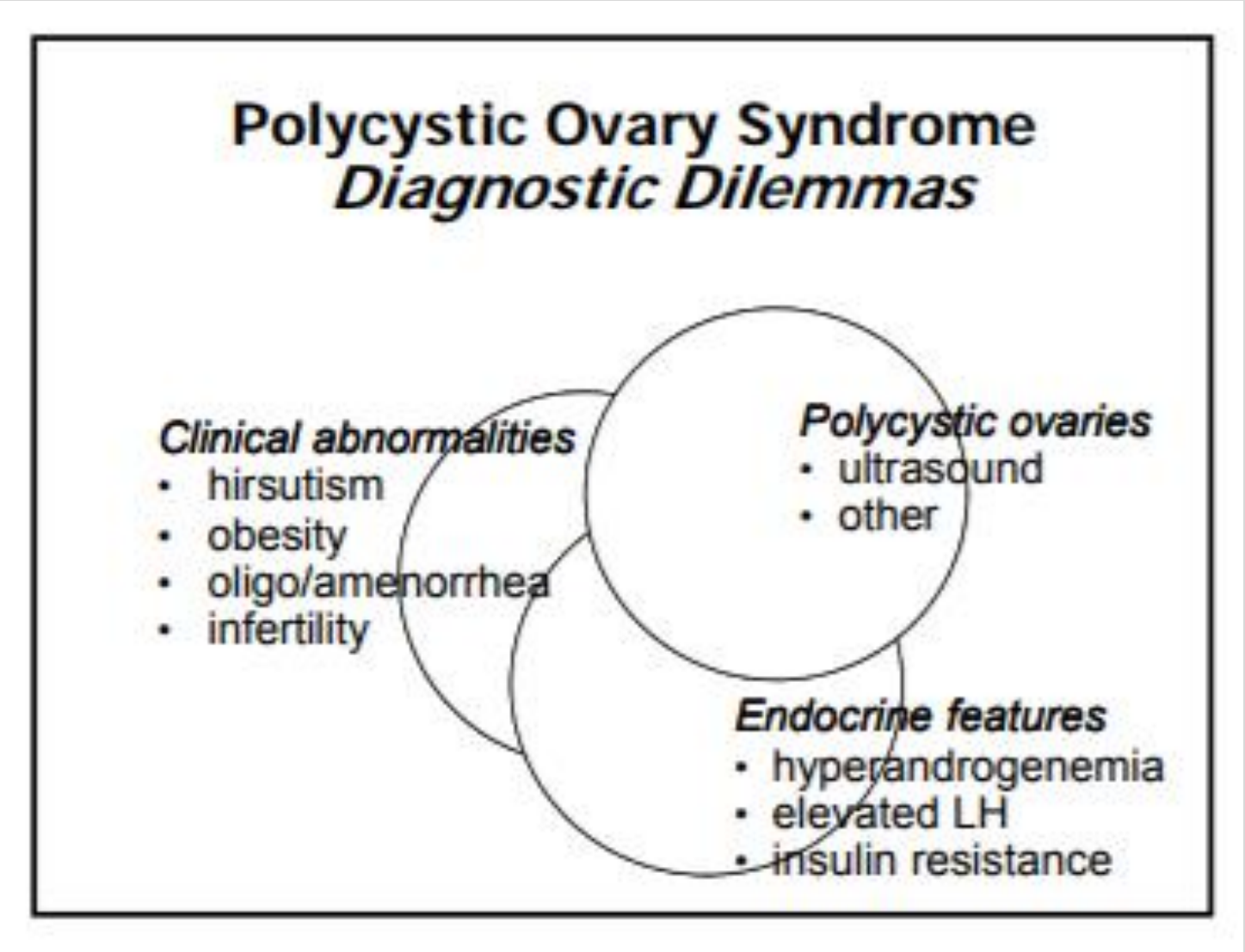
PCOS Diagnosis Criteria

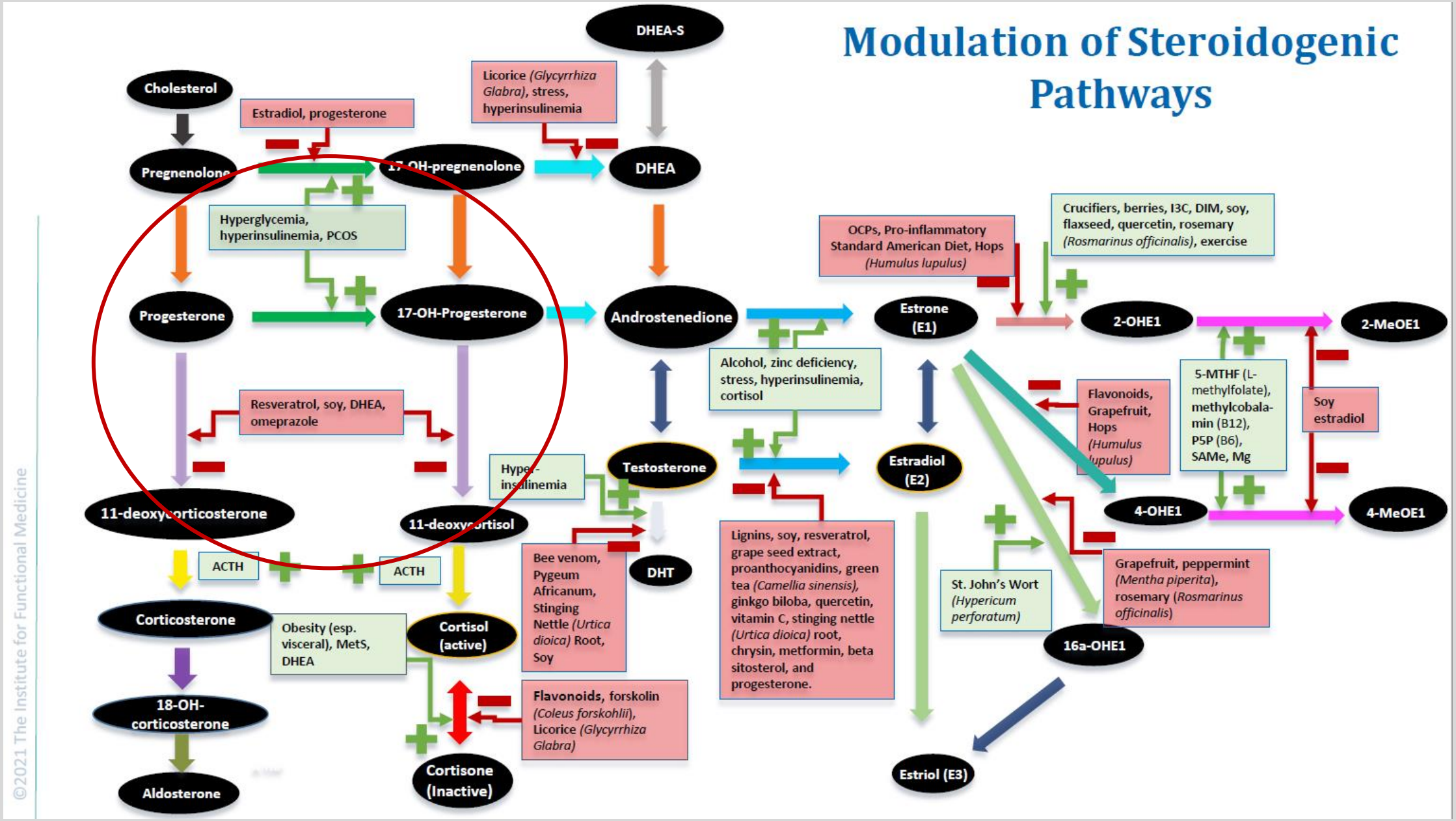
- PCOS: American Society of Reproductive Medicine (ASRM),the European Society of Human Reproduction and Embryology (ESHRE) joint consensus agreed that the diagnosis of PCOS should be made when <u>two of the following three</u> criteria are met (2017)
  - Oligo-ovualtion or anovulation
  - Clinical or biochemical hyperandrogenism (HA)
    - Excess hair growth, acne, raised LH, and raised androgen index
  - Polycystic ovarian morphology (PCOM) on ultrasound scan (and/or)
    - >12 follicles measuring between 2 and 9mm in diameter
    - ovarian volume >10ml
    - Distribution of the follicles are not required and with one ovary sufficient for diagnosis
    - Because AFC can be subjective, look to AMH
      - Levels high in PCOS esp. with HA

Female Conditions: PCOS

- Insulin regulation / resistance issue (insulin is responsible for androgen production)
  - TCM: SP yang and KD yin xu if overweight

- Stress and or excess exercise and can be “skinny” PCOS – cortisol steal = less P4 in relationship to E2 therefore relative estrogen dominance
  - TCM = KD yin xu




Modulation of Steroidogenic Pathways
DHEA-S
Cholesterol
Licorice (Glycyrrhiza Glabra), stress, hyperinsulinemia
Estradiol, progesterone
Pregnenolone
17-OH-pregnenolone
DHEA
Hyperglycemia, hyperinsulinemia, PCOS
Progesterone
17-OH-Progesterone
Androstenedione
OCPs, Pro-inflammatory Standard American Diet, Hops (Humulus lupulus)
Crucifiers, berries, I3C, DIM, soy, flaxseed, quercetin, rosemary (Rosmarinus officinalis), exercise
Estrone (E1)
2-OHE1
2-MeOE1
Alcohol, zinc deficiency, stress, hyperinsulinemia, cortisol
Resveratrol, soy, DHEA, omeprazole
Flavonoids, Grapefruit, Hops (Humulus lupulus)
5-MTHF (L-methylfolate), methylcobalamin (B12), P5P (B6), SAMe, Mg
Soy estradiol
Hyper-insulinemia
Testosterone
Estradiol (E2)
11-deoxycorticosterone
11-deoxycortisol
4-OHE1
4-MeOE1
ACTH
ACTH
Bee venom, Pygeum Africanum, Stinging Nettle (Urtica dioica) Root, Soy
DHT
Lignins, soy, resveratrol, grape seed extract, proanthocyanidins, green tea (Camellia sinensis), ginkgo biloba, quercetin, vitamin C, stinging nettle (Urtica dioica) root, chrysin, metformin, beta sitosterol, and progesterone.
St. John's Wort (Hypericum perforatum)
Grapefruit, peppermint (Mentha piperita), rosemary (Rosmarinus officinalis)
Corticosterone
Obesity (esp. visceral), MetS, DHEA
Cortisol (active)
16a-OHE1
18-OH-corticosterone
Flavonoids, forskolin (Coleus forskohlii), Licorice (Glycyrrhiza Glabra)
Estriol (E3)
Cortisone (Inactive)
Aldosterone
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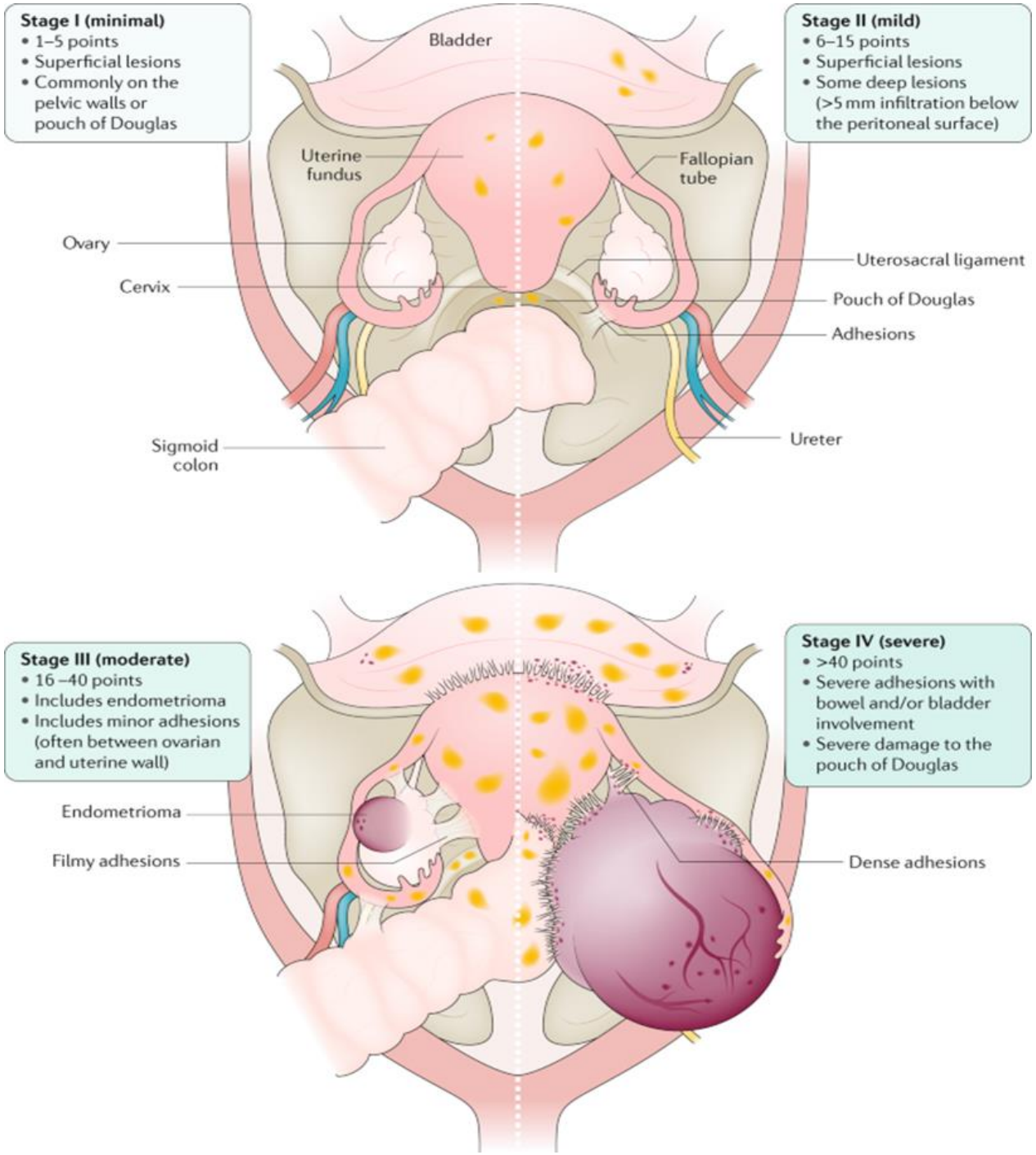
Nutraceuticals to Support PCOS Health

Botanicals	Berberine: 250–500 mg per meal Rose hip: 200 mg per meal Burdock root: 200 mg per meal Gymnema sylvestre: 200–500 mg per meal
Antioxidants	Resveratrol: > 1000 mg per day Curcumin: > 1000 mg per day Liposomal Glutathione: > 10 ml per day
Other Nutraceuticals	EPA and DHA: 2000–5000 mg per day Vitamin D: 2000–1000 IU per day Alpha Lipoic Acid: 200–400 mg per day Fiber Supplements: > 1 gram per day Short-Chain Fatty Acids: > 1000 mg butyrate per day General B vitamin and mineral supplement



Endometriosis

- Dysmenorrhea (before / during); may be heavy and abnormally long / spotting
- Dyspareunia / dysuria / pain with BM urination and or global dysfunction
- May have neuropathy and fatigue
- <u>Three main classification systems</u>
  - rASRM most widely used (see pic)
    - Not as reproducible or predictive for fertility
    - Helpful to explain severity to patients
    - Does not consider deeply infiltrating endometriosis (DIE) in uterosacral ligaments, bladder, vagina, and bowel (ENZIAN)
  - EFI score appears to be a reliable system to predict IVF outcomes
    - Predicts the pregnancy rate in patients with surgically documented endometriosis who have not attempted to become pregnant with in vitro fertilization

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score		Description		Left	Right
4	=	Normal	Fallopian Tube		
3	=	Mild Dysfunction			
2	=	Moderate Dysfunction	Fimbria		
1	=	Severe Dysfunction			
0	=	Absent or Nonfunctional	Ovary		

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

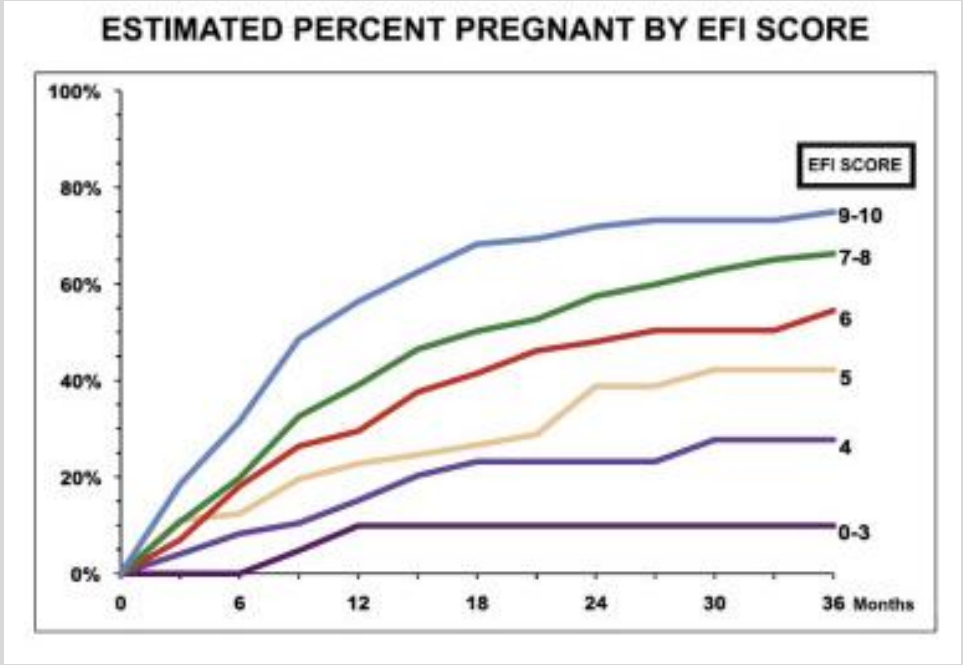
	Left		Right		LF Score
Lowest Score		+		=	

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	**Description**	**Points**	**Factor**	**Description**	**Points**
Age			LF Score		
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	0
Total Historical Factors			**Total Surgical Factors**		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS:

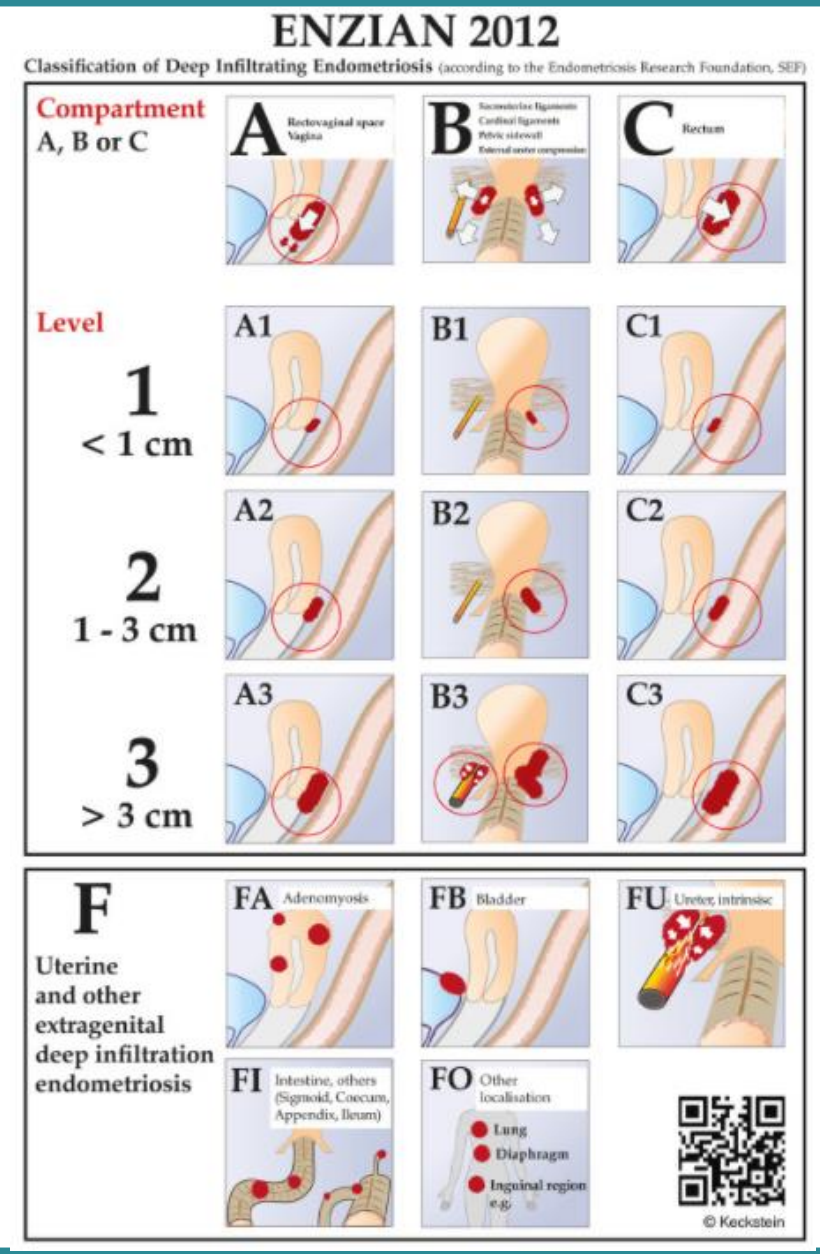
Historical		Surgical		EFI Score
	+		=	

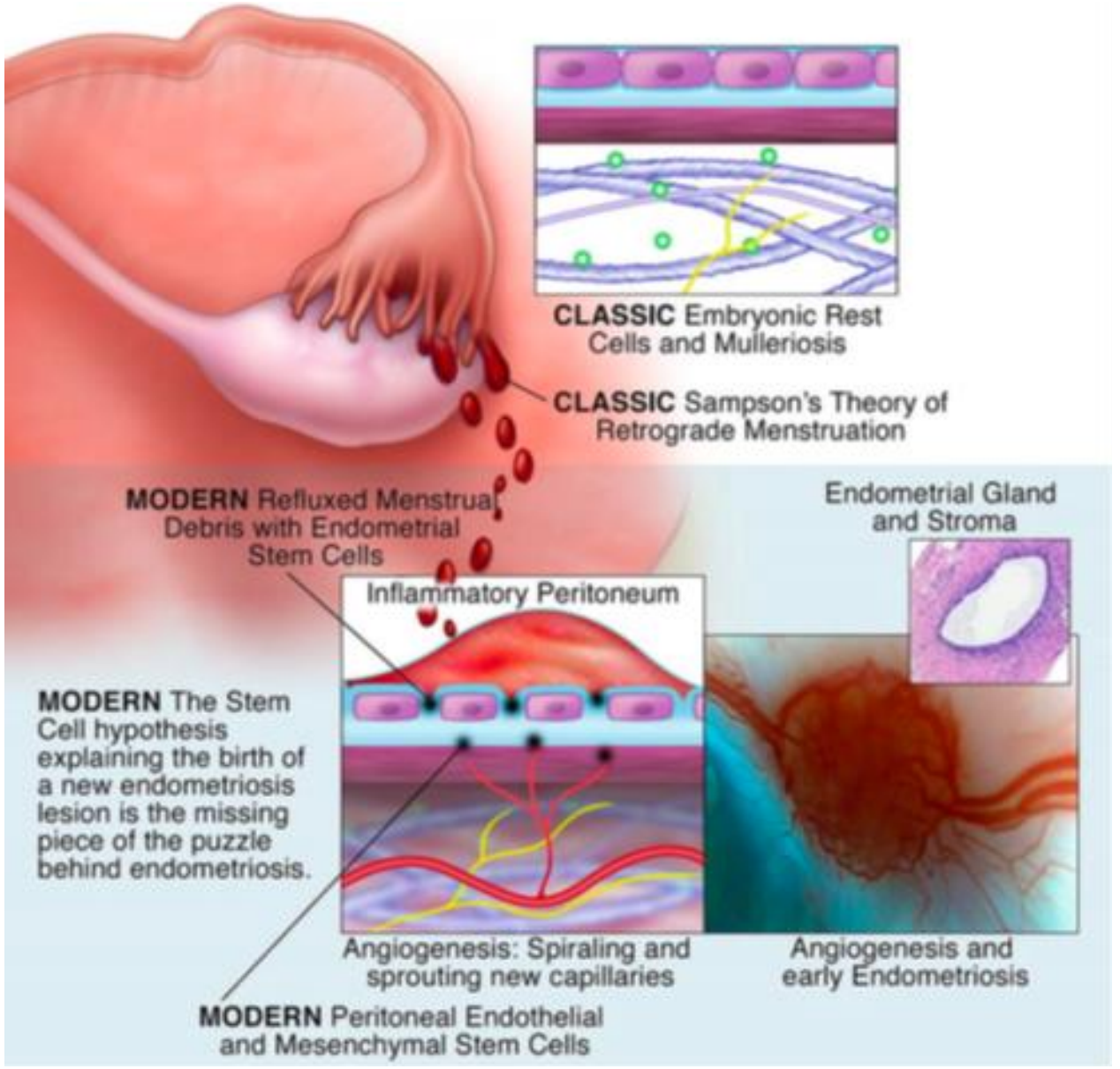


EFI is surgically determined: absent or nonfunctional = 0; severe dysfunction = 1 moderate = 2; mild = 3; normal = 4

rASRM is included (same as AFS)

Final EFI score = historical + surgical scores and ranges from 0 (worst) to 10 (best) prognosis.


ENZIAN 2012
Classification of Deep Infiltrating Endometriosis (according to the Endometriosis Research Foundation, SEF)
Compartment
A, B or C
A
Rectovaginal space
Vagina
B
C
Rectum
Level
1
< 1 cm
2
1 - 3 cm
3
> 3 cm
A1
B1
C1
A2
B2
C2
A3
B3
C3
F
Uterine and other extragenital deep infiltration endometriosis
FA Adenomyosis
FB Bladder
FU Ureter, intrinsic
FI Intestine, others (Sigmoid, Coecum, Appendix, Ileum)
FO Other localisation
Lung
Diaphragm
Inguinal region
e.g.
© Keckstein


CLASSIC Embryonic Rest Cells and Mulleriosis
CLASSIC Sampson's Theory of Retrograde Menstruation
MODERN Refluxed Menstrual Debris with Endometrial Stem Cells
Endometrial Gland and Stroma
Inflammatory Peritoneum
MODERN The Stem Cell hypothesis explaining the birth of a new endometriosis lesion is the missing piece of the puzzle behind endometriosis.
Angiogenesis: Spiraling and sprouting new capillaries
Angiogenesis and early Endometriosis
MODERN Peritoneal Endothelial and Mesenchymal Stem Cells

Nutraceuticals to Support Uterine Fibroid Health Health

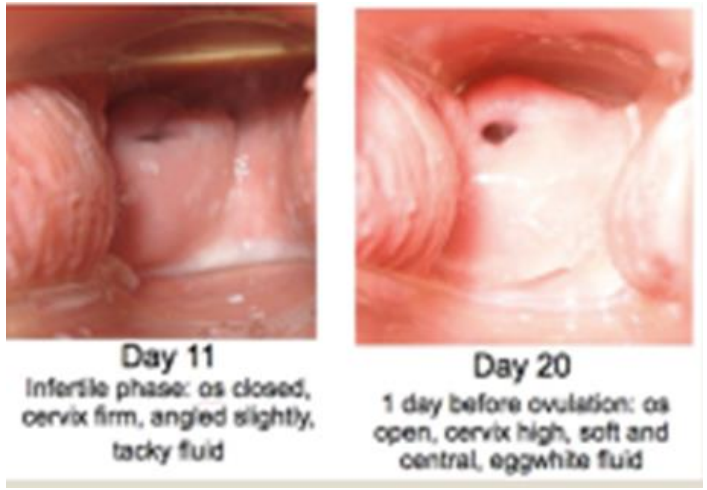
Botanicals	Green tea extract (ECGC): 500–3000 mg per day
Vitamin	Vitamin D: > 1,000–10,000 mg per day
Antioxidant	Resveratrol: > 1000 mg per day

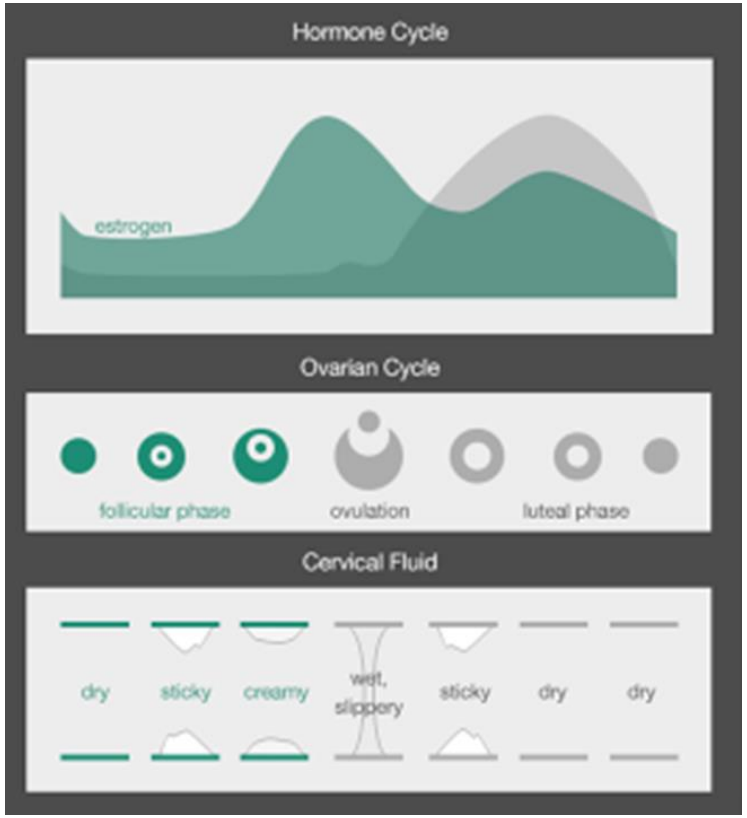
Nutraceuticals to Support Endometrial Health

Fatty Acid Balance	Fish Oils (EPA/DHA): 1000–5000 mg per day Flaxseed Oil: 1000–5000 mg per day Evening Primrose Oil: 1000–5000 mg per day Black Current Seed Oil: 1000–5000 mg per day Borage Oil: 1000–5000 mg per day
Antioxidants	Resveratrol: > 1000 mg per day Curcumin: >1000 mg per day Liposomal Glutathione: >10 ml per day
Other Nutraceuticals	General B vitamin and mineral supplement Vitamin A: 1500 IU per day Vitamin D: 2000–1000 IU per day Vitamin E: 200 IU per day Vitamin K: 50 mcg per day

Medications Impacting Fertility

- Ovary egg quality / quantity
  - Steroids
  - Autoimmune medications
- Sperm quantity / quality
  - Ca channel blockers
  - Psoriasis medication
  - Antifungals
  - Ulcer medication
  - Steroids
  - Seizure medication
  - Antidepressants
- Chemotherapy & Antineoplastics affect both males and female gametes
- Cervical mucus
  - Antihistamines / sinus congestion meds
  - Cough suppressants (guaifenesin)
  - Atropine
  - Propantheline
  - Epilepsy drugs
  - Clomid
  - Anti-depressants
- Ovulation / Menses
  - Antihypertensives
  - Antipsychotics
  - Tricyclic antidepressants
  - Hallucinogens and Opioids
  - Estrogen
  - Antiulcer medications
  - Metoclopramide (intestinal motility)





Cervical Mucous/ Secretions

- Fills the endocervical canal & controls entry of sperm / microorganisms into upper genitalia
  - Produced in the crypts of endocervical columnar epithelium
  - Before ovulation = large increase in the surface of the endocervical epithelium and increased secretion of clear mucus
  - From 20-60 mg/day to 600 mg/day at mid-cycle; and cervical os diameter increases from I to 3 mm and the cervix raises in the vagina
  - pH of endocervical secretions changes from 6.0-6.6 normal to at ovulation 6.8-7.4

Cervical Mucous/ Secretions

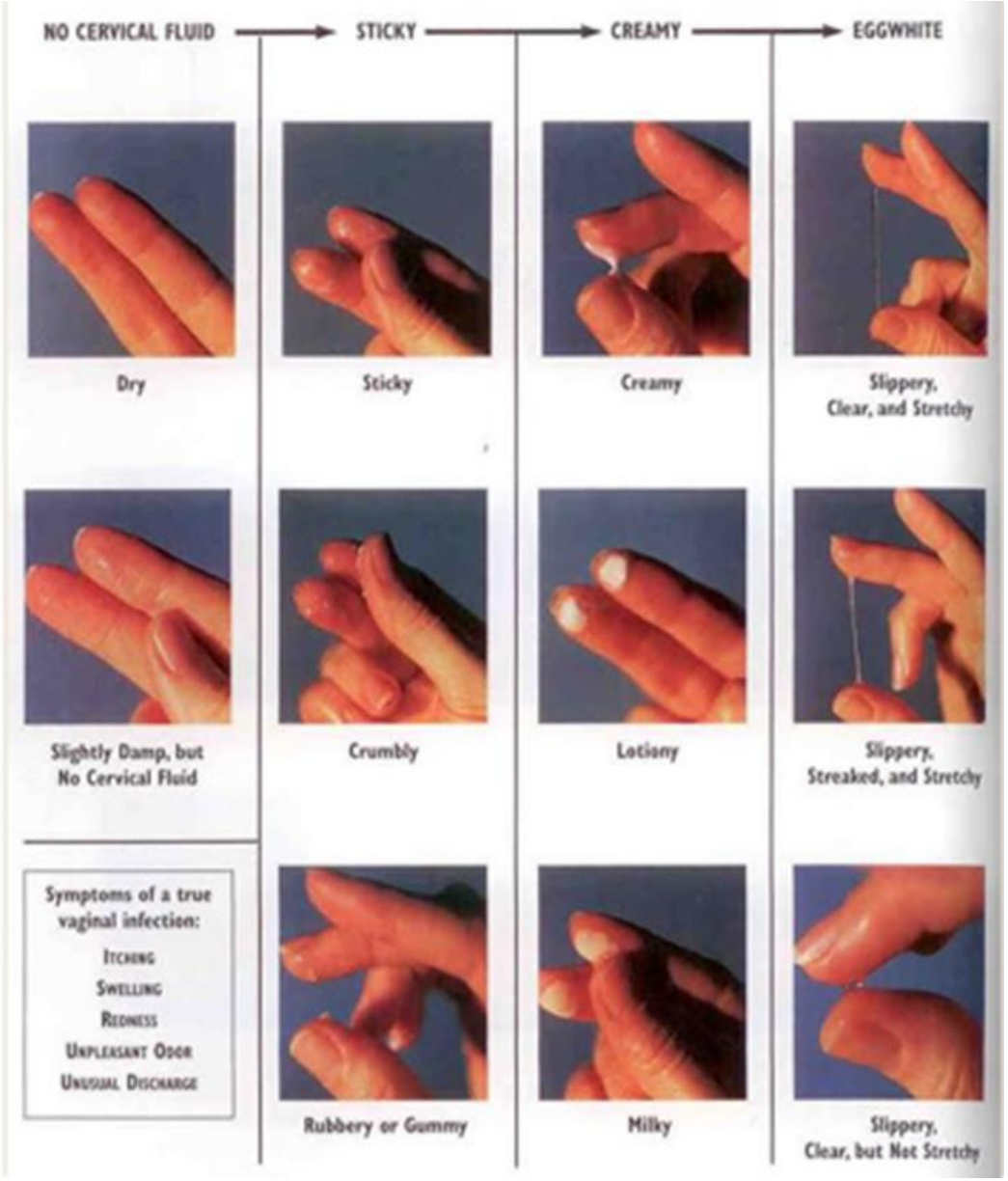
Functions dependent on its physical properties and the presence of key enzymes and proteins – dependent on E2 and P4 levels

Ovulation = cervical mucus contains 98% water (0.5% proteins); 90% water at other times (2.5-3.0% proteins)

Soluble proteins originate from serum and from secretions of the reproductive tract

Aqueous mucous contains NaCl, calcium, other ions; 30% is soluble proteins (are albumin, transferrin, haptoglobins, immunoglobulins IgG, IgA, and IgM, a-amylase, alkaline phosphatase, lactoferrin, peroxidases,12 lysozymes, plasminogen activator, a l-antitrypsin, and several other proteinase inhibitors) and 70% mucins

High estrogen levels decrease protein and proteinase concentrations; progesterone w/estrogens during the secretory phase, increases protein and proteinase concentration



Cervical Mucous

Mucus Type	Characteristics	Function
G type	Thick, pasty, impenetrable	Blocks uterus entrance
L type	Sticky / wet; dried makes branched ferns	Filters abnormal / poor quality sperm (slight fertile)
S type	Stretchy / slippery egg white; dried makes pine needles	Facilitates sperm entry into the uterus (elastic- fertile - spinn)
P type	Lubricative; dried makes hexagons (high potassium)	Activates sperm as they pass through the cervix (most fertile)

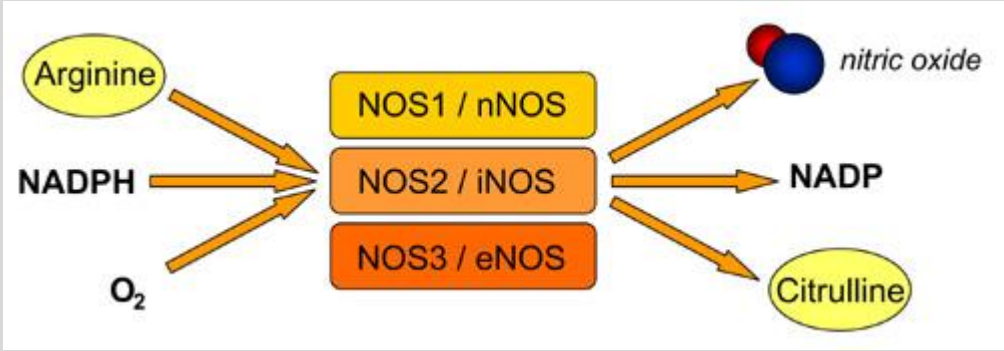
Meds & Mucus: Long term BCPs make more G type; NSAIDS lower prostaglandins and thus mucus production; antibiotics promote Candida growth masking mucous; anti-depressants, Clomiphene and anti-histamines all dry up the mucus (reduce time, anti-estrogen, or dry the body respectively)

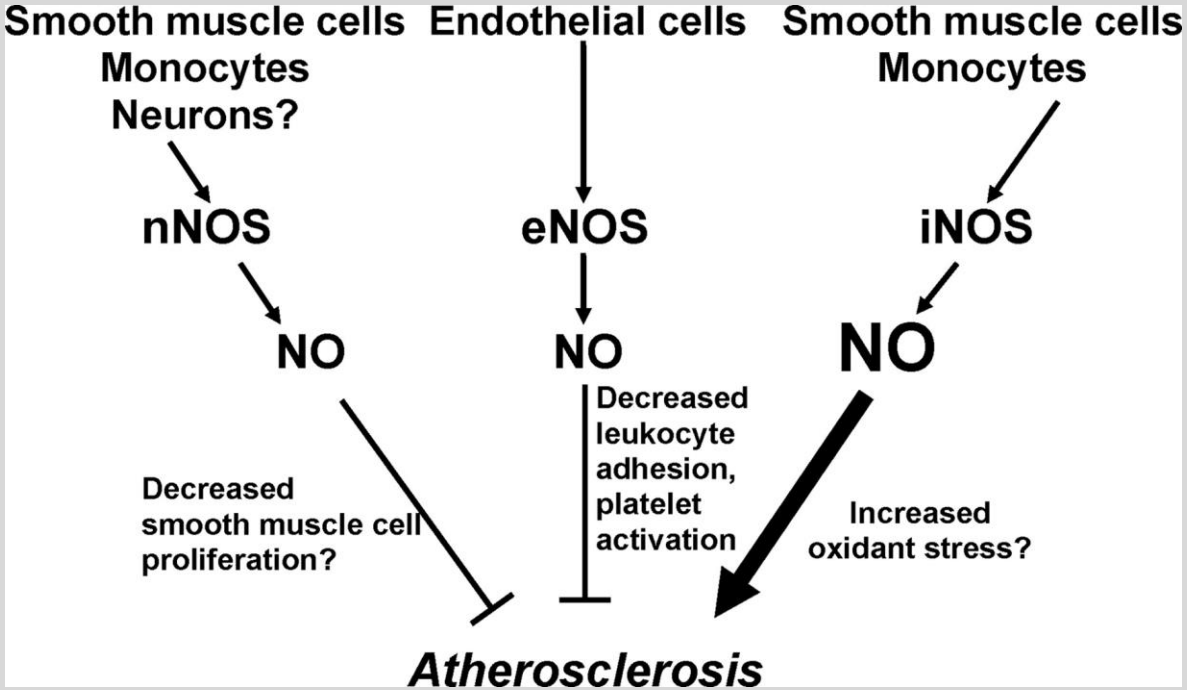
Guaifenesin for Fertile Cervical Mucous

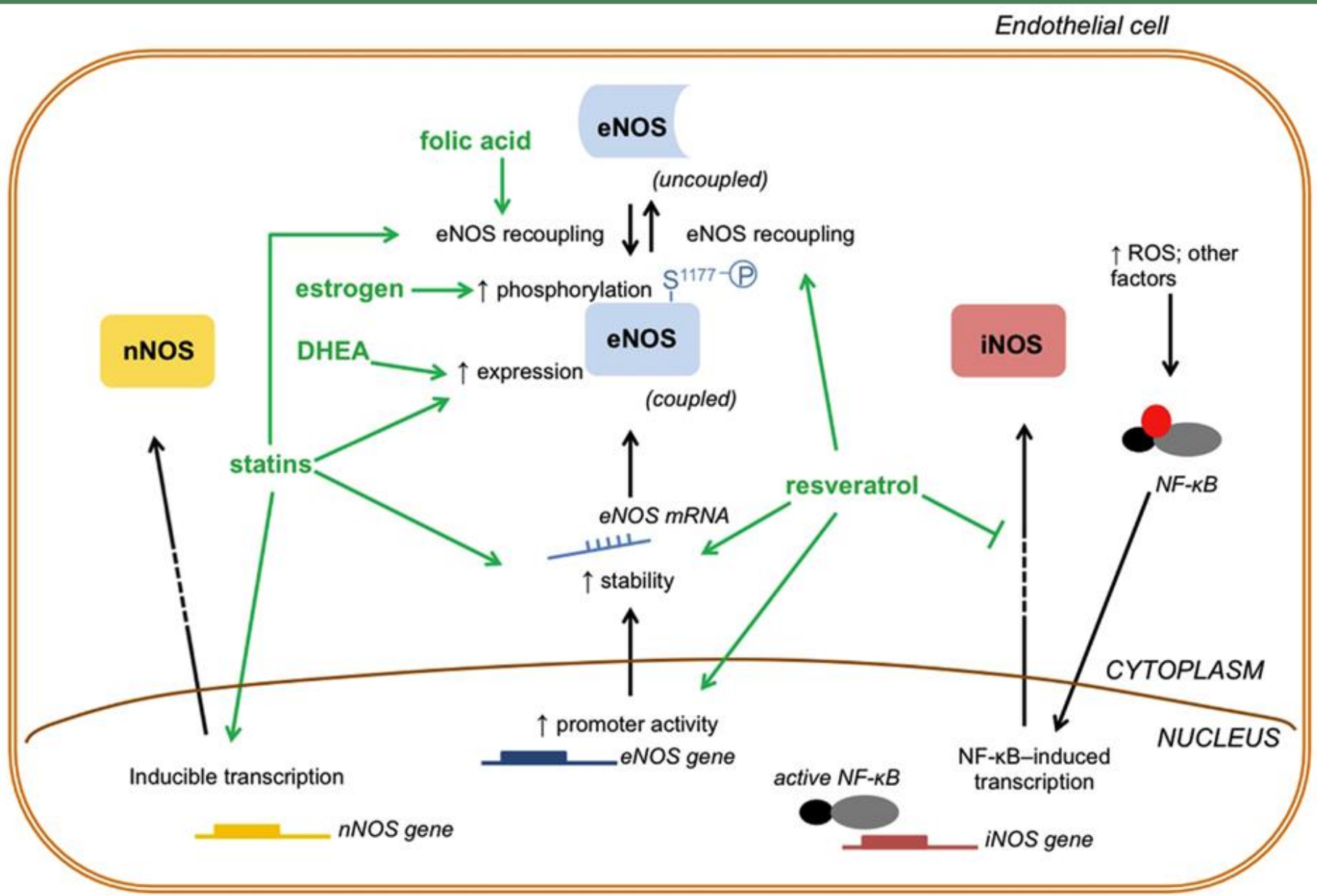
- Commonly given with Clomid
- Recommended dose 200 mg TID from cycle day 5 to ovulation
  - If poor spinnbarkeit (S type), can take as much as 400 mg QID – ensure well hydrated
- Studies state that it will thin cervical secretions but does not work as well as ethinyl estradiol
  - Longer use of ethynyl estradiol will suppresses follicular maturation, so exogenous gonadotropin must be used to counteract suppression

Fertile CM & Sperm

- What about better vascular flow = acetylcholine-induced vasorelaxation by NO
  - Studies using nitroglycerine to form NO and changing amount and quality of cervical mucous
  - Can work for CM and Sperm
    - Overproduction of excessive exposure to oxidative conditions and NO will reduce sperm motility
    - ED Meds: phosphodiesterase type 5 (PDE 5) inhibitor that enhances nitric oxide (NO)-mediated vasodilation in the corpus cavernosum by inhibiting cyclic guanosine monophosphate breakdown
- Must ensure proper form of NO
  - Neuronal = nNOS, endothelial NOS = eNOS and inducible = iNOS







https://www.frontiersin.org/articles/10.3389/fphys.2012.00218/full

Ovarian Reserve Depleting Red Flags

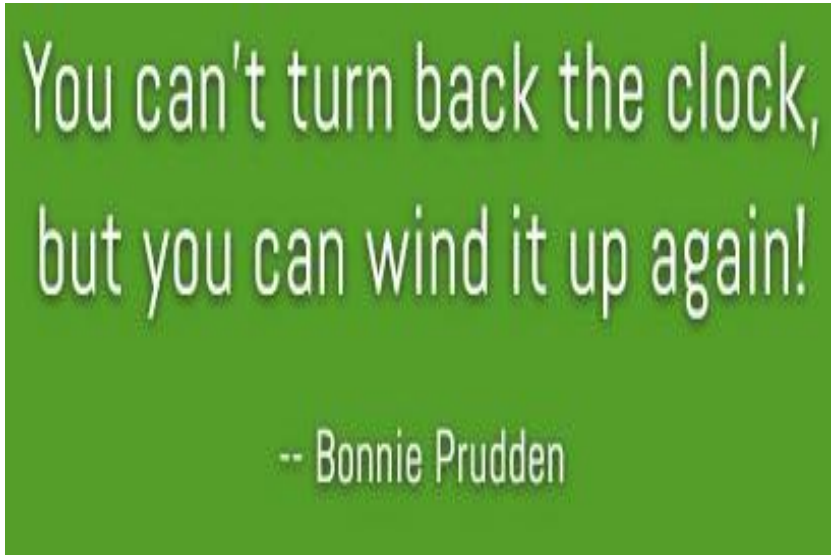
1. **Shorter menstrual cycles**

(25–26-day cycles from a 28-30 day cycle)

2. Missing menstrual cycles

3. Age above 35 years old

4. History of miscarriages

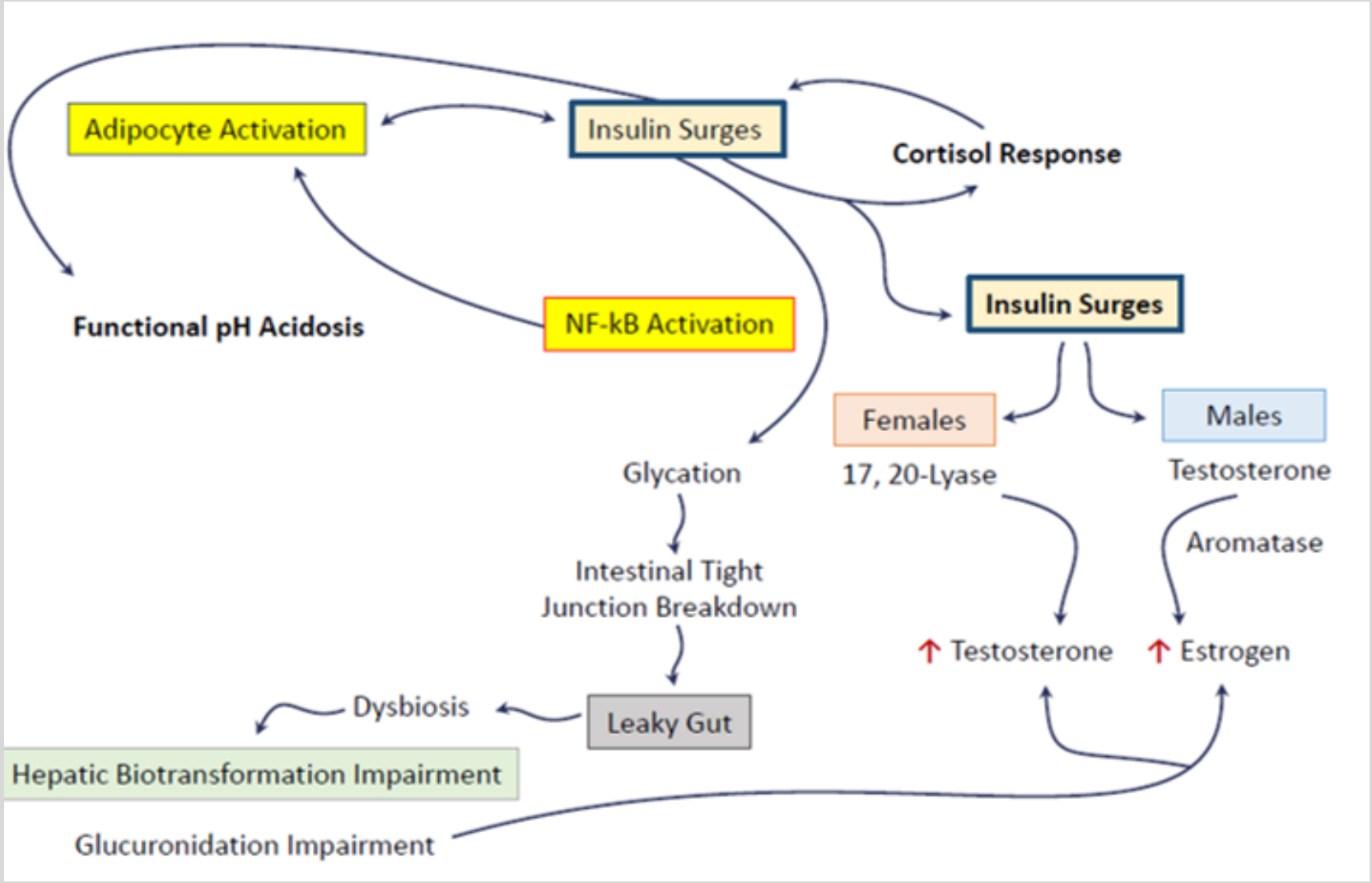


Labs & Testing – Regular & Advanced

- Hierarchy of treatment: once anatomical considerations are removed - normalize all the factors that will still lead to greater hormonal dysfunction
  - Blood sugar / dysglycemia
  - Optimize BMI / waist / hip
  - Anemias / vitamin deficiency
  - Adrenal
    - Work on stress / lifestyle factors
  - Thyroid
  - Then Hormones

BLOOD SUGAR

Cycle of Metabolic Syndrome



Blood Sugar

Hypoglycemia: Regular meals with adequate protein and fat, adaptogens, general B-vitamin and mineral supplements for glucose and adrenal support, fiber, plant sterols, and BCAA

Insulin resistance: Low carb / mito-keto diet with timed eating, resveratrol (liposomal in a trans-isoform), berberine (other AMPK activators like rose hip, burdock root, and ALA), SCFA (all 3), glutathione (liposomal), Gymnema sylvestre, EPA/DHA, fiber supplementation (diverse fibers) and general B-vitamin and mineral supplements for glucose and adrenal support


BMI & BODY WEIGHT

Body Mass Index and Infertility

Body Mass Index

Low Body Mass Index
< 18.5

↓

Suppression of Gonadotropin Release

↓

Anovulation (sporadic or constant)

↓

Infertility

High Body Mass Index
> 25

↓

Insulin Resistance — **PCOS** — **↑ Androgens**

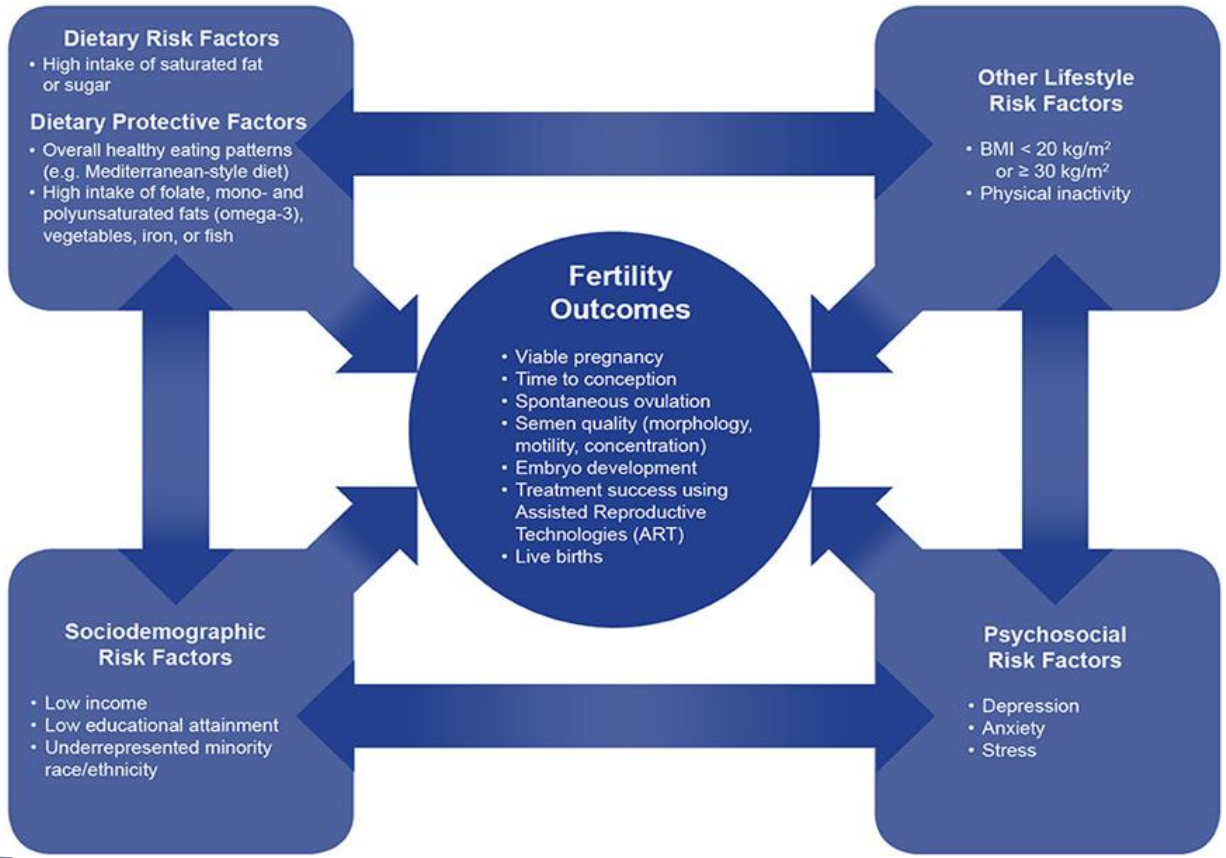
↑ Adipokines

↓

Pituitary Feedback Dysregulation

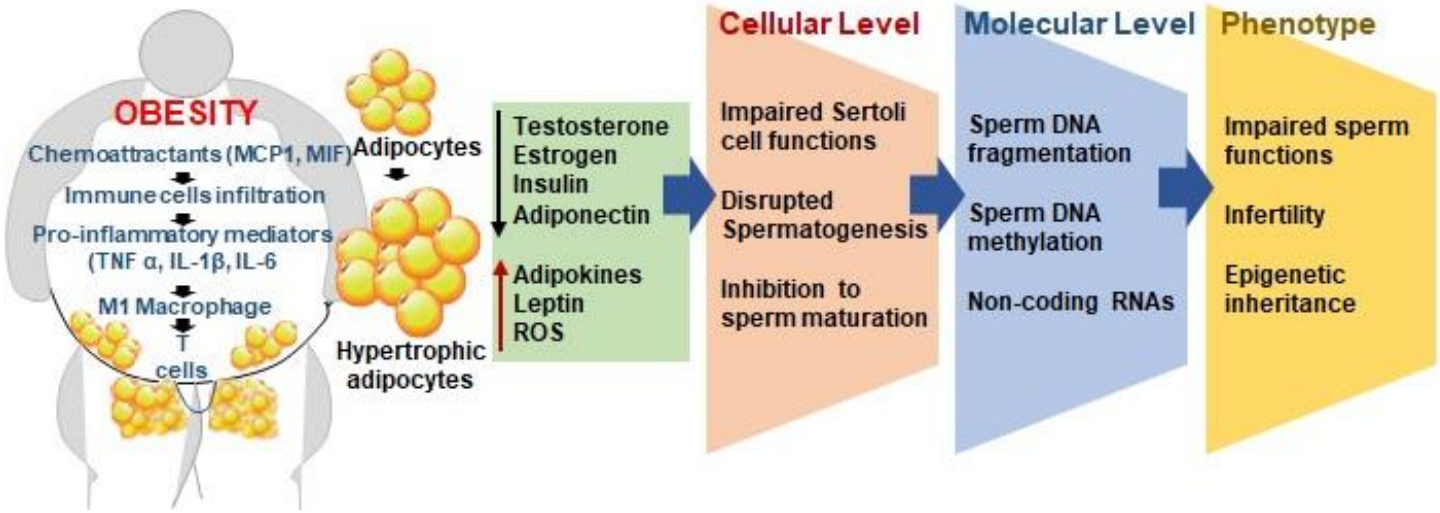
↓

Infertility



OBESITY AFFECTS MEN & WOMEN

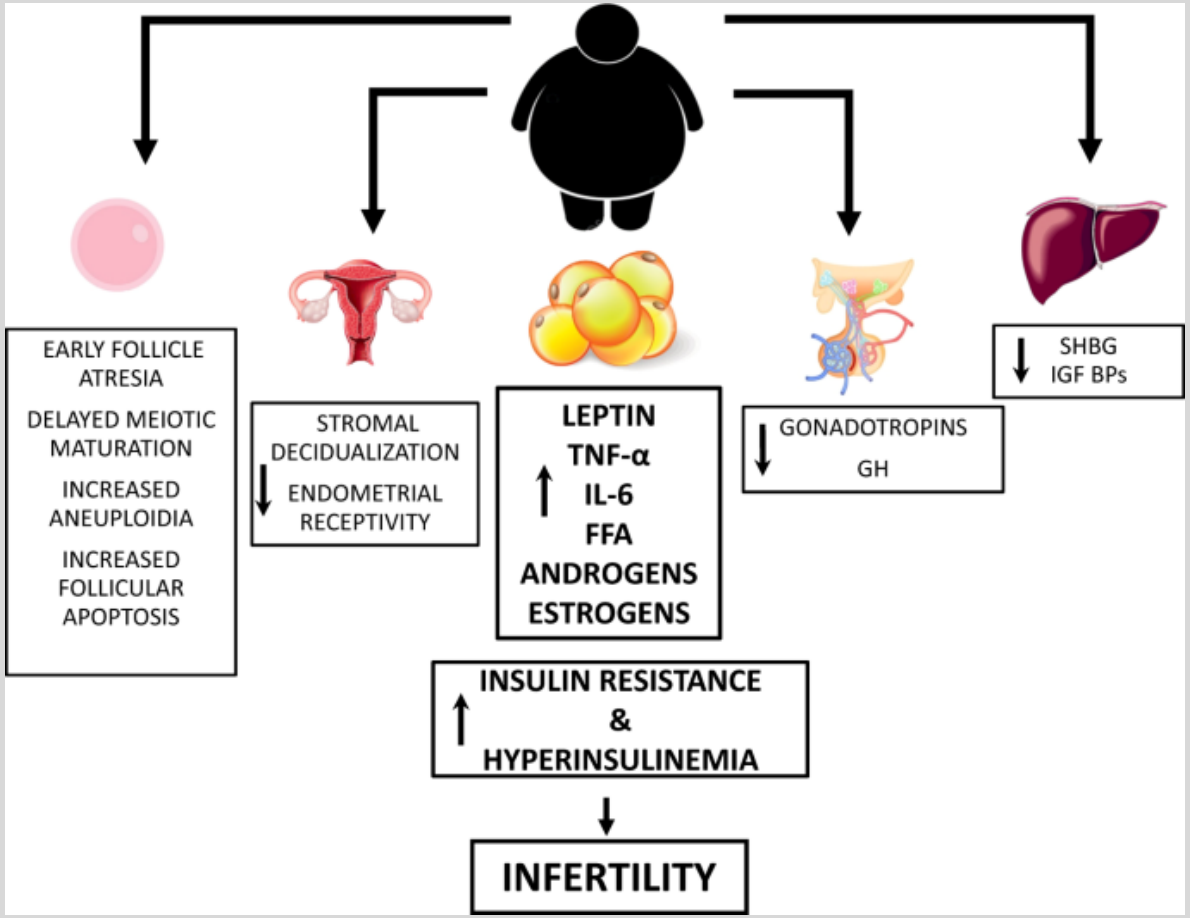
Obesity, systemic inflammation, and male infertility



Obesity, systemic inflammation and male infertility

Chem. Biol. Lett. 2020, 7(2), 92-98

Obesity & Women's Fertility



obesity and infertility

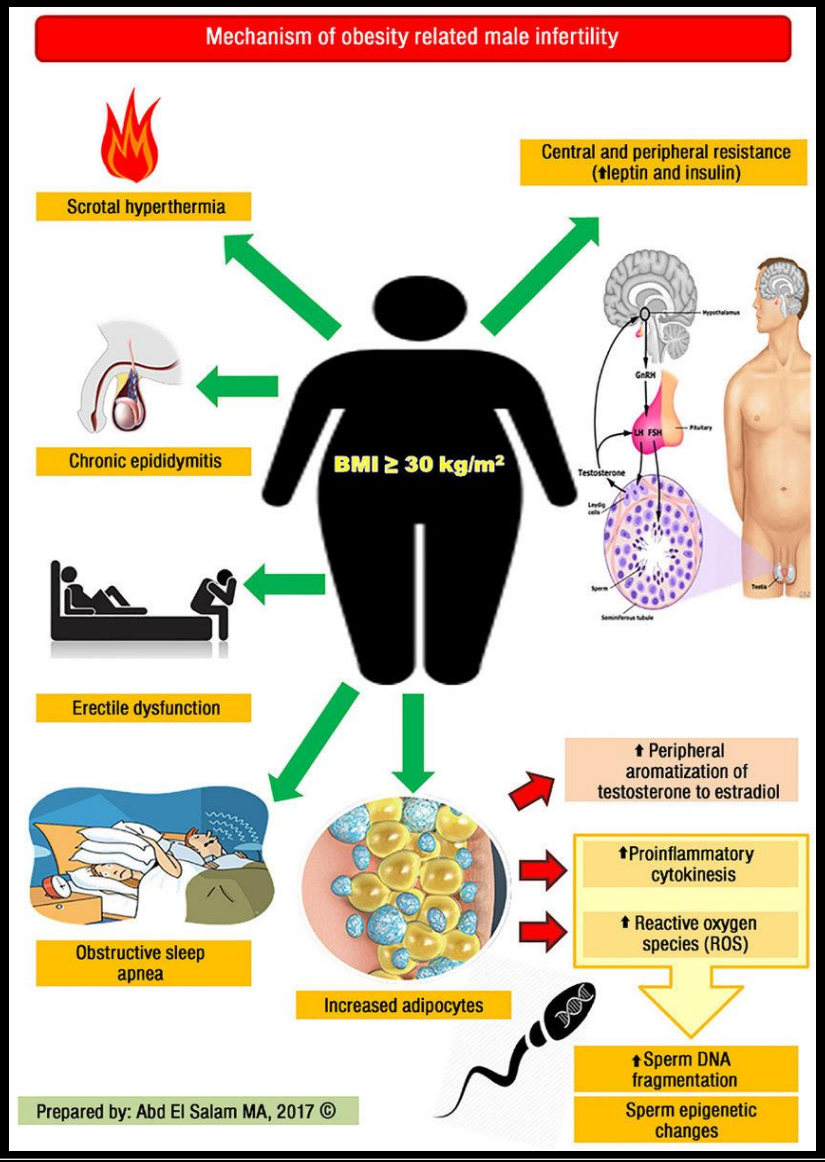
- obese women: x3 times at risk of infertility
  - ✓ in the presence of irregular cycles
    - associated with oligo-anovulation
  - ✓ in the presence of regular cycles
    - probability of pregnancy is reduced by 5% for every BMI unit that exceeds 29 kg/m^2
      - ✓ anovulation even with regular cycles
      - ✓ release of oocytes with reduced fertilization potential
      - ✓ endometrial abnormalities
- underlying mechanisms
  - ✓ insulin resistance
  - ✓ hyperandrogenism
  - ✓ elevated leptin levels and leptin resistance

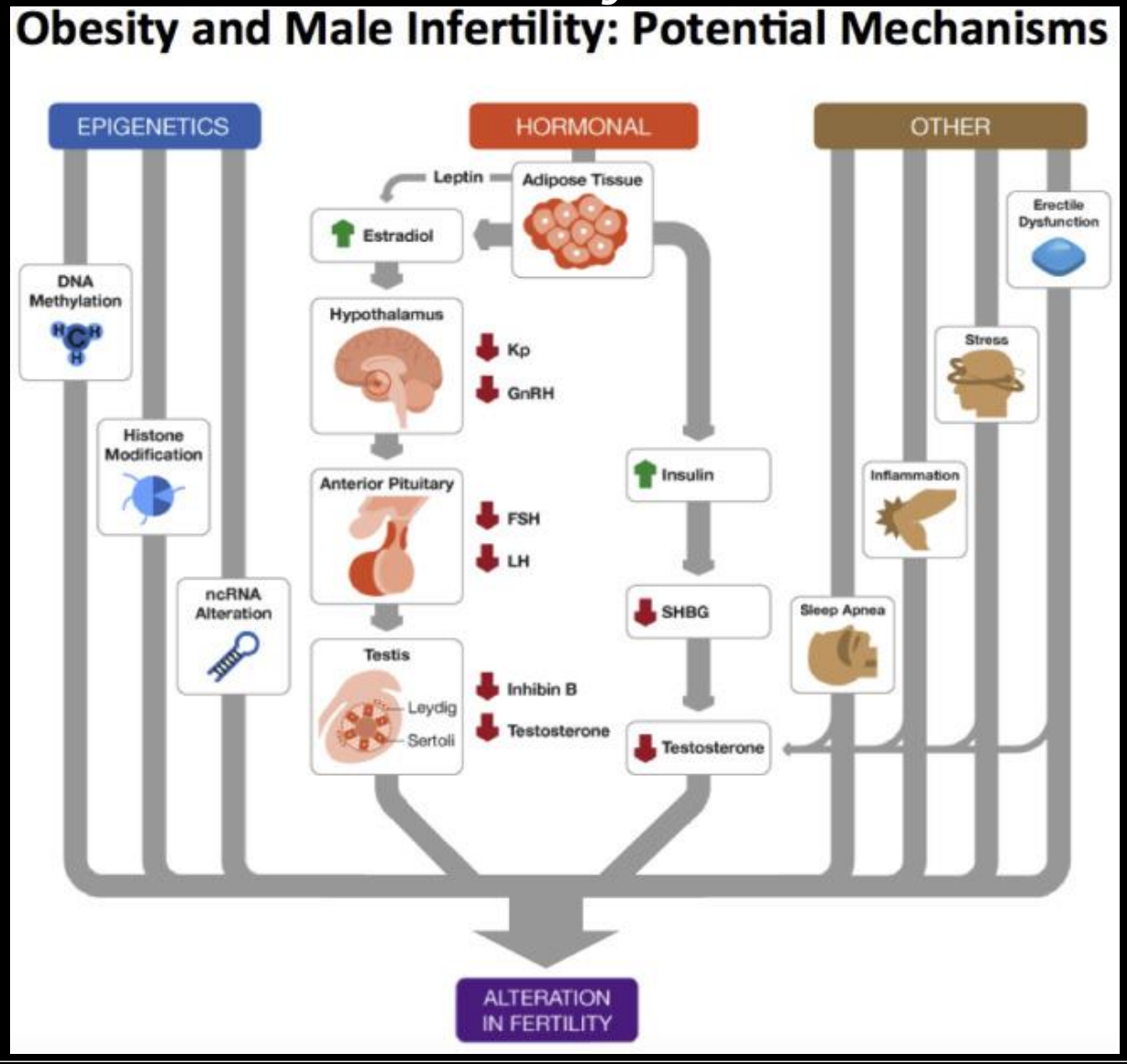
EMBRYO ART

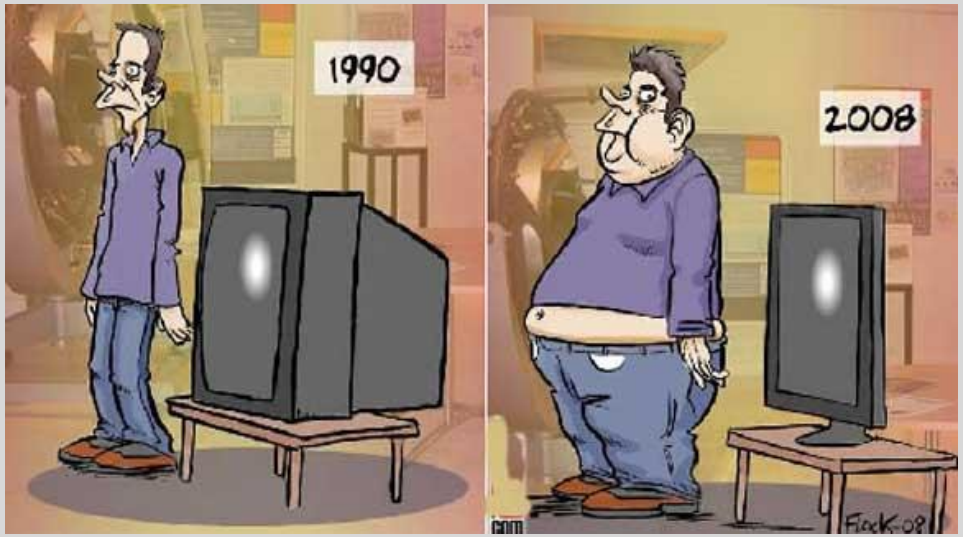
OBESITY AND IVF - 2010

E. MAKRAKIS

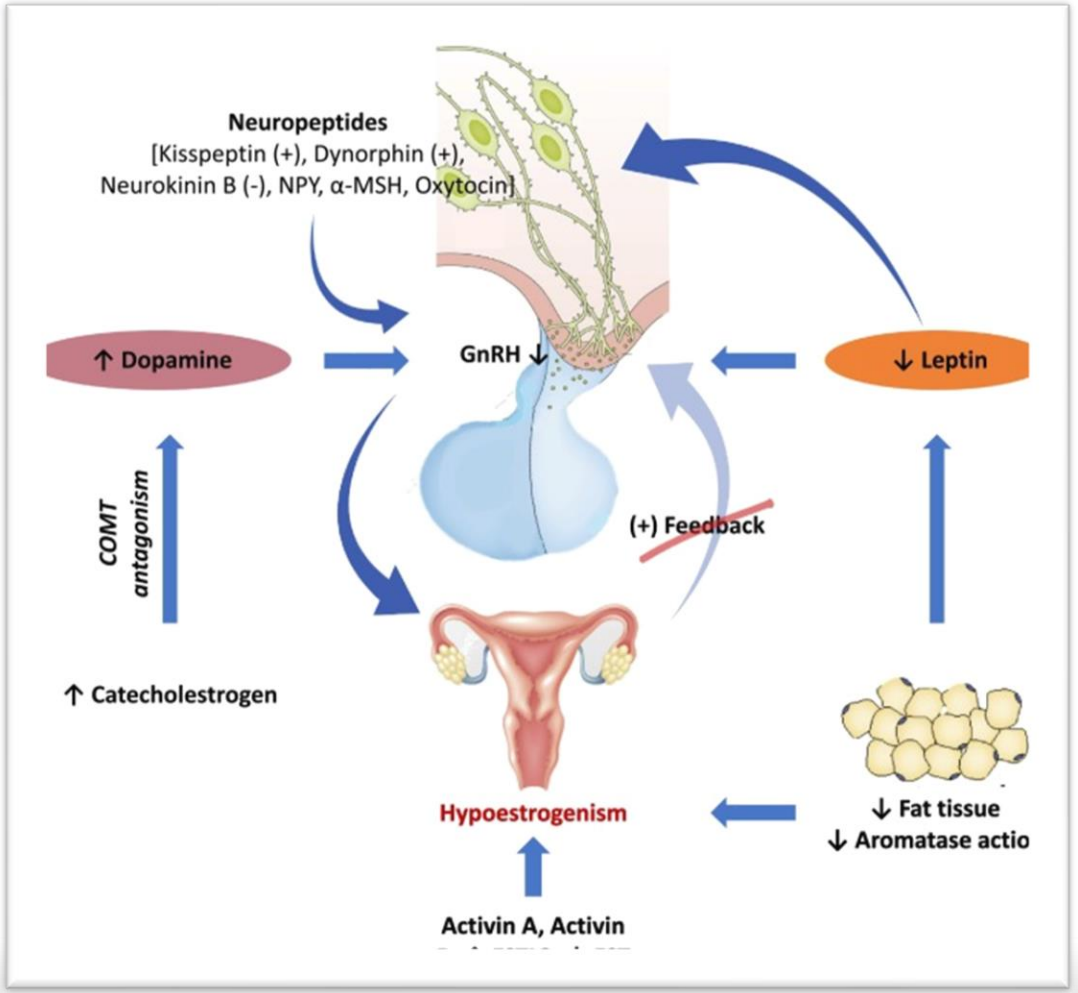
Obesity & Male Fertility







Over the five years to 2022, IBISWorld estimates that the obesity rate among adults aged 18 and older has increased an annualized 1.8% to 33.0 people per 100 individuals. There are a multitude of factors influencing this increase during the period, as well as over the long-term. Our modern work environment, which has become increasingly less physical, has drastically increased inactivity. The COVID-19 (coronavirus) has further introduced a sedentary lifestyle through mandated stay at home orders and business closures. Individuals reported weight gain during the first year of the pandemic, likely due to stress surrounding the virus coupled with lack of access to recreational activities and food insecurity. Compounding this effect, individuals are not offsetting this with increased exercise during their leisure time. A study by Harvard University found that heavy-duty TV watchers ate fewer fruits and vegetables, had larger waistlines and higher levels of blood pressure, blood sugar, and triglycerides. In addition, food marketing and an emphasis on consumption has driven an attitude around eating that favors large portion sizes and excess.



UNDERWEIGHT AND FERTILITY

ANEMIA

Iron

- Used in many metabolic processes
  - Oxygen transport
  - Deoxyribonucleic acid (DNA) synthesis
  - Manufacture thyroid
  - Electron transport / cofactor in oxidative phosphorylation
    - Cytochrome enzymes bind heme iron, and some protein complexes in the oxidative phosphorylation process have iron-sulfur centers that are crucial to their function
  - Watch the heavy menses ladies
  - TCM = blood and yin xu

Serum iron status in association with pregnancy outcomes in infertile women undergoing IVF/ICSI

B S Kadhum[1] and S A Wadood Al-Shammaree[1]

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Journal of Physics: Conference Series, Volume 1853, The International Conference of Chemistry 17-18 December 2020, Bagdad, Iraq

Citation B S Kadhum and S A Wadood Al-Shammaree 2021 *J. Phys.: Conf. Ser.* **1853** 012025

Article PDF

References

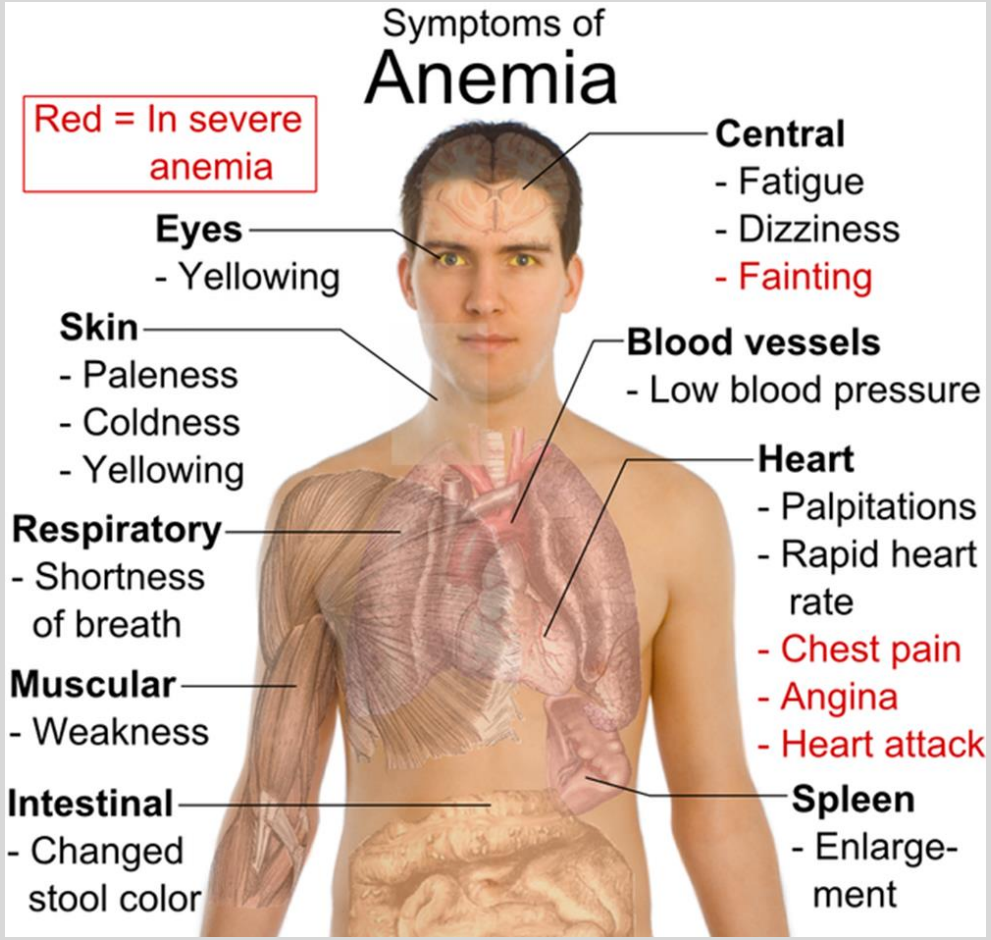
+ Article information

Abstract

Iron status can affect the outcome of *in* vitro-fertilization (IVF) in infertile women who undergoes this process. The aim of this study is to evaluate iron status, ceruloplasmin ferroxidase activity and their association with outcome of pregnancy prior to initiation of IVF/ICSI procedure. The participants were fertile women with male cause infertility (control; n=25), women with polycystic ovary syndrome (PCOS; n=21), women with low anti-Müllerian hormone level (AMH; n=26), and women with unexplained infertility (UI; n=27). Blood samples were obtained on the day of oocyte aspiration. Serum iron, ferritin, transferrin level, and ceruloplasmin ferroxidase activity were measured; the transferrin saturation, Total Iron Binding Capacity (TIBC), and Unsaturated Iron Binding Capacity (UIBC) were calculated. In the low AMH group, Ferritin showed a significantly lower level compared to the control and UI groups. In the PCOS group, ferritin, transferrin, TIBC, and UIBC showed a significantly lower level compared to the control and UI groups. Cp. ferroxidase activity in the PCOS group showed a lower level but of no significance compared to the other groups. In this study, it can be concluded that higher levels of iron, ferritin, and lower transferrin in pregnant PCOS women lead to increase chances of pregnancy following an IVF protocol.

Don’t Forget the Other Anemias

- B12 – watch the vegetarians
- Pernicious
- Thalassemia
- Hemolytic
- Faconi’s
- Sickle cell



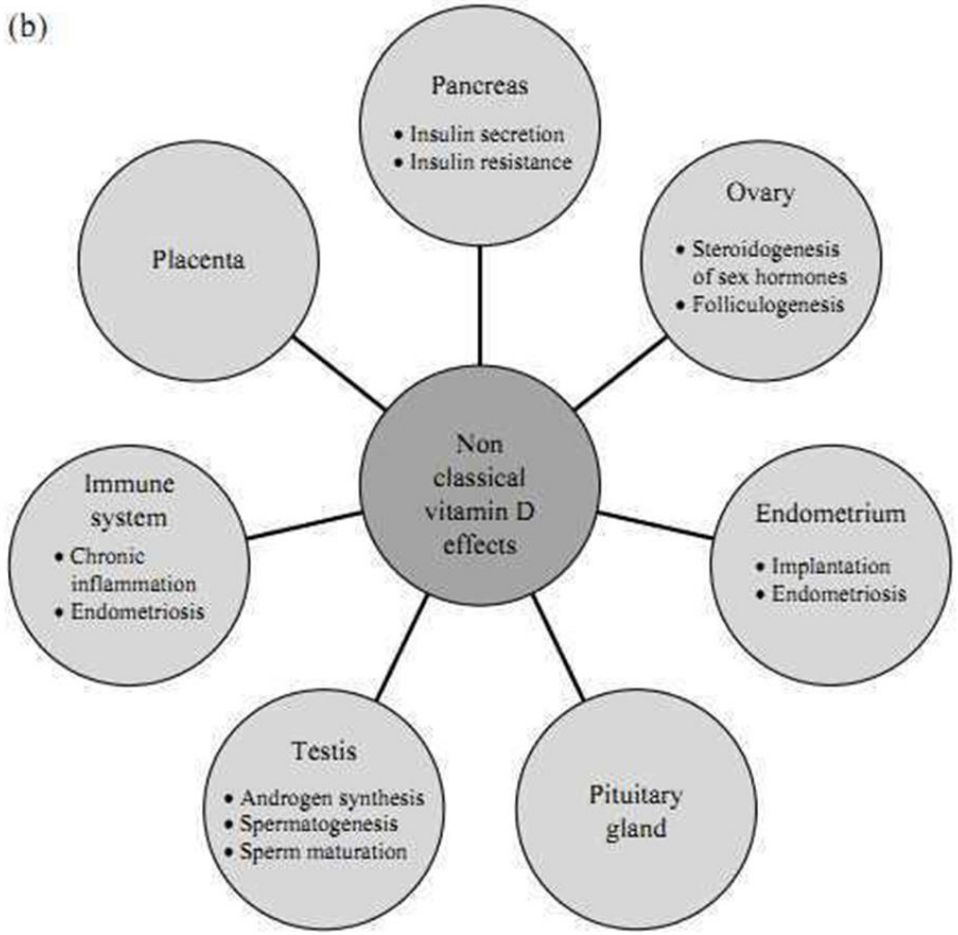
OTHER VITAMIN DEFICIENCIES

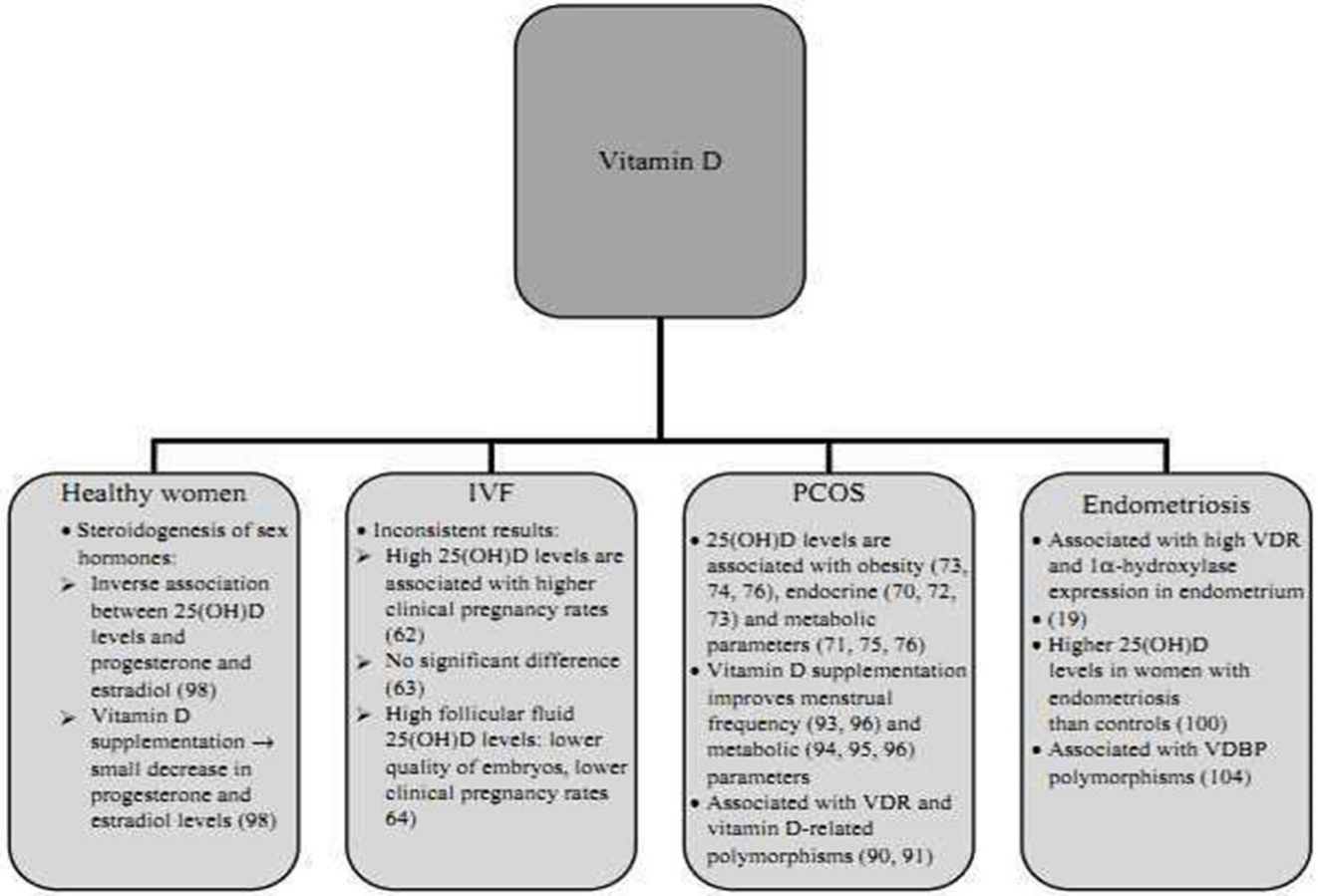
Effect of Micronutrient Supplements on Fertility

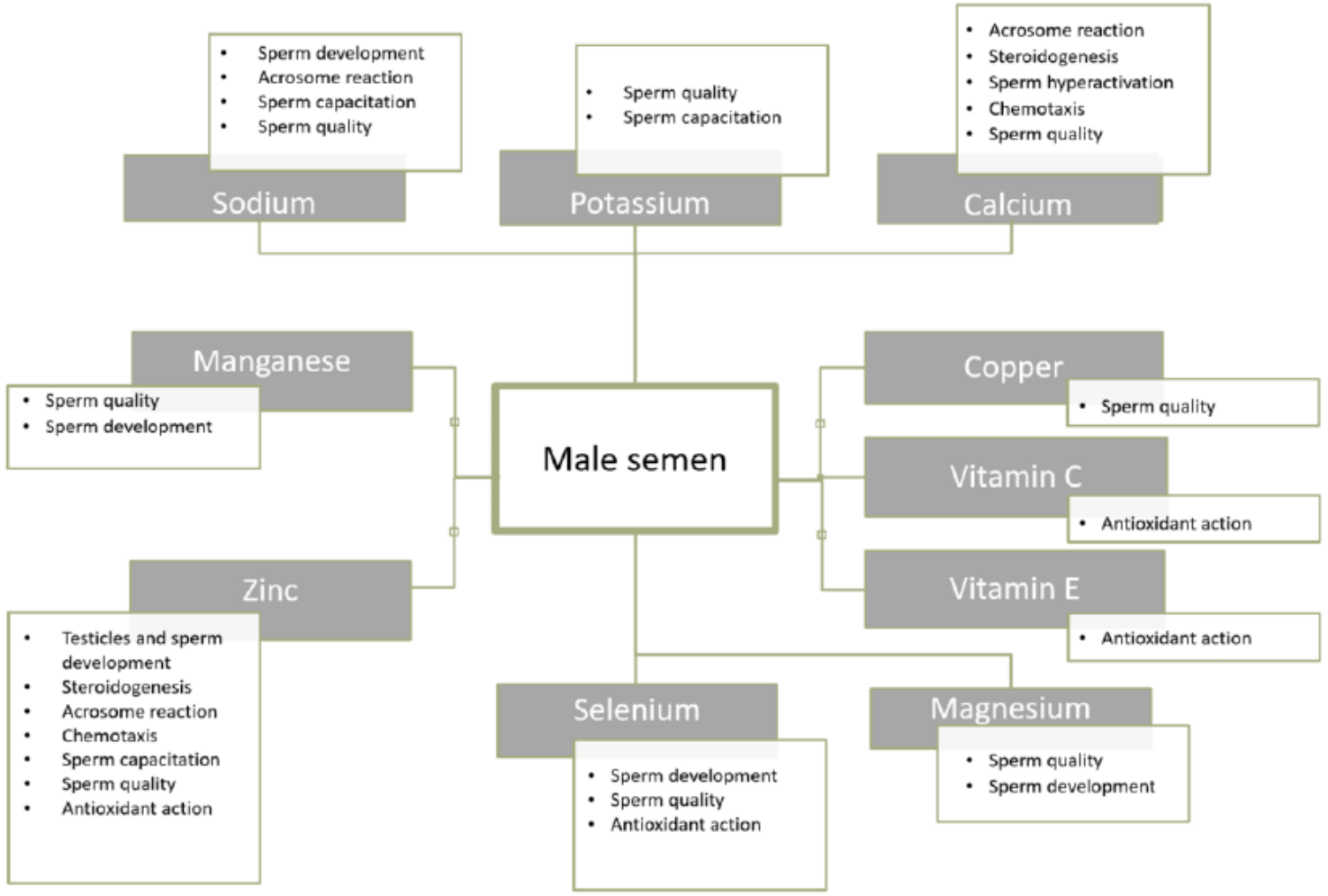
- Female conclusion: Aside of lowering the malformation risk by periconceptional supplementation of folic acid, substitution with different micronutrients, particularly folic acid, vitamin B6, vitamin C, vitamin D, vitamin E, iodine, selenium, iron, and DHA might have a positive impact on infertility treatment
  - Multivitamin formulation should take the pathophysiology, clinical studies, and upper limits into account

- Male conclusion: In addition to the avoidable risk factors (alcohol and smoking), unchangeable factors are also likely involved in the genesis. Modern reproductive medicine methods help resulting in decent pregnancy rates in subfertile men.
  - Several studies have reported a significant increase in sperm quality and pregnancy rates when the men were supplemented by specific vitamins and micronutrients

Role of Vitamin D in Fertility







Diet and Nutritional Factors in Male (In)fertility—Underestimated Factors

J. Clin. Med. **2020**, *9*, 1400; doi:10.3390/jcm9051400

Micronutrient Testing

	Micronutrient	Plasma			WBC			RBC		
		Current	Previous	Ref	Current	Previous	Ref	Current	Previous	Ref
Vitamins	Vitamin A	74.86 (mcg/dL)		32.96–82.27	0.21 (pg/MM WBC)		0.21–21.08			
	Vitamin B1	304.99 (nmol/L)		164.71–397.23	0.47 (pg/MM WBC)		0.34–3.77			
	Vitamin B2	38.91 (mcg/L)		23.41–358.56	0.45 (pg/MM WBC)		0.07–4.23			
	Vitamin B3	8.25 (ng/mL)		5.05–84.36	8.01 (pg/MM WBC)		0.99–14.76			
	Vitamin B5	66.03 (mcg/L)		23.23–269.15	0.07 (pg/MM WBC)		0.02–0.39			
	Vitamin B6	1.94 ↑ (ng/mL)		0.46–1.76	0.010 (pg/MM WBC)		0.003–0.040			
	Vitamin B12	>2000 (pg/mL)		≥211						
	Vitamin C	0.71 (mg/dL)		0.34–0.71	41.06 ↑ (pg/MM WBC)		0.55–28.77			
	Vitamin D3	1.77 (ng/mL)		0.74–2.46	10.74 (pg/MM WBC)		7.68–84.76			
	Vitamin E	20.8 (mg/L)		7.6–24.6	10.45 ↓ (pg/MM WBC)		11.34–116.04			
	Vitamin K1	3.05 ↑ (ng/mL)		0.22–2.50	0.004 (pg/MM WBC)		0.003–1.440			
	Vitamin K2	0.18 (ng/mL)		≥0.08	0.004 ↓ (pg/MM WBC)		0.005–5.152			
	Folate							172.5 (ng/mL)		≥71.4

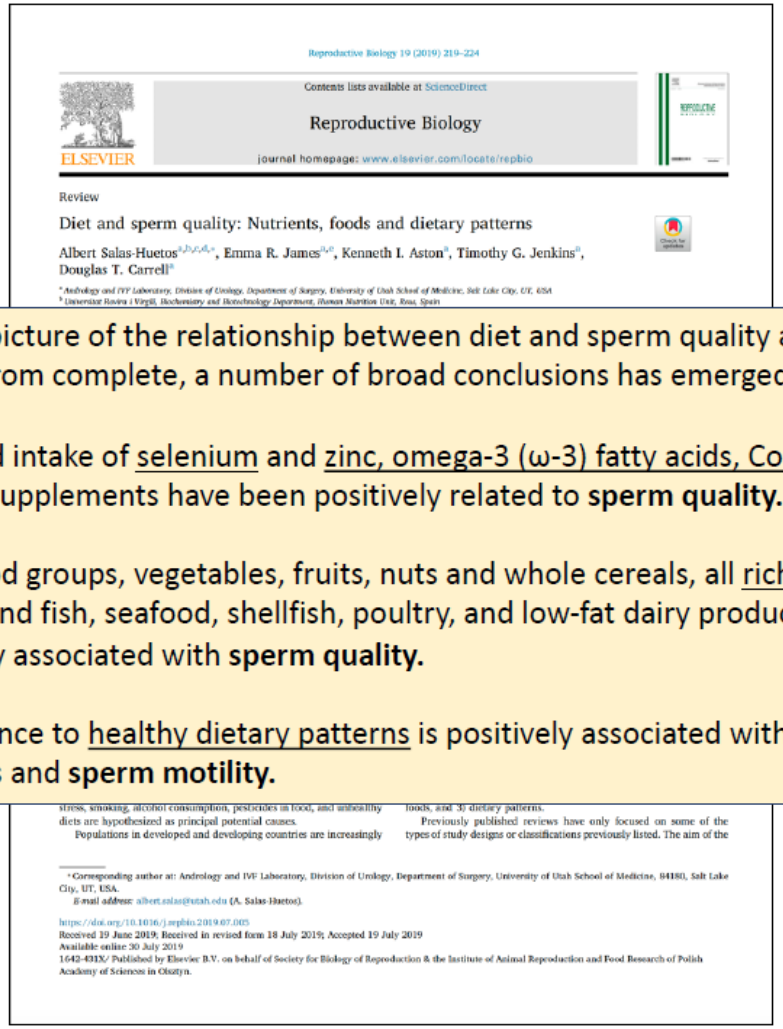
Comprehensive Nutritional Panel

Vitamins	Minerals	Amino Acids	Antioxidants	Carbohydrate Metabolism, Fatty Acids & Metabolites
Biotin	Calcium	Asparagine	Lipoic Acid	Carnitine
Folate	Copper	Glutamine	Coenzyme Q10	Choline
Pantothenate	Magnesium	Serine	Cysteine	Chromium
Vitamin A	Manganese		Glutathione	Fructose Sensitivity
Vitamin B1	Zinc		Selenium	Glucose/Insulin Metabolism
Vitamin B2			Vitamin E	Inositol
Vitamin B3			SPECTROX™ (Total Antioxidant Function)	Oleic Acid
Vitamin B6				
Vitamin B12				
Vitamin C				
Vitamin D				
Vitamin K2				

Table 1
Most studied supplements (and antioxidants), foods and dietary patterns that positively affect (or are associated with) sperm quality, main benefits, evidence level and primary references.

Variables	Main benefits: associations (from observational studies) or effects (from RCT)	Problems in the evidence	Main references
Antioxidants			
Selenium	Beneficial effect on sperm concentration, total sperm motility and morphology	RCTs of low-quality and small population	[5,6]
Zinc	Beneficial effect on sperm concentration and total sperm motility	RCTs of low-quality and small population	[5,6]
Other supplements			
ω-3 fatty acids	Beneficial effect on sperm count and concentration, total motility and normal morphology	RCTs of low-quality and small population	[6]
CoQ10	Beneficial effect on sperm count and concentration, total motility and normal morphology	RCTs of low-quality and small population	[6]
Carnitines	Beneficial effect on sperm progressive and total motility and normal morphology	RCTs of low-quality and small population	[6]
Foods			
Vegetables and fruits	Positively associated with sperm motility	No RCTs to date	[17]
Cereals	Positively associated with sperm motility	No RCTs to date	[17]
Fish, shellfish and seafood	Positively associated with total sperm count, concentration and morphology	No RCTs to date	[17]
Poultry	Positively associated with sperm motility	No RCTs to date	[17]
Low-fat dairy and skimmed milk	Positively associated with sperm concentration and motility	No RCTs to date	[17]
Nuts	Beneficial effect on sperm count, vitality, total and progressive motility and normal morphology	RCTs of small population	[30,31]
Dietary patterns			
Health conscious	Positively associated with sperm concentration and lower sperm DNA damage	No RCTs to date	[17,32]
Prudent	Positively associated with sperm concentration and decreased frequencies of sperm disomy	No RCTs to date	[17,32]
Mediterranean	Positively associated with sperm concentration and sperm motility	No RCTs to date	[17,32,39]

Diet & Sperm Quality: Nutrients Food & Dietary Patterns; *Reproductive Biology 19 (2019) 219-224*



Reproductive Biology 19 (2019) 219–224

Contents lists available at ScienceDirect

Reproductive Biology

journal homepage: www.elsevier.com/locate/repbio

Review

Diet and sperm quality: Nutrients, foods and dietary patterns

Albert Salas-Huetos[a,b,c,d,*], Emma R. James[a,e], Kenneth I. Aston[a], Timothy G. Jenkins[a], Douglas T. Carrell[a]

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[b] Universitat Rovira i Virgili, Biochemistry and Biotechnology Department, Human Nutrition Unit, Reus, Spain

stress, smoking, alcohol consumption, pesticides in food, and unhealthy diets are hypothesized as principal potential causes.

Populations in developed and developing countries are increasingly

foods, and 3) dietary patterns.

Previously published reviews have only focused on some of the types of study designs or classifications previously listed. The aim of the

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Received 19 June 2019; Received in revised form 18 July 2019; Accepted 19 July 2019
Available online 30 July 2019
1642-431X/ Published by Elsevier B.V. on behalf of Society for Biology of Reproduction & the Institute of Animal Reproduction and Food Research of Polish Academy of Sciences in Olsztyn.

Although the picture of the relationship between diet and sperm quality and fertility is far from complete, a number of broad conclusions has emerged.

First, increased intake of selenium and zinc, omega-3 (ω-3) fatty acids, Coenzyme Q10 and carnitine supplements have been positively related to **sperm quality.**

In terms of food groups, vegetables, fruits, nuts and whole cereals, all rich in fiber and antioxidants, and fish, seafood, shellfish, poultry, and low-fat dairy products have been positively associated with **sperm quality.**

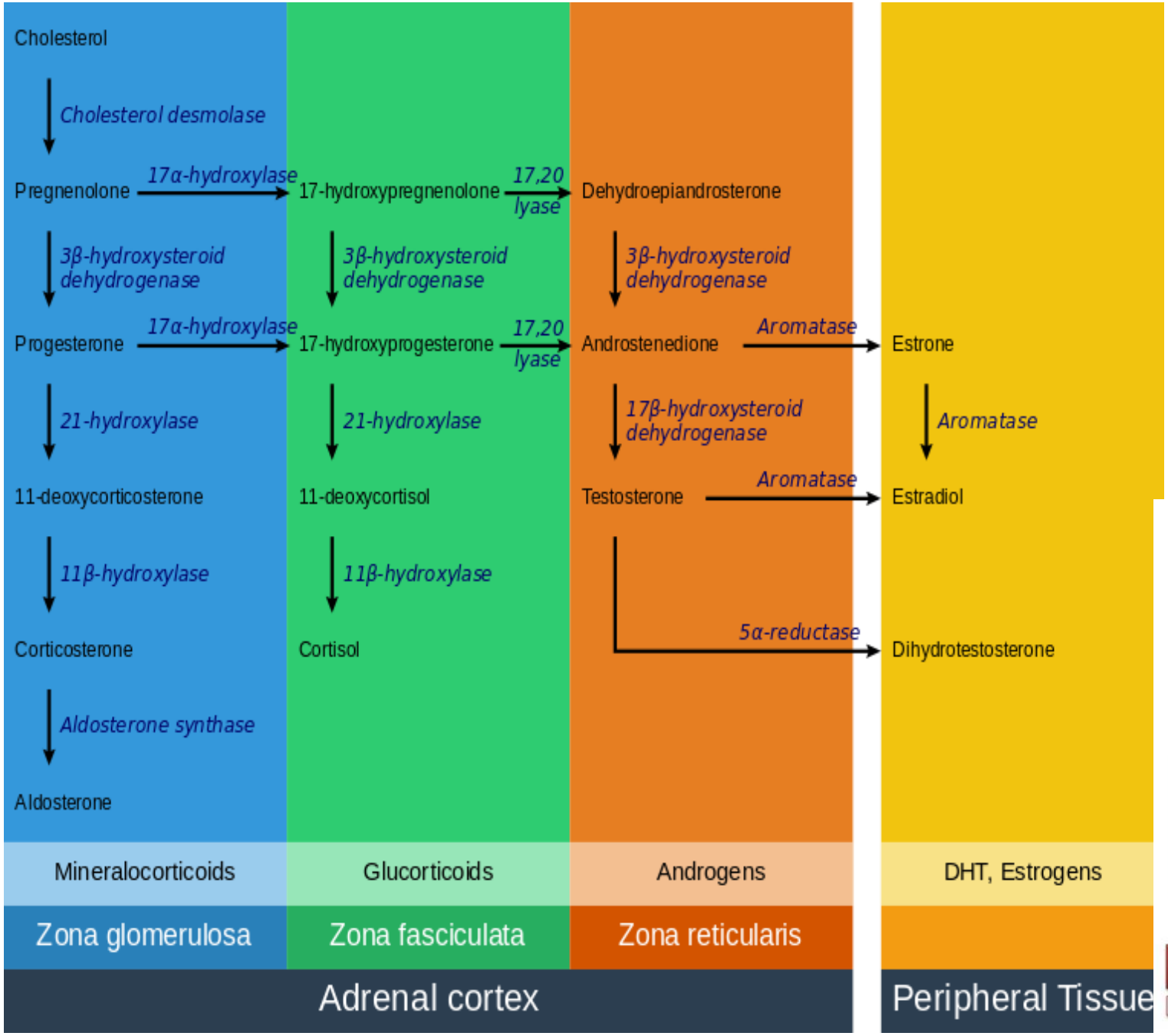
Finally, adherence to healthy dietary patterns is positively associated with sperm concentrations and **sperm motility.**

For Women: Dietary change will depend on conditions treated

- PCOS
  - Blood sugar mgt, fiber and Mg
- Anovulation d/t low BMI
  - Healthy weight gain
- Endometriosis
  - Fiber, EFA (control prostaglandins), green tea, AI diet
- Fibroids
  - Fish, EFAs fruit / veggies

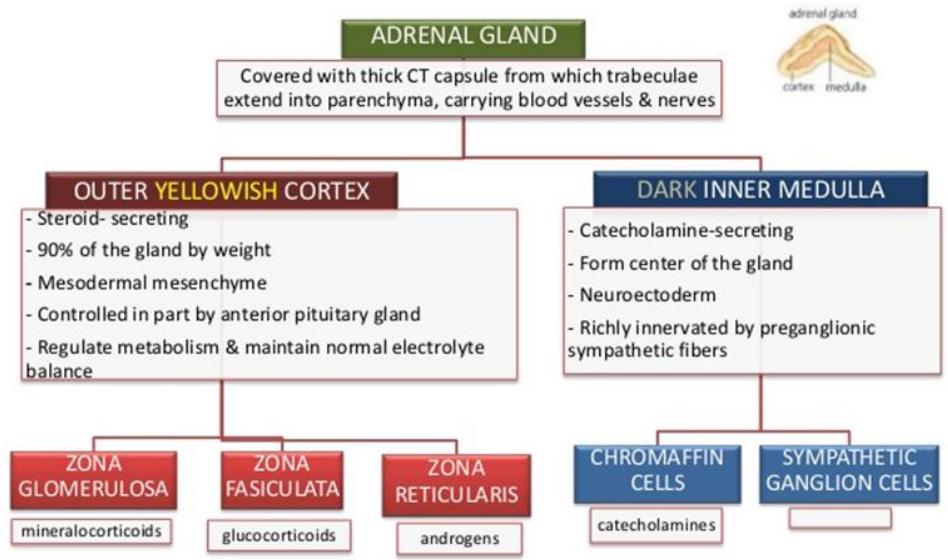
- For all caffeine and alcohol cut

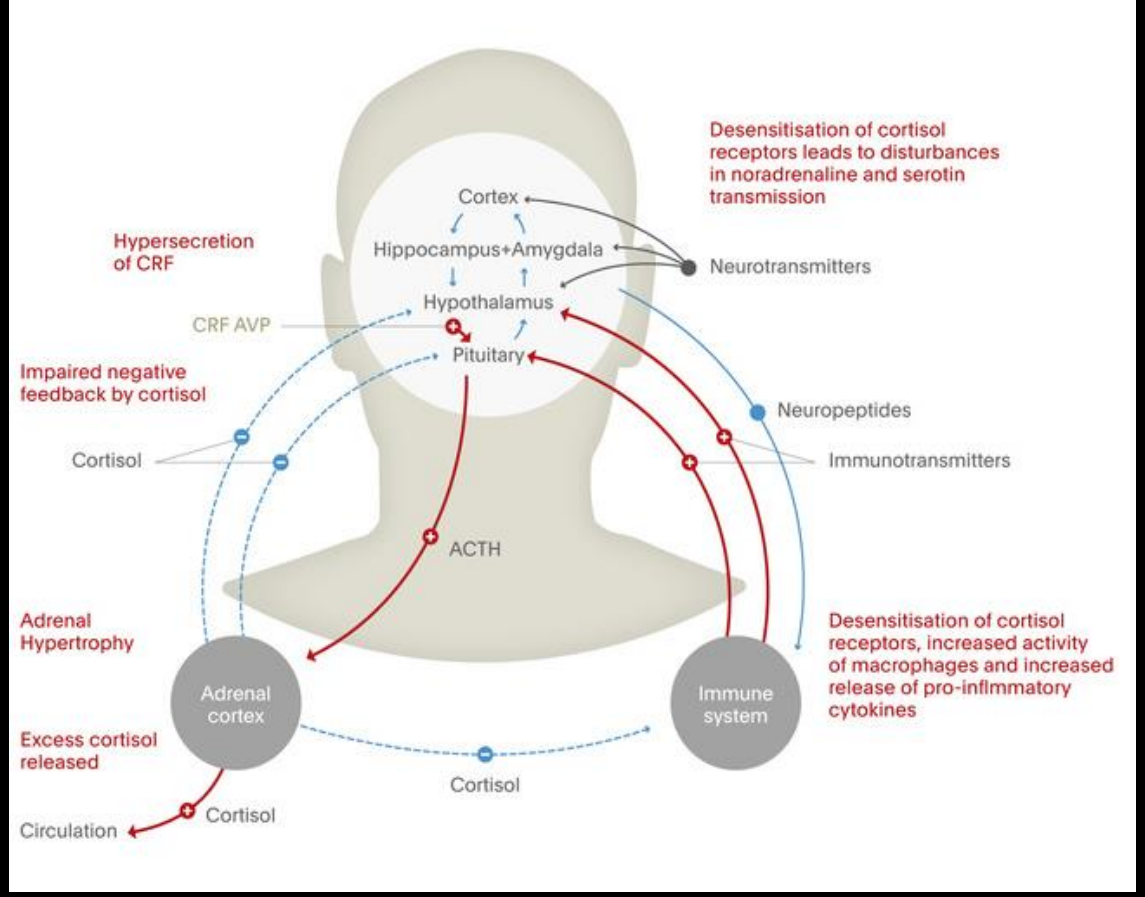
ADRENAL PROBLEMS

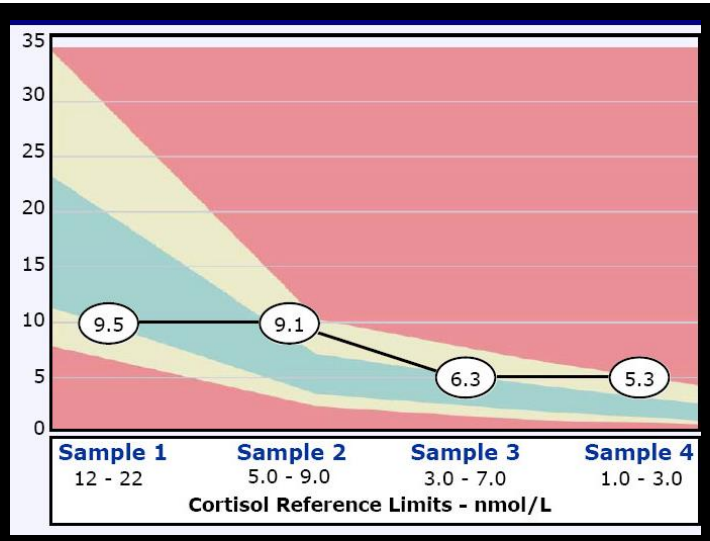


ADRENAL GLAND HORMONE PRODUCTION

OVERALL ADRENAL GLAND







"Adrenal Fatigue"

- Organ is not "tired"; feedback is maladaptive
- Don't get less production – get cortisol resistance
- Healthy individuals = distinct diurnal pattern
  - Peak cortisol in the morning, declines during the day, and lowest level around 2 or 3 AM
  - CAR: Levels slowly rise before waking in the morning and quickly peak 30-45 minutes post-awakening and then begin a gradual descent thereafter
- Maladaptive stress response = support HPA axis
- In TCM – KD yang and essence xu
  - With KD yang xu = yin xu = SP qi xu

Common Adrenal Dysregulation

- High AM cortisol levels
  - "Pre-clinical" biomarker of health and psychosocial status
  - Older age, smoking, increased BMI and waist circumference
- High PM cortisol levels
  - Marked sleep disturbances (difficulty falling / staying asleep, easy wakening, and AM fatigue, low positive affect (men only) and depressive symptoms
  - Older age common
- Low/flattened cortisol profile "exhaustion"
  - Chronic stress alters HPA axis = no recover
  - Low DHEA and low sex steroid hormones
  - Increased atherosclerosis, BMI, PTSD, athlete overtraining and increased risk of all-cause mortality
- Flat pattern/no diurnal variation
  - R/O Addison's Disease, pituitary pathologies, chemicals, drugs, infections, cancer, infarction or hemorrhage.
  - If negative = "overuse"

Adrenal Signs & Symptoms

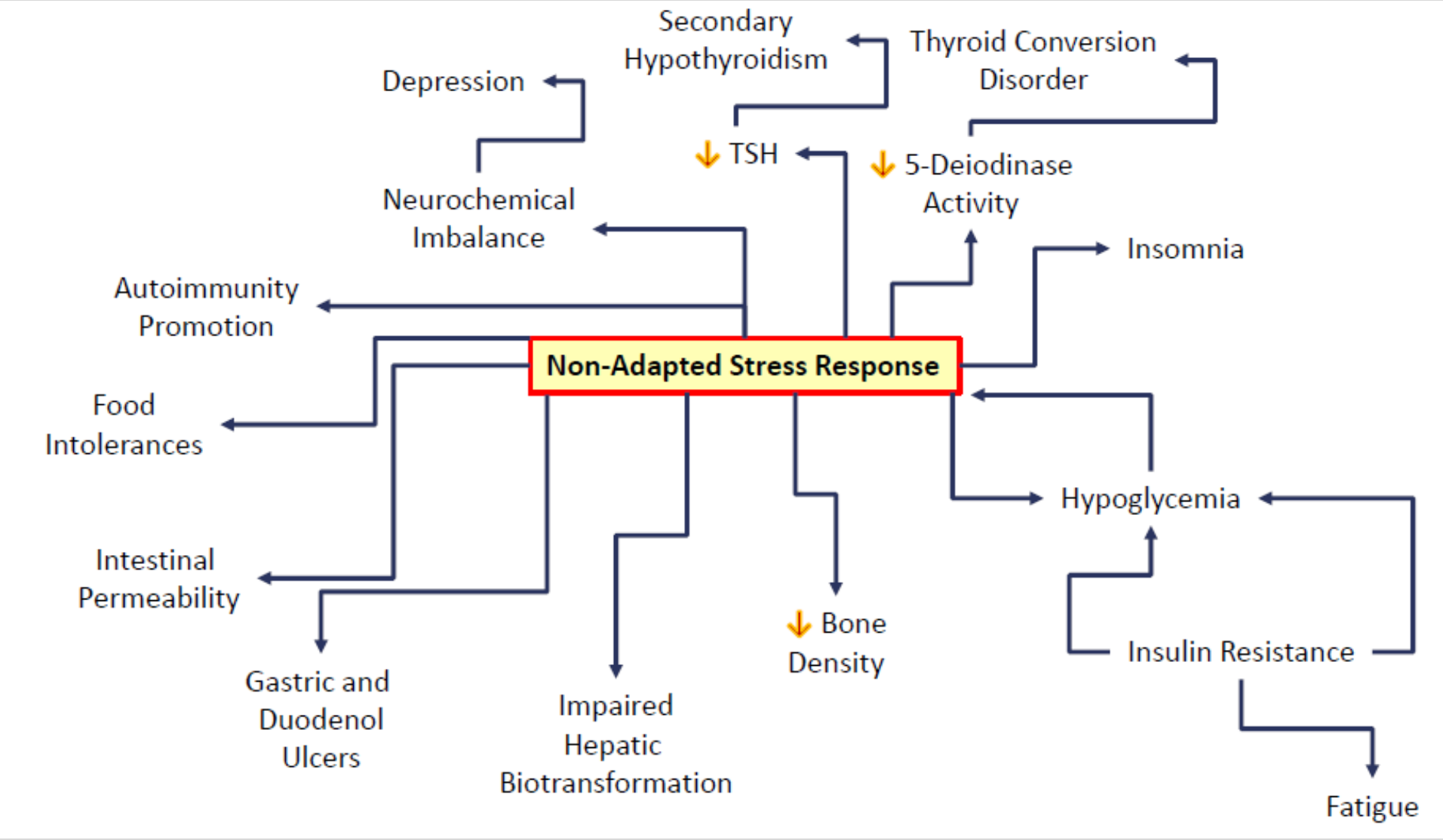
Low / Flattening

- Orthostatic hypotension (low aldosterone)
- Fatigue- especially AM, **mid-afternoon, or after a stressor**
- Apathy and anxiety / **inability to cope with stress**
- Memory loss/poor concentration
- **Crave salty foods**
- Increased sleep but poor quality: **more nocturnal awakenings**
- Hypoglycemia
- **Depression, worse in the evening, and particularly under stress**
- **Early onset perimenopause** or menopause
- Muscle pains and/or weakness

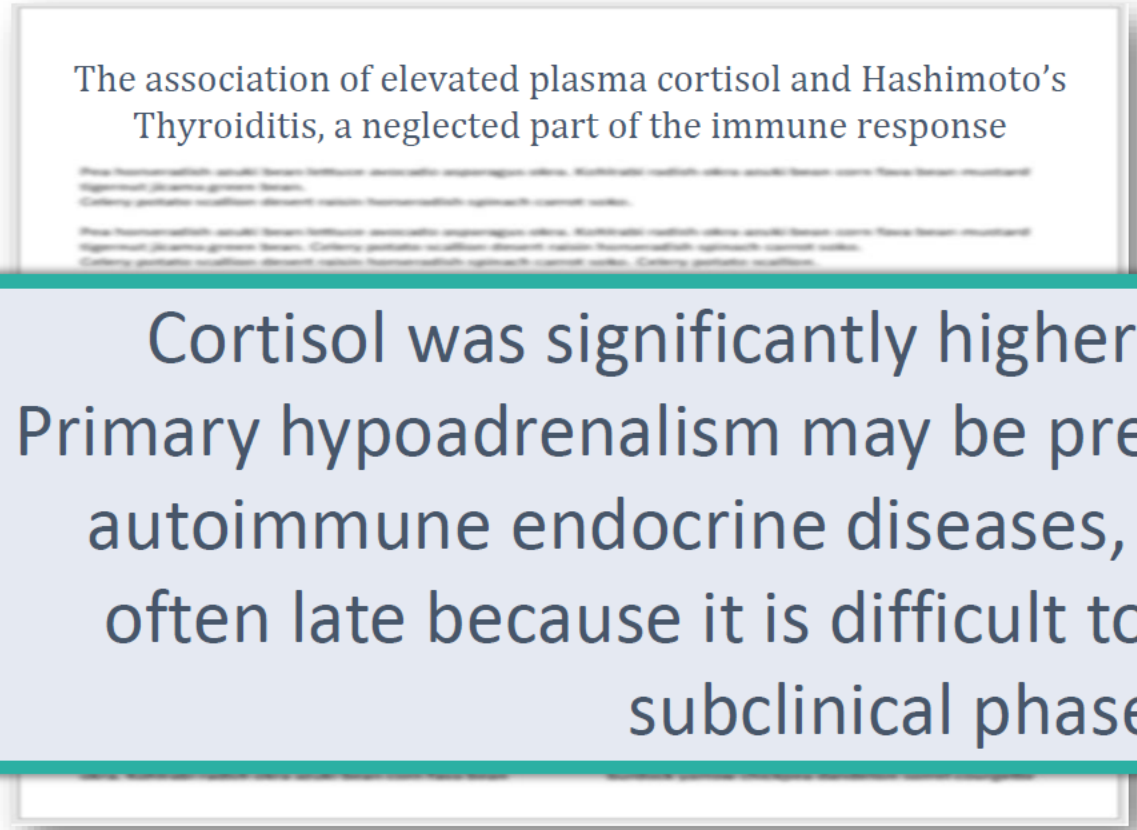
No Pattern / Flat

- Low blood pressure/orthostatic hypotension
- Chronic fatigue
- Loss of appetite and weight loss
- Abdominal pain, N/V, diarrhea
- Irritability and depression
- Craving salty foods
- Hypoglycemia
- *Headache*
- *Sweating*
- **Irregular or absent menstrual periods**
- ***In women, loss of libido***
- Muscle weakness

Physiology is Non-Adapted Stress Response

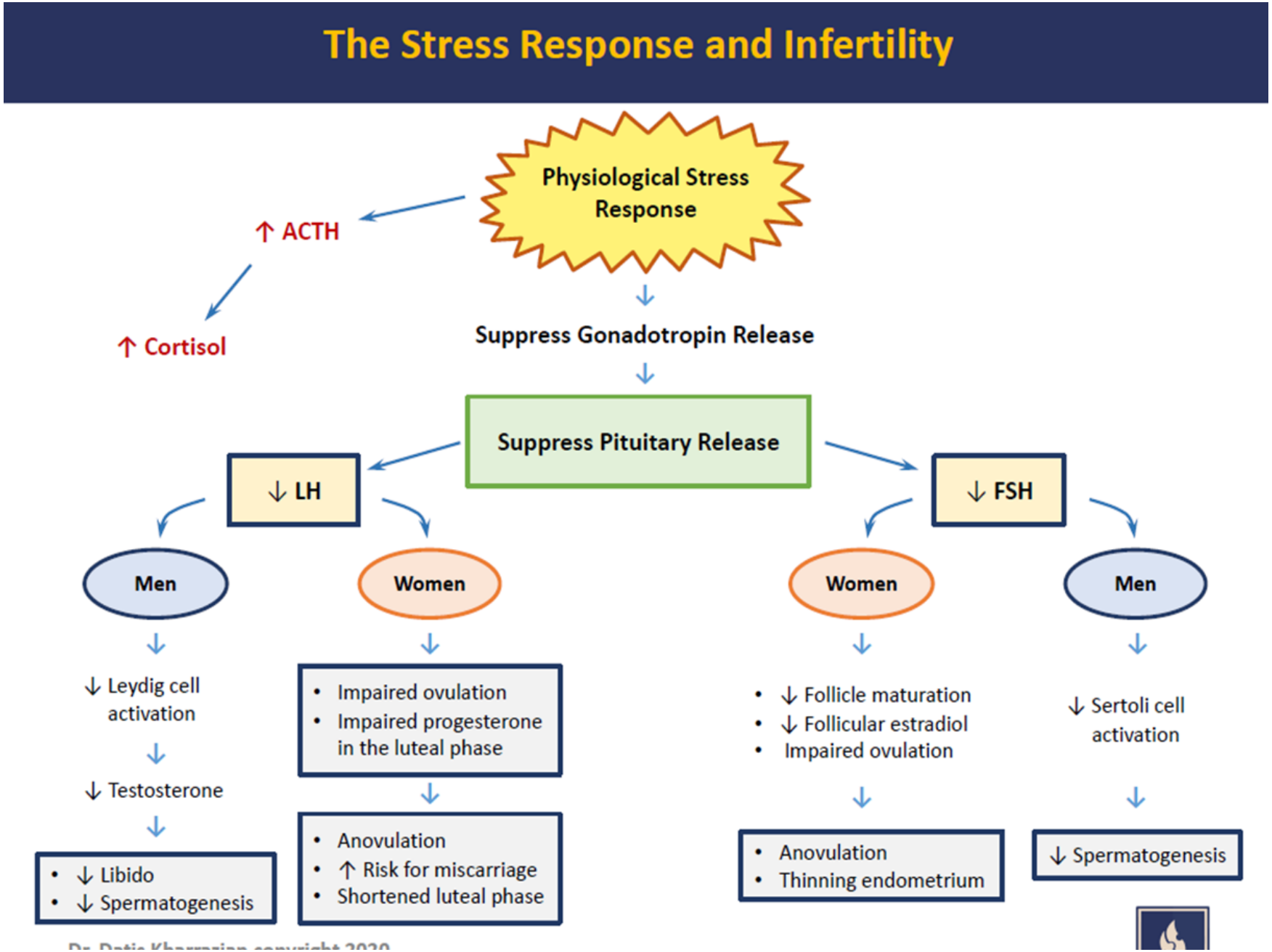


Hashimoto's Thyroiditis Associated With Elevated AM Cortisol


The association of elevated plasma cortisol and Hashimoto's Thyroiditis, a neglected part of the immune response

Cortisol was significantly higher in the HT group. Primary hypoadrenalism may be present in patients with autoimmune endocrine diseases, but its diagnosis is often late because it is difficult to demonstrate in a subclinical phase.

Agha-Hosseini F, Shirzad N, Moosavi MS. The association of elevated plasma cortisol and Hashimoto's Thyroiditis, a neglected part of immune response. Acta Clin Belg. 2016 Apr;71(2):81-5. doi: 10.1080/17843286.2015.1116152.



Stress Response & Fertility

Egg health reflects the state of the body

- Poor nourishment
- Hormonal cues interrupted
  - Follicles become resistant to FSH
- Compromised blood flow
  - Increased vascular endothelial cells in the follicular fluid (same found in damaged heart muscle)
- Any sub-standard factors affect health of the egg

USE LIFESTYLE + ADAPTOGENS

FOR PROPER PHASE OF ADRENAL DYSFUNCTION

Rating of Adaptogens Clinically

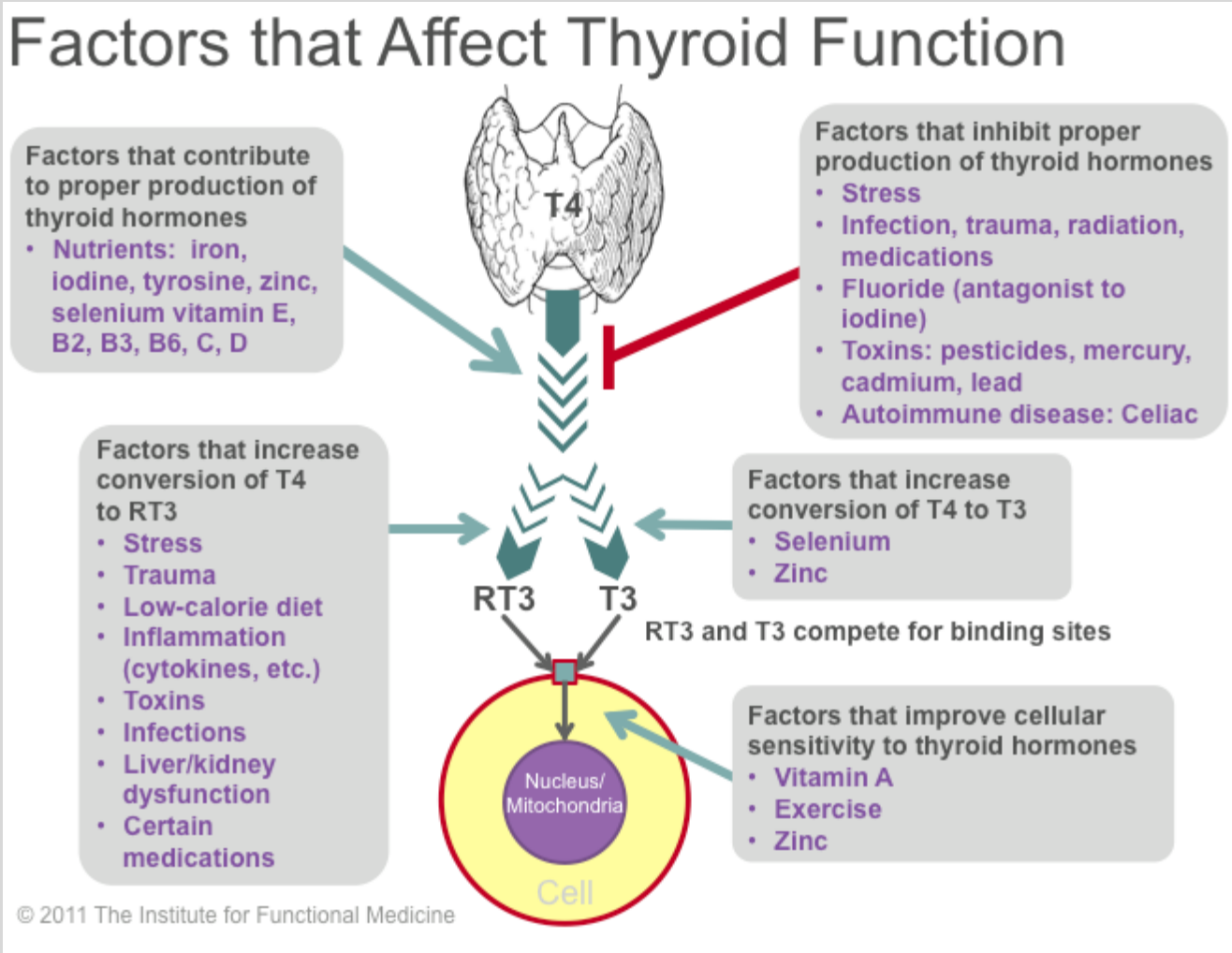
Panax ginseng extract Ashwagandha extract Holy basil extract Rhodiola rosea extract Siberian ginseng extract	★★★★★
Phosphatidylserine	★★★★
Boerhaavia diffusa Plant sterols	★★★
B-vitamins Magnesium Vitamin C	★★

**** Adaptogens have a synergistic amplifying effect when taken in combination ****

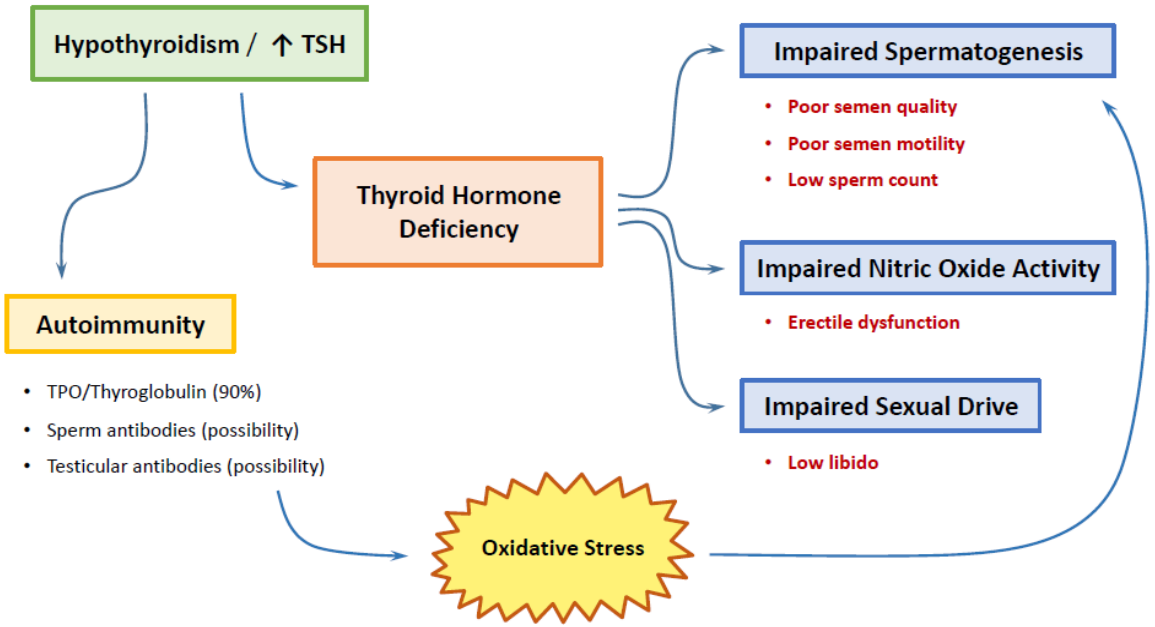
THYROID

Thyroid

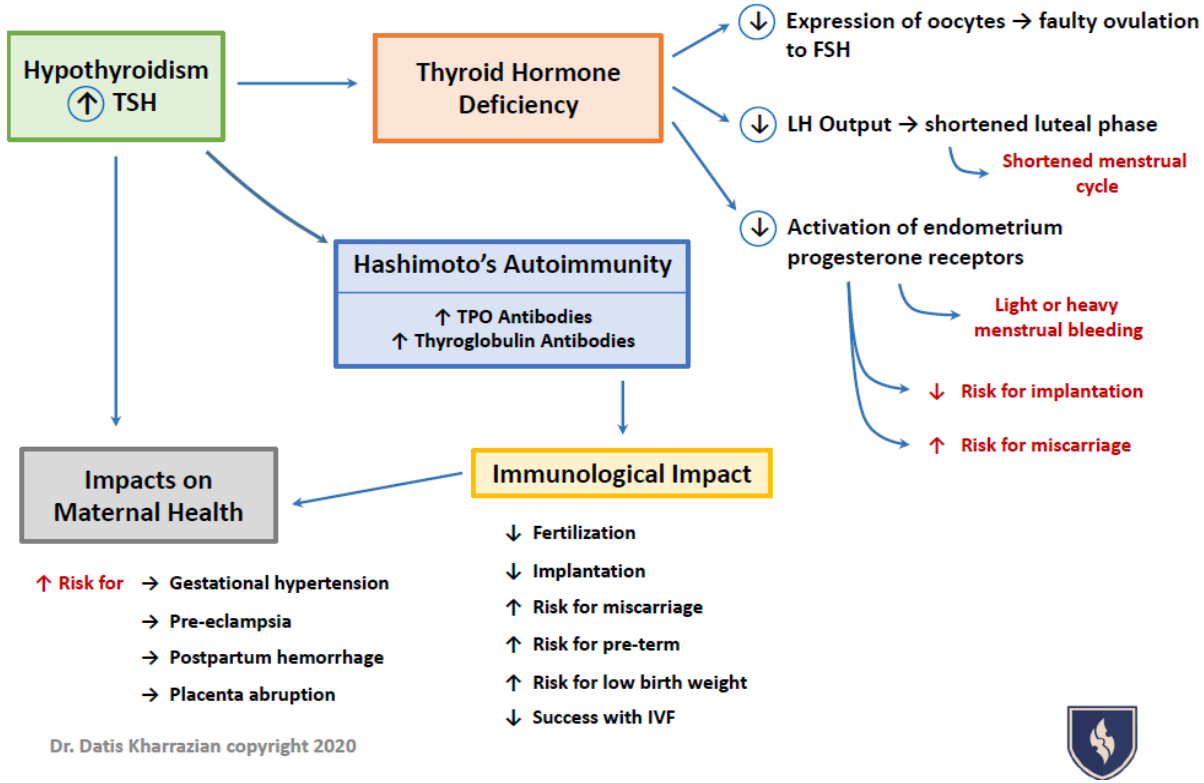
- TSH: baseline for thyroid problems
  - TRH (thyrotropin releasing hormone) from hypothalamus triggers TSH release from anterior pituitary causing thyroid to make T3 and T4 - possible
  - Miscarriages, PCOS, premature births, and intrauterine growth retardation; hypothyroidism can increase prolactin leading to anovulation
  - Optimal level of TSH 1.0-1.8 mIu/ml for fertility; fT4 1.0-1.5 ng/dl; fT3 3.0-4.0 pg/ml; - Abs
  - Remember to also check T3 uptake and rT3 (markers for cell health, GI health and detox)



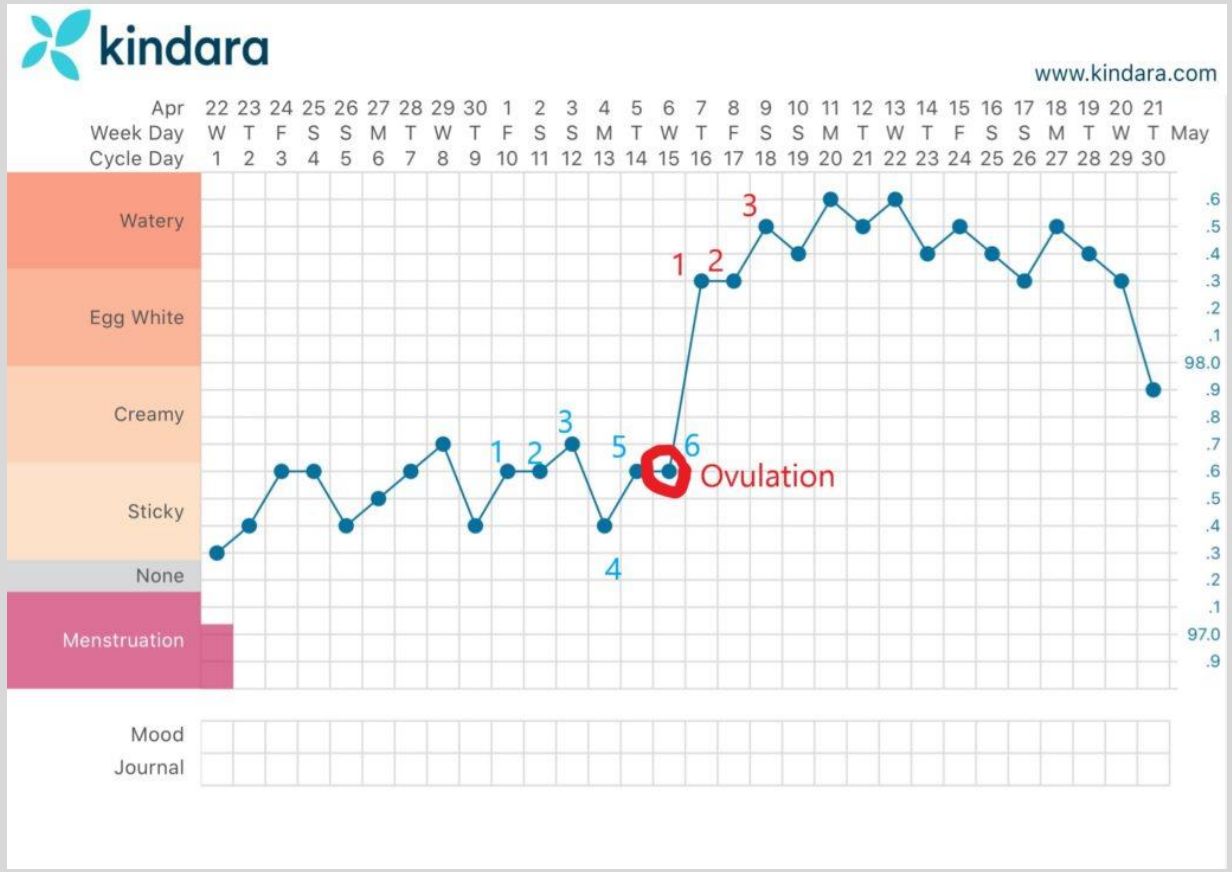
The Impact of Hypothyroidism on Male Fertility

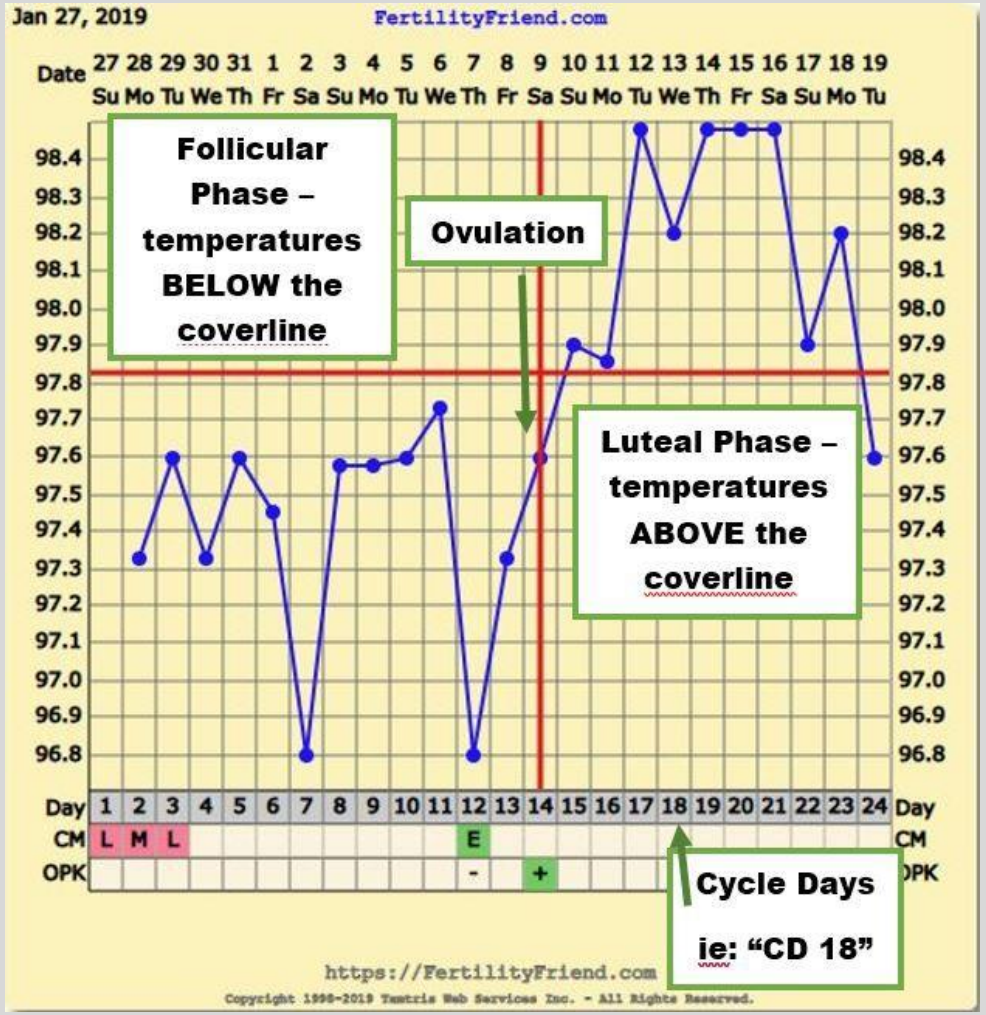


The Physiological Web of Hypothyroidism and Female Infertility



BBT Variations with Stress/ Thyroid





Follicular Phase Chart Variations

Normal temp is 97.16-97.70 F (36.2-36.5C) – if consistently lower =hypothyroid / Hashi's

BBT Pattern	Diagnosis	Treatment
Low follicular phase	Generalized Yang xu (SP/KD)	Warm Yang through the cycle
Long follicular phase	KD Jing, Yin or Blood Xu (qi stag or shen disordered)	Nourish blood, reinforce KD Jing and Yin after menses
Short follicular phase	Yin Xu heat (hyperthyroid)	Clear heat, nourish yin from early in cycle (creates acidic mucus / antisperm abs)
High follicular phase	Yin Xu heat (hyperthyroid; illness or alcohol)	Clear heat, nourish yin from early in cycle (creates acidic mucus / antisperm abs)
High follicular phase initially	Obstruction of Yang conversion to Yin	Promote KD Yang to Yin conversion, regulate menses
Unstable follicular phase	LV or HT Fire	Clear fire of HT or LV and calm the mind

Luteal Phase Chart Variations

General temperature variations should not be more than 0.2F (thermal shift is over 0.6 F); should remain elevated 12-14 days

BBT Pattern	Diagnosis	Treatment
Short luteal phase	KD Yang xu arising from KD Yin xu	Strong supplement KD Yin in follicular phase to create luteal phase Yang
Slight short luteal phase	KD Yang xu	Boost KD Yang in luteal phase
Low luteal phase	KD Yang xu	Nourish KD Yin and blood, boost KD Yang in luteal phase
Saw tooth luteal phase (unstable)	LV/HT Qi unstable, KD Yang xu (poss. LV Fire)	Regulate LV/HT Qi, calm LV fire, boost KD Yang by nourishing blood; stress reduction!
Saddle luteal phase (unstable)	KD Yang xu, LV/HT Qi unstable	Reinforce KD Yang, regulate LV/HT Qi; Western med indicates rise in estrogen or drop in progesterone
Slow rise luteal phase (>2 days)	KD Yang xu and SP Qi / Yang xu or Yin xu	Reinforce KD Yin after period, invigorate SP Qi early mid cycle to boost luteal phase KD Yang (check not LV qi stag)
Early decline luteal phase	KD Yang xu and SP Qi xu	Invigorate SP Qi and boost KD Yang in luteal phase
Long luteal phase	Pregnancy	Support KD Yang if necessary

TCM Menstruation: 4 Phases

Menstrual Phase: (day 1-4) Blood movement dependent on free flow of Liver qi and blood

- Fall in the estrogen and progesterone levels
- Necrosis of compact and spongy layers of endometrium

Follicular / Proliferative Phase: (day 4-12) Blood and yin are empty and CV & GV are depleted

- Follicular Phase-follicle grows and estrogen rises under influence of FSH

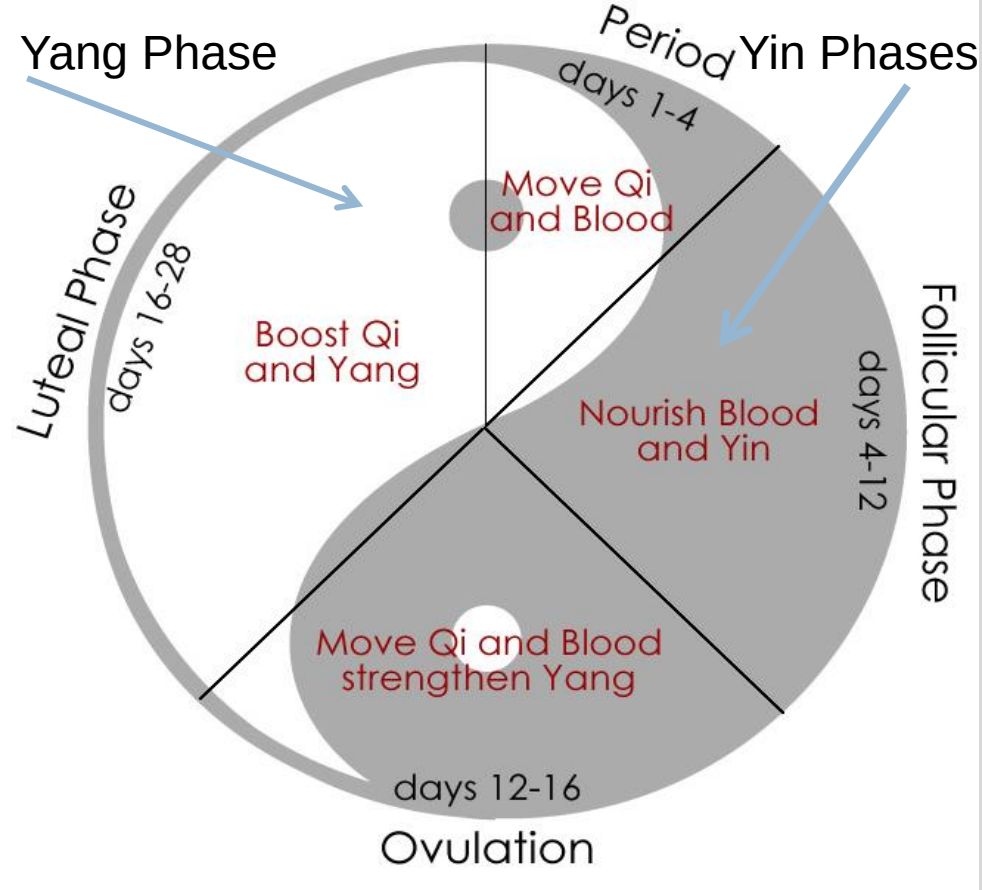
Mid-Cycle / Ovulation Phase: (day 12-16) Blood and yin fill up CV & GV

- Ovulatory Phase-ovum released and corpus luteum develops under LH

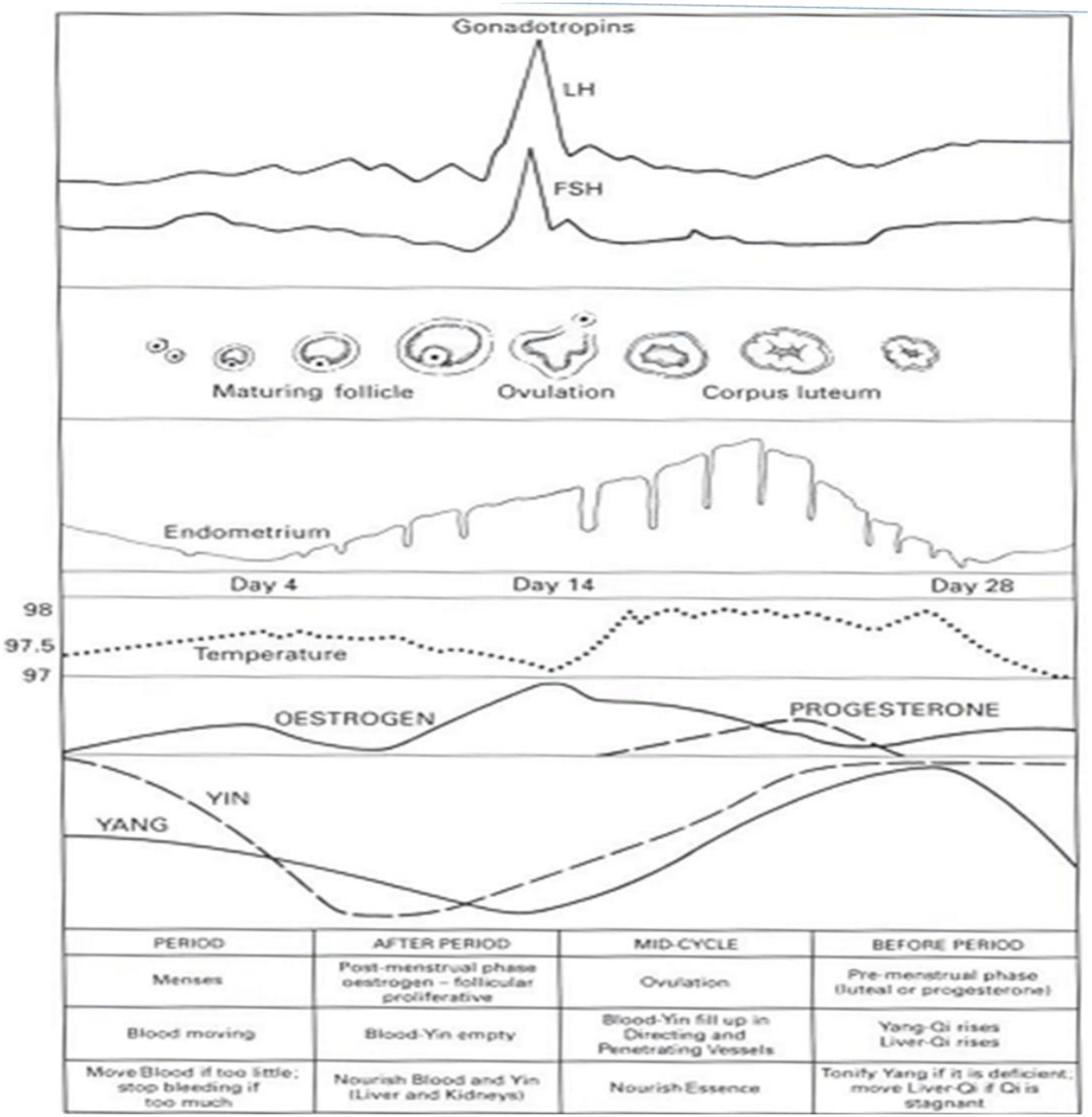
Luteal Phase: (day 16-28) Yang qi rises and Liver qi moves in to prep for the period. Liver qi movement is essential to move the Liver blood during the period

- Luteal Phase-corpus luteum grows and secretes progesterone

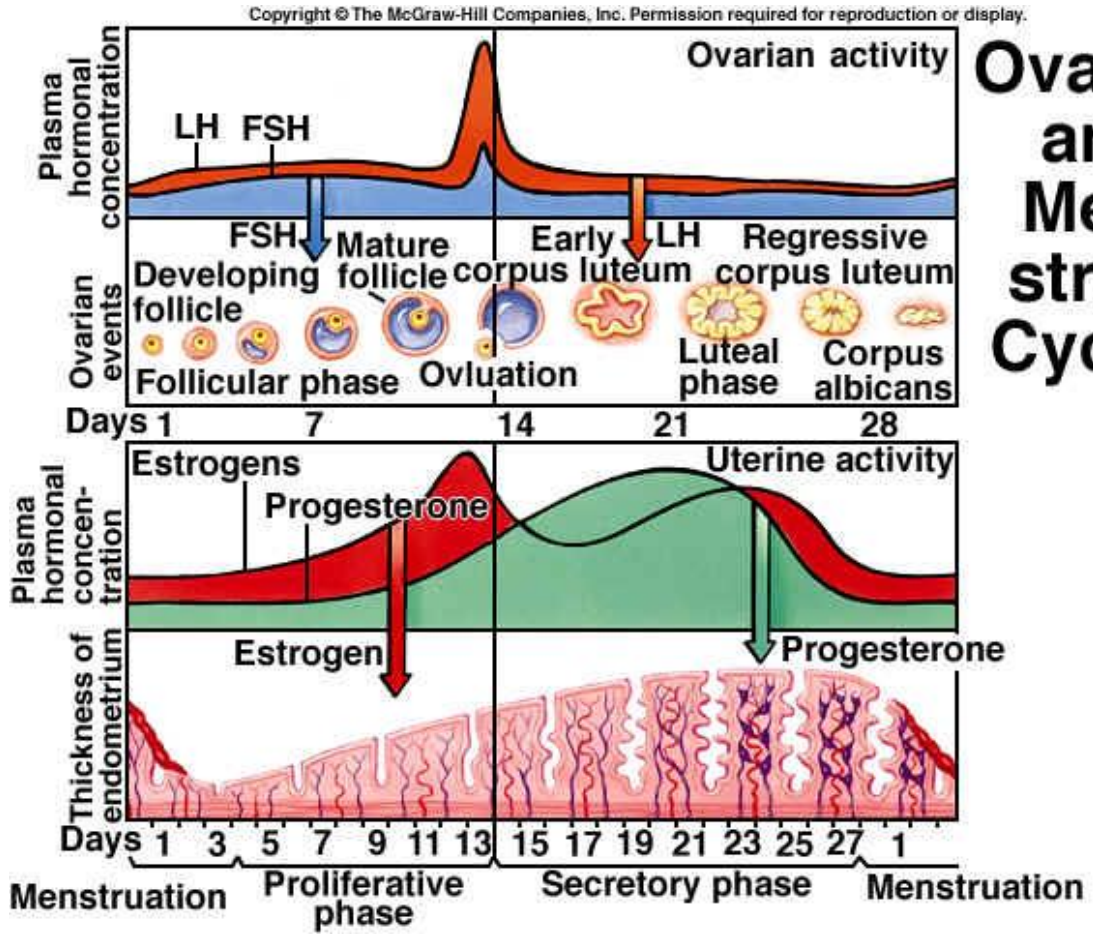
TCM Menstruation: 4 Phases



- Menstrual Phase: Regulate menses
  - Scanty period-move blood/ enrich the blood and essence
  - Heavy bleeding-stop bleeding
- Follicular Phase: Nourish blood & yin
  - Liver, Kidneys and Spleen
- Ovulatory Phase: Promote ovulation
  - Tonify Kidneys nourish the Essence and consolidate CV, GV and Chong Mai
- Luteal Phase
  - Tonify Yang if deficient
  - Move Liver qi if stagnant

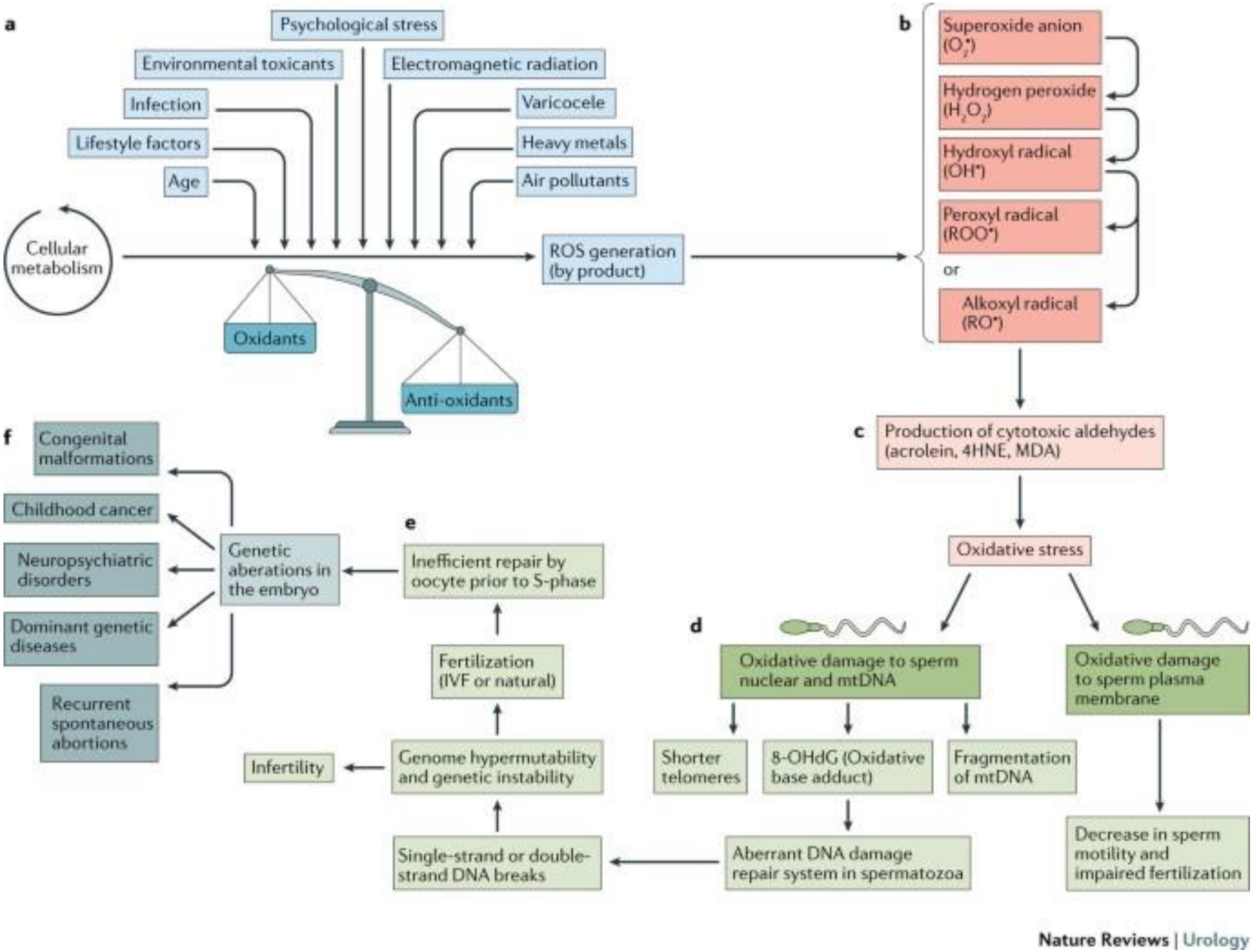


PERIOD	AFTER PERIOD	MID-CYCLE	BEFORE PERIOD
Menses	Post-menstrual phase oestrogen – follicular proliferative	Ovulation	Pre-menstrual phase (luteal or progesterone)
Blood moving	Blood-Yin empty	Blood-Yin fill up in Directing and Penetrating Vessels	Yang-Qi rises Liver-Qi rises
Move Blood if too little; stop bleeding if too much	Nourish Blood and Yin (Liver and Kidneys)	Nourish Essence	Tonify Yang if it is deficient, move Liver-Qi if Qi is stagnant



Ovarian and Men-strual Cycles

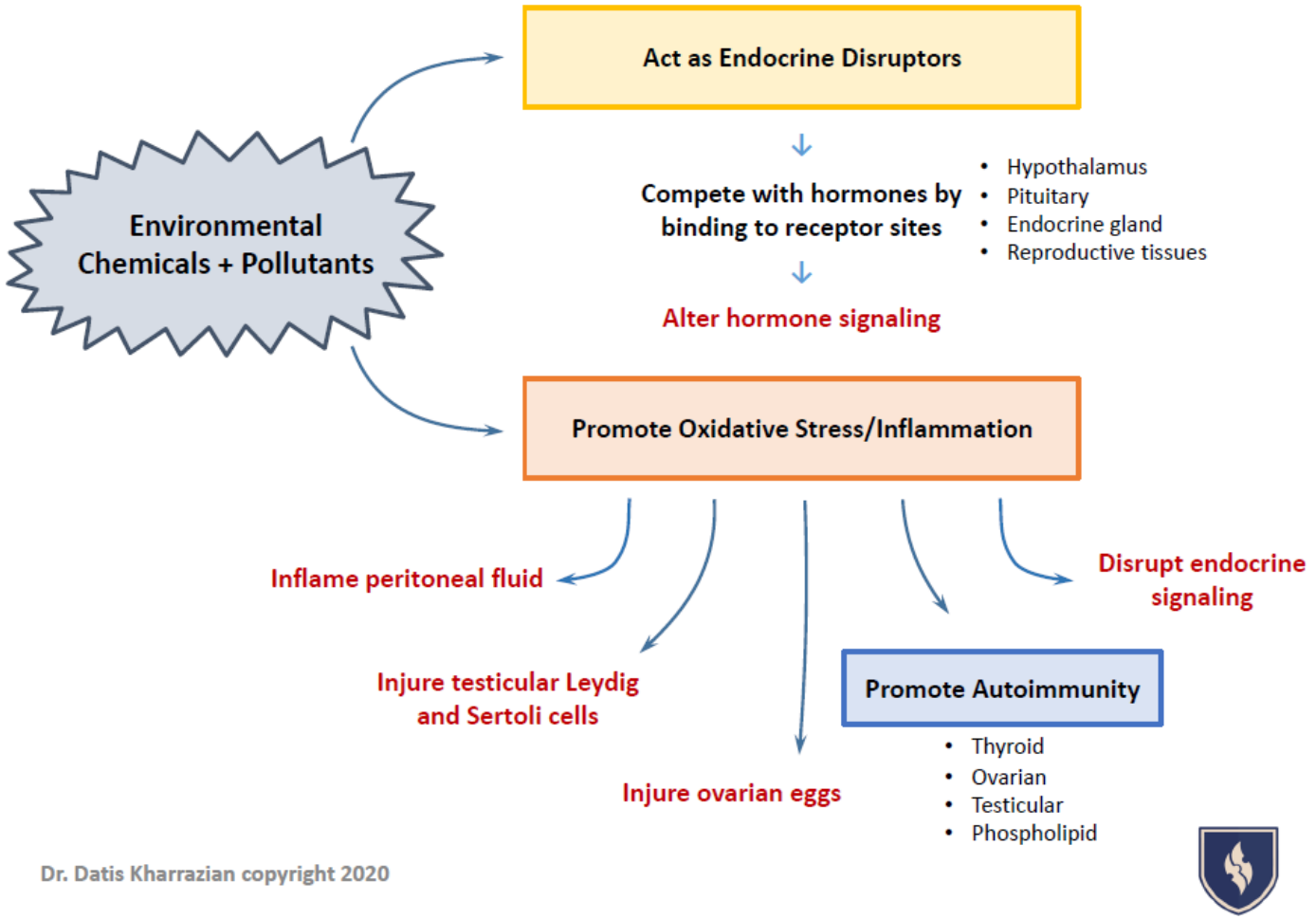
OXIDATIVE STRESS AND POLLUTION

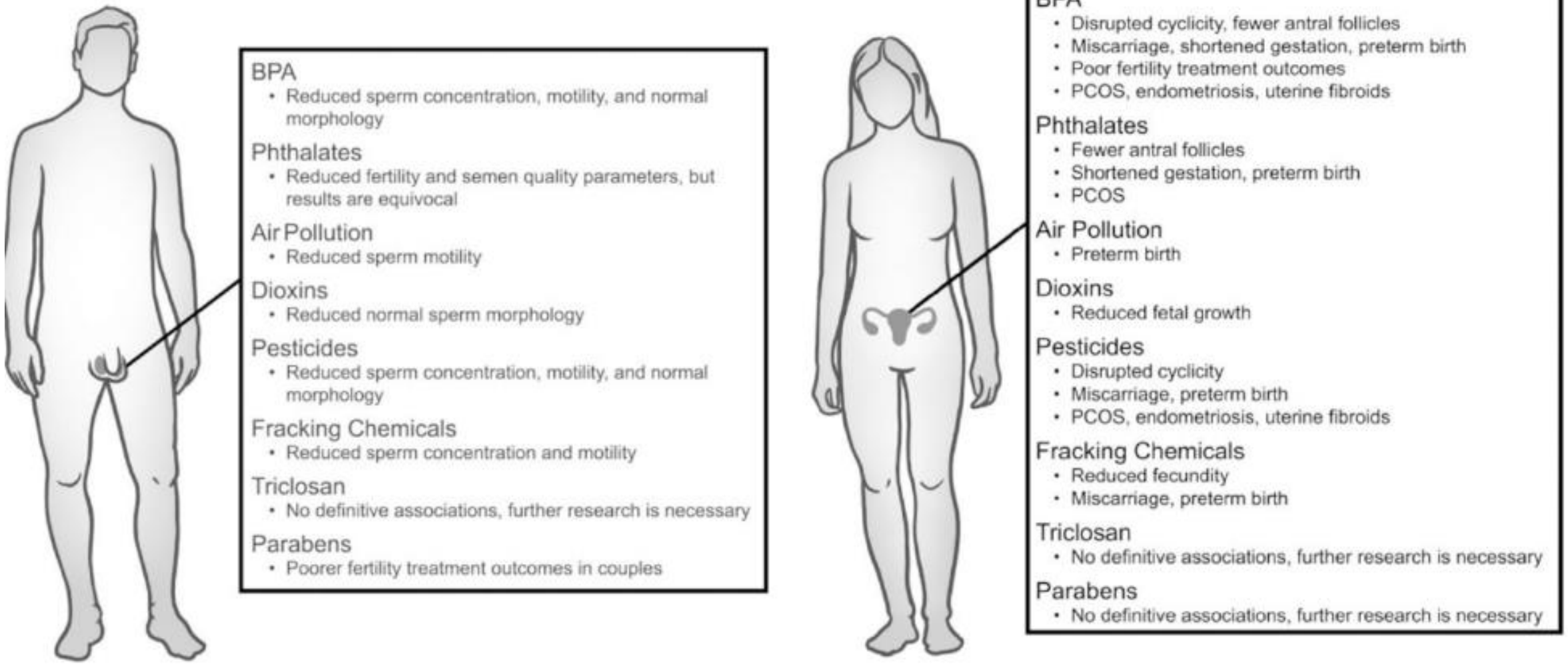


Oxidative Stress & Male Infertility

- Oxidative stress causes damage to both mitochondrial and nuclear DNA, the sperm epigenome, resulting in infertility, recurrent pregnancy loss, poor pregnancy outcomes and an increased disease burden in the offspring
- Sperm are most vulnerable to oxidative stress and oxidative DNA damage (ODD) as these cells have limited antioxidant defense mechanisms and a limited capacity for detection and repair of DNA damage

The Role of Environmental Chemicals in Infertility





Environmental Contaminants Affecting Fertility and Somatic Health *Semin Reprod Med.* 2017 May ; 35(3): 241–249. doi:10.1055/s-0037-1603569.

Table 1 – The most widely studied bioactive nutrients for optimizing mitochondrial function.

	Strategy	Possible effects on fertility
Abdulhasan et al., 2017; Ben-Meir et al., 2015; Bentov et al., 2014; Boots et al., 2016	Coenzyme Q10	Lowers the aneuploidy rate[a] Delays ovarian reserve depletion Restores oocyte mitochondrial gene expression Improves mitochondrial activity and distribution Lowers the ROS level in oocytes Increases mitochondrial mass and polarization Increases ATP levels in oocytes
Liu et al., 2013; Sugiyama et al., 2015; Takeo et al., 2014	Resveratrol	Increases the follicle pool and embryo development Improves the number and quality of oocytes Improves fertilization and developmental ability Increases ATP in oocytes Increases the mtDNA level and membrane potential
Talebi et al., 2012; Zhang et al., 2013	Alpha-lipoic acid	Improves in-vitro follicle development Decreases follicular ROS production Improves oocyte maturation rates Enhances the antioxidant ability of oocytes

[a] This was the only clinical trial in humans. It was discontinued before recruiting enough patients to achieve statistical power due to proof of negative effects on embryogenesis associated with polar body biopsy, such as higher rates of embryonic cleavage arrest and fragmentation. The remaining evidence listed in the table was obtained in animal-based models.

Role of Mitochondrial Activity in Female Fertility and Assisted Reproductive Technologies: Overview and Current Insights

- Studied in Spain and Brazil; published 2018
- Embryo selection is critical for ART success
  - Predicated on morphological and morphometric embryonic scoring system however is inaccurate in predicting embryo quality (40% with normal morphology have chromosomal disorder
- Senescence stands out among the predisposing factors for embryonic metabolic stress
- Calorie restriction by 40% sees occurrence of germline cell division errors and mitochondrial damage significantly decreases
  - Diet composed of a protein >25% with carbohydrate < 40% is related to better blastocyst development and pregnancy rates especially with PCOS

Radiofrequency Electromagnetic Fields (RF-EMF) Effect on Brain and Testicular Organ

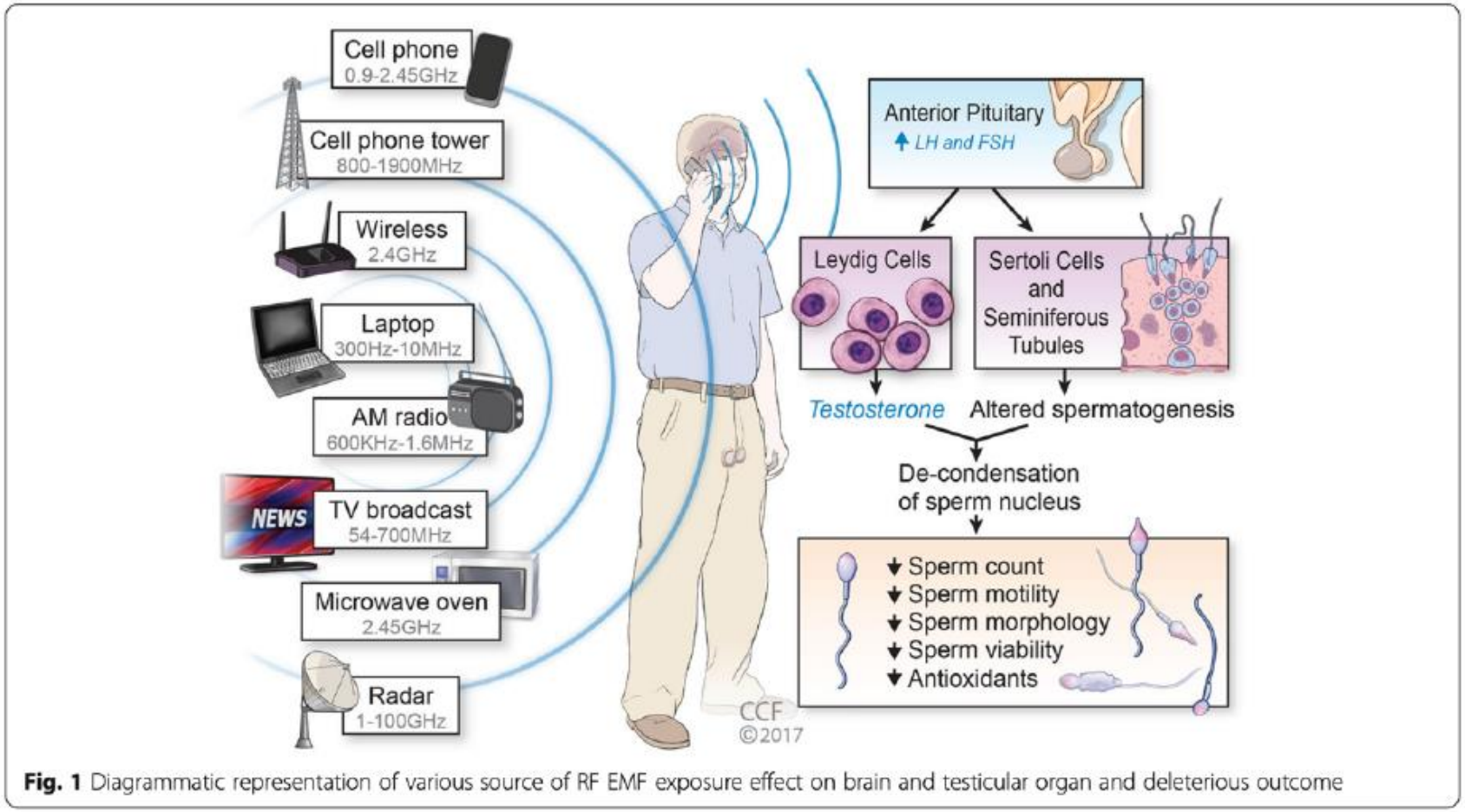
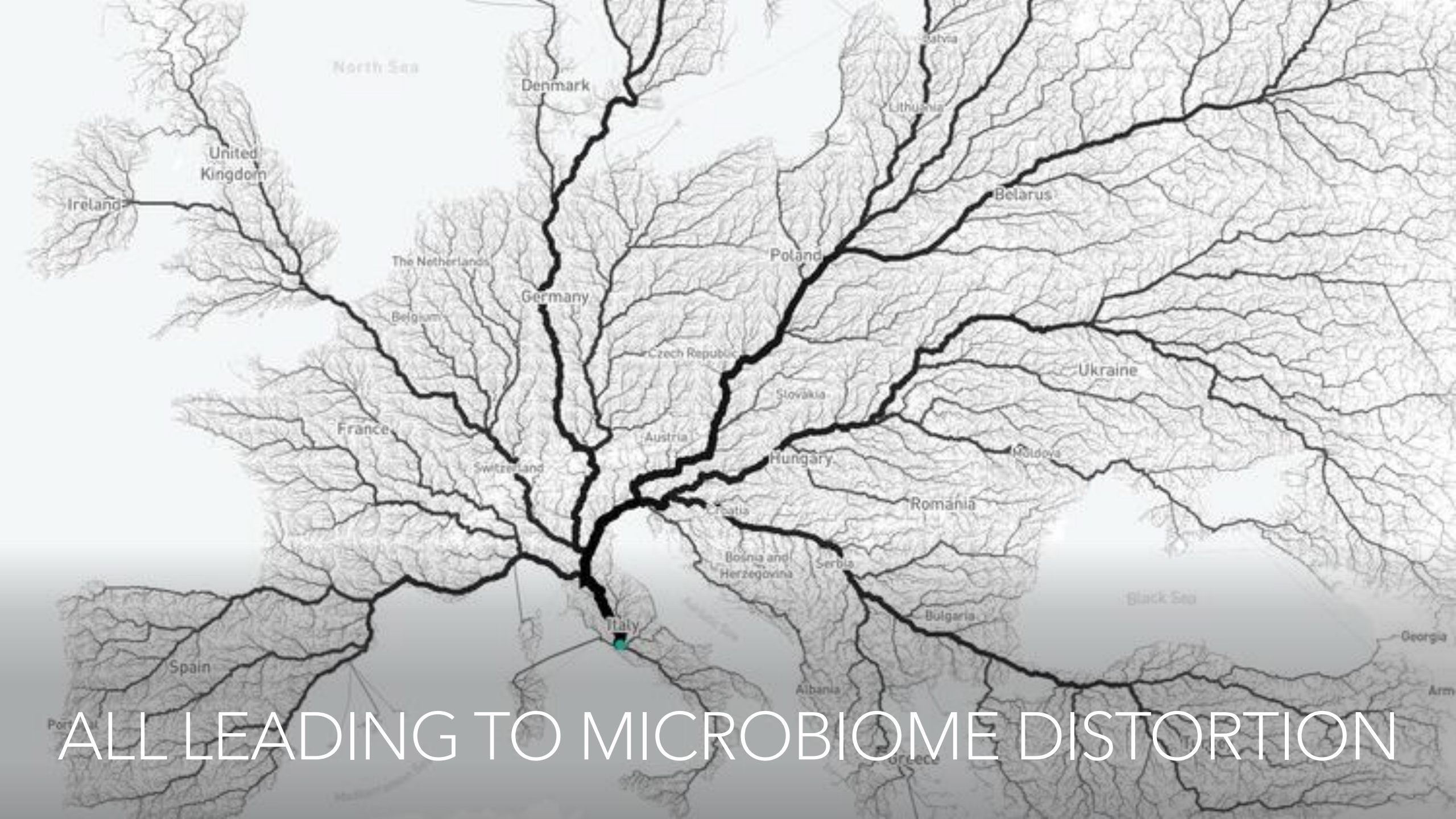


Fig. 1 Diagrammatic representation of various source of RF EMF exposure effect on brain and testicular organ and deleterious outcome

Radiations and male fertility

Kesari *et al. Reproductive Biology and Endocrinology* (2018) 16:118

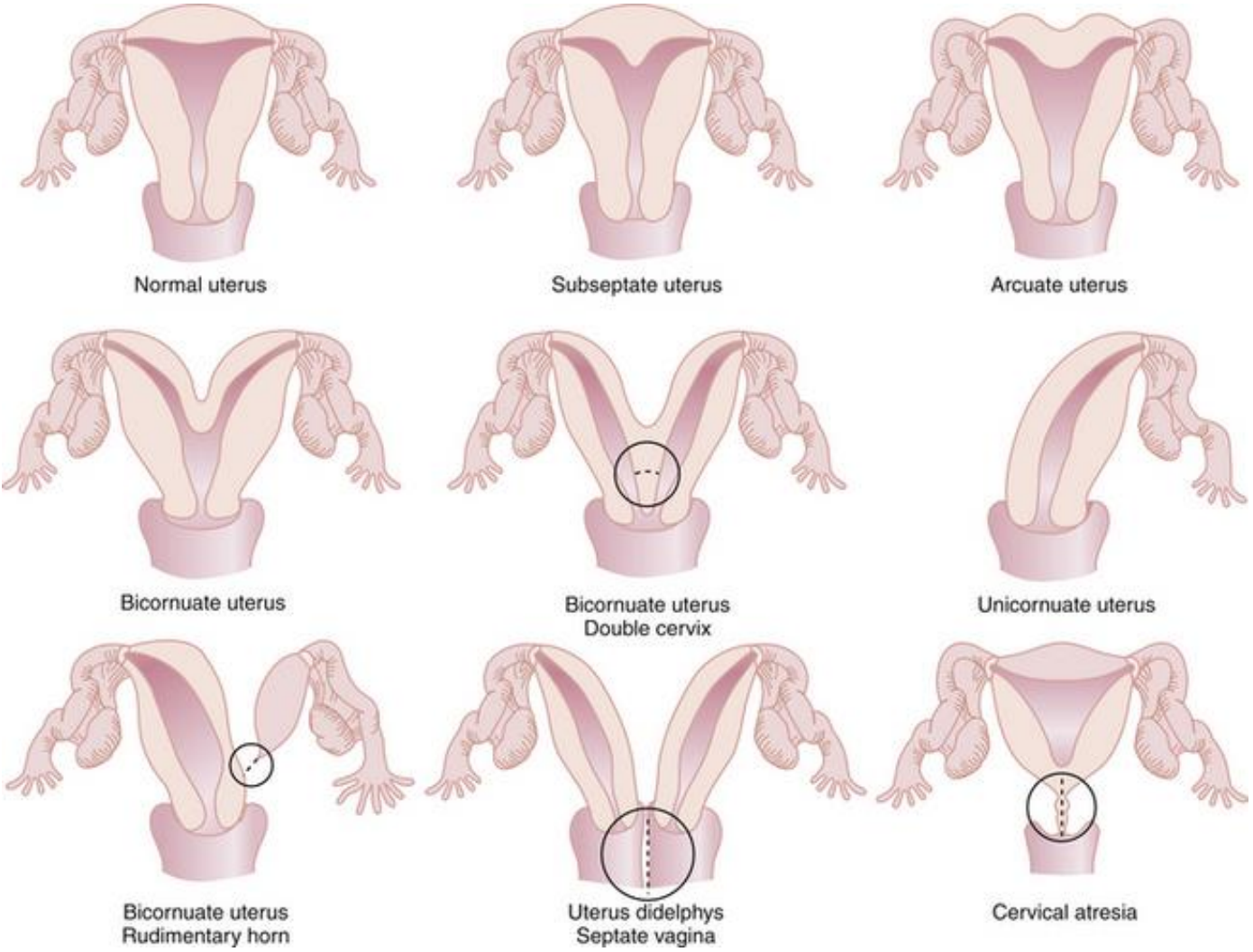


ALL LEADING TO MICROBIOME DISTORTION

Testing Specific for Women

Common Fertility Problems: Female

- Ovulation problems: anovulation or oligoovulation
  - Primary: issue with ovary directly
  - Secondary: lack of hormones from pituitary or hypothalamus
    - Affected by stress, weight change, excess prolactin, thyroid/adrenal gland issues
- Luteal phase defect:
  - Decreased progesterone via corpus luteum or uterine lining defect
- Cervical Factor
  - Thickened cervical mucus
  - Cervical stenosis
  - Sperm antibodies in female or male
- Tubal Factor:
  - History of PID or STI, ectopic pregnancy, endometriosis, Hydrosalpinx or abdominal infections / surgery = non patent tubes / inflammatory prostaglandins in fluid
- Uterine factor: endometrium must have adequate surface area to nourish and support normal embryo growth and development
  - Submucosal leiomyoma
  - Endometrial polyps
  - Intrauterine adhesions from infection or past surgeries
  - Chronic endometritis
  - Adenomyosis



Common Fertility Problems: Female

- Aside of growths & endo…
- Congenital uterus malformation
- Hostile cervical mucus
  - Antisperm antibodies
  - Poor estrogen stimulation makes thick mucus
  - pH alterations (dietary, bacteria)

Mechanisms that Reduce Ovarian Egg Quantity and Quality

Senescence →
- Aging = Quality and quantity decline with age

Endocrine Imbalances →
- Hypothyroidism
- ↓ FSH
- ↑ Androgens
- ↑ Prolactin

Oxidative Stress →
- Air pollution
- Environmental toxins
- Cigarette smoking
- Illicit drugs
- Radioactive exposure

Medications →
- Antineoplastic medications
- Autoimmune medications
- Steroids

Genetic Disorders →
- Chromosome abnormality

Endometriosis →
- Ovarian inflammation

Testing Specific For Men

Common Fertility Problems: Male

No sperm (azoospermia)

Poor sperm quantity (oligospermia) or quality

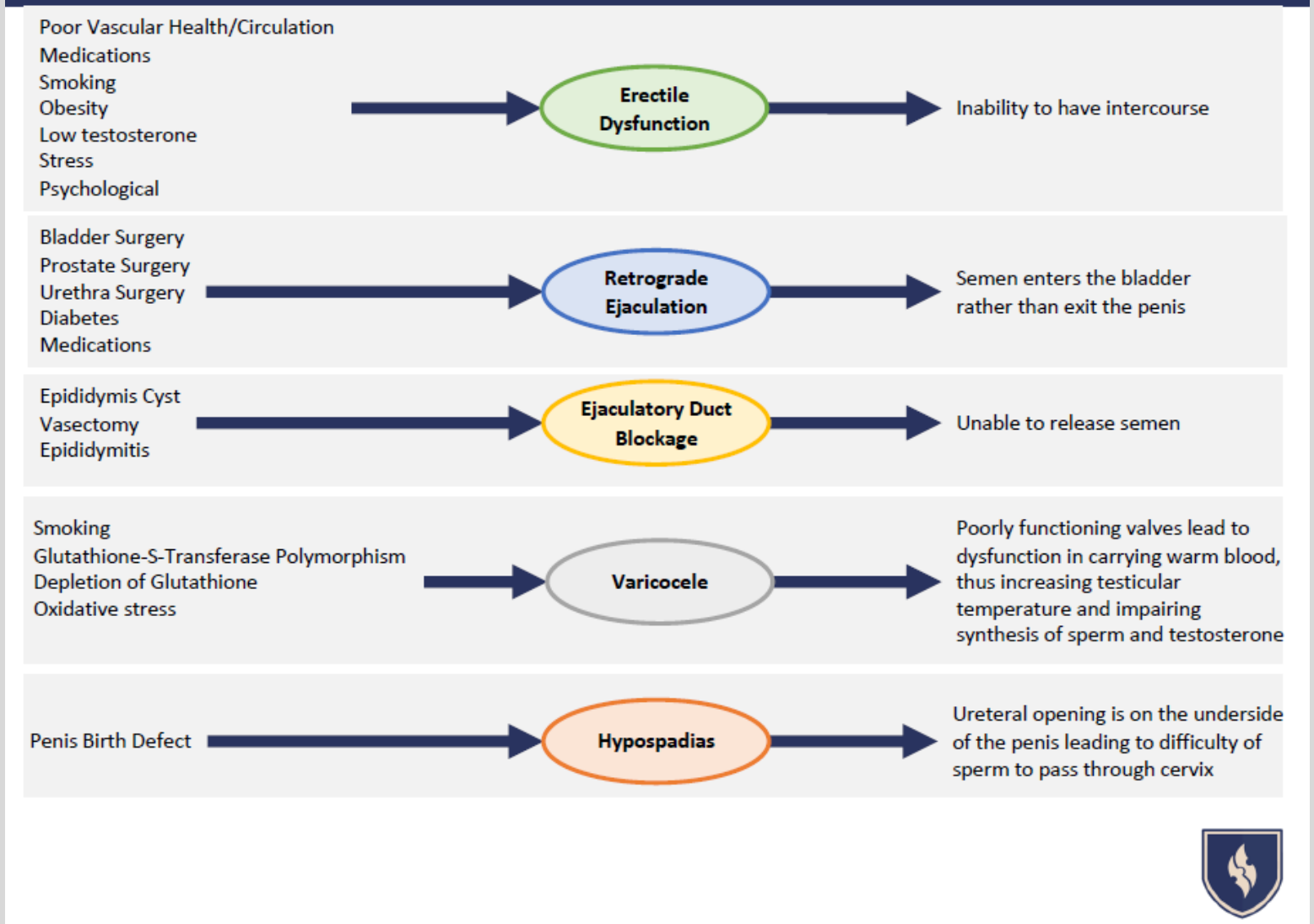
- Low motility (asthenozoospermia)
- High percentage of abnormal sperm (teratozoospermia)
- Antisperm antibodies
- Affected by medications / drugs: antidepressants, antihypertensive, anabolic steroids, marijuana and cocaine, heavy smoking and excess alcohol
- Varicoceles, frequent hot baths, tight underwear, cycling and saunas
- Nutritional deficiencies – micronutrient testing

Sperm dysfunction

- Normal semen analysis but the sperm lack or have a defective fertilizing capacity, resulting in complete failure of fertilization or poor fertilization of the eggs in IVF

Inability to ejaculate into the vagina

Anatomical Causes of Male Infertility




FERTILITY
TESTING

Common Testing

- Basic bloodwork and urinalysis
  - CBC with differential
  - Complete chemistry panel
  - Iron Panel: iron, TIBC, % saturation and ferritin
  - Blood sugar: HgA1C and fasting insulin
  - Adrenal: salivary cortisol is best look
  - Thyroid complete: TSH, TT4 and TT3, fT4 and fT3, T3 uptake, rT3, and Antibodies – TPO and anti-thyroglobulin
  - STI screen: Hep B and C, HIV, syphilis, rubella; some TB and vaginal bacteria / swabs for gonorrhea / chlamydia if indicated
  - ABO and Rh factor
  - UA

  - All specialty hormone labs…

Common Testing

- FSH: produced by anterior pituitary
  - Women: FSH controls menstrual cycle and production of eggs by the ovaries; levels flux in women (gauge of ovarian reserve)
  - Day 3 level: < 6mIu/ml excellent; 6-9mIu/ml: good; 10-13: diminished reserve; 13+: very hard to stimulate; menopause >40 mIU/ml
    - High estrogen can suppress day 3 FSH into normal (PCOS)
  - Men: FSH helps control the production of sperm; levels remains constant in men - 5 to 20 mIU/mL is normal level

- LH: produced by anterior pituitary (day 3) – optimal <7 mIU/ml; normal LH to FSH 1:1; LH > FSH is one indication of PCOS – Surge day >20mIu/ml
  - Women: regulates menstrual cycle and ovulation
  - Men: stimulates the production of testosterone, for spermatogenesis

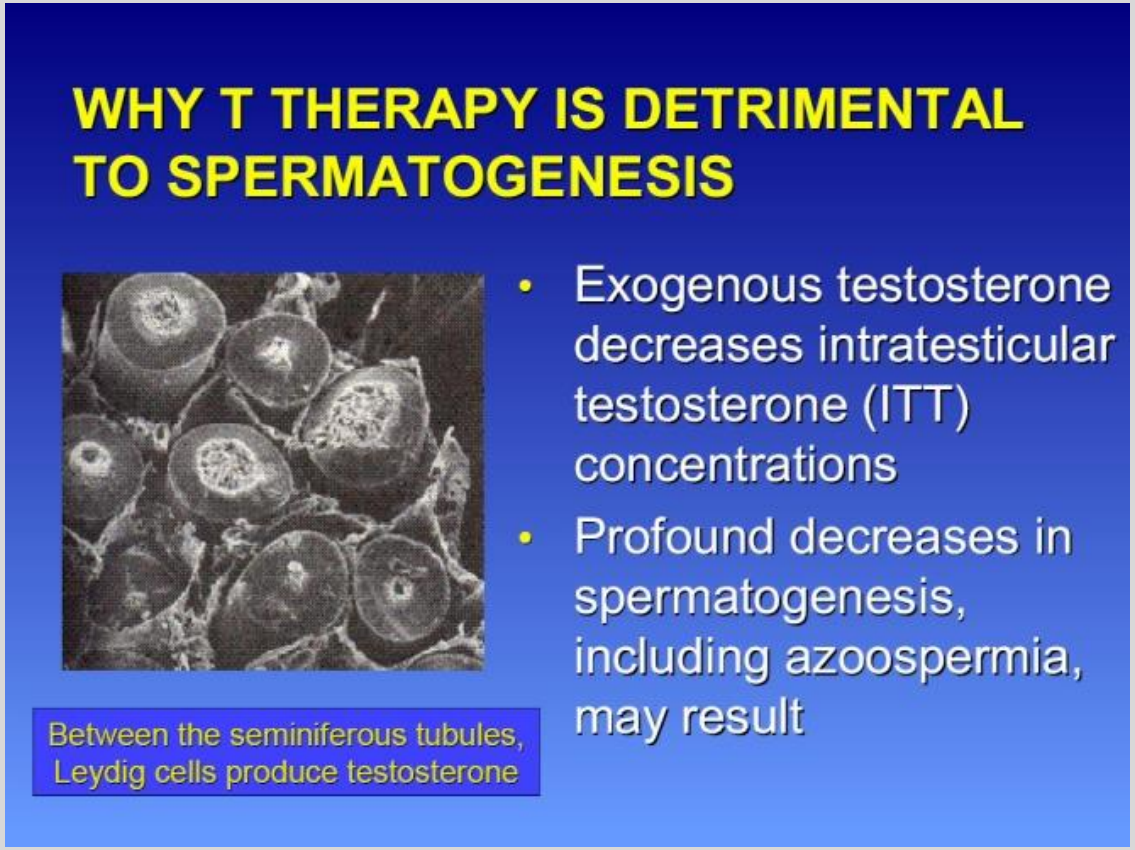
Common Testing

- AMH: anti-Mullerian hormone – optimal 2.0 - 6.8 ng/ml (low < 2.2) - anytime
  - Predict ovarian reserve in females; early indicator of aging – must correlate with FSH – can be affected by acupuncture and TCM / nutrition
  - Produced in antral follicles measuring < 6 mm – levels decline with age and are lower around ovulation and with obesity; high with PCOS

- Prolactin: produced by anterior pituitary; men: 2-18 ng/mL; females: 2-24 ng/mL; pregnancy: 10-209 ng/mL (<20 optimal)
  - Post-partum: Breast-feeding levels return to normal gradually; if not breast-feeding return to normal within 1-week post birth
  - Both male and female levels vary throughout the day
    - Highest levels occur during sleep and shortly after awakening; increase with physical / emotional stress
  - Medicines can cause levels to go up; tumors of the pituitary gland or damage to the gland can also change levels

Common Testing

- Testosterone: low sex drive or low sperm count
  - Men: large amounts by the testicles; small amounts in adrenals (Normal 270-1,070 ng/dL)
  - Women: small amounts in adrenals and ovaries (Normal Day 3: 6-50 ng/dl; >50 = PCOS possible)
  - Pituitary gland controls the level of testosterone in the body. Low levels cause the pituitary gland to releases LH
  - Most bound to SHBG: check levels of free VS bound
    - Free T: Ladies Day 3 – Normal Range: 0.7-3.6 pg/ml



Common Testing

- Estrogen (estradiol, estriol, and estrone): both sexes; optimal day 3 = <80 pg/mL
  - B-estradiol (E2): m/c in non-pregnant women; post menopausal levels drop to a low but constant level
  - Day 3 – Normal: 25-75 pg/ml; each 18mm mature follicle is 150-300 pg/ml
- Abnormally high levels on day 3 may indicate existence of a functional cyst (normal) or Diminished Ovarian Reserve (DOR)
  - Estriol (E3): made by the placenta is only measured during pregnancy
  - Estrone (E1): menopausal women; may be measured in men or women who might have cancer of the ovaries, testicles, or adrenal glands. Made in most tissues especially fat and muscle
- Women: produced in the ovaries, in the placenta; small amounts by adrenal glands

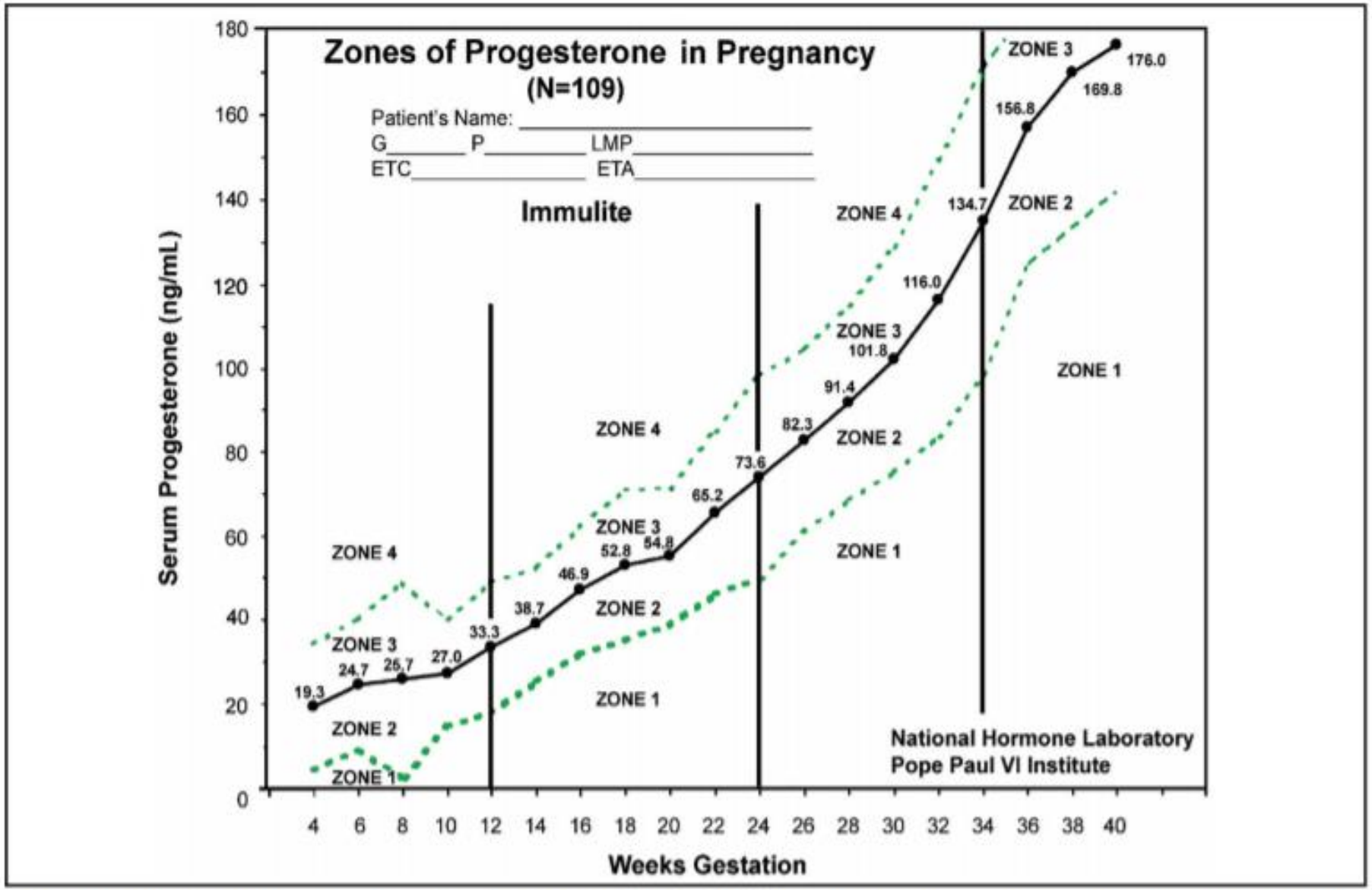
Common Testing

- Progesterone (P4): produced by the ovaries, corpus luteum and placenta (10X normal)
  - Progesterone helps form / fluff the endometrium
  - Egg is not fertilized, progesterone levels drop, and menstruation begins
  - High LH signals body to make progesterone; negative feedback to LH
  - Day 3: <1.5 ng/ml; 7 days past ovulation (~Day 21): >15 ng/ml
  - Can be used to confirm ovulation; general results indicate the following:
    - 10+: is normal on a natural cycle; 15+: is normal on a medicated cycle

- 17-Hydroxyprogesterone: Day 3: 20-100 ng/dl
  - Mid cycle peak would be 100-250 ng/dl, luteal phase100-500 ng/dl
  - Too high interferes with ovulation - congenital adrenal hyperplasia

Creighton Method

- The Pope Paul VI Institute has a National Hormone Laboratory
- Normal pregnancy serum progesterone developed at this laboratory
- https://www.popepaulvi.com/PDF/N_PPBrochure.pdf



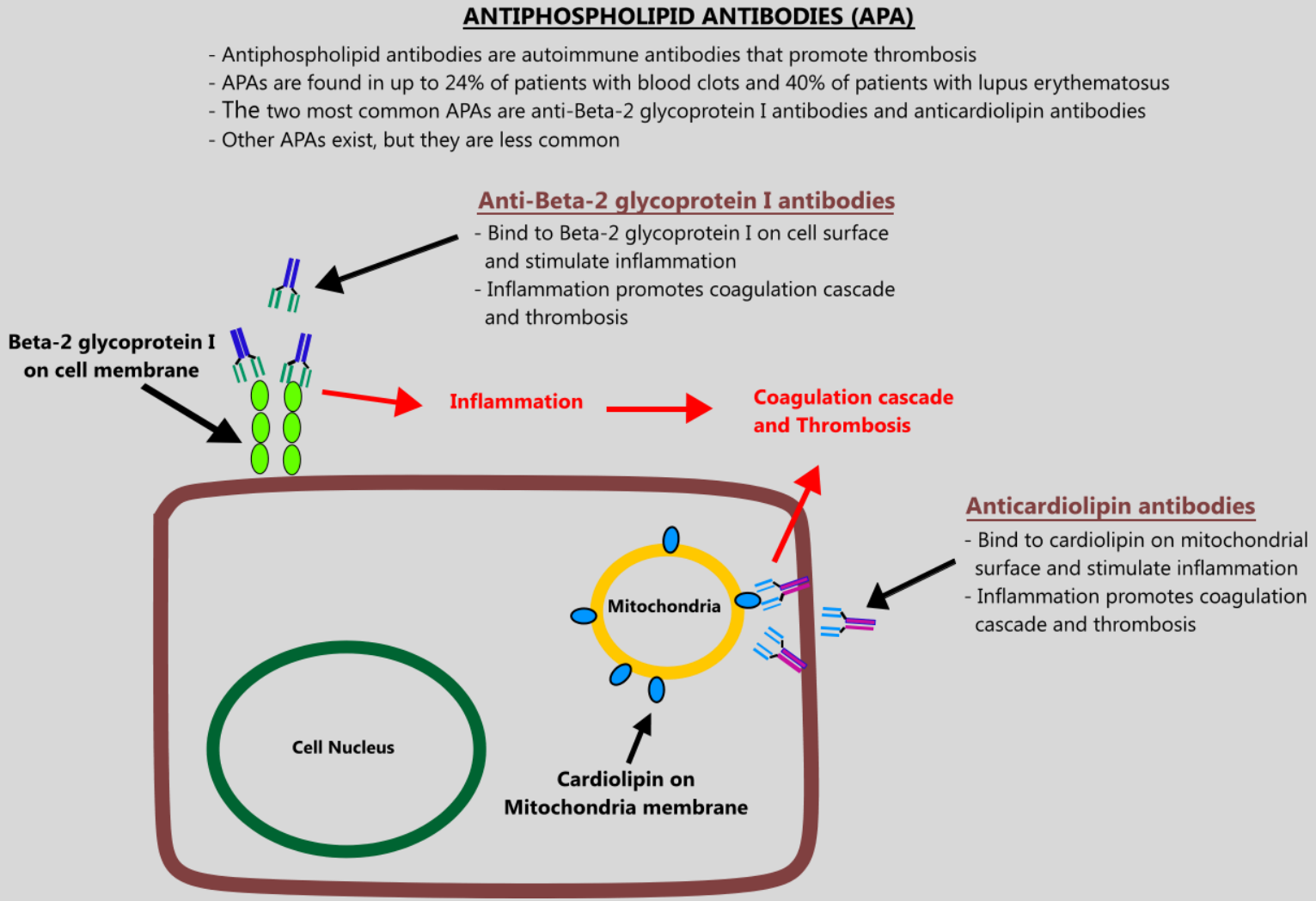
This graph shows the average level of serum progesterone during the course of pregnancy. It also shows the four zones that have been developed through research done at the Pope Paul VI Institute.

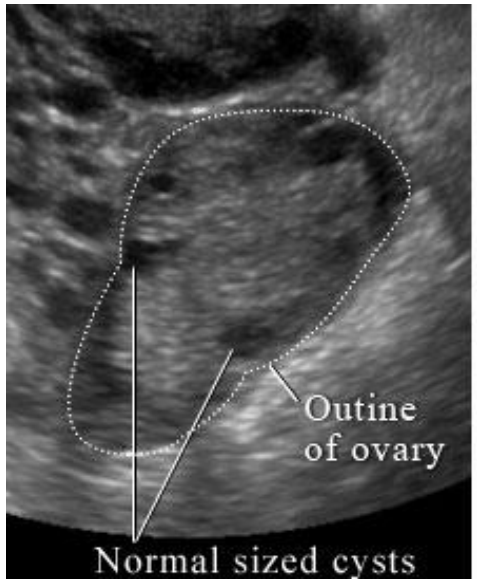
Common Testing

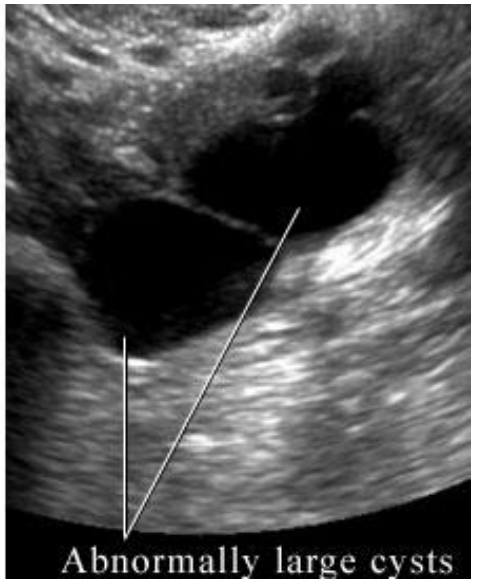
- Dehydroepiandrosterone Sulfate (DHEA-S): Day 3 Normal: 35-430 ug/dl
  - Elevated DHEA-S is often seen in PCOS; levels improve when working with insulin-sensitizing medications and herbs (DIM, I3C, Berberine, Maca)
- Sex Hormone Binding Globulin (SHBG): Day 3 Normal: 18-114 nmol/l
  - Increased androgen production often leads to lower SHBG levels
- Fasting Insulin: Done 8-16 hours after fasting; Normal <30 mIU/ml
  - Fasting insulin of 10-13 generally indicates some insulin resistance, with levels above 13 indicating greater insulin resistance
- Inhibin B: made in ovaries and testes – helps suppress FSH for follicle maturation = normal: $\geq$ 45 pg/mL
  - In women = maturation of follicles / ovarian reserve – test day 3: $\leq$45 = declining ovarian function
  - In men = helps sperm production - higher in men with normal fertility (says nothing of quality) but better marker than FSH

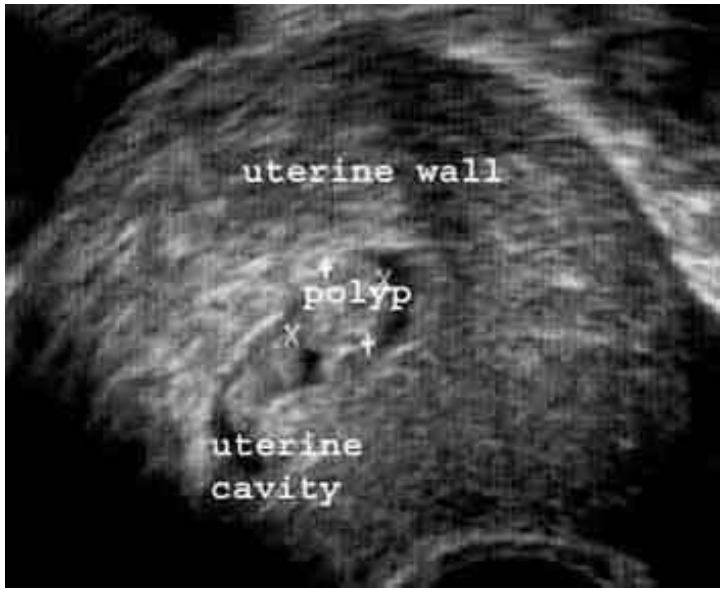
Other Testing

- Anti-Cardiolipin Antibody (aCL) and Anti-Phospholipid antibodies (aPL) : both regulates blood clotting – used in 2+ miscarriages
  - R/O Antiphospholipid syndrome (APS); commonly comes with Lupus
  - Reason for Implantation failure
- For aPL – test anti-β2glycoprotein I (aβ2GPI IgA) should be important to exclude thrombotic state and autoimmune disease
- aCL rises with ovarian puncture (IVF)









Common Testing

- <u>Ultrasound (trans-abdominal, vaginal or rectal):</u> to evaluate the uterus, prostate, and fallopian tubes – with or without saline
  - Women: Look for PID, IUD placement, size and shape of the uterus and ovaries, thickness of endometrium, confirm a pregnancy and placement, cervical length in preterm labor, uterine fibroids / lumps during a pelvic examination, guide a procedure to assess size of follicles, uterine lining or remove an ovarian follicle for in vitro fertilization
  - Men: Look at seminal vesicles and the prostate gland and check for prostate cancer

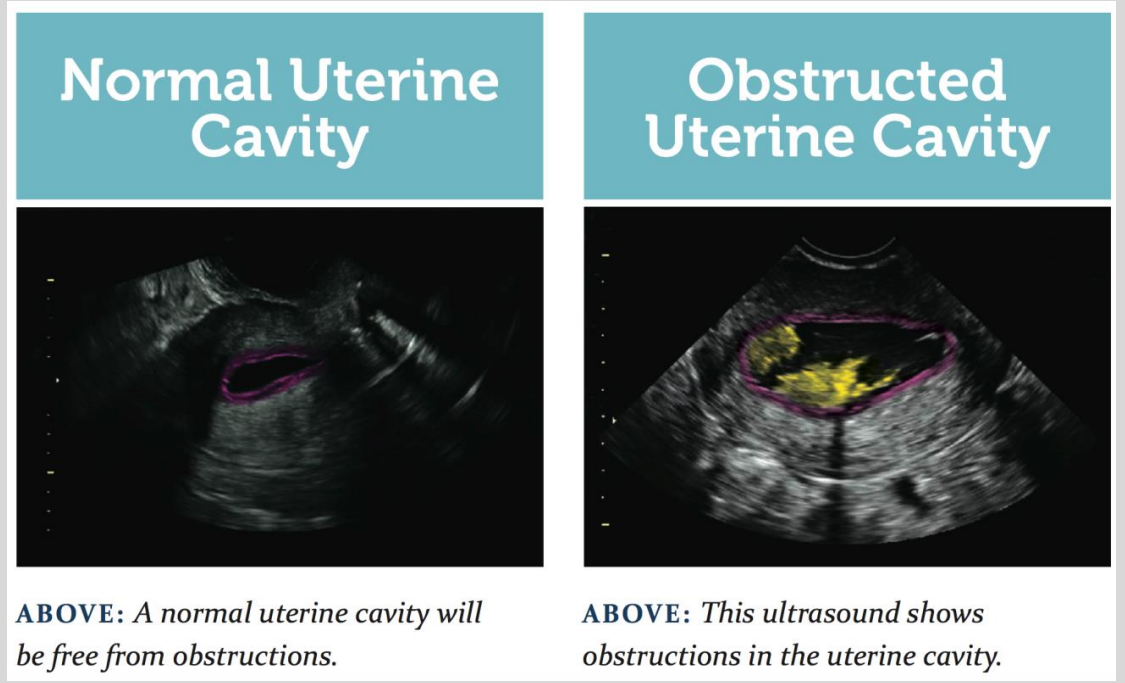
Common Testing

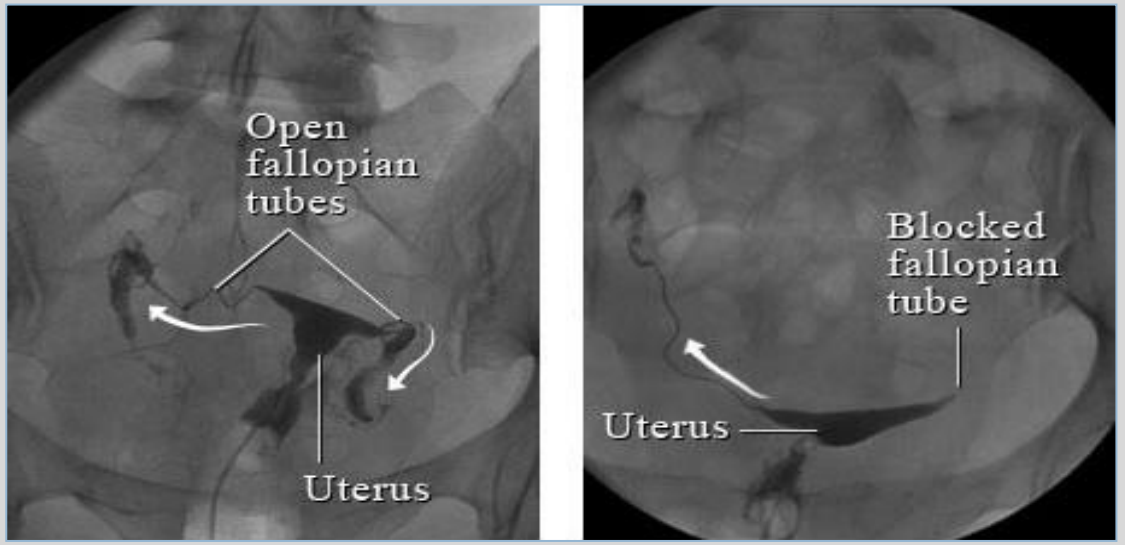
- Saline Hysterosonogram (SHG): like HSG - used to detect any abnormal structures on the inside of your uterus and possible fallopian tube blockage

- Hysterosalpingogram (HSG): looks inside fallopian tubes and uterus (fibroids / polyps) via fluoroscopy with contrast to check for blocked tubes or hydrosalpinx

- Cervical mucous culture: checks for infections (gonorrhea, chlamydia; mycoplasma, which can be normal) and post coital tests for antibodies

- Also check for group B-strep and staph: alter vaginal pH & can lead to miscarriage



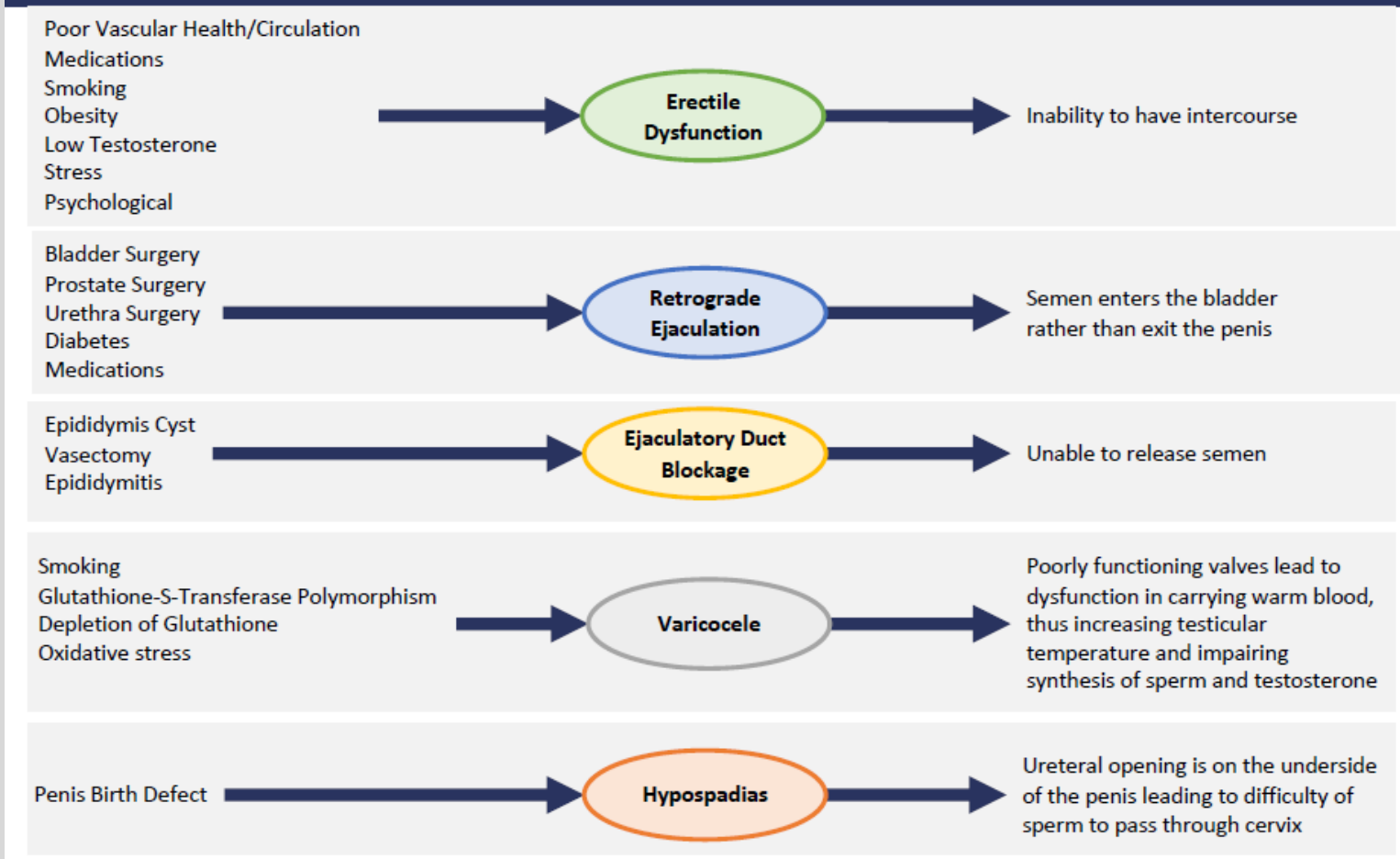


Common Testing

- Hysteroscopy (HSC)
  - Alone it may be done at the beginning of a cycle; with a laparoscopy around ovulation; with a biopsy - a few days before the menstrual cycle (for luteal phase defects done 11-13 days post LH surge)
  - Done under local or general anesthesia - cervix is dilated, a small scope inserted into the uterus with CO2 to expand the uterus for better visualization
  - Minor abnormalities may be fixed during this procedure, and it is sometimes done in conjunction with a laparoscopy, and/or an endometrial biopsy;
  - Commonly used for abnormal bleeding or bleeding that occurs after a woman has passed menopause; to treat growths in the uterus, such as fibroids or polyps; take biopsy

- Laparoscopy (Lap)
  - To look for endometriosis, adhesions and organ malformations
  - Done under general anesthesia; Typical 3 scope site incisions (navel and 2 lower abdomen – 1 for instruments, one for CO2 and one for tools)
  - If found, endometriosis and adhesions may be removed during this surgery

Anatomical Causes of Male Infertility



Common Testing: Men

- Sperm & semen analysis: determines amount of semen combined with quantity, quality and morphology of sperm
  - Volume, liquefaction time, sperm count (morphology and motility), pH, white blood cell count, fructose level
  - No ejaculation for 2-5 days before the test (no abstinence for more than 1 week; no alcohol / drugs for 1-3 days before the test; report medications, herbs, vitamins and supplements
  - Can culture if needed

Normal sperm quality:
Count: >20 × 10^6/mL
Morphology: >30%
Motility: >50%

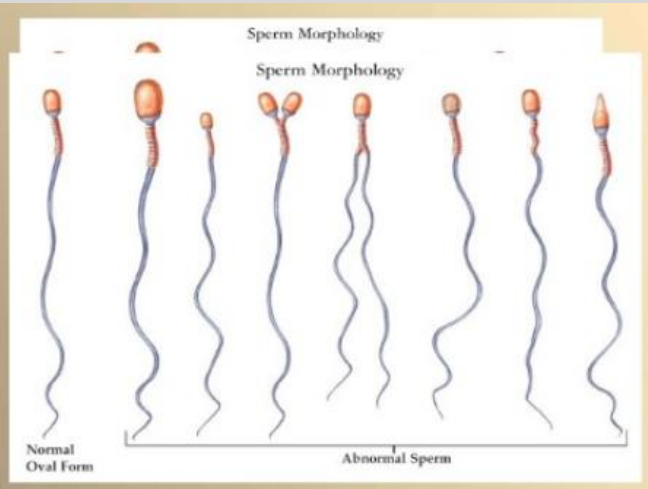


Image on file with Organon, a part of Schering-Plough
Male Infertility Best Practice Policy Committee of the American Urological Association; Practice Committee of the American Society for Reproductive Medicine. *Fertil Steril.* 2006;86(5 suppl):S202. Taylor. *BMJ.* 2003;327:494.

WHO reference values changed

	1980	1987	1992	1999	2010
Volume (mL)	ND	≥2	≥2	≥2	≥1.5
Count (10^6/mL)	20-200	≥20	≥20	≥20	≥15
Total count (10^6)	ND	≥40	≥40	≥40	≥39
Motility (%)	≥ 60	≥50	≥50	≥50	≥40
Progressive (%)	≥ 2	≥25%	≥25% (a)	≥25% (a)	≥32%
Vitality (%)	ND	≥50	≥75	≥75	≥58
Morphology (%)	80.5	≥50	≥30	(14)*	≥4*
Leukocytes (10^6/mL)	<4.7	<1.0	<1.0	<1.0	1.0

*Strict criteria (Tygerberg); Esteves et al. *Urology* 2012

Parameter	(WHO 1999) 4th Edition	(WHO 2010) 5th Edition
Volume	≥ 2.0 ml.	≥ 1.5 ml.
pH	7.2 - 8.0	≥ 7.2
Sperm Concentration	≥ 20.0x106 Spermatozoa / ml.	≥ 15.0 x106 Spermatozoa / ml.
Total Sperm Count	≥40.0 x 106Spermatozoa / Ejaculate	≥ 39.0 x106 Spermatozoa / Ejaculate
Motility	≥ 50 % with forward progression (categories a and b)	≥ 40 % (Progressive motility and Non-progressive motility)
: Grading	A = ≥ 25 % ; ≥ 25µm/s at 37°C & ≥ 20µm/s at 20°C	Progressive motility ≥ 32% : moving active, either linearly or in a or in a large circle, regardless of speed
	B = ≥ 50 % with forward progression (categories a and b)	Non-progressive motility : all other patterns of motility with an absence of progression
	C = Non-progressive motility (< 5 µm/s)	
	D = Immotility.	

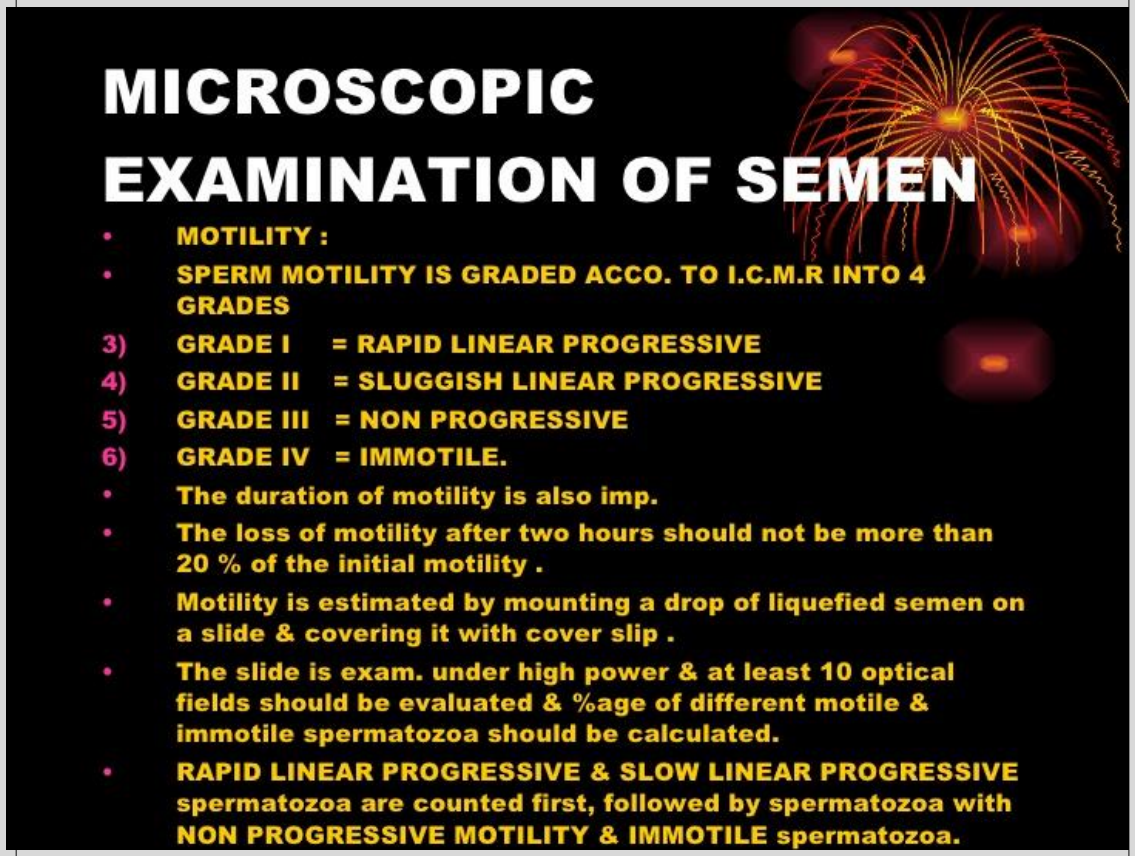
Morphology	≥ 30 % with normal forms	≥ 4 % with normal forms
Vitality	≥ 75 % live	≥ 58 % live
White Blood Cells	≤ 1.0 x 10 6 / ml. ; should not exceed 1 x106/ml.	< 1x106/ ml.
Immunobead Test	< 20 % motile spermatozoa with adherent particles	< 50 % motile spermatozoa with adherent particles
MAR Test	< 10 % motile spermatozoa with adherent particles	< 50 % motile spermatozoa with adherent particles
Seminal Zinc	≥ 2.4 µmol/Ejaculation	≥ 2.4 µmol/Ejaculation
Seminal Fructose	≥ 13 µmol/Ejaculation	≥ 13 µmol/Ejaculation
Seminal Neutral Glucosidase	≥ 20 mU/Ejaculation	≥ 20 mU/Ejaculation

*Preference should always be given to total number, as this parameter take precedence over concentration.

SEMEN ANALYSIS PARAMETERS

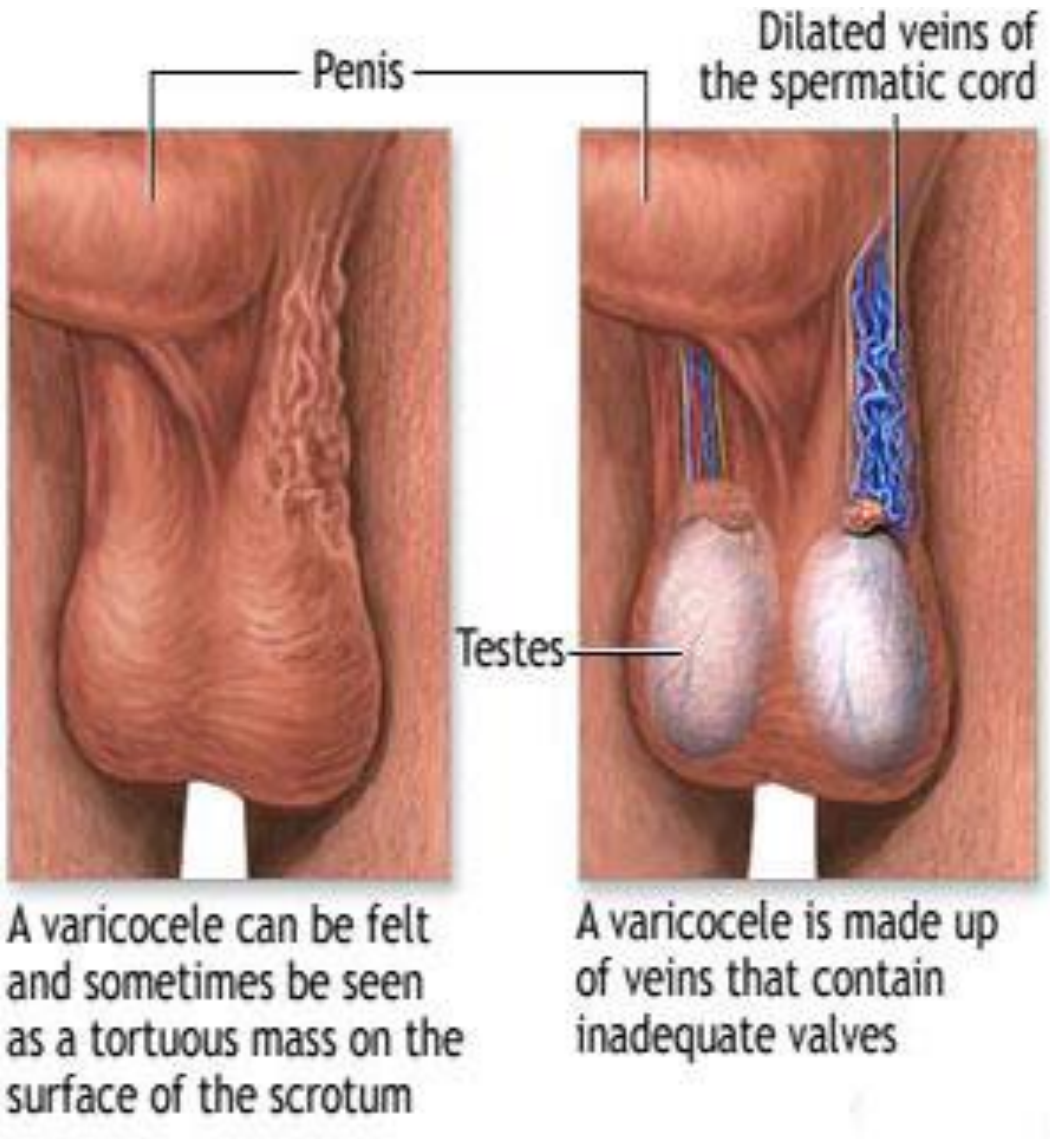
Terminologies of Semen Analysis

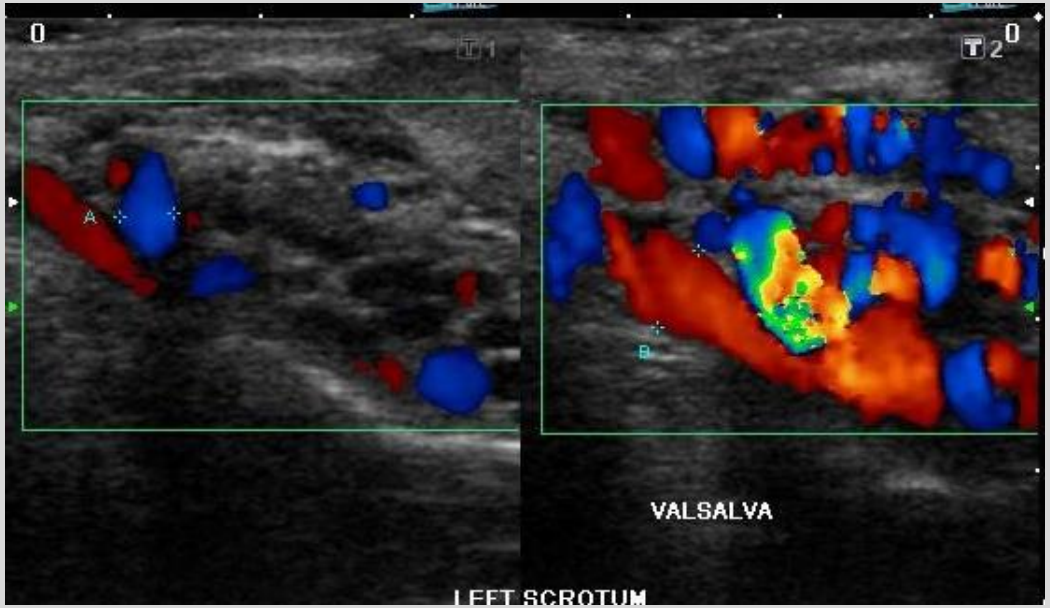
- Oligospermia – sperm concentration <15 million/ml
- Asthenozoospermia – <40% grade (PR+NP) or < 32 PR%
- Teratozoospermia – <4% spermatozoa
- OAT =Oligo-astheno-teratozoospermia
- Azoospermia – no spermatozoa in semen
- Polyzoospermia – ++ high sperm concentration, >200M/ml
- Hypospermia – semen volume < 1.5 ml
- Hyperspermia – semen volume > 4.5 ml
- Aspermia – no semen volume
- Pyospermia – leukocytes present in semen, >1M/ml
- Hematospermia – red blood cell present in semen
- Necrozoospermia – "dead" sperm



https://www.slideshare.net/RaviJain7/semen-analysis

Testicular Ultrasound





- Evaluate masses in the testes (varicocele m/c L>R)
  - Monitor infection or inflammation
  - Testicular cancer reoccurrences
  - Twist in spermatic cord
  - Check non-descended testes
  - Identify fluid in the scrotum (hydrocele)
    - Fluid in the epididymis (spermatocele)
    - Blood in the scrotum (hematocele)
    - Pus in the scrotum (pyocele)

Common Testing: Men

- Sperm antibody test (not used much anymore): Sperm come into contact with male's immune system (injured testes, prostate infection, or biopsy) or from female allergic reaction
  - Poor mobility or agglutination
  - Preparing for testing
    - Males-see sperm count
    - Female-blood test
- Testicular biopsy: collection of sperm and sample of testicular tissue to evaluate men with normal hormone levels and abnormal or dead sperm on semen analysis - Not used routinely

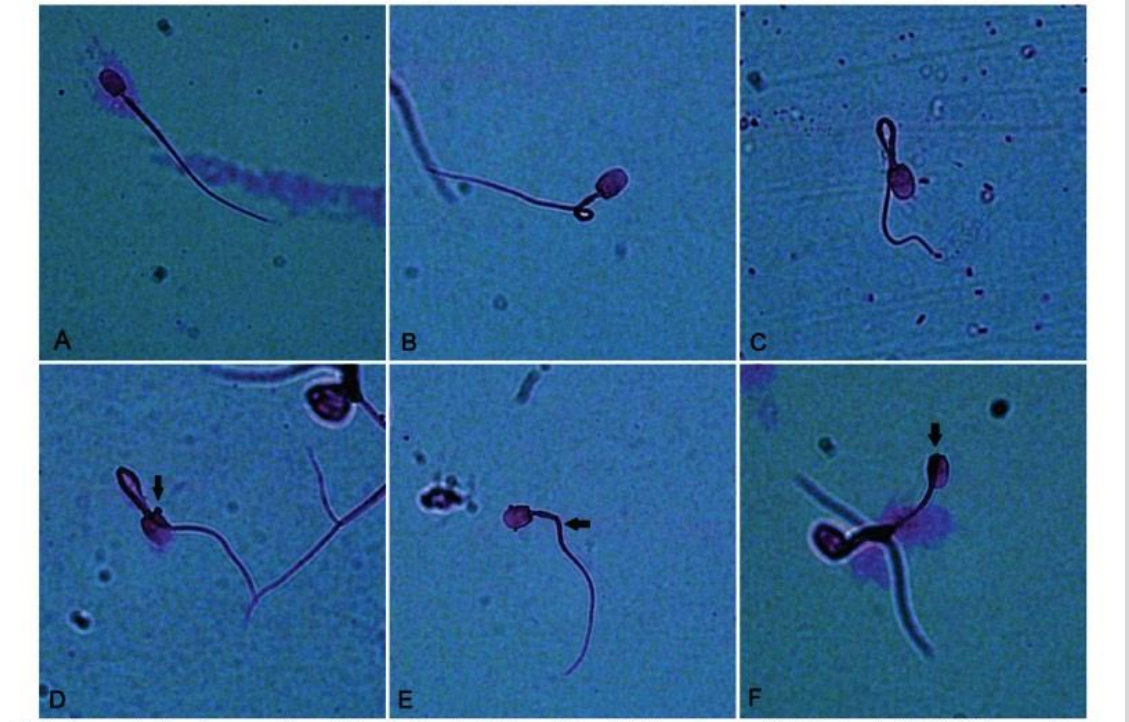
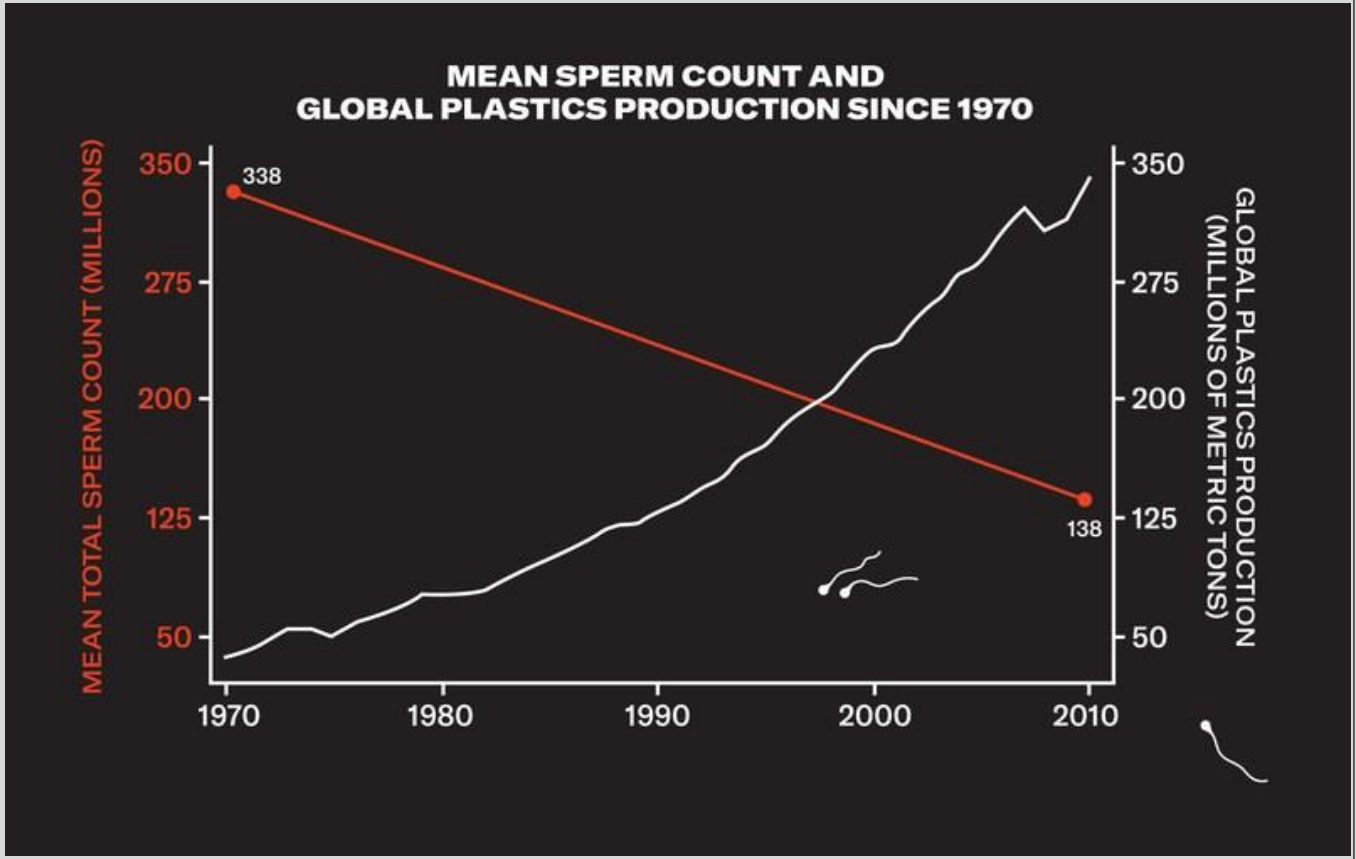


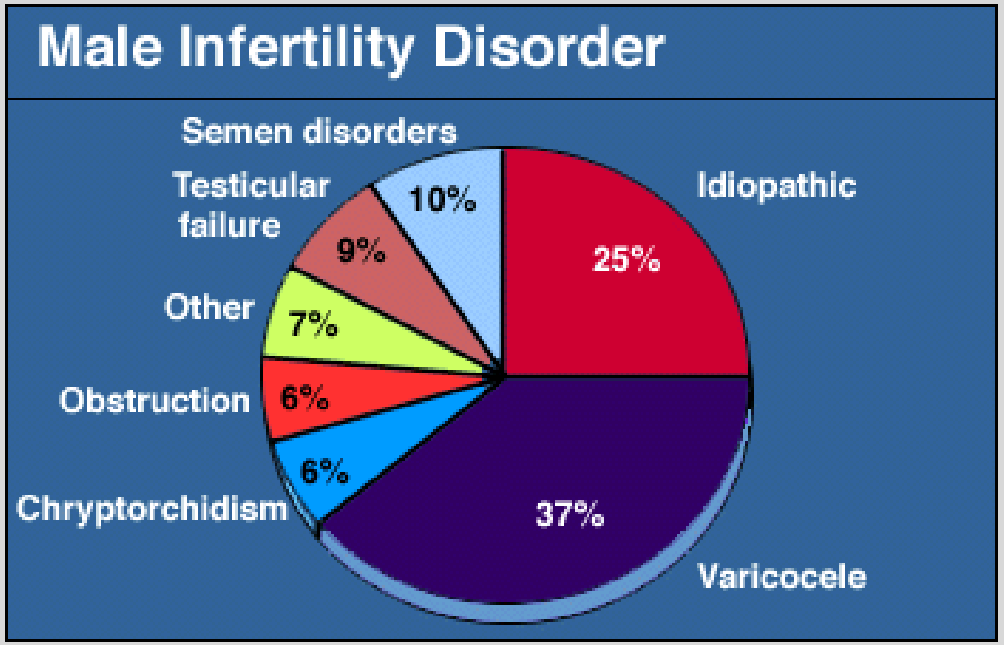
Fig.1. Sperm of collared peccary (*Pecari tajacu)* stained with Bengal Rose. (A) Normal sperm. (B,C) Bent coiled tail. (D) Abnormal shape of the head. (E) Broken midpiece. (F) Broken neck. Light microscopy, 100x.

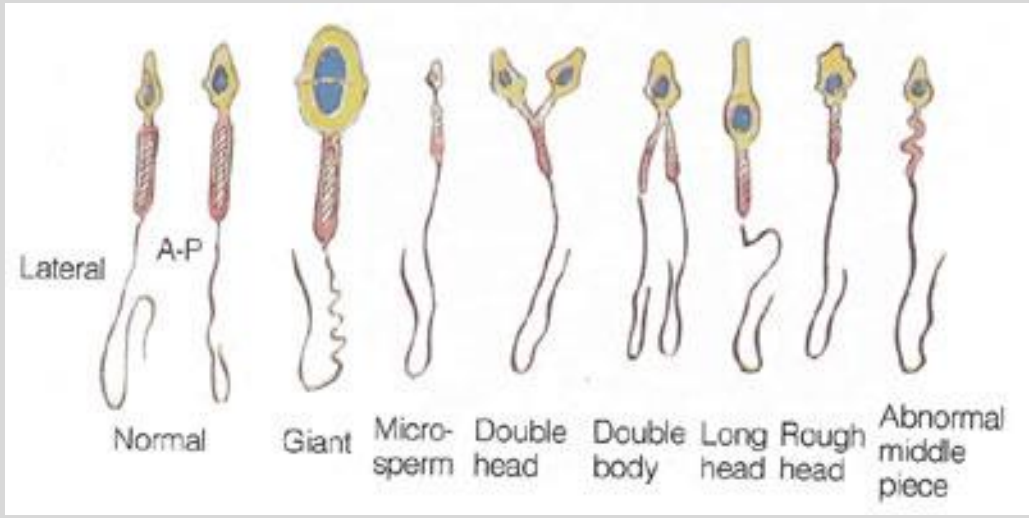
Sperm Count Zero??

- Sperm counts are declining since the ‘70s
- Welcome to plastics
  - Phthalates and BPA mimic E2 and drop T
  - Lower sperm counts
  - In utero – boys with smaller penis, less male characteristics and girls with PCOS like syndromes or precocious puberty



https://www.gq.com/story/sperm-count-zero





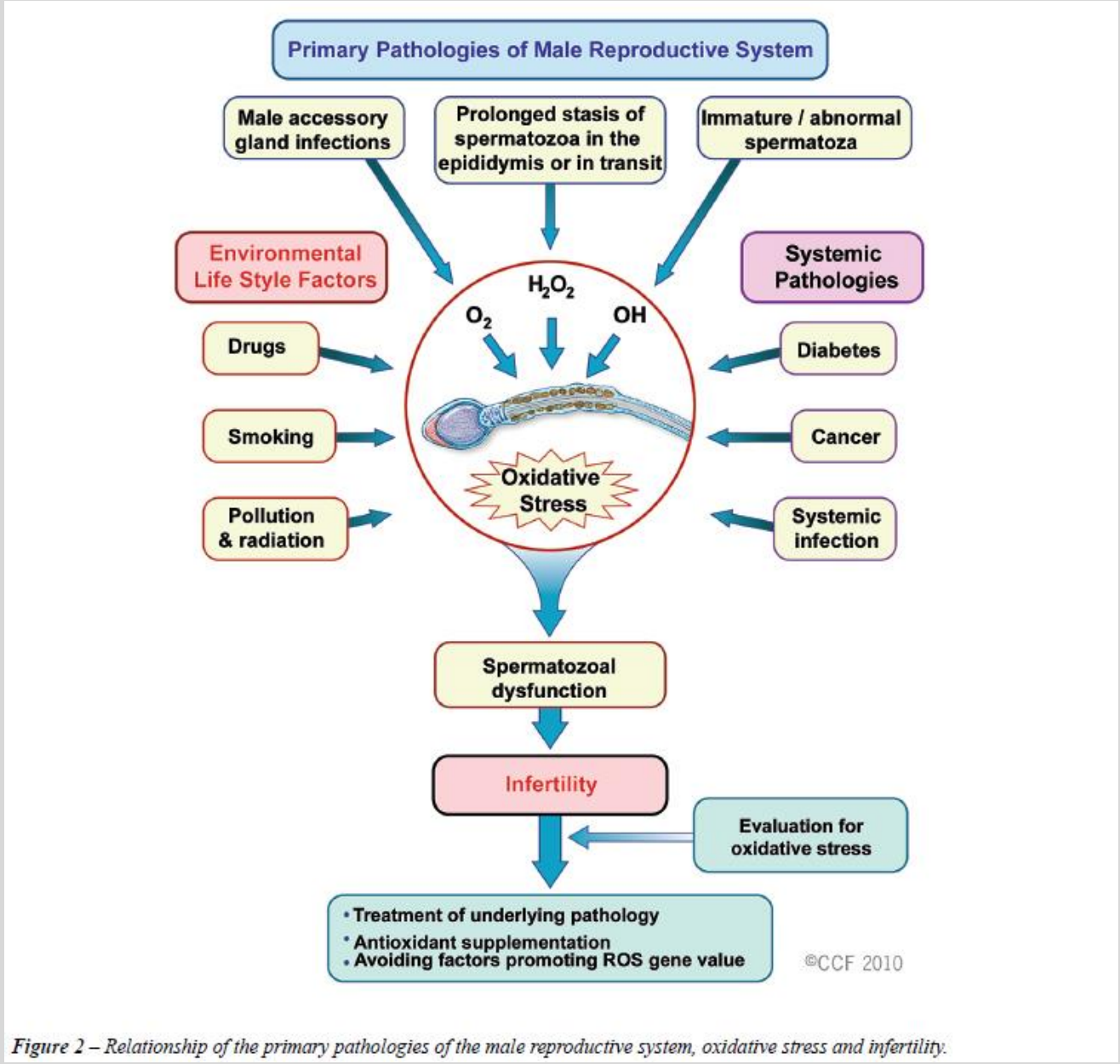
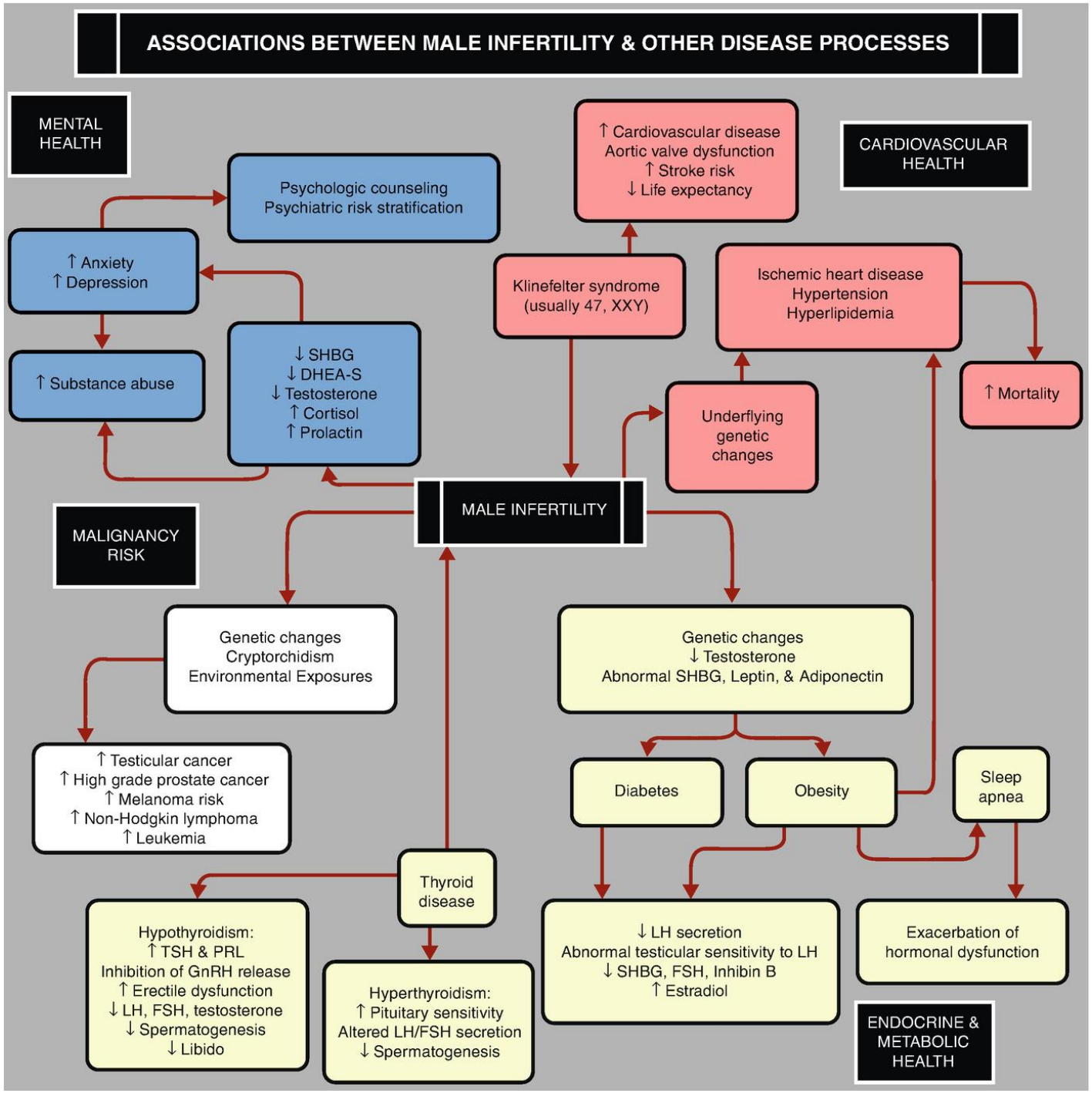


Figure 2 – Relationship of the primary pathologies of the male reproductive system, oxidative stress and infertility.



Emerging Topics in Reproduction: Male Infertility as a Marker of Future Health

April 2018: Underlying genetic or epigenetic abnormalities, hormonal imbalances, and environmental factors have been proposed as possible explanations

Men who are diagnosed with infertility appear to have a higher risk of developing depression, anxiety, alcohol abuse, drug abuse, cardiovascular disease, obesity, and diabetes. Risks of specific malignancies such as testicular germ cell tumors, prostate cancer, melanoma, and non-Hodgkin's lymphoma

Nutraceuticals to Support Sperm Health

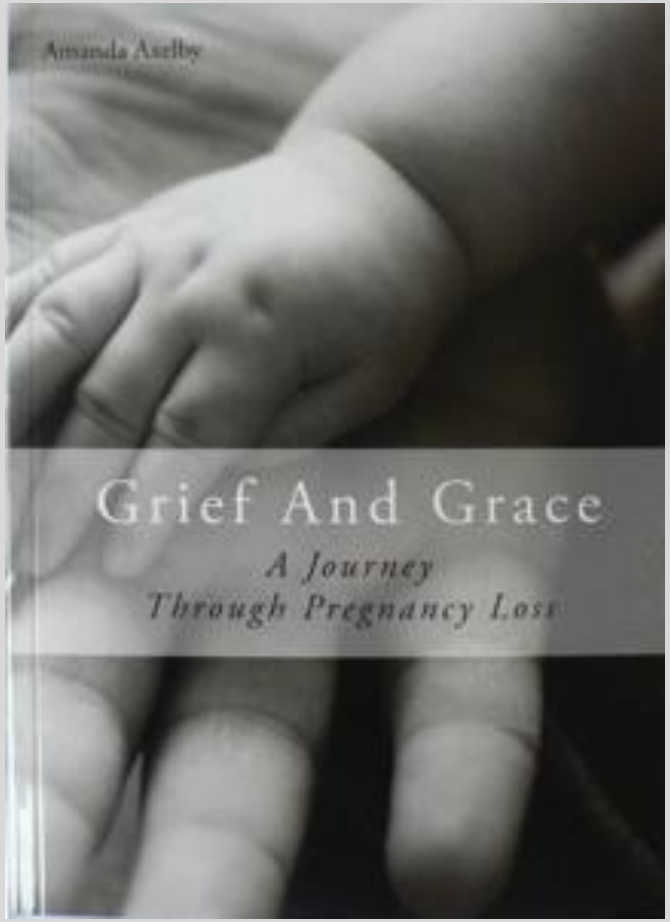
Botanicals	Tribulus Terrestris: 500–1500 mg per day
Antioxidants	Glutathione: > 1000 mg per day N-Acetyl L-Cysteine: > 1000 mg per day Alpha Lipoic Acid: > 500 mg per day Lycopene: > 50 mg per day
Nutrients	Zinc: 100–300 mg per day Selenium: 300–500 mg per day Folic Acid: 1000–3000 mg per day B12 (Methylcobalamin): 5000 mcg per day Vitamin C: 1000–5000 mg per day
Other Nutraceuticals	Myo-inositol: 2000–4000 mg per day L-Carnitine: 2000–4000 mg per day Coenzyme Q10: 100 mg per day Omega 3 Fatty Acids: 3000–5000 mg per day


GENETIC TESTING

Genetic Testing

Done commonly for previous miscarriages

- MTHFR (Methylene-Tetra-Hydro-Folate-Reductase):
  - Homozygous MTHFR mutation have elevated homocysteine levels, thus increased clots (correlate with fasting elevated homocysteine)
    - 12% of people are homozygous
- Hereditary thrombophilia (Factor V Leiden, prothrombin, etc…)
- Autoimmune issues (Hyper T-cell, other Abs)
- Molecular aneuploidy screening of extracted abortus material by multiplex ligation-dependent probe amplification (MLPA)



Genetics VS DUTCH Testing

Genetics

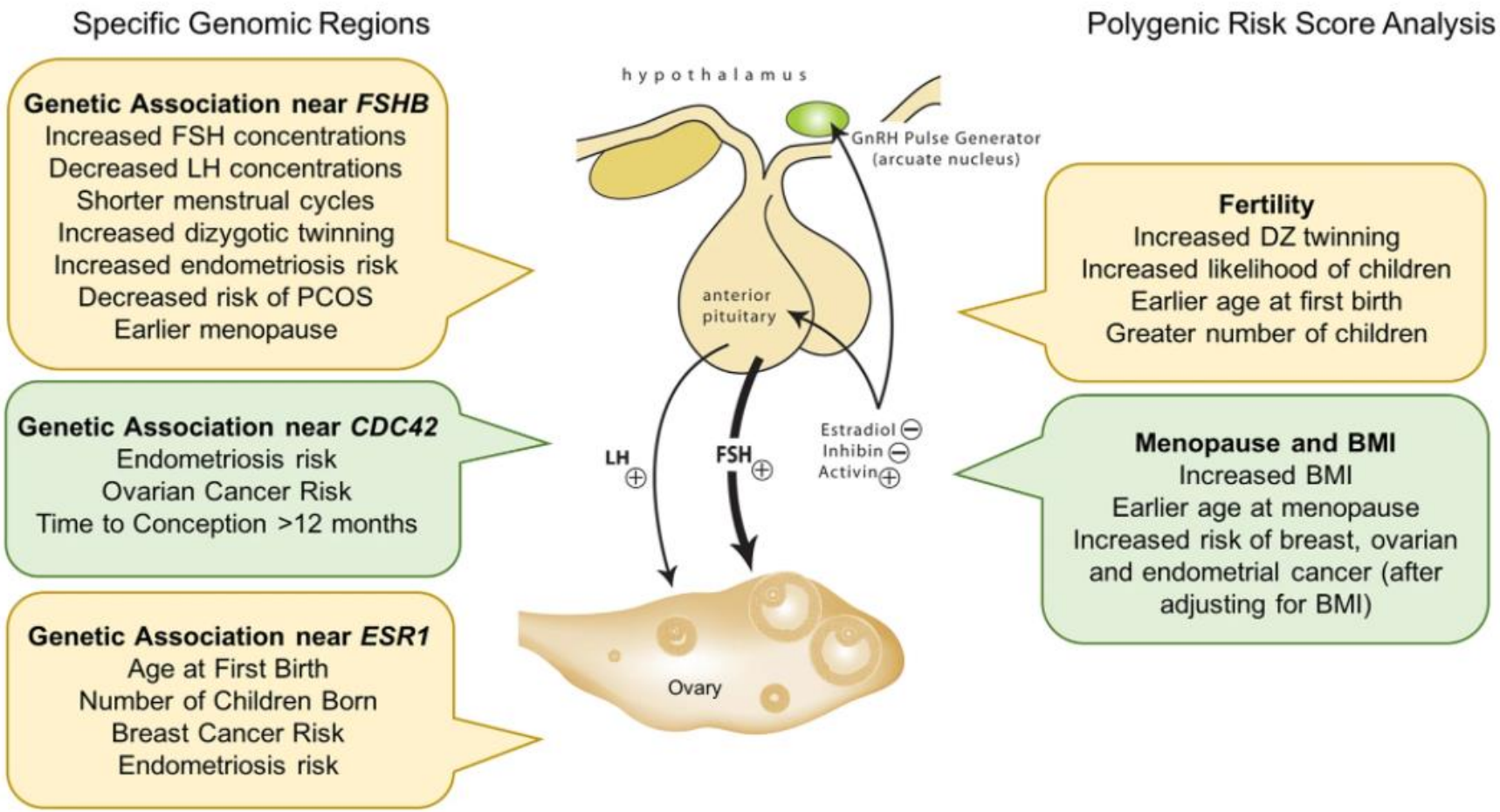
- Not variable
  - Can have triggers to “turn on” specific genes
- Looks at larger picture than just specific hormones to better support pathways that maybe dysfunctional
  - But are they now?
- How to integrate this into history
- Cost / training for good tests?

DUTCH

- Variable from month - month
- For E2 and P4, the dried urine assay is a good surrogate for serum testing
  - 4-spot or 24-h urine collections
  - BMC Chemv.13(1); 2019 DecPMC6661742
- Reference ranges change from lab to lab
- How are the breakdown process of the hormones going?
  - Hints to LV and GI function

Genetic Testing

- Several genomic regions with strong associations for multiple reproductive traits
- The Polygenic risk score (PRS): combines association results from genome-wide genotyping into a single estimate of the genetic risk for a disease or trait and is calculated from the number of risk alleles carried by an individual, weighted by the effect size estimated from the discovery sample.
- The polygenic risk scores calculated from the results of large GWAS data provide insights into shared genetic risk between traits and help to understand the complex relationships between related traits



Genetic studies reveal several genomic regions with strong associations for multiple reproductive traits with three examples shown on the left-hand side of the figure. The Polygenic risk score (PRS) combines association results from genome-wide genotyping into a single estimate of the genetic risk for a disease or trait and is calculated from the number of risk alleles carried by an individual, weighted by the effect size estimated from the discovery sample. The polygenic risk scores calculated from the results of large GWAS data provide insights into shared genetic risk between traits and help to understand the complex relationships between related traits with two examples shown on the right-hand side of the figure. The examples are redrawn with permission from a figure published in Nature[105] on age at menarche [Perry, J. R. et al.[105]]

https://www.nature.com/articles/s41525-018-0068-1

IVF MEDICATIONS & PROCESS

IVF and ART: Why?

- **According to Society for ART and the CDC, IVF is considered when couples have failed to conceive after at least one year of trying and who also have one or more of the following fertility issues:**
- Blocked fallopian tubes or pelvic adhesions
- Severe male factor infertility (low sperm count or low motility)
- Failed 2-4 cycles of ovarian stimulation with IUI
- Advanced female age - over 38 years old
- Reduced ovarian reserve (Day 3 FSH, ovarian antral follicle counts and AMH blood levels screens for egg quantity)
- Severe endometriosis

Fertility Medication

- Estrogen antagonists (anti-estrogen): first choice therapy
  - Block estrogen receptor (ER) and / or inhibiting or suppressing estrogen production
    - Thus, perceived as low estrogen levels in ovary
  - More GnRH released from hypothalamus, driving FSH and LH secretion leading to higher ovulation rate
  - 10-15% higher rate of twin pregnancy (< with Letrazole); good for PCOS
  - Come in types:
    - SERMs: selective estrogen receptor modulators (SERMs) like tamoxifen (breast CA), **clomifene,** and raloxifene (osteoporosis / breast CA)
    - SERD: selective estrogen receptor degrader (SERD) fulvestrant (breast CA)
    - AIs: aromatase inhibitors- anastrozole (breast CA) and **letrazole**

- Side effects: flushing, abdominal discomfort, visual blurring, and/or reversible ovarian enlargement and cyst formation; possible alopecia, N/V, uterine bleeding, decreased uterine lining and thicker cervical mucous
- Other uses: end of an anabolic steroid cycle to block estrogen effects

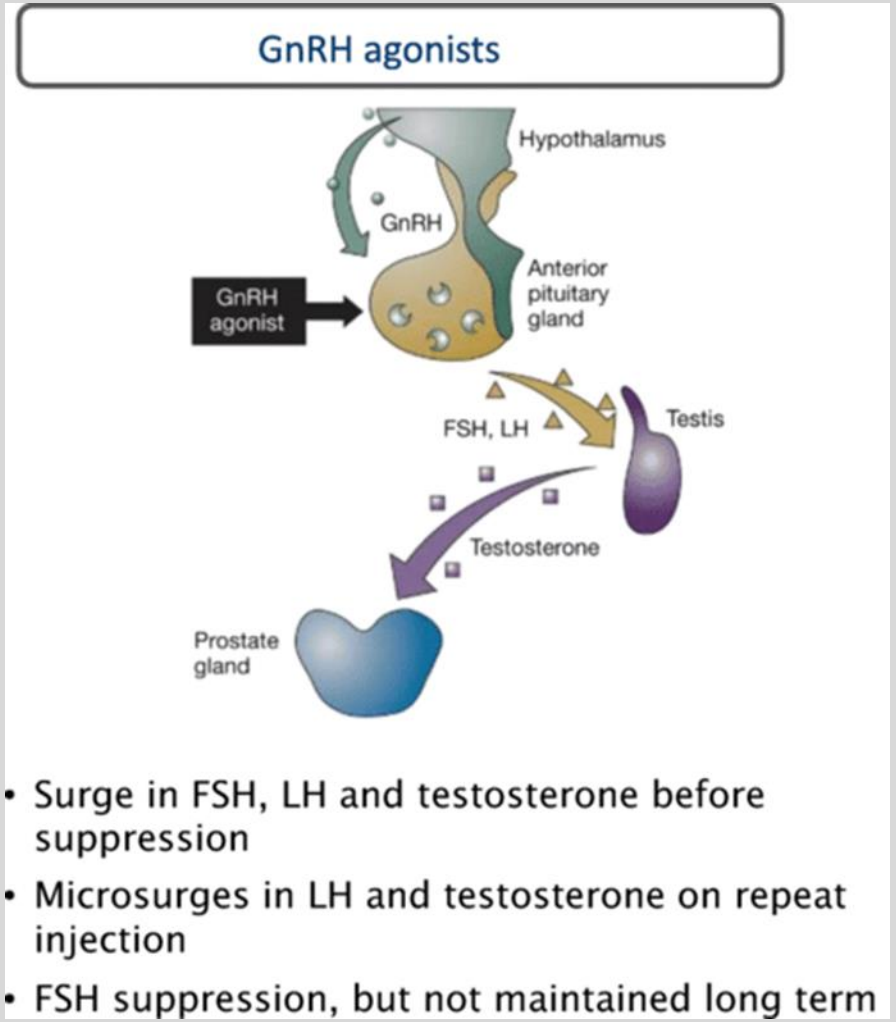
Fertility Medication

- Bromocriptine (Cycloset, Parlodel): elevated prolactin
  - Dopamine agonists
  - Growth hormone overproduction, Parkinson's disease, and pituitary tumors
    - Can also stop breast milk production
  - Side effects: nausea and dizziness during the first few days of use

- Metformin (Glucophage, Glyciphage): helps lower endogenous production of glucose from the liver; used in cases of insulin resistance and/or PCOS
  - Can be combined with Clomid
  - Interferes with B12 absorption and can cause lactic acidosis
  - Studies of its usage are no better than placebo in fertility

Fertility Medications

- Gonadotropin releasing hormone (GnRH) agonists: do not quickly dissociate from the GnRH receptor; stop premature LH surge for poor responders
  - Increase in FSH and LH secretion called "flare effect" before a “down regulation” in about 10 days; can do a shorter micro flare
  - Leuprolide (**Lupron**, Eligard); Buserelin (Suprefact, Suprecor); Nafarelin (Synarel);Histrelin (Supprelin)
  - Goserelin (Zoladex); Triptorelin (Gonapeptyl, Trelstar)
- Used to treat endometriosis, prostate CA and precocious puberty
  - Now being evaluated for treatment of uterine fibroids, PCOS, breast cancer, fibrocystic breast disease, benign prostatic hypertrophy, and irritable bowel syndrome



Side effects: lower E2 and T if not given FSH analogs at the same time

Lupron Down Regulation VS Microflare

Lupron Down Regulation Protocol

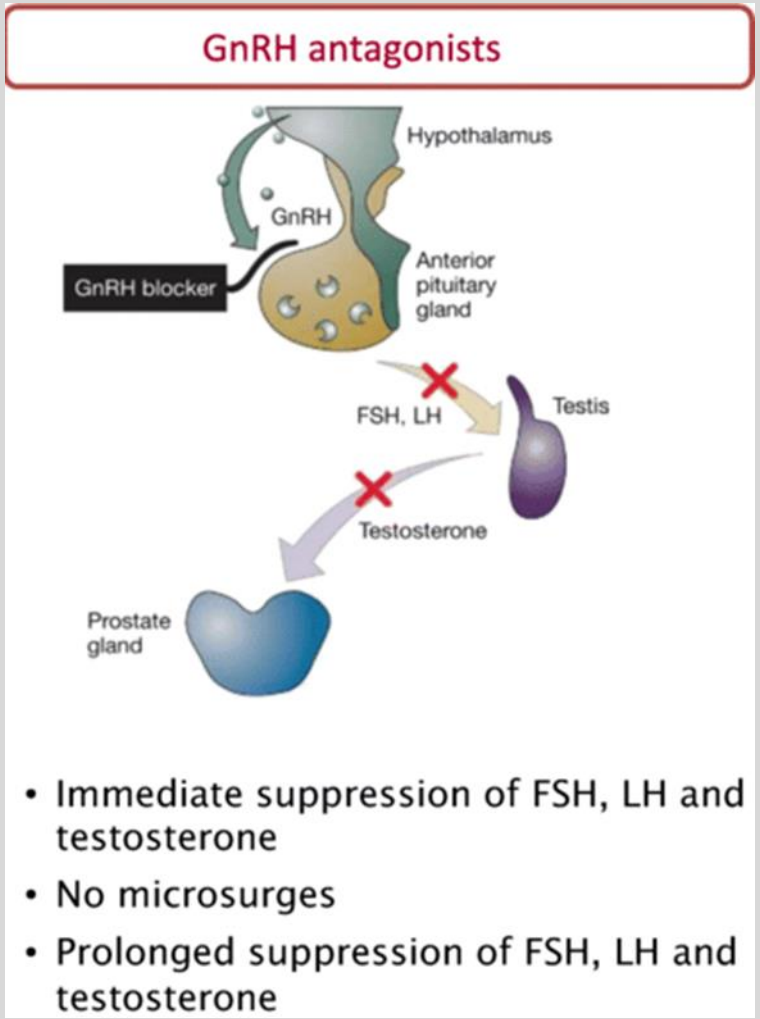
- Lurpon started 1 week before menses / drop of OCP
- Birth control pills are usually given for the month before to avoid corpus luteum cysts that could become reactivated by the high LH levels at the onset of the flare stimulation
- Continue to take for up to 3-4 weeks with slow down dosing as begin FSH analogs
- Can cause excess suppression / poor response to FSH analogs

Microflare

- Lupron started CD2- to take advantage of an initial "flare-up" response of FSH and LH release in the first 3 days of agonist administration.
- FSH analogs (Follistim, Gonal-F) are started CD3 now will release of a large amount of FSH (and LH) that will jump-start (flare-up) the follicles = more mature follicles and more eggs
- Birth control pills are usually given for the month to avoid corpus luteum cysts that could become reactivated by the high LH levels at the onset of the flare stimulation

Fertility Medications

- Gonadotropin releasing hormone antagonists: immediately block the GnRH receptor in 4-5 days
  - Cetrorelix (Cetrotide)
  - Orgalutran (Antagon)
  - GnRH antagonists used to prevent early ovulation by decreasing LH; may allow for shorter treatment cycles and lower doses of gonadotropin injections but are associated with lower pregnancy rates
  - Used as part of downregulation protocol
- Side effects of both: (hypoestrogenism) hot flashes, headaches, and osteoporosis, night sweats, mood changes & vaginal dryness
- Other uses of both: CA (men), female-male sexual reassignment, endometriosis, menorrhagia



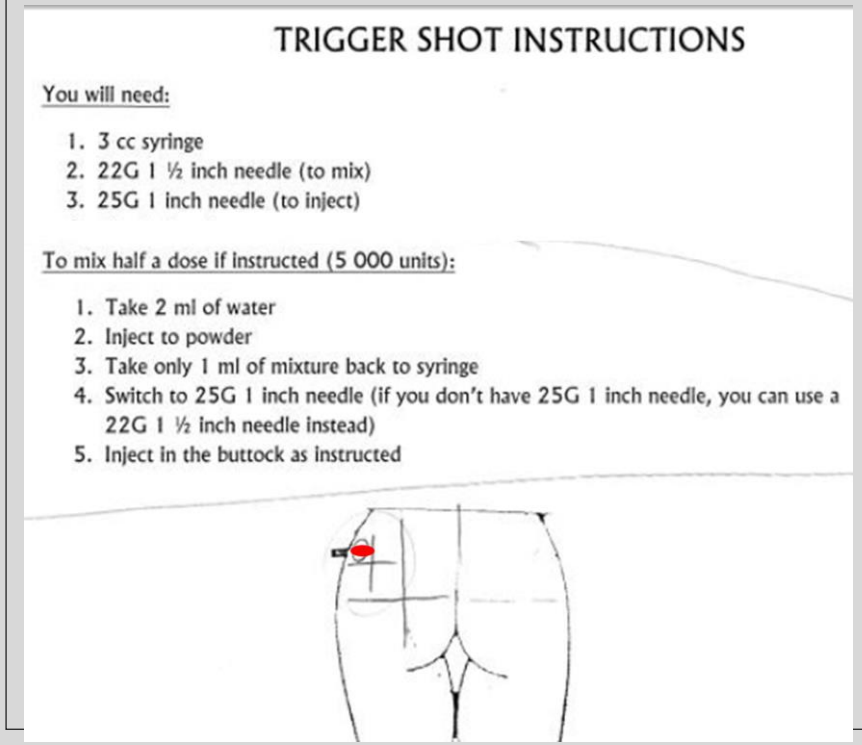
Fertility Medications

- Human Menopausal Gonadotropin (hMG): contain LH and FSH made from menopausal women's urine
  - **Menopur,** Pergonal, **Repronex,** Mentrodin, Menogon, Nugon
- Recombinant Gonadotropins: created by inserting the DNA coding it into bacteria in hamster ovary cells
  - Recombinant FSH: **Follistim, Gonal F,** Recagon
  - Recombinant LH: Luveris

FSH/LH combo is better for amenorrhea / hypomenorrhea

Fertility Medications

- Human Chorionic Gonadotropin (hCG):
  - Pregnyl, Novarel, Ovidrel, and Profasi
  - Used to trigger the ovaries to release the mature egg or eggs from a stimulation cycle



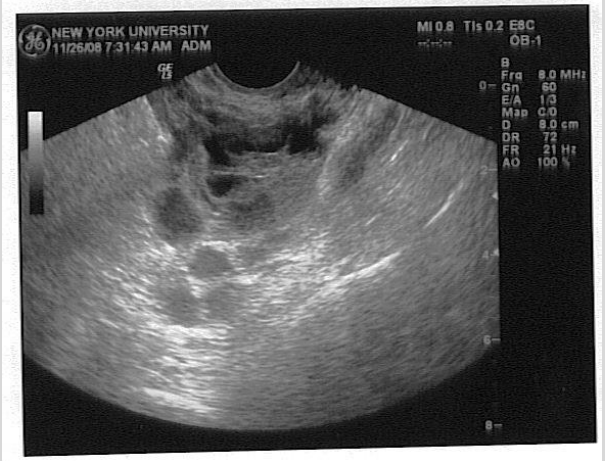
TRIGGER SHOT INSTRUCTIONS

You will need:

1. 3 cc syringe
2. 22G 1 ½ inch needle (to mix)
3. 25G 1 inch needle (to inject)

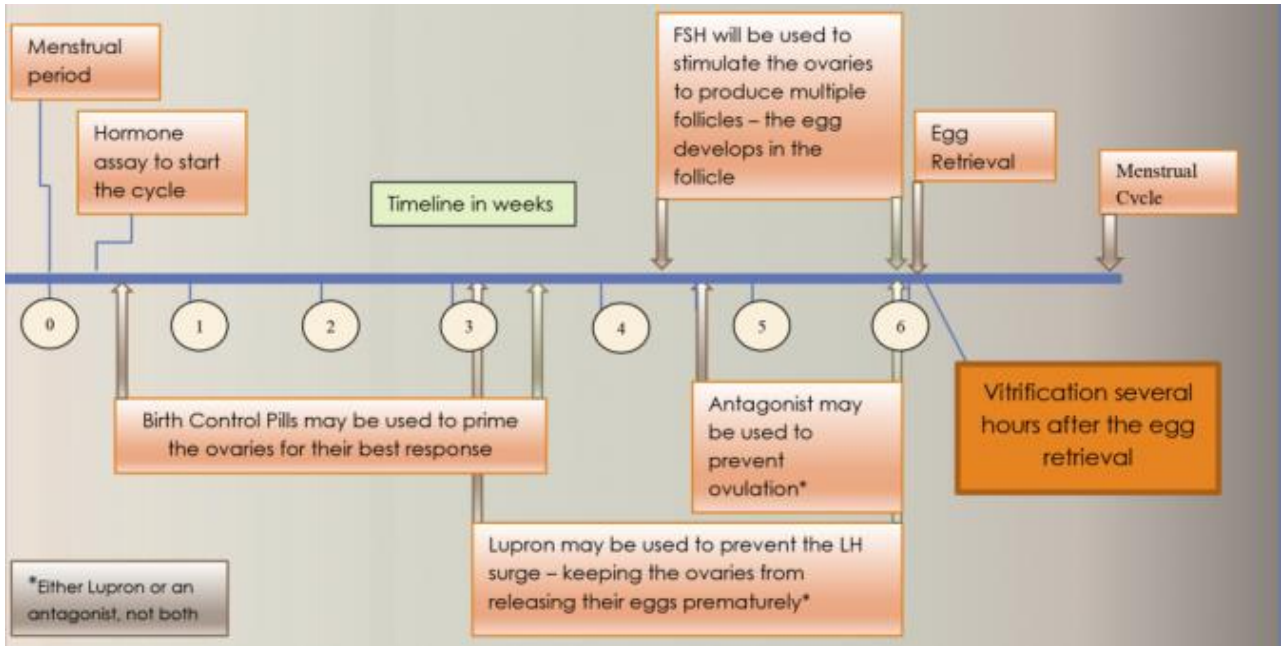
To mix half a dose if instructed (5 000 units):

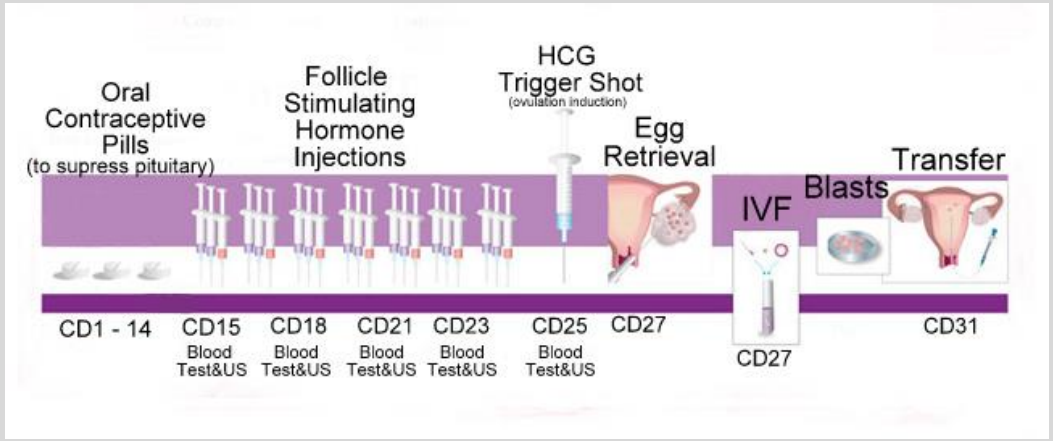
1. Take 2 ml of water
2. Inject to powder
3. Take only 1 ml of mixture back to syringe
4. Switch to 25G 1 inch needle (if you don't have 25G 1 inch needle, you can use a 22G 1 ½ inch needle instead)
5. Inject in the buttock as instructed



ART Techniques

- Medical stimulation + sex
- Medical stimulation + insemination
  - Vaginal / cervical (ICI)
  - Uterine (IUI)
- Added procedure for IVF:
  - ICSI: Intra-cytoplasmic sperm injection (common)
  - Frozen embryo transfer (FET)
  - REE: Rectal electro ejaculation
  - Assisted hatching to help implantation (common)
  - GIFT: Gamete intra-fallopian transfer
  - ZIFT: Zygote intra-fallopian transfer
    - Both GIFT and ZIFT have higher risk for same reward but is not against Roman Catholic belief of IVF (not common)

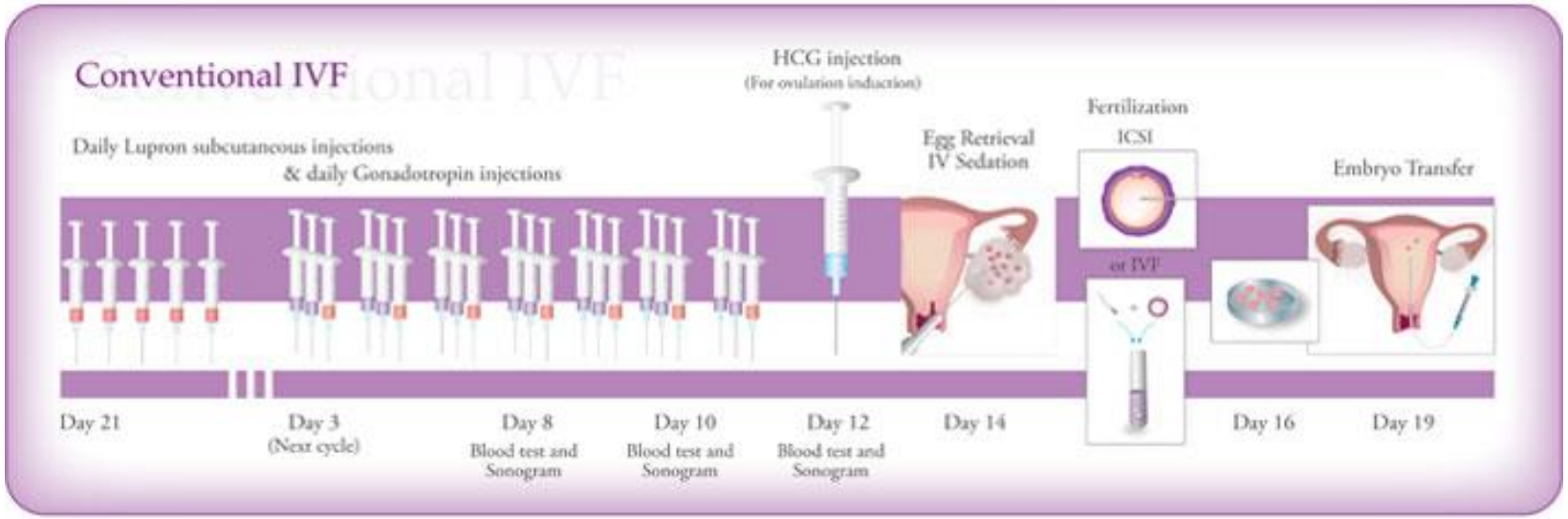


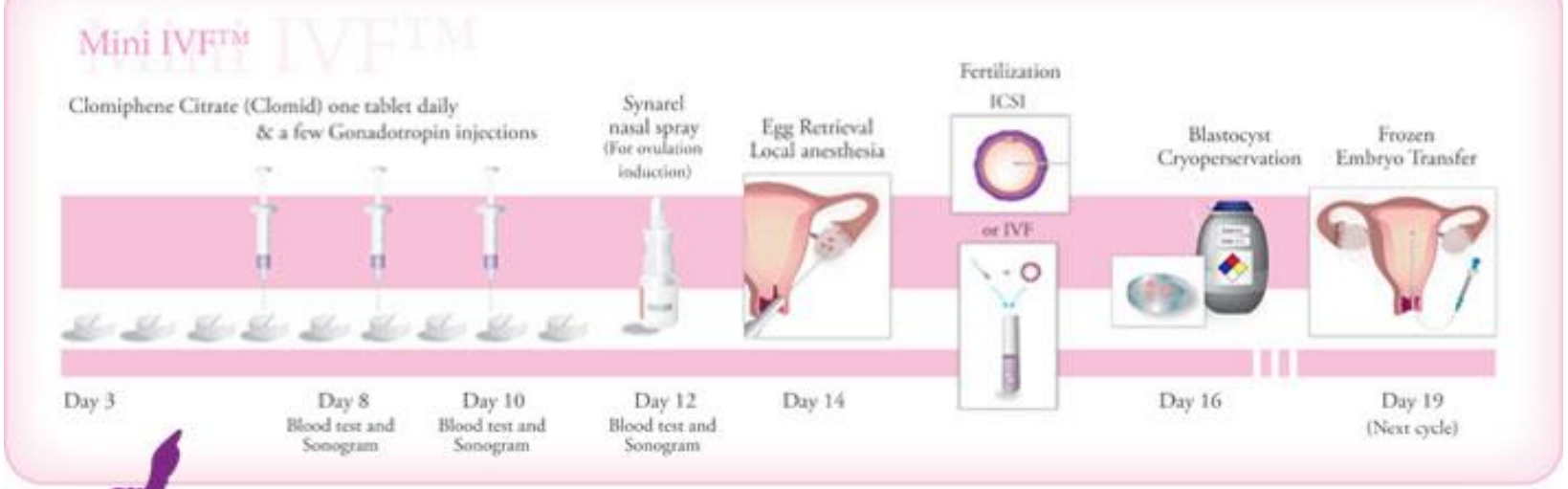


IVF Procedure

- Superovulation: use of fertility drugs to stimulate the ovaries to grow several mature eggs – each drug regime is supposed to be customized

Comparison between Conventional IVF and Mini-IVF™





New Hope Fertility Center

IVF Procedure Steps

BCPs to cycle a group of women all at the same time; some clinics no longer doing this

Possible addition GnRH analogues via injection

Vaginal ultrasound: ovaries are inactive; thin uterine lining

- Blood test to estimate the hormone levels for down regulation

Gonadotropin injections (FSH and or hMG) to stimulate the ovaries for 10-12 days QD

- Dose is adjusted depending on the response (blood tests, ultrasound for follicle development and uterine lining thickness)
- <3 mature follicles develop, the doctor may cancel the cycle
- Production of many follicles (above 17) are at risk of developing ovarian hyperstimulation syndrome

IVF Procedure Steps

hCG shot given at night; all GnRH and gonadotropins are stopped when:

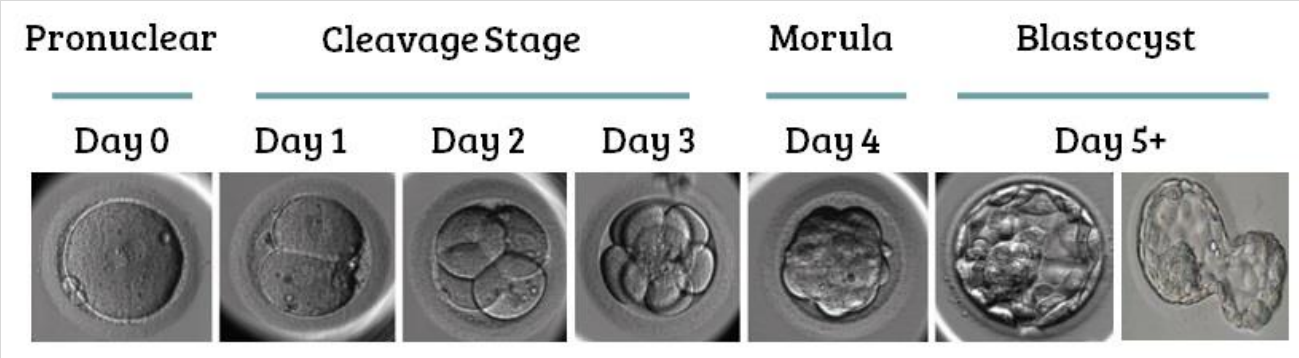
- Reasonable number of follicles are developed
- Follicles are of descent size; leading follicles are 17-19 mm diameter ideal
- Endometrium is thick enough
- Estrogen levels correlate to number of developed follicles

Stimulates a natural LH surge to allow follicles to get a bit bigger for collection

Eggs collected 36 hours later via sedated ultrasound (either through the vaginal wall or abdomen); antibiotics and steroids are commonly given post procedure

IVF Procedure Steps

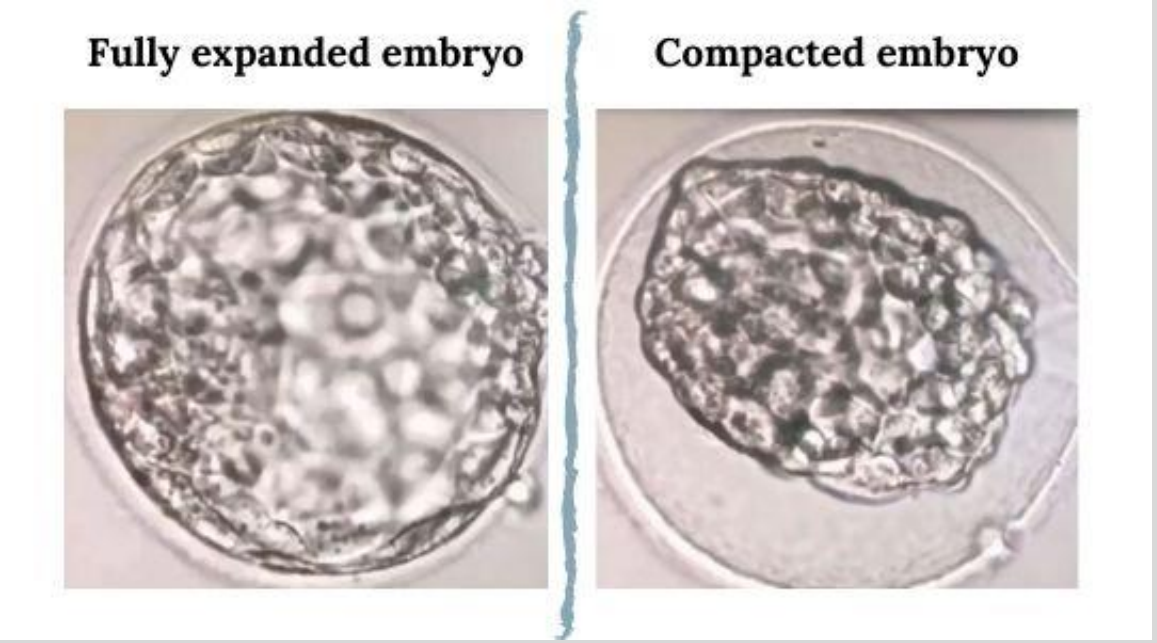
- IVF: eggs are incubated ~ 3-8 hours; later mixed with washed sperm
  - ICSI used commonly used; takes about 18 hours for the egg to be fertilized
  - 12 hours later they divide
  - 48-72 hours from collection, the embryos will consist of 4-8 blastocyst embryos ready
  - Quoted pregnancy rates are significantly higher w/ good quality blastocysts transferred



- Usually, no more than 2 embryos are transferred via a catheter into the uterus under mild sedation
  - Either day 3 or 5 (better quality – less common now)
  - FET (frozen embryo transfer) = now more common

Compaction for FET

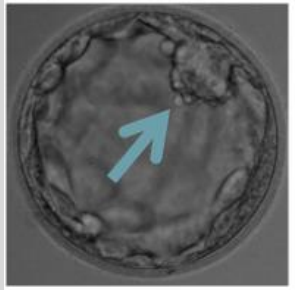
- Embryos can be artificially compacted by using a laser
  - Done before freezing to remove the water from inside the embryo
  - Darwish 2016 found that embryos that were artificially collapsed before freezing had improved survival compared to those that weren't
    - Less sharp shards = less damage to the embryo during thaw
- After thaw, the embryo will re-expand in a couple of hours



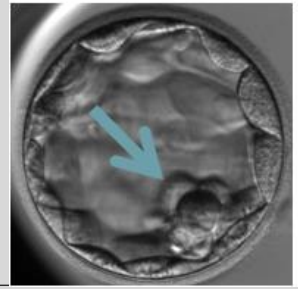
Embryo Development Grading

Inner Cell Mass

ICM Grade "A" (good):
The ICM is composed of many cells that are all compacted
(note the large ICM that is highly compacted)



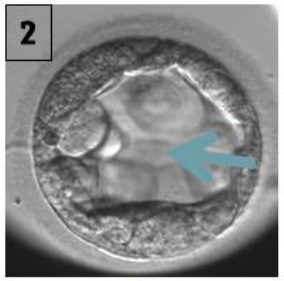
ICM Grade "B" (fair):
The ICM is composed of fewer cells with less compaction
(note the smaller ICM with some cells that are not compacted)



ICM Grade "C" (poor):
The ICM is composed of very few cells that may not show compaction at all.
(note that there's very few cells and no compaction)

Expansion

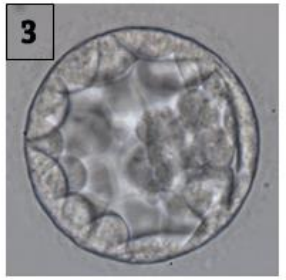
Early Blast



Expansion 1:
Blastocoel occupies <50% of embryo

Expansion 2:
Blastocoel occupies >50% of embryo
(note larger blastocoel)

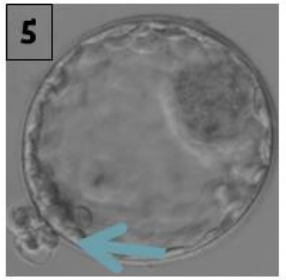
Expanding Blast

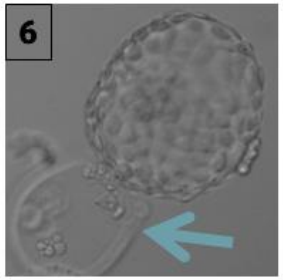


Expansion 3:
Blastocoel occupies 100% of embryo

Expansion 4:
Embryo grows in size, zona thins out
(note zona)

Hatching Blast





Expansion 5:
Cells herniate (hatch) from embryo
(note cells)

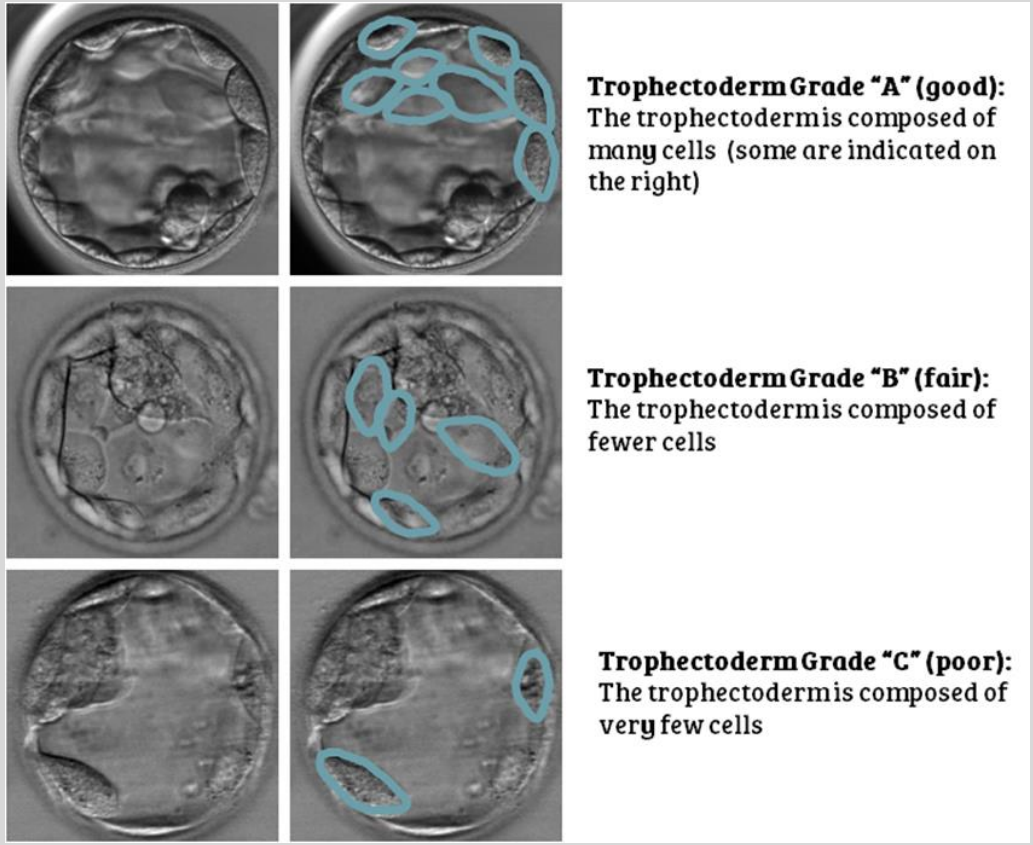
Expansion 6:
Embryo completely hatched
(note zona)

Embryo Development Grading

Gardner System = Grade

- Expansion of the embryo (1-6) + ICM quality (A, B or C) + trophectoderm
- Morbeck (2017) review of 8 studies that drew conclusions based on whether the ICM, trophectoderm, or expansion were the most predictive for implantation:
  - 2 studies = ICM was predictive
  - 4 studies = trophectoderm was predictive
  - 1 study = expansion was predictive
- Irani et al. (2017): Poor graded euploid embryos have reduced pregnancy rates vs excellent graded embryos (35.8% vs 84.2%) with increased miscarriage rates (25.7% vs 0%). Average /fair quality embryos had a 10.5% miscarriage rate. (ages 35-37)

Trophectoderm = placenta



Notes About Grading

- Age matters = According to Goto et al. 2011
  - <33 years old, with high quality blasts: 59.9% chance of live birth.
  - >38 years old, with high quality blasts: 32.6%
  - <33 years old, with fair quality blasts: 41.9%
  - >38 years old, with fair quality blasts: 20.0%
- Embryo grading is subjective = Storr et al. 2017
  - 10 top-notch embryologists graded embryos
  - Although they could consistently choose the same embryo for transfer, they **weren't as consistent when grading blastocysts**
- Becoming a blastocysts on Day 5??
  - Ferreux et al. (2018) found that **Day 5 embryos performed better than Day 6** regardless of grade (29.6% live birth vs 17.0%)
  - Du et al. (2018) found live birth rates from Day 7 embryos were about half of Day 5 and Day 6 (~25% vs ~45%) with no differences in low birth weight, malformations or early neonatal death
- Craciunas et al. (2019) state "It is estimated that embryos account for one- third of implantation failures
  - **Suboptimal endometrial receptivity and altered embryo–endometrial dialogue are responsible for the remaining two-thirds**"

IVF Procedure Steps

Embryos are assessed by their appearance

- Number and characteristic of cells and fragmentation
- Good quality embryos divide rapidly, have equal cells with clear cytoplasm, and have only few fragments
- Some IVF clinics classify into grade one, two, three and four (or A-C); grade one are the best quality embryos and are more likely to implant
- **Research has shown that up to one third of embryos are genetically abnormal**

PGT (pre-implantation genetic testing)

Embryo cryopreservation

- M/C used now that thawing has gotten better
- Better outcomes for pregnancy

Types of Pre-Genetic Testing

- Preimplantation genetic testing (PGT): global term for testing an embryo before IVF implantation; comes in 3 types
- 1. Preimplantation genetic screening (PGT-A): for abnormal chromosome number
- 2. Preimplantation genetic testing for monogenic (individual) disease (PGT-M)
- 3. Preimplantation genetic testing structural rearrangement (PGT-SR) for known chromosomal mis-arrangements such as inversion and translocation
  - Testing techniques include fluorescent in situ hybridization (FISH), microarray, and single-nucleotide polymorphism (SNP)
  - Biopsy of the blastocyst (day 5 - 6) from trophectoderm (TE - placenta) and inner cell mass (ICM - baby) removes 3-10 cells
  - 5% are destroyed by accident and not 100% accurate results

Other Genetic Testing

- Karyotype: done during pregnancy via chorionic villus sampling (CVS - weeks 10-12) or amniocentesis (week 15-19)
  - This test shows if the fetus has more or fewer chromosomes than the usual 46. Having too many or too few chromosomes can cause disorders such as Down syndrome (Trisomy 21) or Edward's (Trisomy 18) or Patau (Trisomy 13); or translocations impacting health
- Children can only survive one type of monosomy, Turner syndrome (-X)
- Trisomy's: Down syndrome (21), Edward's syndrome (18), and Patau syndrome (13)
- Aneuploidy is one of the greatest causes of failed implantation for pregnancy and miscarriage, as well as a major cause of birth defects in children

Why Test Embryos?

Candidates for PGT-A

- Couples who have had a previous pregnancy with aneuploidy
- Women who have had two or more miscarriages
- Women who have experienced previously failed embryo implantation
- Women diagnosed with unexplained infertility
- Women older than age 35
- Women who have undergone numerous unsuccessful fertility treatments

Candidates for PGT-M w/family history

- Huntington's disease
- Sickle cell anemia
- Muscular dystrophy
- Cystic fibrosis
- BRCA1 & BRCA2 mutations
- Fragile-X syndrome
- Tay-Sachs disease

Candidates for PGT-M w/family history

- Robertsonian translocations
- Reciprocal; translocations
- Nonreciprocal translocations

IVF Procedure Steps Post Transfer

Luteal phase support (progesterone) for at least two weeks to assist implantation – some start earlier if testing reveals need

- Daily intramuscular injections (Gestone) – sesame oil or Prometrium (peanut oil)
- Daily vaginal suppositories (Endometrium or Cyclogest)
- Daily vaginal tablets (Utrogestan)
- Daily vaginal gel (Crinone)

Want tri-laminar endometrial layer ≥ 8mm thick for good implantation

Two weeks after transfer, B-hCG blood test

- If positive repeated in 2-5 days to ensure levels double daily
- Ultrasound at 5 weeks to ensure good placement
- Progesterone stopped at 10-12 weeks gestation