Female Fertility and Infertility; Understanding Common Lab Indicators

Alison McAllister, ND

Objectives for today:

Understand the menstrual cycle

PCOS and its role in infertility

Hypothyroidism and infertility.

Alison McAllister, N.D.

Lead Clinical Consultant
ZRT

Teaching doctors for
over 20 years

Infertility Definitions

- Defined as the inability to get pregnant in 1 year of unprotected intercourse.

- Inability to get pregnant in 6 months in a woman older than 35 after unprotected intercourse or 3 months in a woman after age 40.

Review of Normal

Ovulatory Cycle

24-36 days long

Day 1 = 1st day of bleeding

Ovulation on day 8 – 22

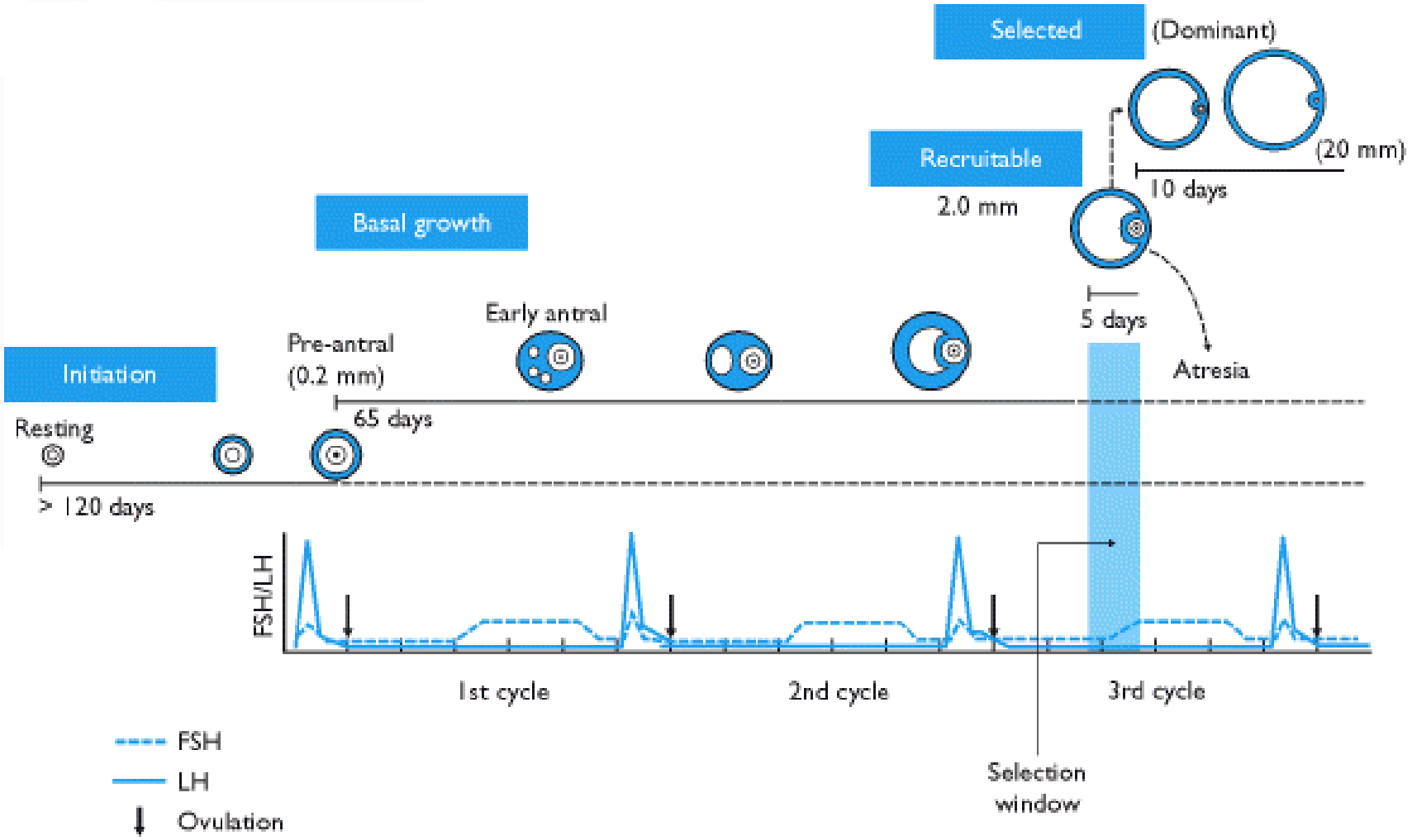
Follicular phase variable length

Luteal phase 12- 16 days. Consistent

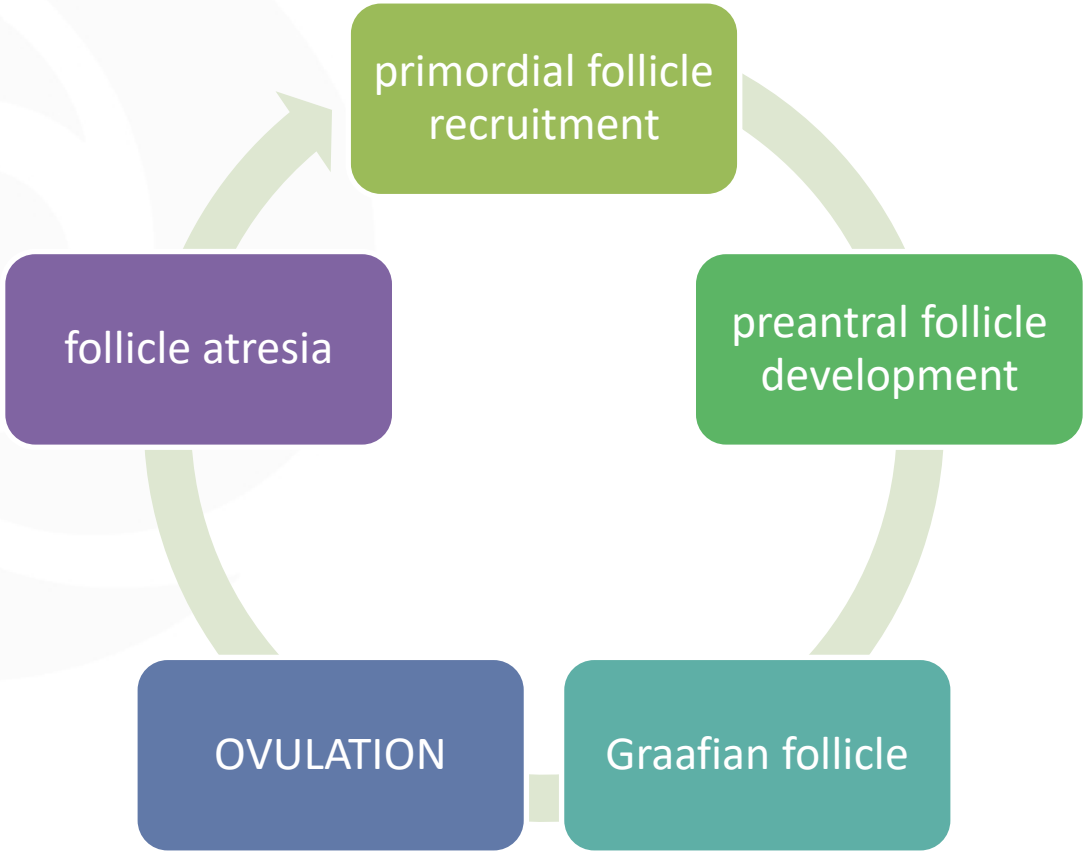
25% pregnancy chance every cycle

Ovarian “Egg” Reserve

- Primordial follicles – develop between fetal 6th and 9th month of gestation.

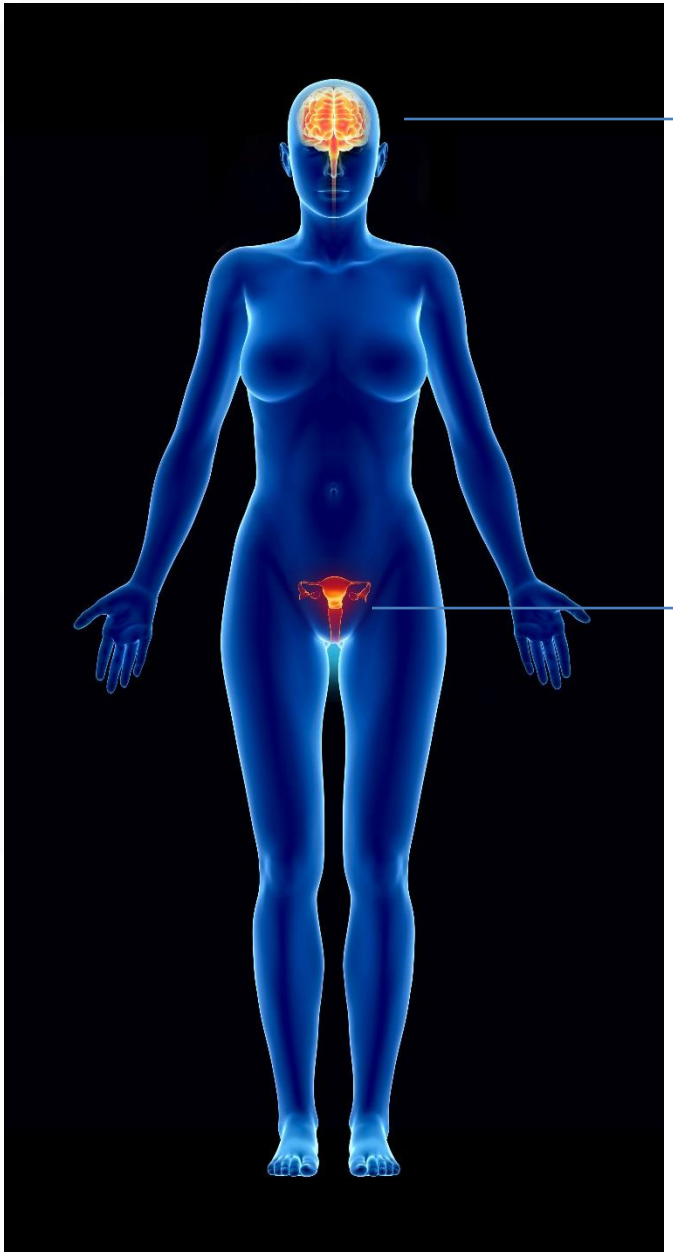

Selected
(Dominant)
Recruitable
2.0 mm
(20 mm)
10 days
Basal growth
5 days
Atresia
Early antral
Pre-antral
(0.2 mm)
Initiation
65 days
Resting
> 120 days
FSH/LH
1st cycle
2nd cycle
3rd cycle
FSH
LH
Ovulation
Selection
window

Ovulation Phases



2 Phases of Folliculogenesis

PreAntral/ Gonadotrophin	Antral/Graafian/
Independent growth and differentiation	Gonadotrophin dependent Growth of the follicle up to 25mm
Locally produced growth factors About 10 cycles	FSH/LH control Growth factors About 2 cycles Then one is chosen and develops in about 14 days



LH

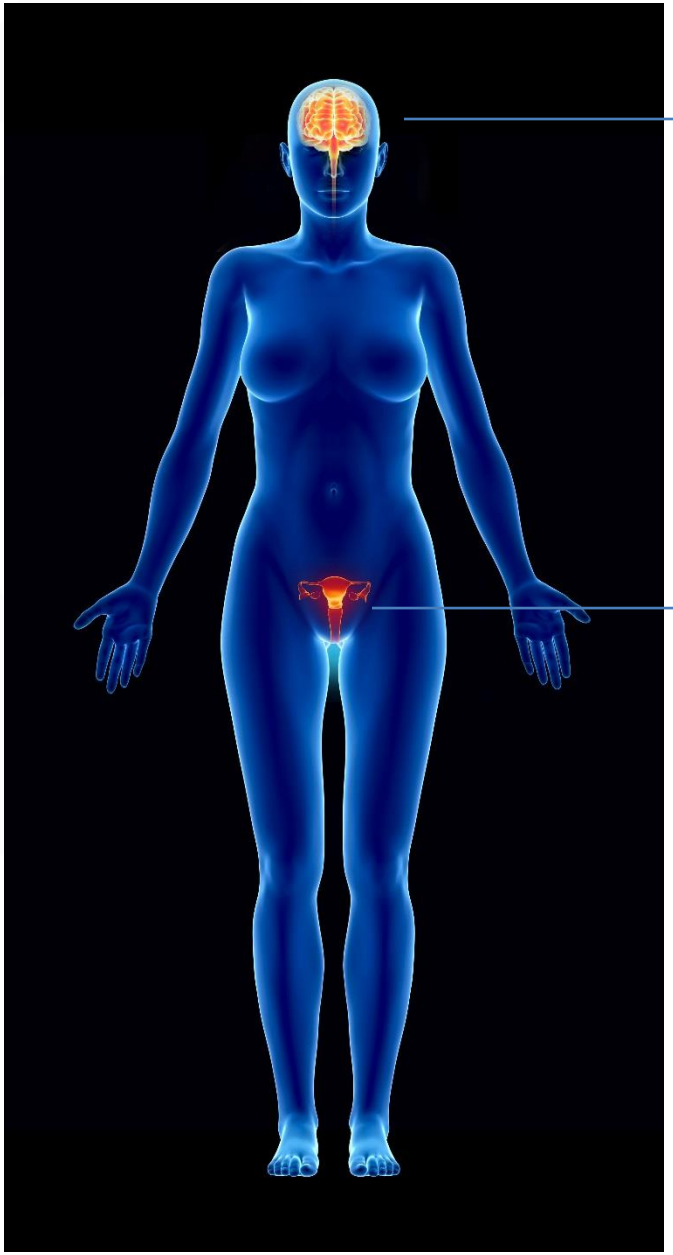
Follicles

Dominant Follicle

Estradiol

ovulation

Corpus luteum



FSH

Follicles

Estradiol
Inhibin

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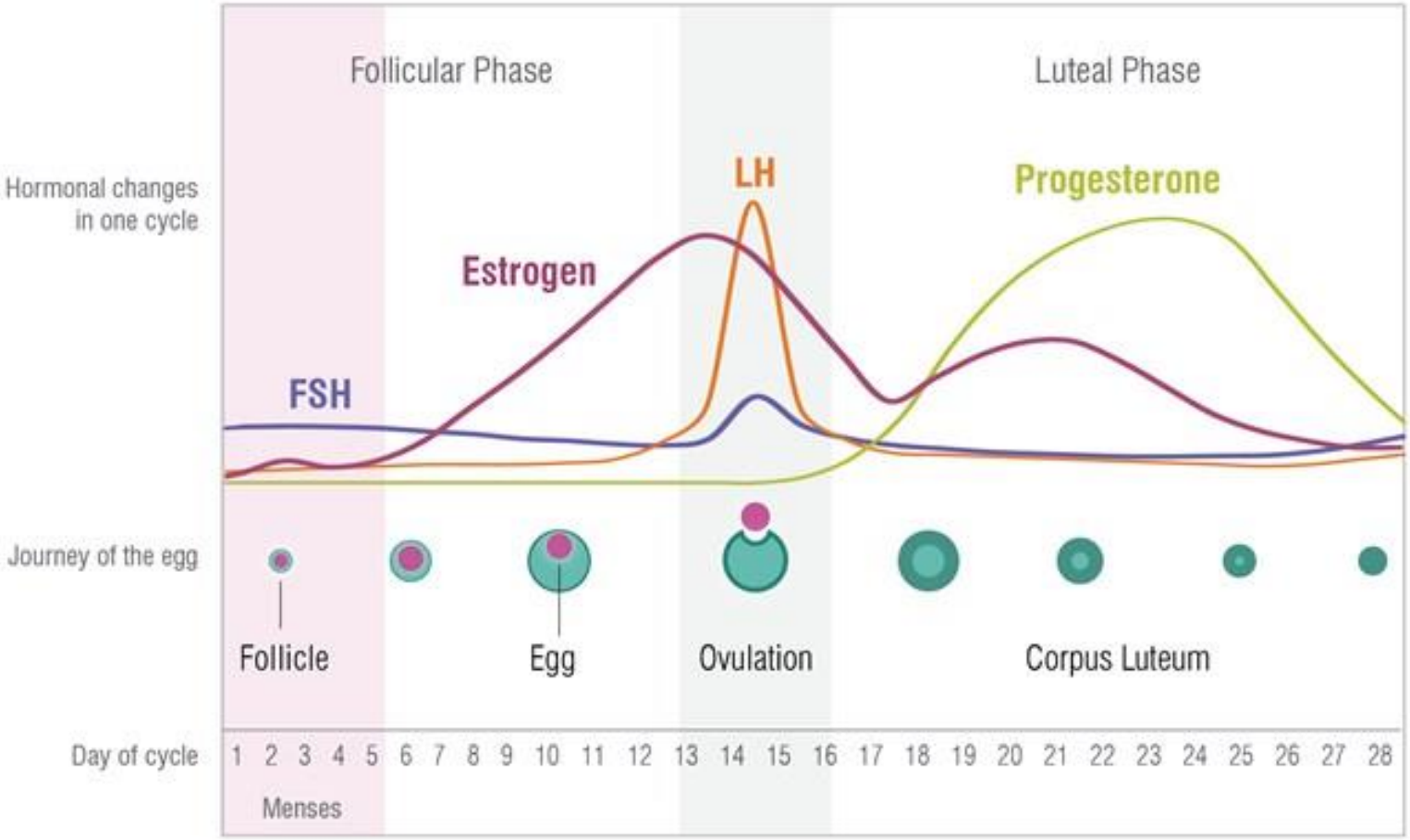


This illustration is an example of a 28-day cycle. Hormonal changes and day of ovulation vary with cycle lengths.

Corpus Luteum

- Produces estradiol and progesterone
- Gains colour from large amount of cholesterol esters
- Expresses large amount of: StAR, P450scc, 3ß-HSD, and P450arom
- Degrades by day 28 ending hormone production and starting the next cycle

Educated House Wife
@SierraHighKey

Uterus: Look! I put up the wall paper for the new baby!

Body: yeah... There isn't a baby. Not this month.

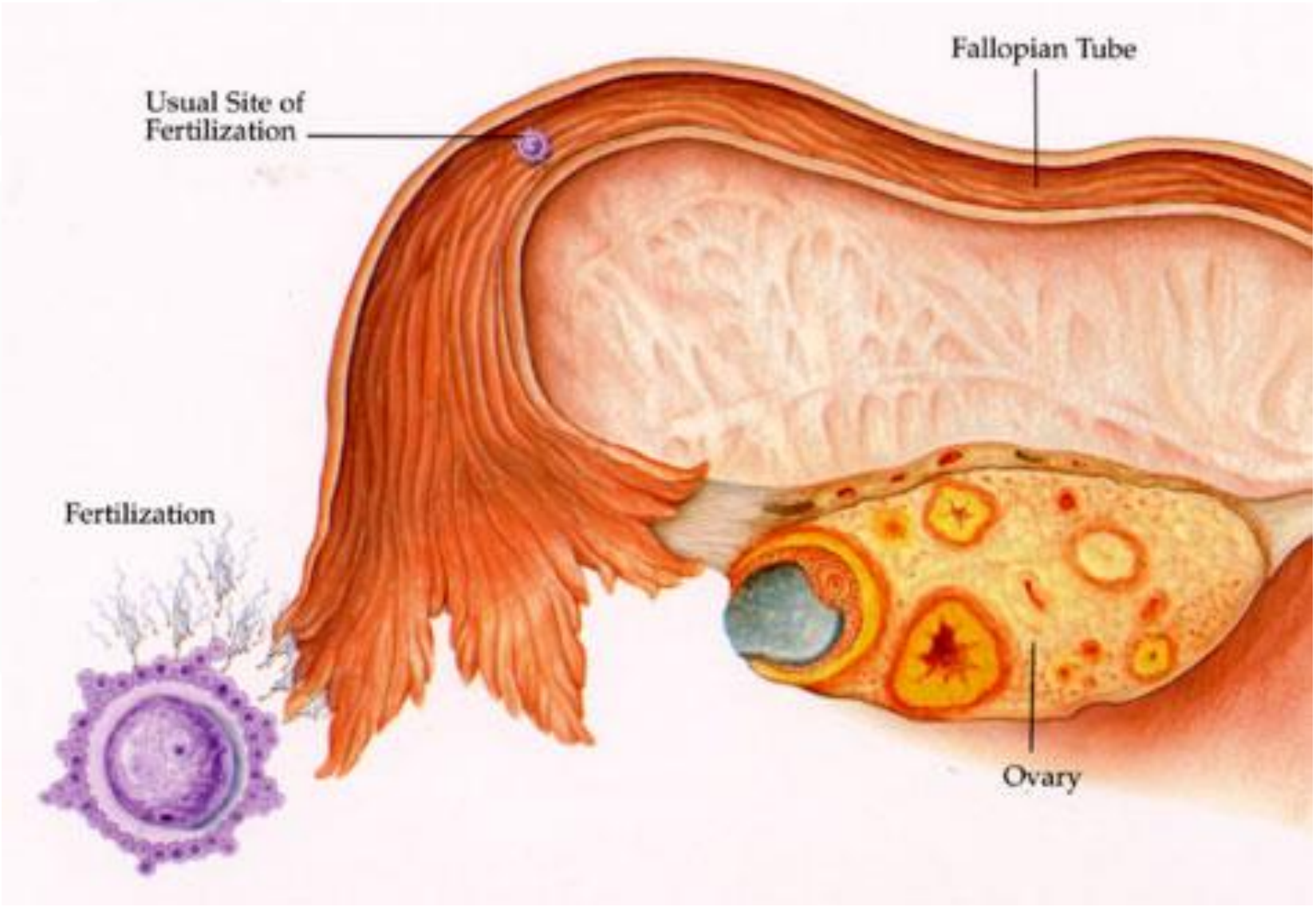
Uterus: ...

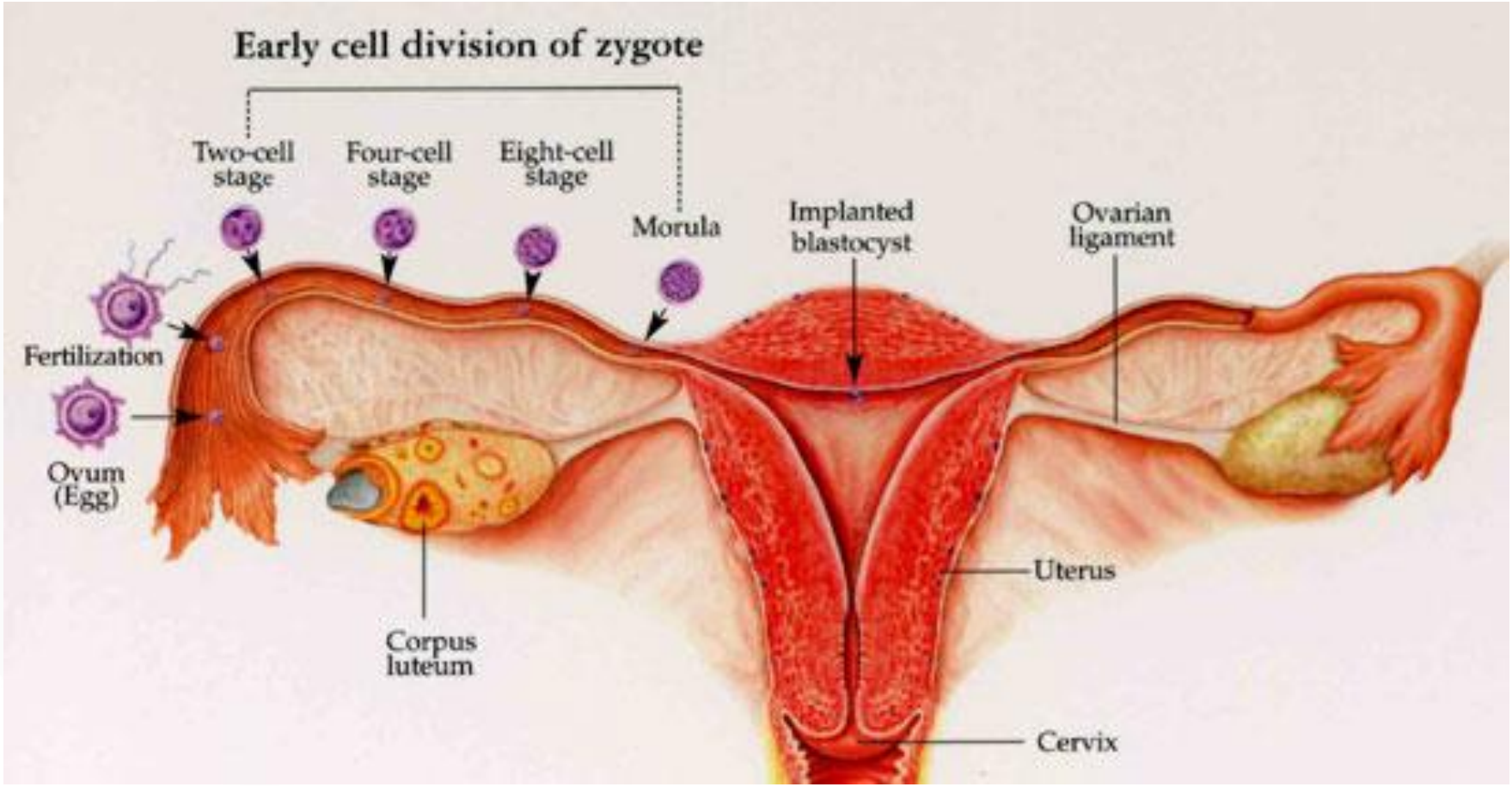
Body: please dont...

Uterus: You do this all the time These false alarms. IM DONE. I CANT TAKE THIS ANYMORE. *Rips down wall paper*

-The menstrual cycle

OR


Fallopian Tube
Usual Site of Fertilization
Fertilization
Ovary



Novaivf.com

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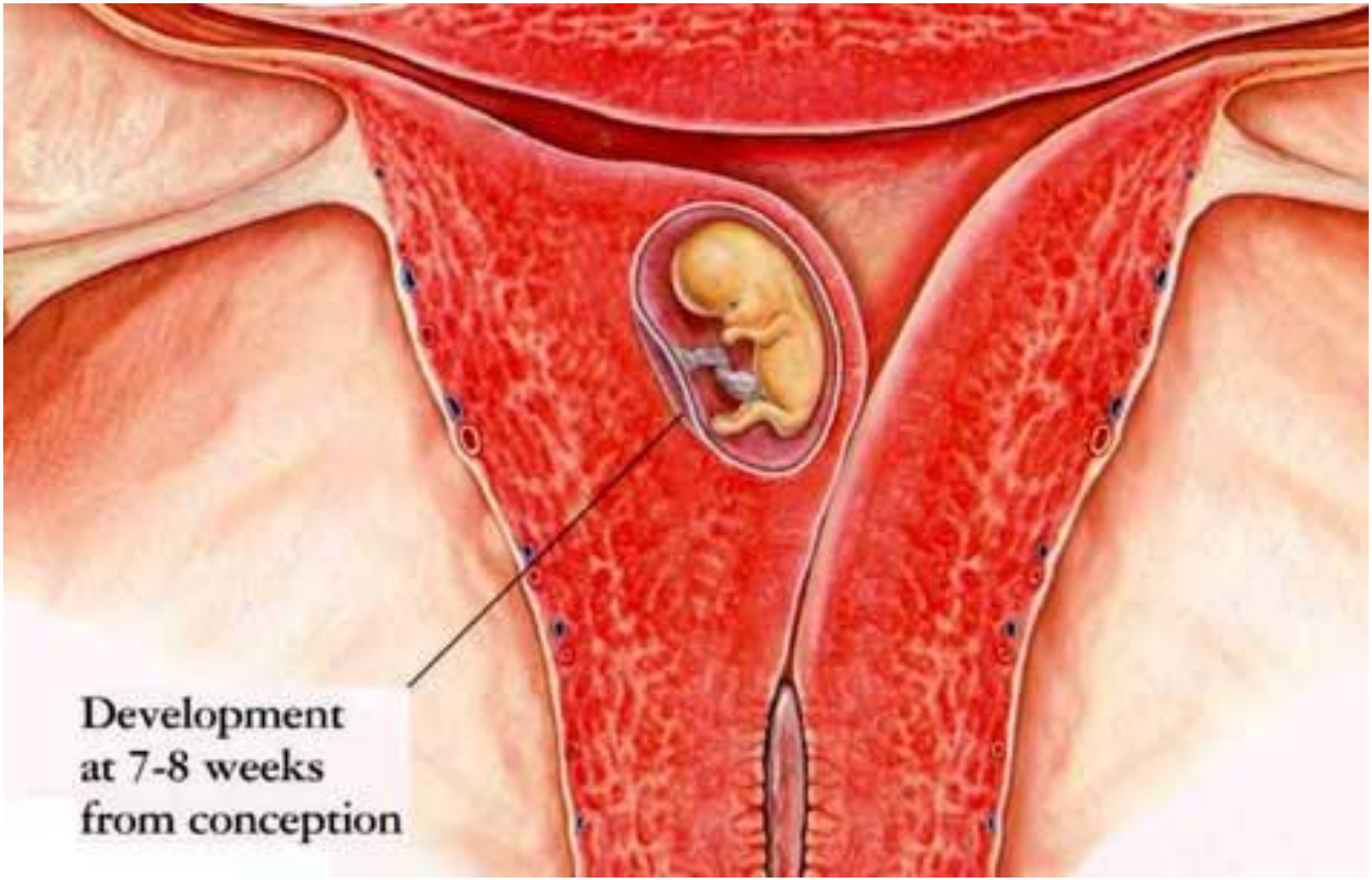

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2 COMMON CAUSES OF INFERTILITY

PCOS

POLYCYSTIC OVARIAN SYNDROME

PCOS is extremely common

4-10% of all women – many who are undiagnosed

Treatable, but not curable

Cause not known, but getting closer

3 SNPs identified w/insulin receptor

SORCS1 polymorphism (rs1358030, rs1416406 and rs11192966)

Abnormal Heat Shock protein 90B1

Mitochondrial SNPs positive (ND5 T12338C and tRNASer C7492T)

Abnormal AntiMullerian Hormone secretion

PCOS Diagnostic Requirement

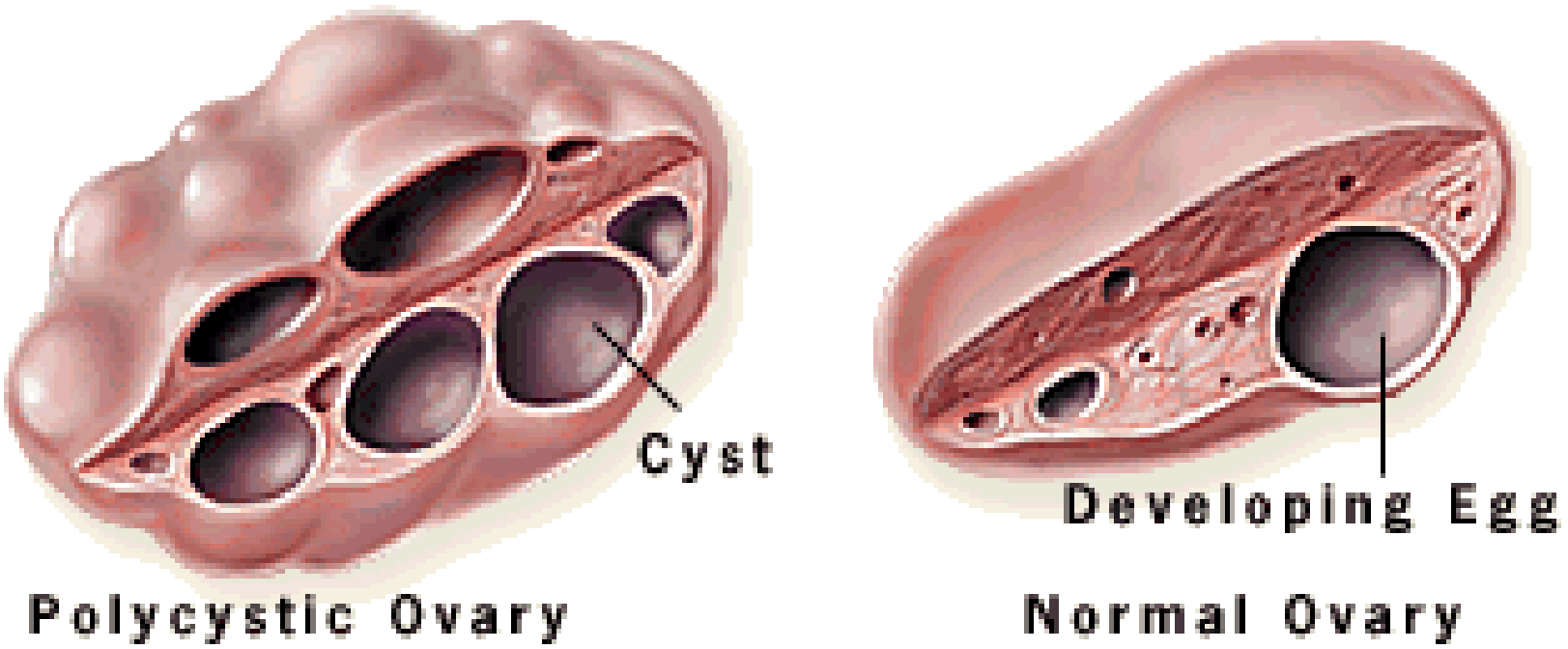
Symptoms of high androgens

High Androgens on testing

There are multiple phenotypes

No cysts need to be seen on ultrasound, although usually are seen

The Polycystic Ovary



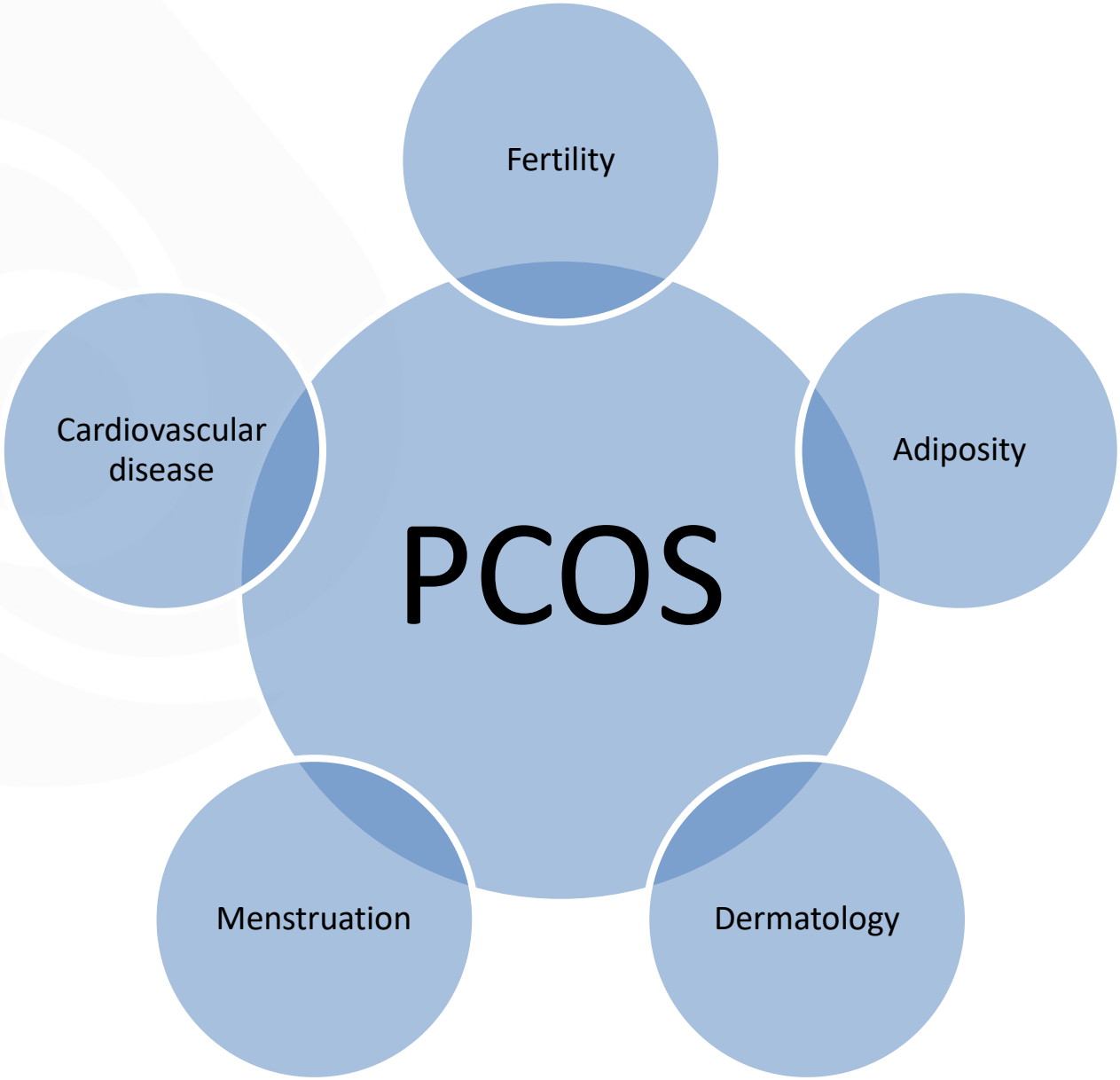
2 Commonly Seen Variants

Ovarian only

- Leaner
- Less hyperinsulinemic
- Difficult infertility
- High Testosterone, but normal DHEAS

Ovarian & Adrenal

- Weight struggles to Obesity
- Hyperinsulinemia
- Oligomenorrhea or regular cycles
- High DHEAS & Testosterone


Fertility
Cardiovascular disease
PCOS
Adiposity
Menstruation
Dermatology

Common signs and symptoms

Overweight/Obese

Acne

Increase facial/body hair

Oligomenorrhea

Amenorrhea

Infertility

Family history

Acanthosis

Type 2 Diabetes

Endometrial hyperplasia

Menorrhagia

Hypertension

Reactive hypoglycemia

Anovulatory cycles

High androgens

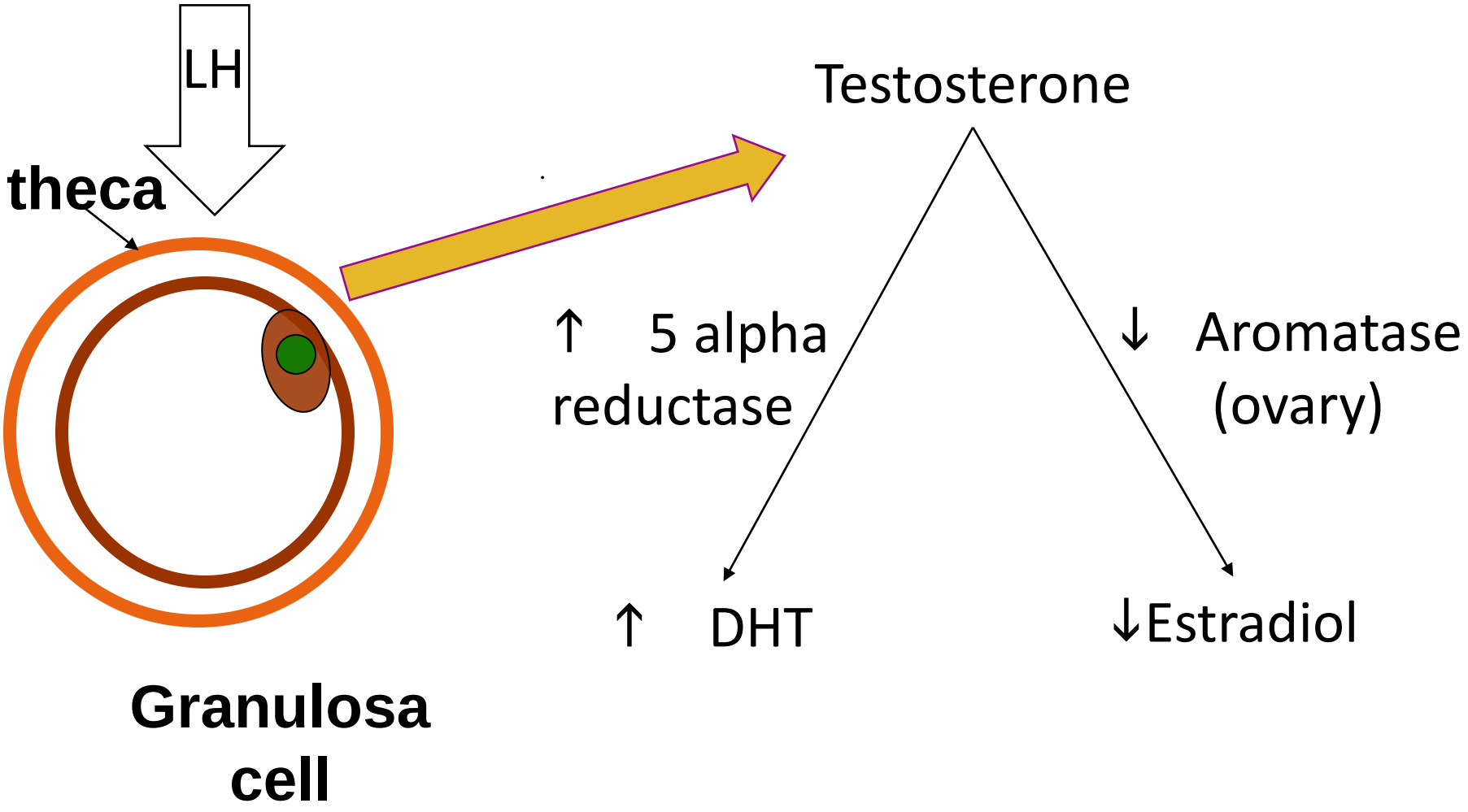
- Acne, facial/body hair, loss of scalp hair

Insulin resistance – hyperinsulinemia

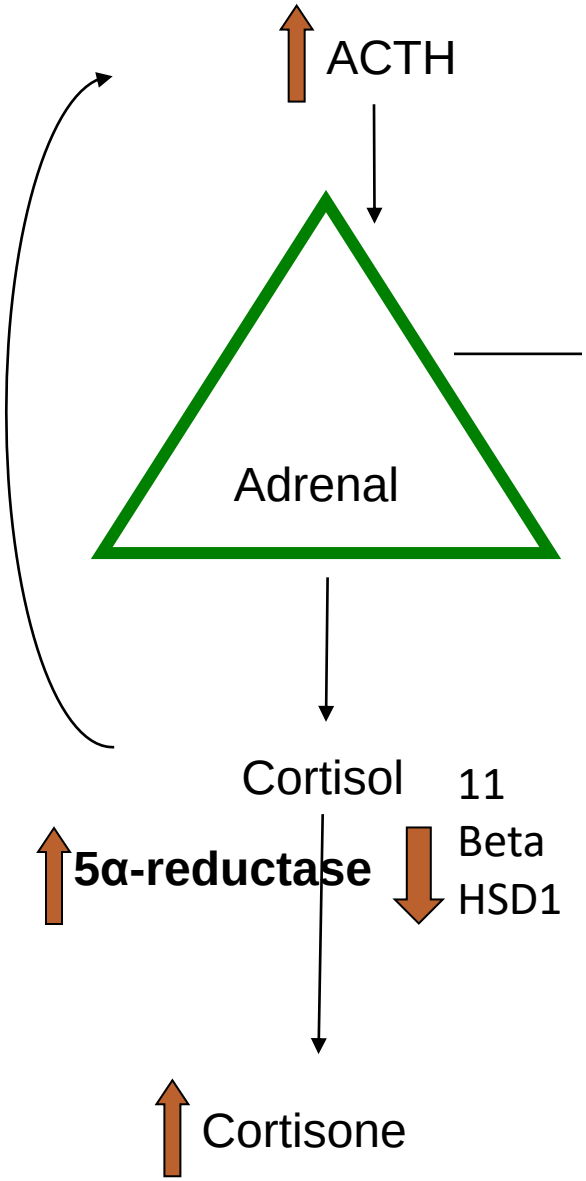
High LH relative to FSH (50%)

Multiple follicles without dominant follicle

Ovarian Component



The Adrenal Component



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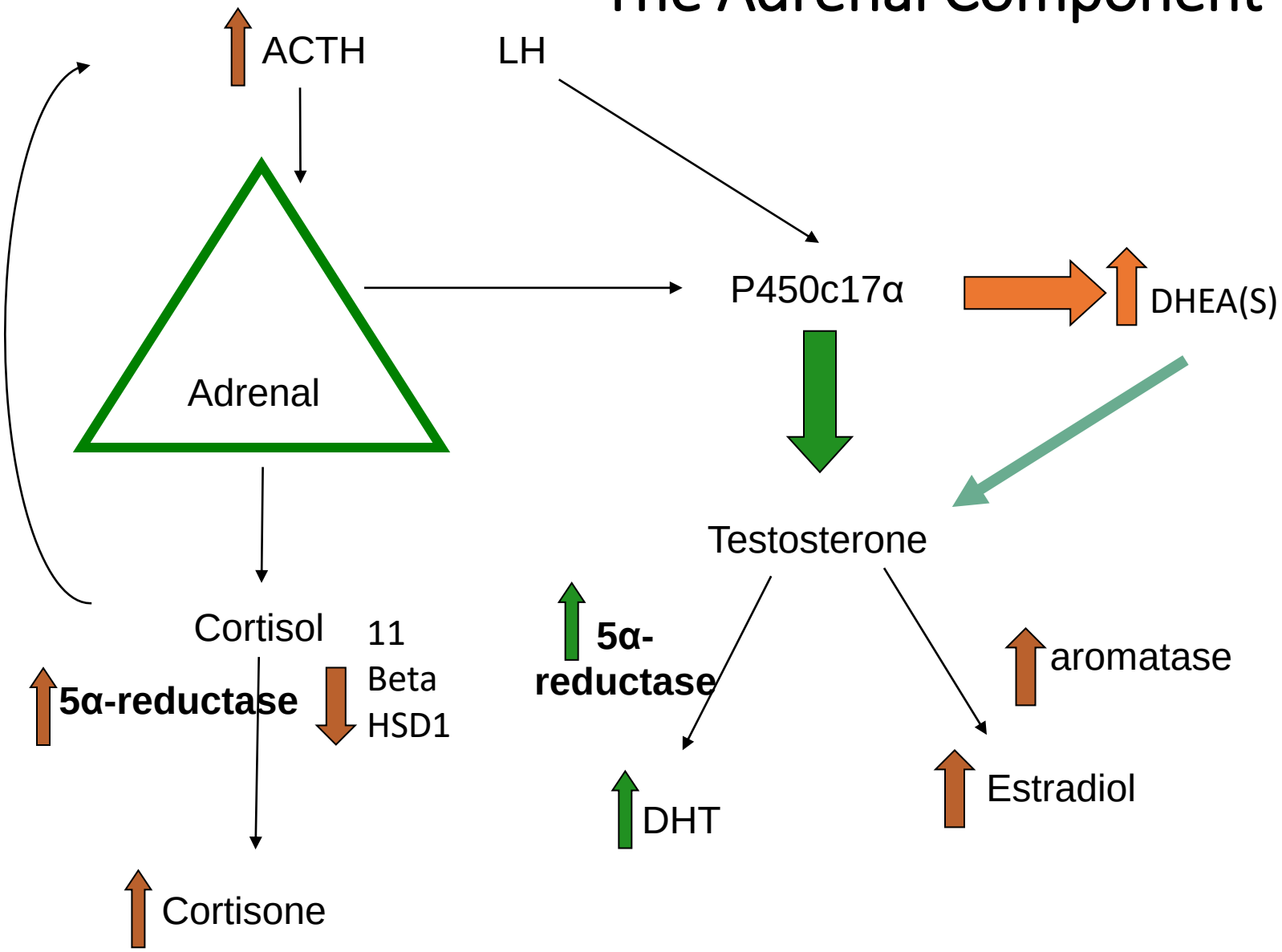


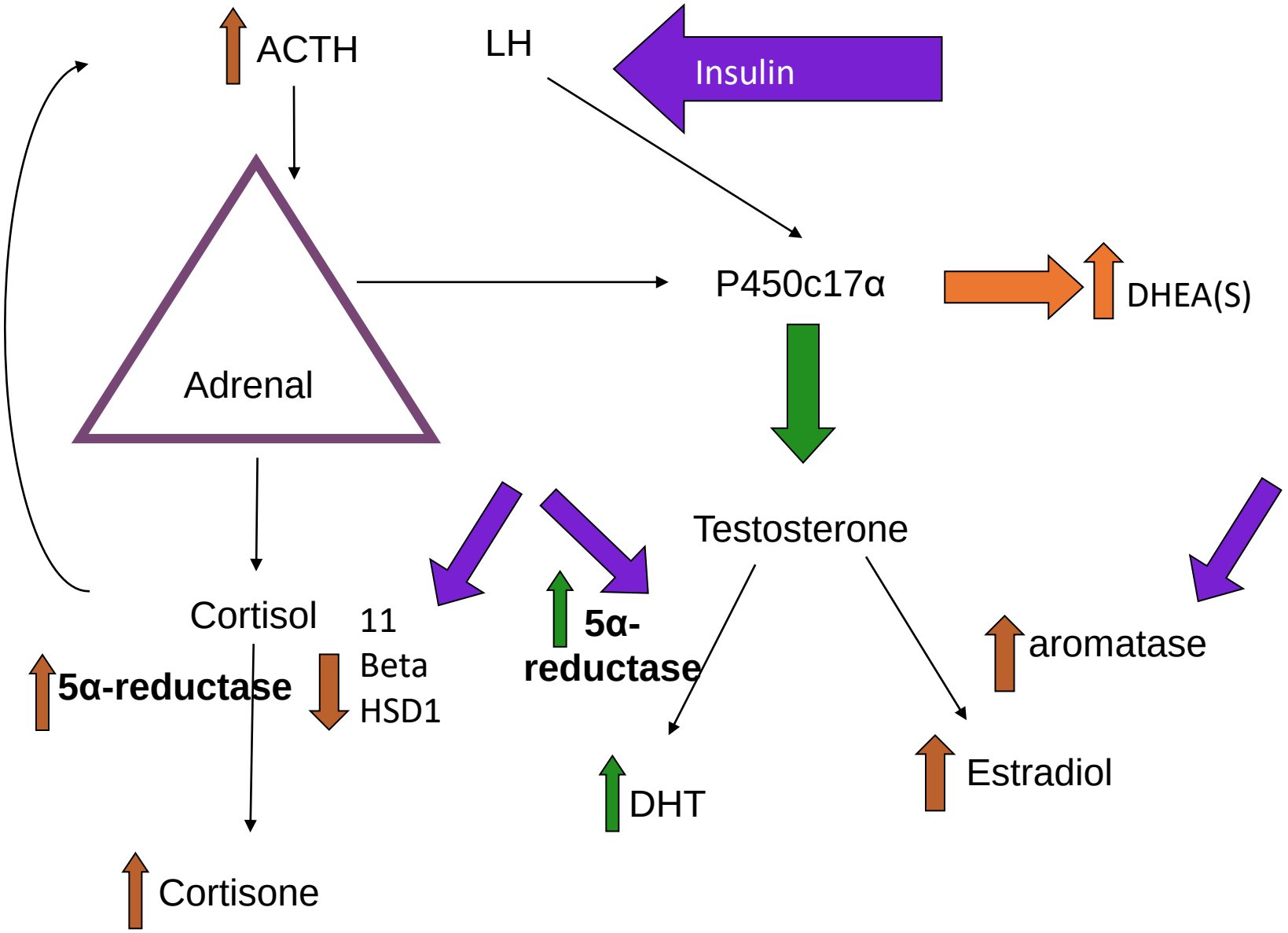
60% of women with PCOS have mental health issues

Gestational hyperandrogenism of the developing fetus

- Increased anxiety
- Changes to the amygdala
  - Androgen receptors changed
  - Estrogen receptors changed
  - Genes changed regulating serotonin and GABA

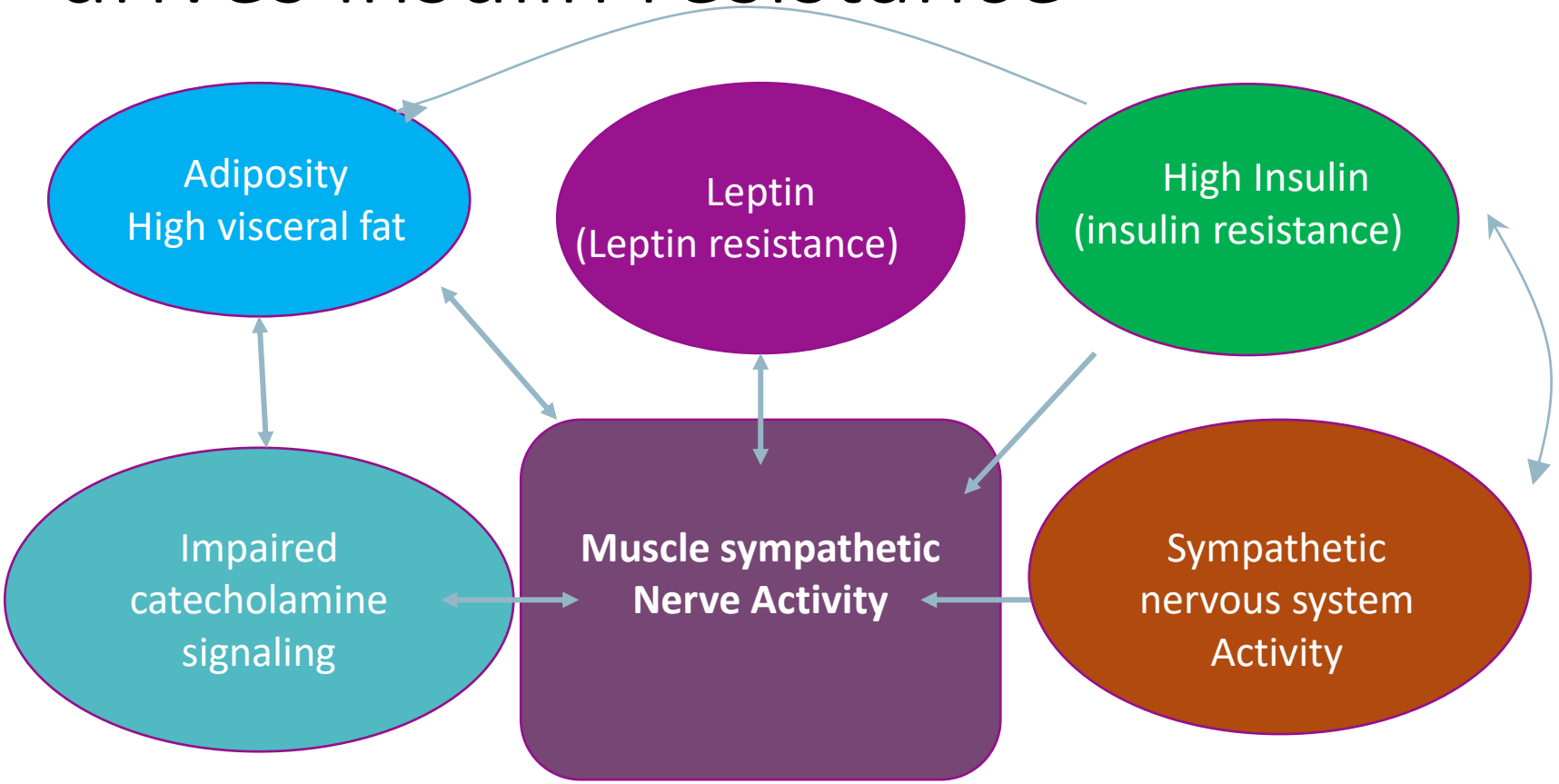
Multigenerational PCOS

Insulin Influences

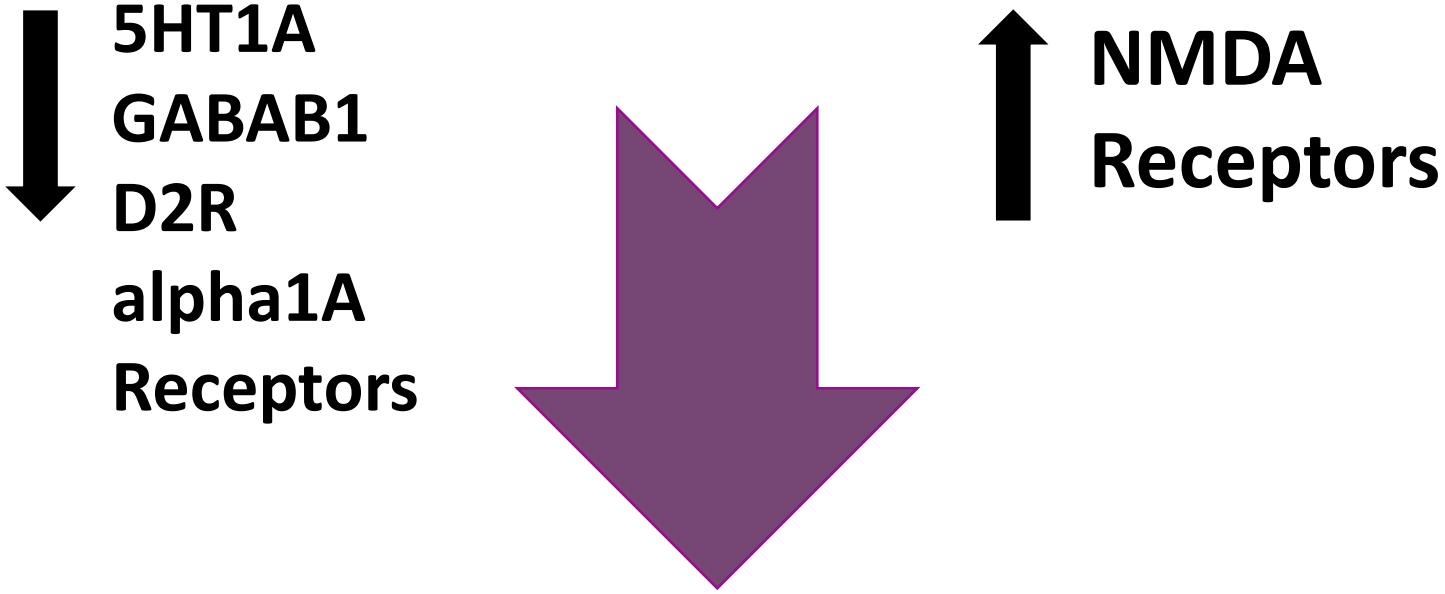



Inc IGF1
Liver
Muscle
Adipose
Ovaries
Dec adiponectin
High Insulin
PAI-1
Clotting
Dec SHBG
Dyslipidemia

Increased sympathetic activity drives insulin resistance



Altered Neurotransmitter Receptors

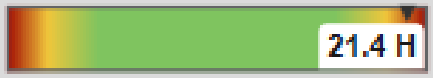
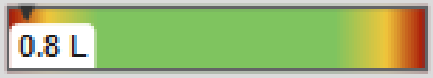


Altered GnRH Pulsatility

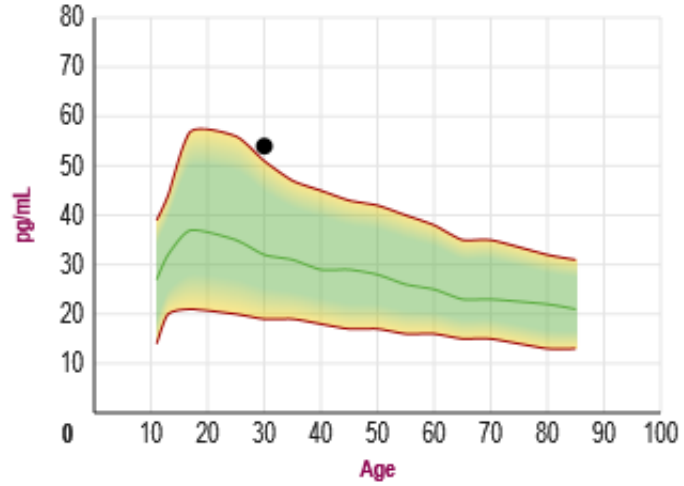
Labs to run on women with suspected PCOS

- Estradiol
- Progesterone
- Testosterone
- DHEAS
- Cortisol
- Thyroid panel & TPOab
- Fasting Insulin/glucose; 2 hour postprandial
- 17a-hydroxyprogesterone
- CBC/Chem screen
- Prolactin
- LH/FSH – day 3 of cycles
- CRP

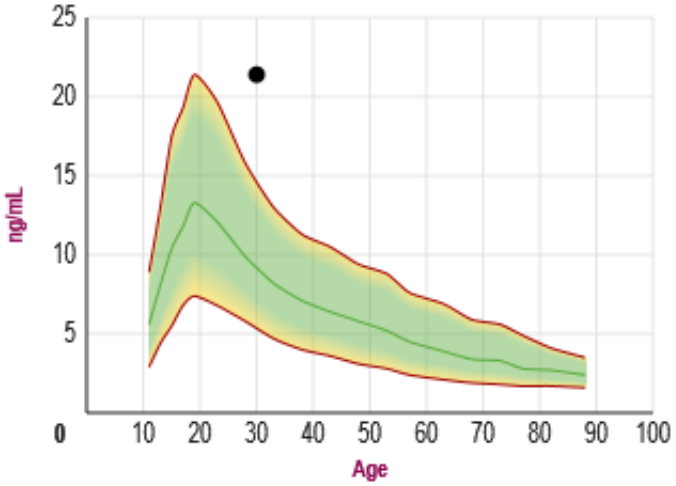
Hormone profile 3

Salivary Steroids		
Estradiol		1.0-5.0 Premenopausal (optimal 1.5-3)
Progesterone		100-600 Premenopausal-luteal (b)
Ratio: Pg/E2		Optimal: 100-500 when E2 1.3-3.3 pg/mL
Testosterone		20-50
DHEAS		3-10
Cortisol		3-8 (morning)
Cortisol		2-4 (noon)
Cortisol		1-2 (evening)
Cortisol		0.5-1.5 (night)

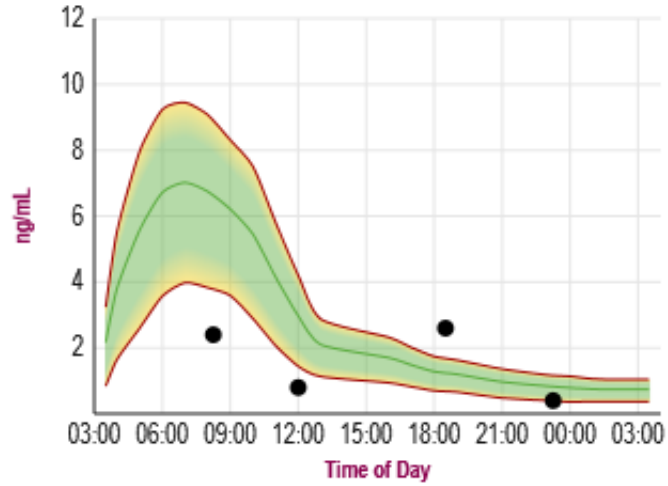
Saliva Testosterone



Saliva DHEAS



Saliva Cortisol



Another variant of PCOS

Salivary Steroids		
Estradiol	1.0	1.0-5.0 Premenopausal (optimal 1.5-3)
Progesterone	12 L	100-600 Premenopausal-luteal (b)
Ratio: Pg/E2	12 L	Optimal: 100-500 when E2 1.3-3.3 pg/mL
Testosterone	50	20-50
DHEAS	14.4 H	3-10

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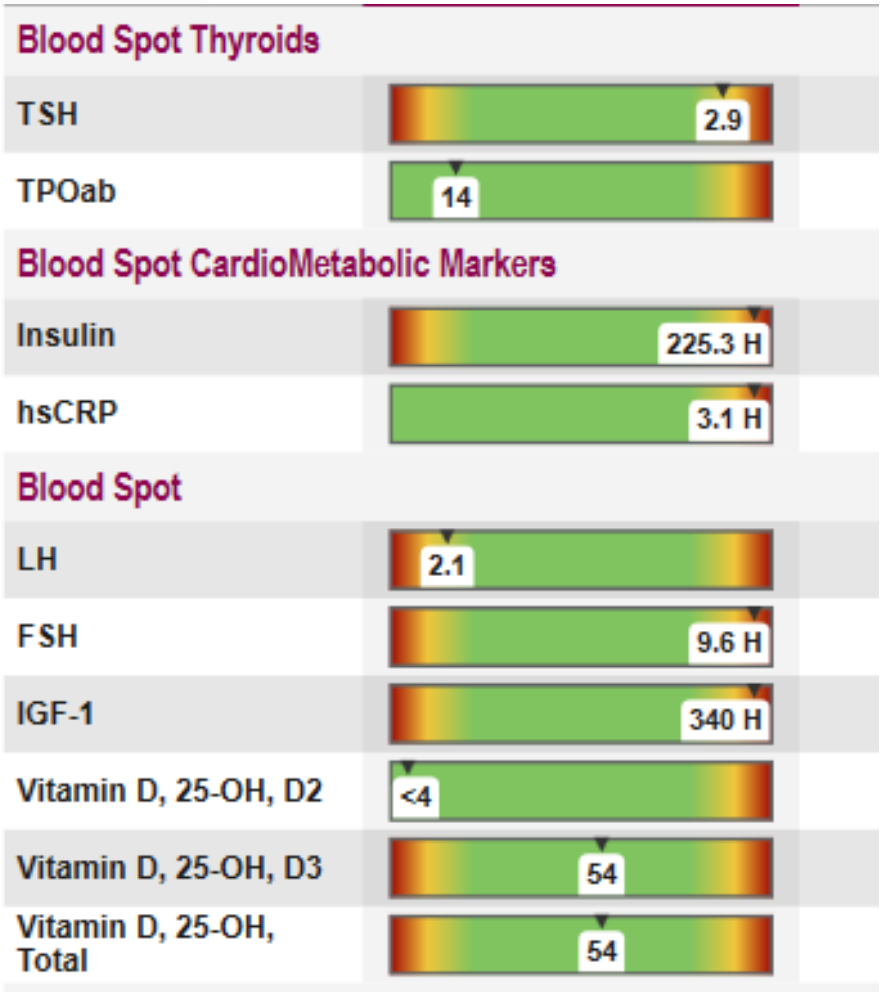
Postprandial Insulin and Day 3 Testing



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PCOS variant?

Salivary Steroids		
Estradiol	1.0 L	1.3-3.3 pg/mL Premenopausal (Luteal)
Progesterone	81	75-270 pg/mL Premenopausal (Luteal)
Ratio: Pg/E2	81 L	Optimal: 100-500 when E2 1.3-3.3 pg/mL
Testosterone	45	16-55 pg/mL (Age Dependent)
DHEAS	6.3	2-23 ng/mL (Age Dependent)
Cortisol	8.0	3.7-9.5 ng/mL (morning)
Cortisol	2.0	1.2-3.0 ng/mL (noon)
Cortisol	0.9	0.6-1.9 ng/mL (evening)
Cortisol	0.6	0.4-1.0 ng/mL (night)
Blood Spot Thyroids		
TSH	1.2	0.5-3.0 µU/mL
Blood Spot CardioMetabolic Markers		
Insulin	2.2	1-15 µIU/mL (optimal 2-6)
Hemoglobin A1c	6.3 H	<6%

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Goals of Treatment

- Lower Androgens – testosterone and DHEAS
- Increase Sex Hormone Binding Globulin (SHBG)
- Normalize insulin resistance and hyperinsulinemia
- Lower sympathetic nervous system tone
- Optimize hormone balance overall
- Reduce inflammatory state

Conventional Medications

Oral Contraceptives

Spironolactone

Metformin HCl

GLP1
:Semaglutide/Ozempic/Wegovy?

Clomiphene

Letrozole

Oral Contraceptives

- Choose: estrogenic, high progestogenic, low androgenic
- Oral contraceptives increase SHBG →↓Free testosterone
- Benefits include
  - Changes in SHBG lasts unknown time after discontinuation of OBCP
  - Dec. skin/hair issues
  - Regulate cycles
- Risks
  - May worsen insulin sensitivity (not thought to be significant)

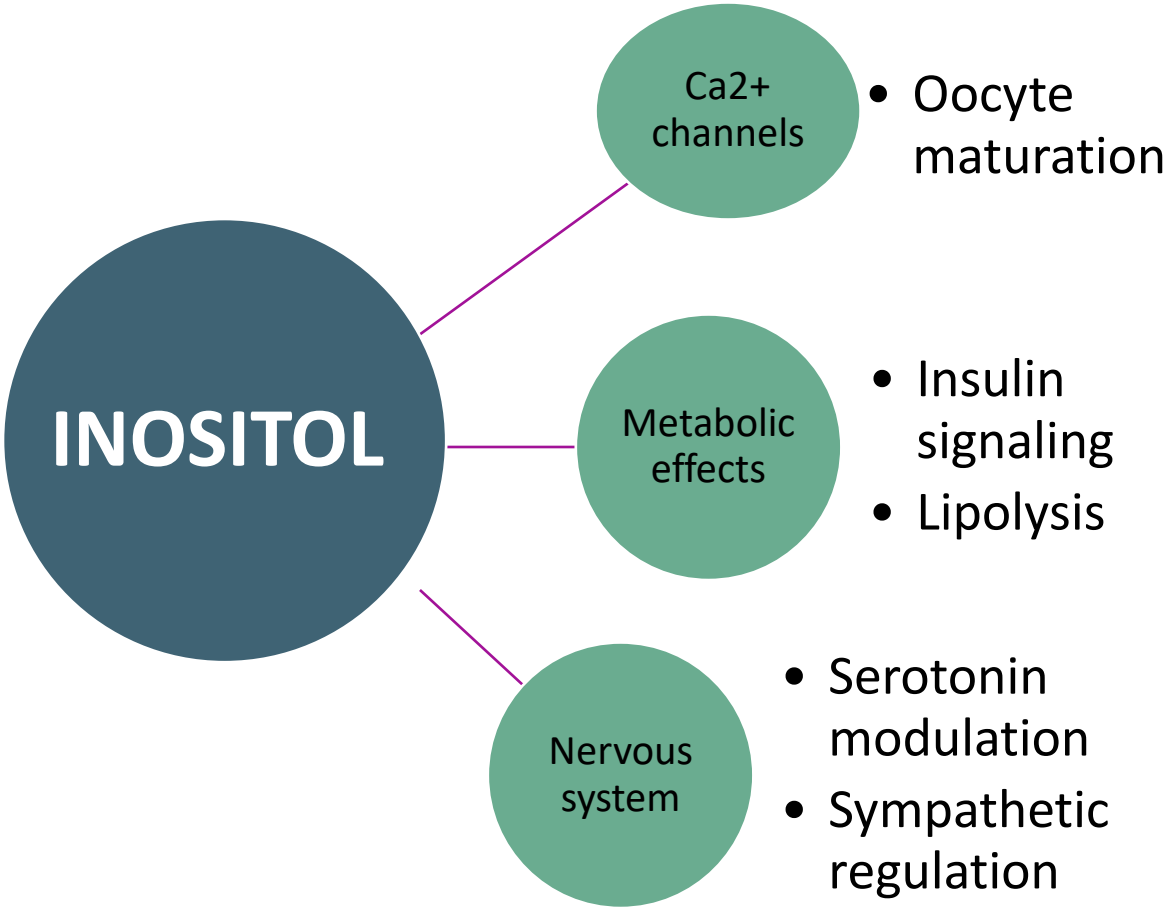
So Many Natural Products to consider

- Progesterone
- Chromium
- Gymnema sylvestre
- GABA
- Licorice
- Green Tea
- Flax seeds
- D-Chiro-Inositol/D-Pinitol/myo-inositol
- Vitamin D
- Calcium/Magnesium
- NAC
- Saw Palmetto

Insulin Sensitizing

- Chromium 200mcg – 500mcg QD-TID cc
- Gymnema sylvestre
- Berberine 500mg TID
- Inositol – 4 gms per day

Multiple functions of Inositol



Alison's Absolutes

- Lifestyle – low carb; higher protein diet
- SLEEP
- Inositol
- Berberine OR Metformin
- Adrenal support including licorice (BP caution)

Resources

- The Natural Diet Solution for PCOS and Infertility by Nancy Dunne, ND
- PCOS the Hidden Epidemic by Samuel Thatcher, MD, PhD
- PCOS by Felice Gersch
- PCOS by Fiona McClaugh
- PCOS by Pamela Smith

HYPOTHYROIDISM

Common signs of hypothyroidism

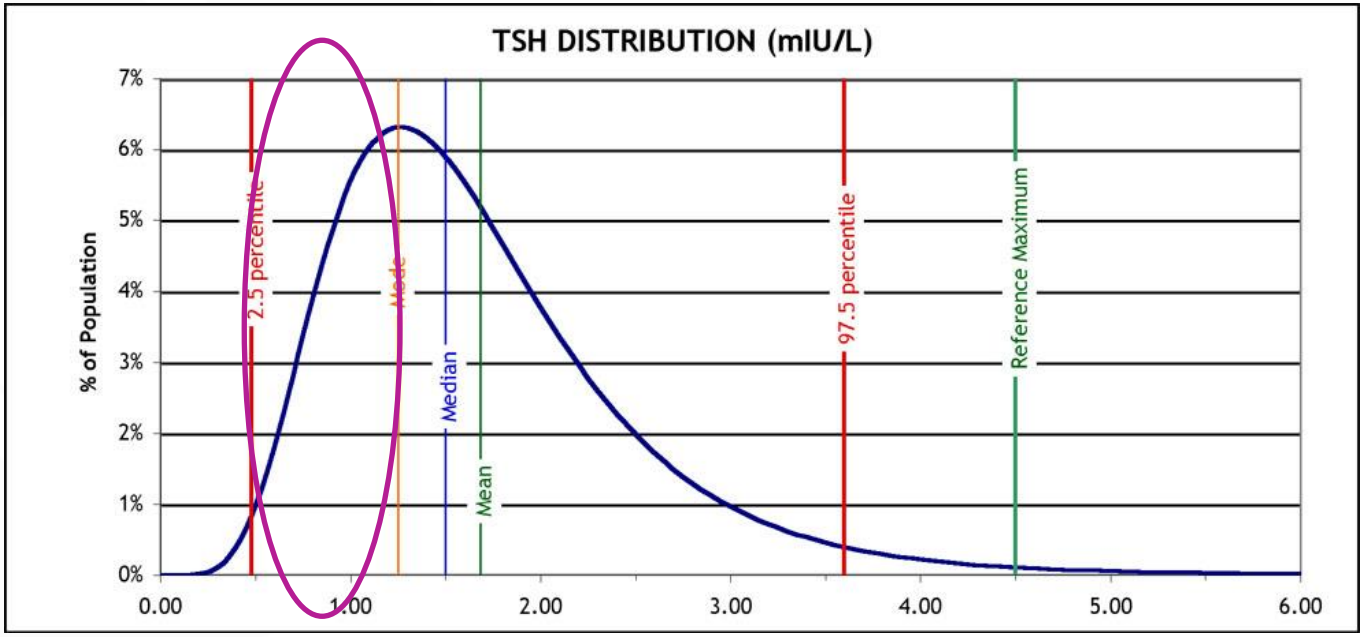
- Hypertention
- Bradycardia
- Coarse hair
- Swelling around the eyes
- Yellow skin
- Carpal tunnel
- Delayed reflexes

- Thyroid may be any size with firm texture.

- Unusual - megacolon, cardiomegally, galactorrhea, congestive heart failure.

Defining Underactive Thyroid

- **Overt Hypothyroidism**
  - TSH is high, T4/3 are low, Sxs are reported
- **Subclinical Hypothyroidism**
  - TSH is mildly elevated, T4/3 are N, Sx are reported.
- **Functional Hypothyroidism**
  - TSH, T4/3 are all N, yet the patient complains of symptoms.



Australian Thyroid Association

Hypothyroidism

Ovulatory dysfunction – amenorrhea or irregularity

Reduces sperm motility

Autoimmune thyroiditis increases SAB not corrected by thyroid replacement

Thyroid & Iodine

- Receptors on the granulosa cells
- Iodine and thyroid may affect ovaries directly
- Iodine concentrated in ovary (2^{nd} to thyroid)
- Iodine aid FSH/LH receptors on ovary
- Low iodine = low T3 in ovary
- Thyroid hormone (T3) found in follicular fluid

Autoimmune Causes are complexed

Viruses - Coxsackie B virus, Yersinia enterocolitica, Escherichia coli, Helicobacter pylori

Covid?

Gliadin cross reaction

Food allergens

Autoimmune diseases

- Diabetes
- Celiac
- Vitiligo

Chemical exposures

Autoimmune Thyroiditis

- Males: Patho-zoospermia and astheno-zoospermia

Female:

- ↑SAB
- Inc 2X risk without abnormal TSH
- Increased preterm deliveries

SCREEN IN FIRST TRIMESTER or better yet, preconception

Postpartum Thyroiditis
10% of women for 6-12 months after delivery.

Treat Subclinical hypothyroidism

- Hypothyroid
  - 30-40% inc. placental requirement
  - Inc. TBG
  - Greater blood volume
- 0-2.5 vs 2.5-5.50 in 1st trimester = 3.6% vs 6.1% SAB
- T4 tx in the 2.5-5.5 w/pos. TPO = 3.5% vs 13.8% SAB.

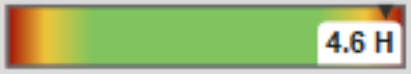
Thyroid Medications

- Synthroid
- T4
- T3
- Cytomel
- Tirosint

- Armour thyroid
- NP Thyroid
- Dessicated thyroid

ALL THYROID IS BIOIDENTICAL!

Blood Spot Thyroids

Free T4		0.7-2.5 ng/dL
Free T3		2.4-4.2 pg/mL
TSH		0.5-3.0 µU/mL
TPOab		0-150 IU/mL (70-150 borderline)

Patient Work-up for Fertility

History

- Menstrual history
- Pregnancy history
- Sexual intercourse – timing and frequency
- Sexual history – PID, Infections, STDs
- Environmental toxicity
- Surgeries
- Infections
- Caffeine intake

Imaging and other labs

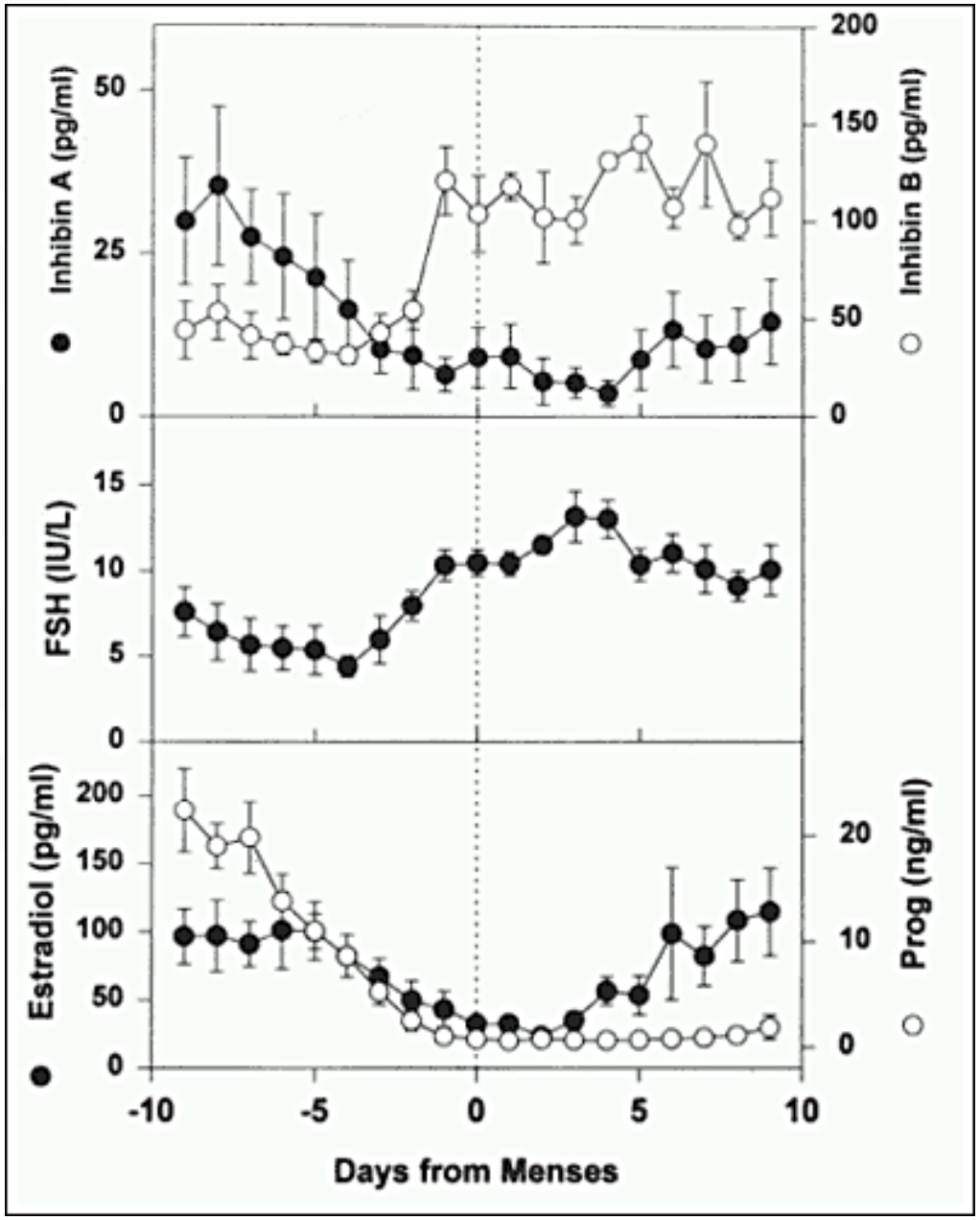
- Ultrasound of uterus
- Hysterosalpingogram

- Sperm analysis for partner

Assessing ovarian reserve

- FSH – Day 3
  - Considered baseline FSH level
  - Associated with number of follicles remaining
  - Lab dependent
  - Approximately < 12 is good (lab dependent)

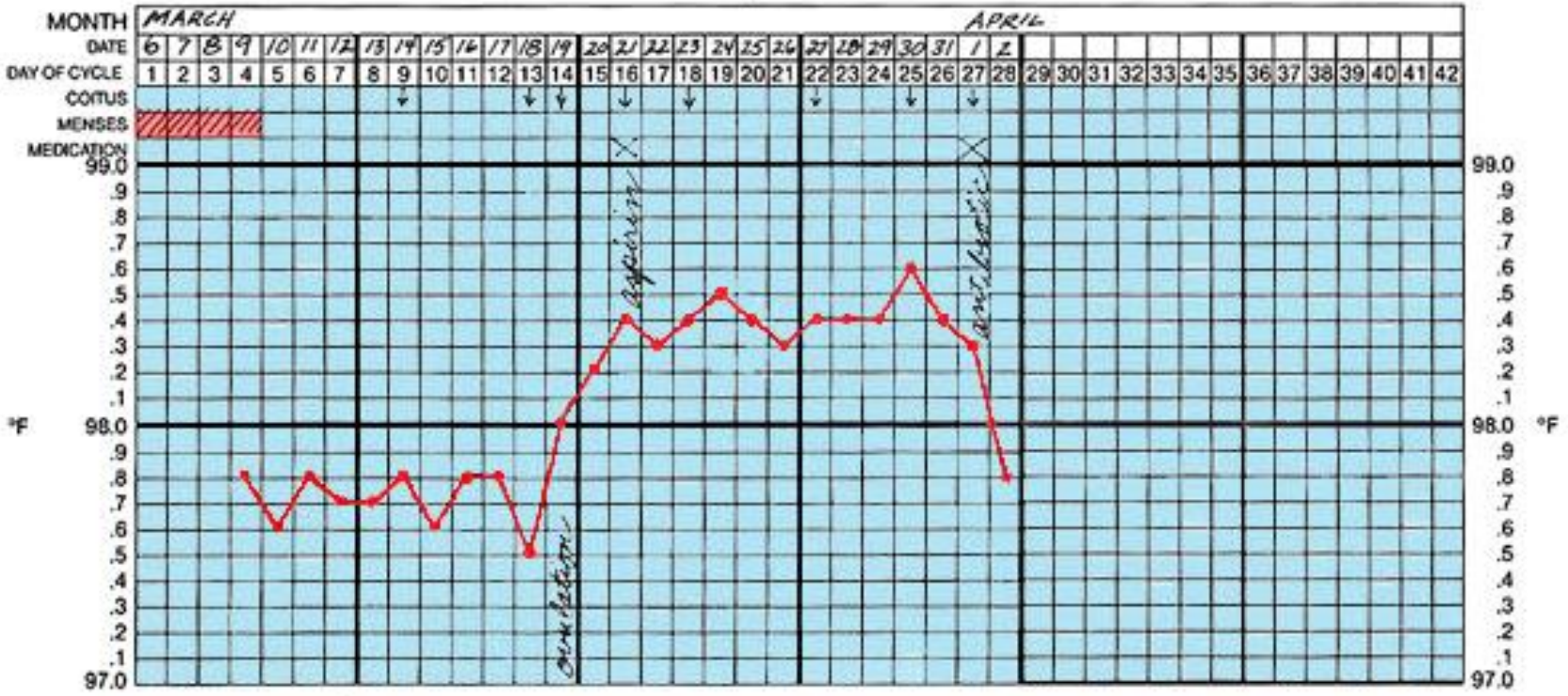
- Anti-Müllerian Hormone
  - Expressed by granulosa cells
  - Inhibits follicular recruitment by FSH
  - Independent of FSH
  - Correlated with antral follicle count (U/S)
  - Proportional to follicles



Assessing Ovulation

- Menstrual cycle- regularity, PMS
- Basal Body Temperatures – spikes 1-2 days after ovulation has already occurred.
- Cervical Mucus – amount and quality
- LH Kits – urine metabolite- ovulation in 24 hours
- Luteal progesterone level
- Salivary ferning - Fertilityscope

Sample Chart



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Conventional Testing

- Day 3 FSH & estradiol
- Day 19-21 – Estradiol, progesterone, testosterone, DHEAS, Cortisols
- Thyroid – TSH, TPO
- CBC, Chemistry
- Ferritin
- Hgb A1c & Insulin

Treatments

Vitex

- Vitex Agnes-Castus
  - Dopaminergic → reduce prolactin
  - Acts in the hypothalamus/pituitary – dec LH, inc FSH
  - Normalizes cycle esp oligomenorrhea
  - Increases corpus luteum health
    - Increases luteal estradiol and progesterone levels
  - Caution with other ovulatory stimulants

Progesterone

- DO NOT STOP IF PREGNANT
- 20mg topical
- 100-200mg po
- 200-400mg vaginally

from ovulation to day 26-28

Switch to vaginally 200-400mg pv once pregnant

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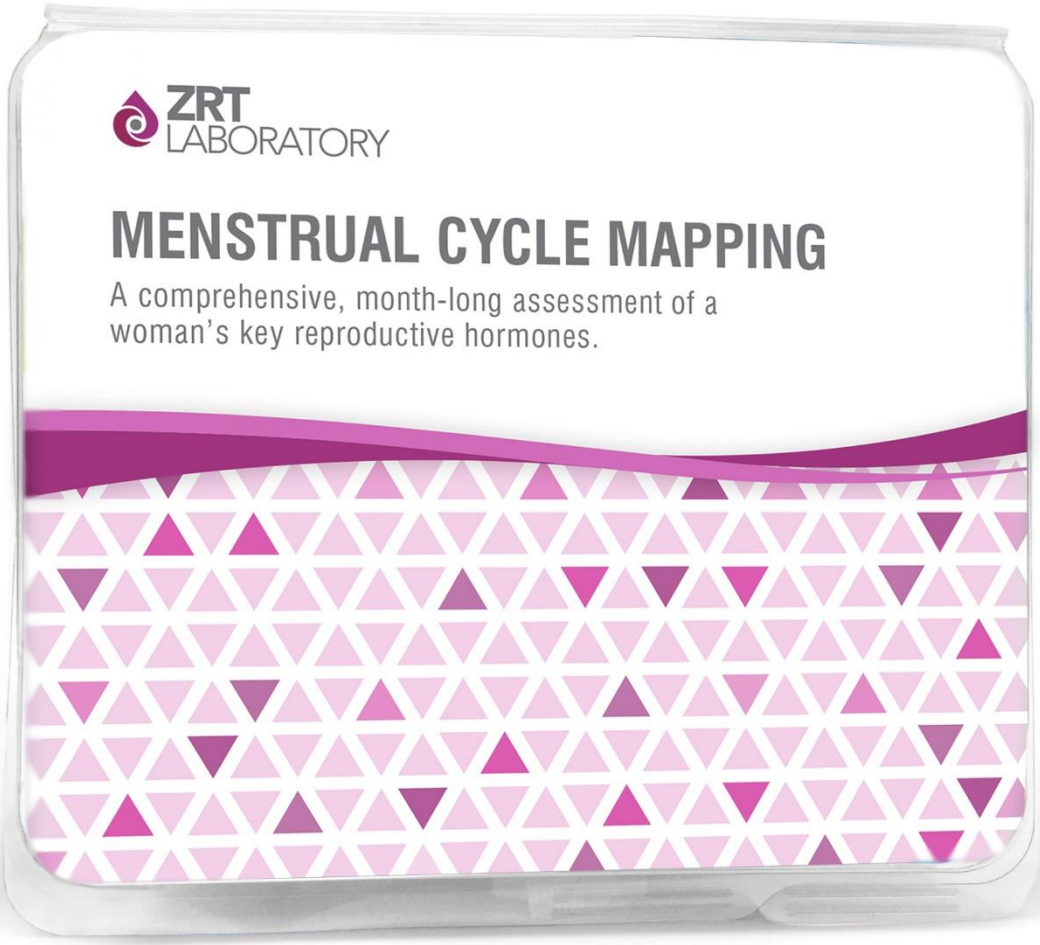
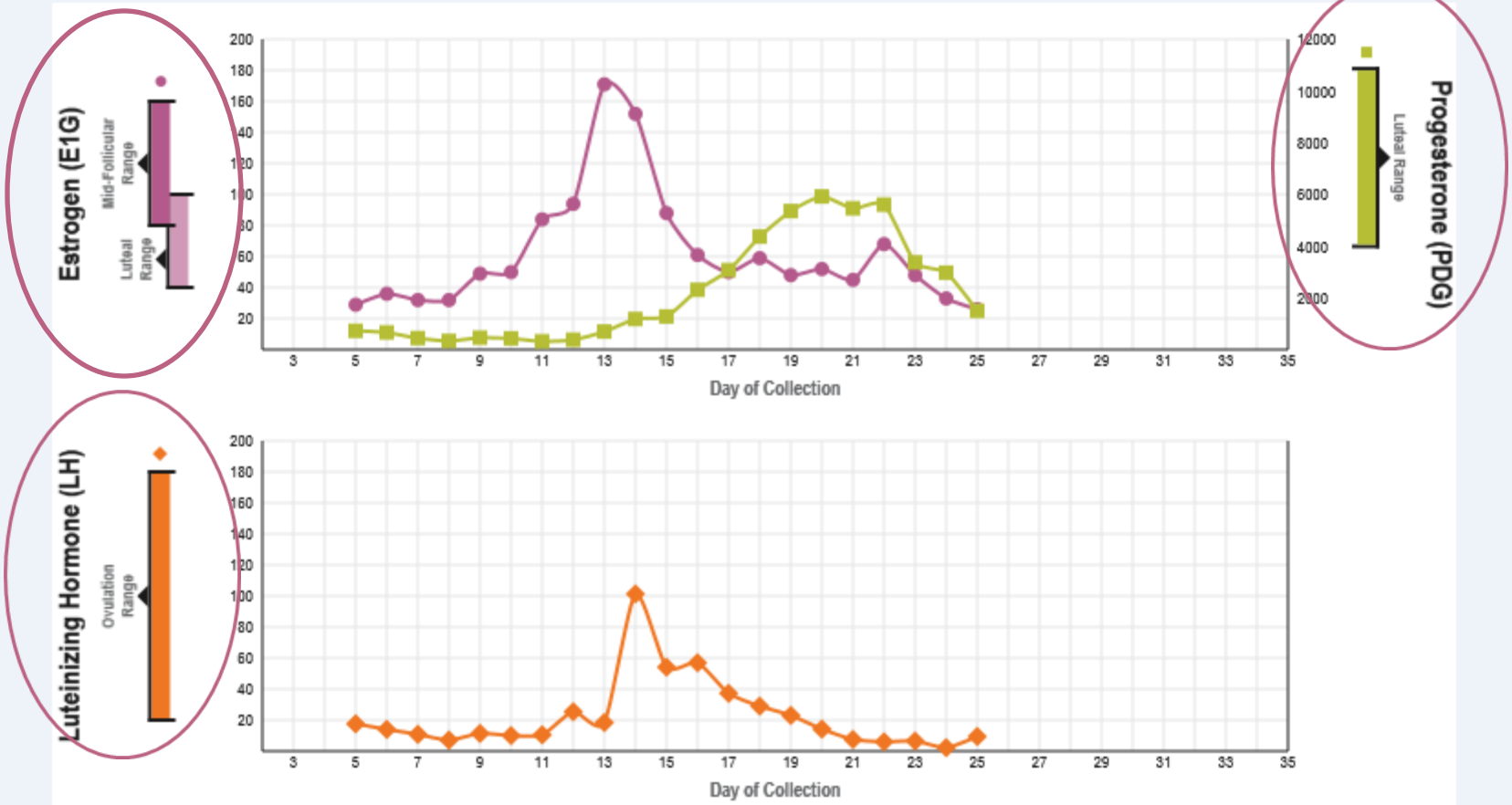
Fertility Profile


zrtlab.com
WELLNESS METRICS
Hormones, Stress
& Metabolism
A simple, convenient, and non-invasive
home-collection kit to evaluate your
health and wellness.
ZRT
LABORATORY

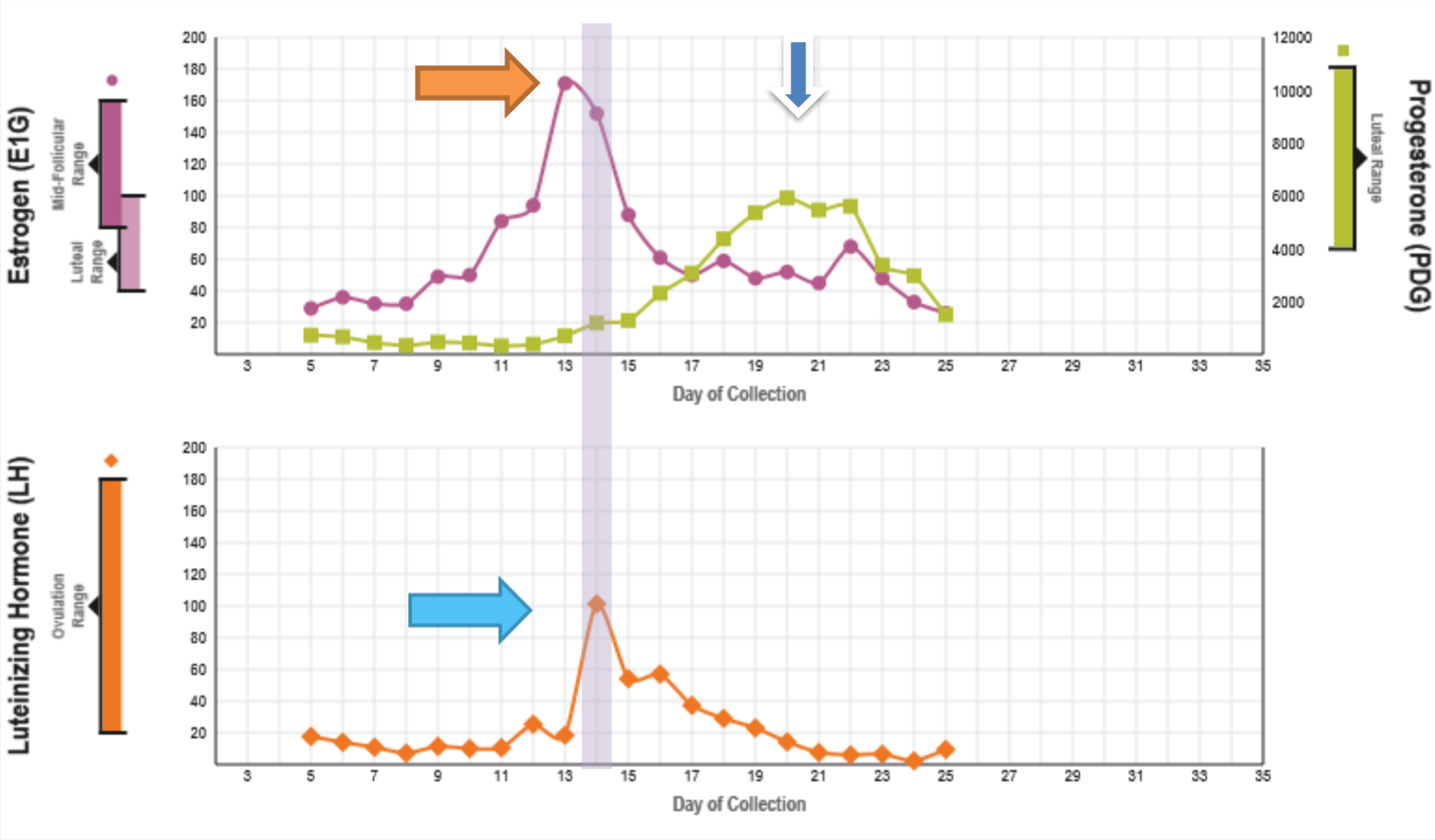

SALIVA + BLOOD
ZRT
LABORATORY


ZRT LABORATORY
MENSTRUAL CYCLE MAPPING
A comprehensive, month-long assessment of a woman's key reproductive hormones.

MENSTRUAL CYCLE MAPPING


Estrogen (E1G)
Mid-Follicular Range
Luteal Range
Progesterone (PDG)
Luteal Range
Day of Collection
Luteinizing Hormone (LH)
Ovulation Range
Day of Collection

ovulation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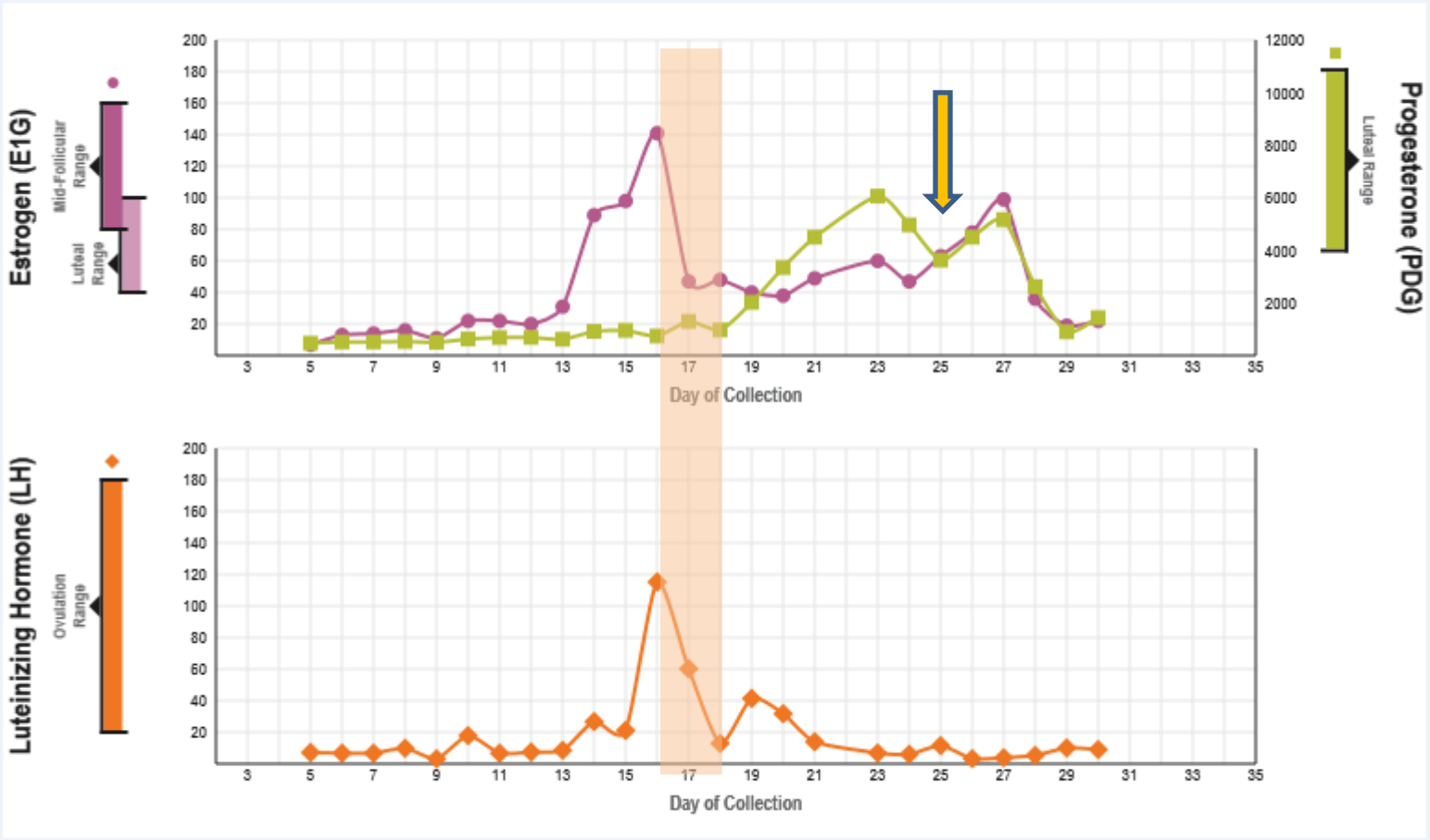
Day of Collection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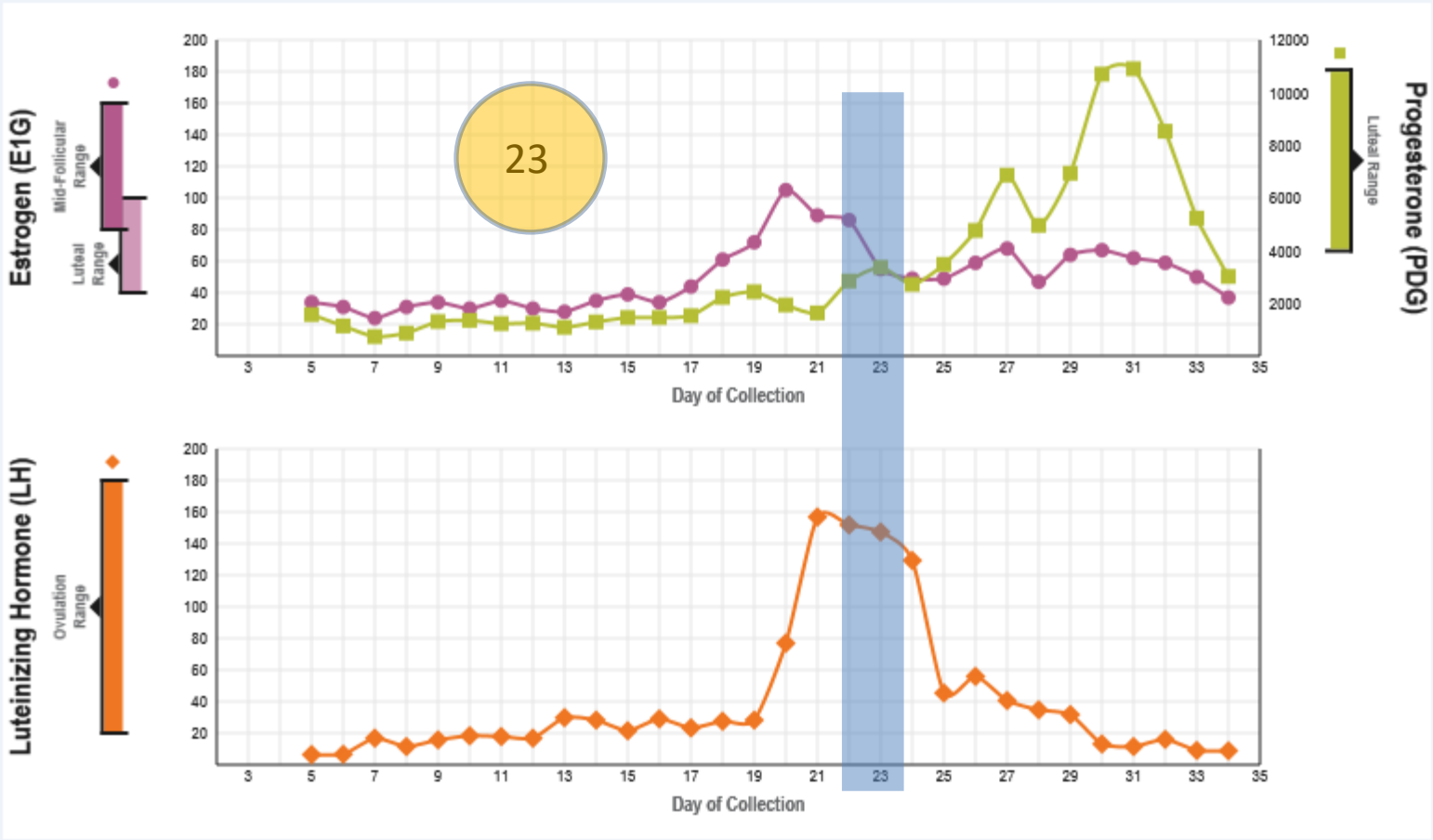
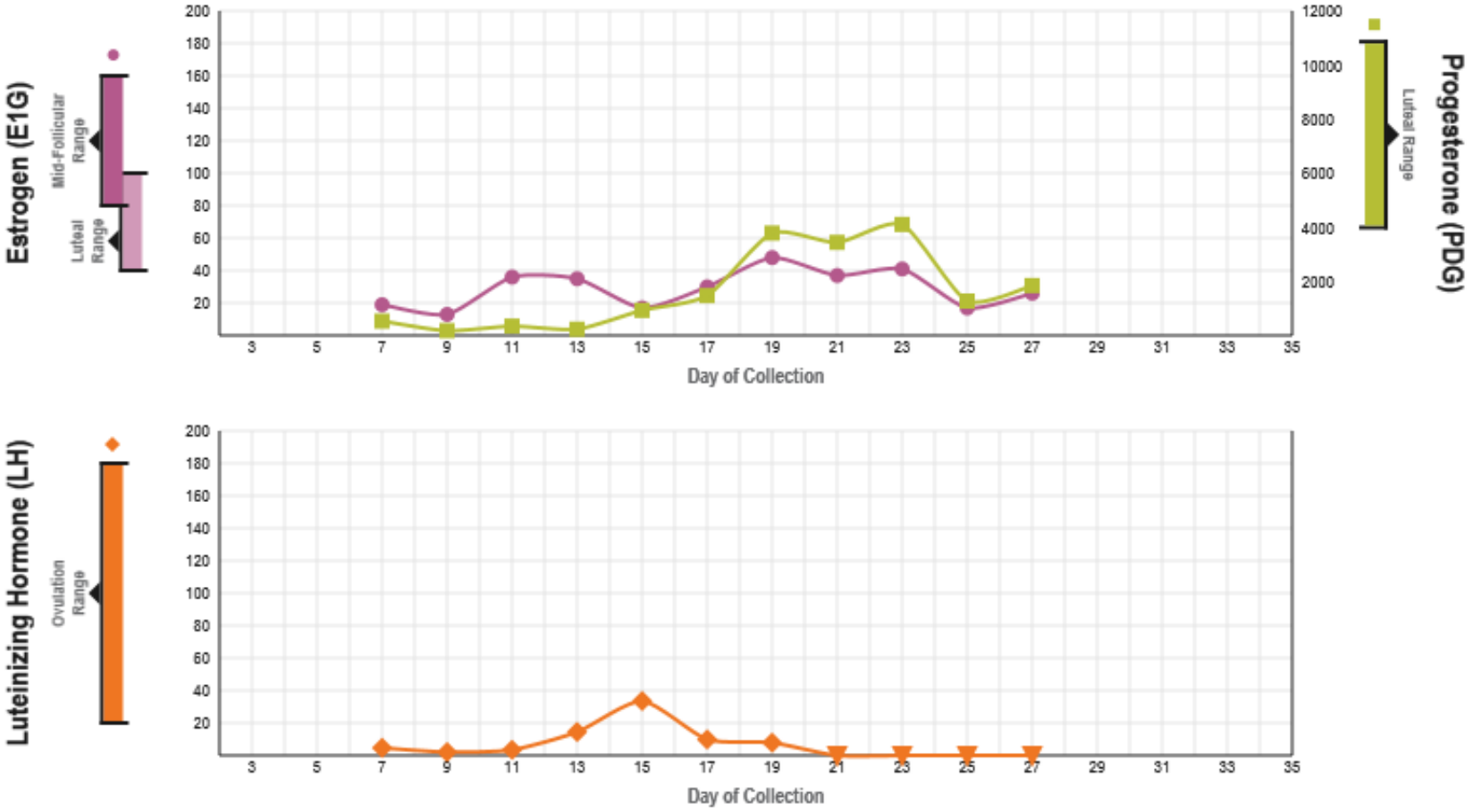
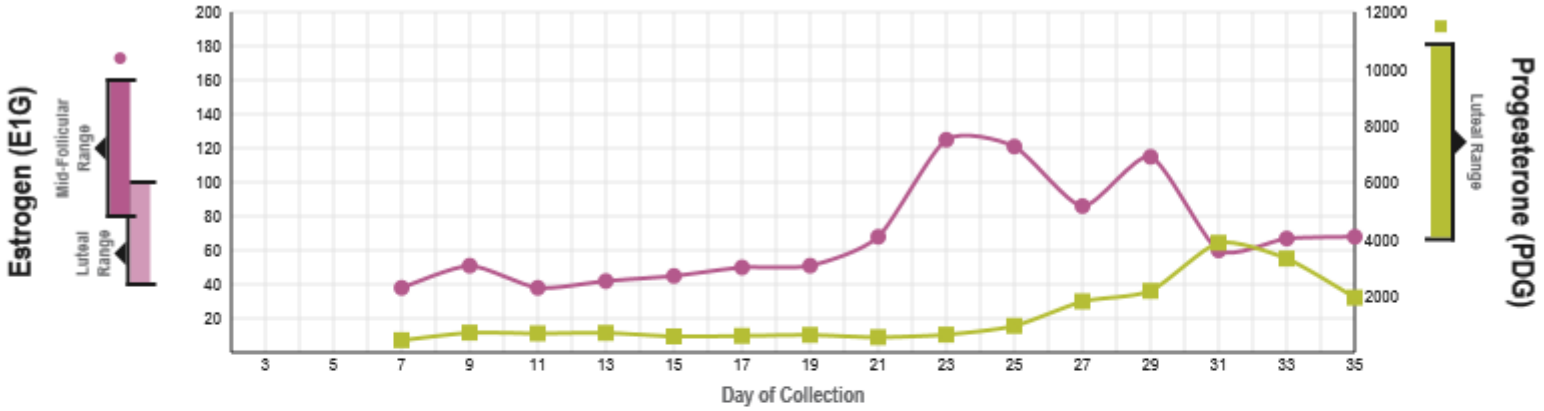
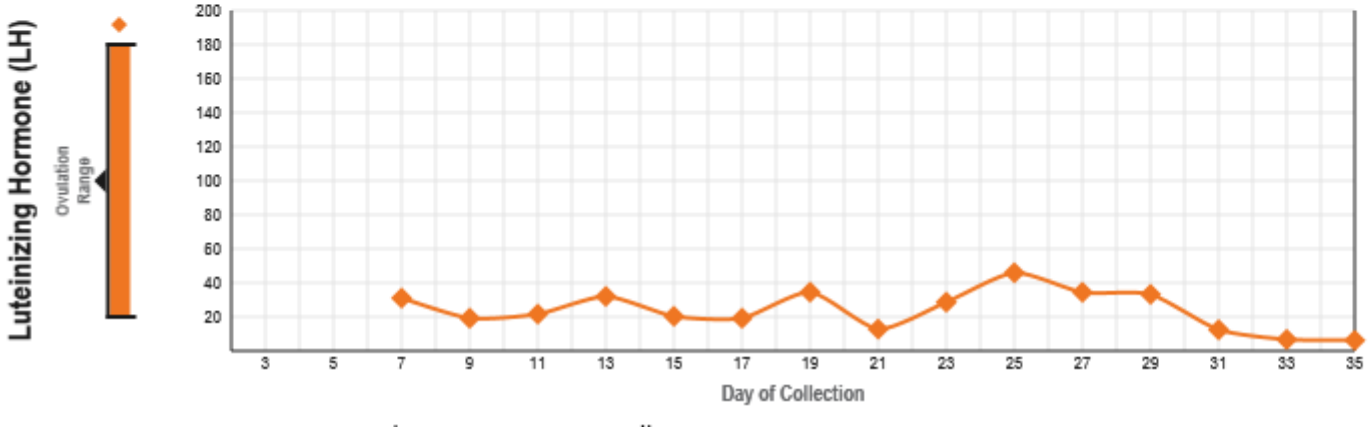
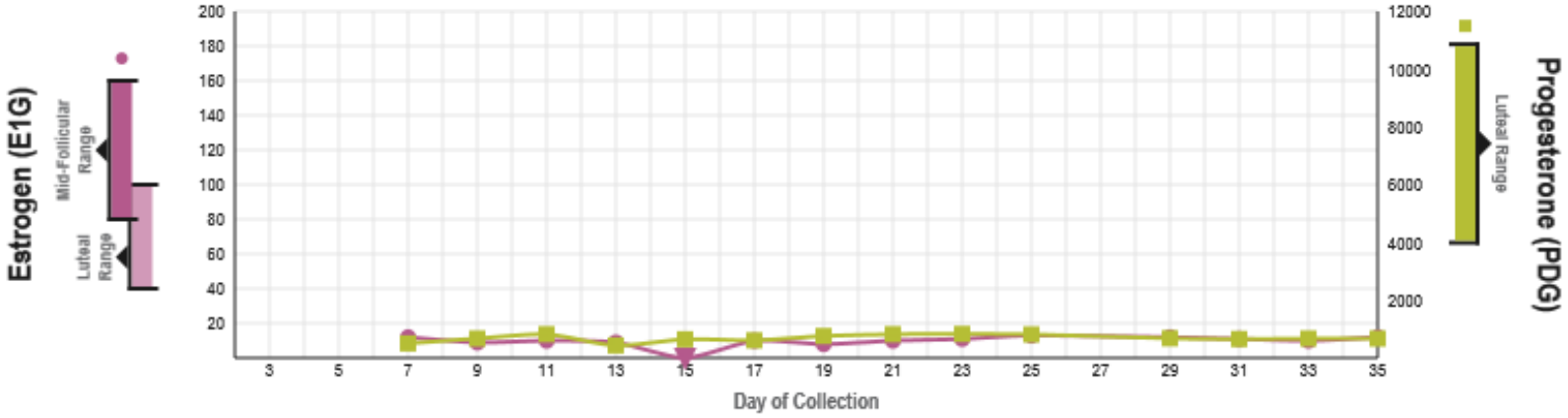
Luteal Range
Progesterone (PDG)
Luteal Range
Day of Collection
Luteinizing Hormone (LH)
Ovulation Range
Day of Collection

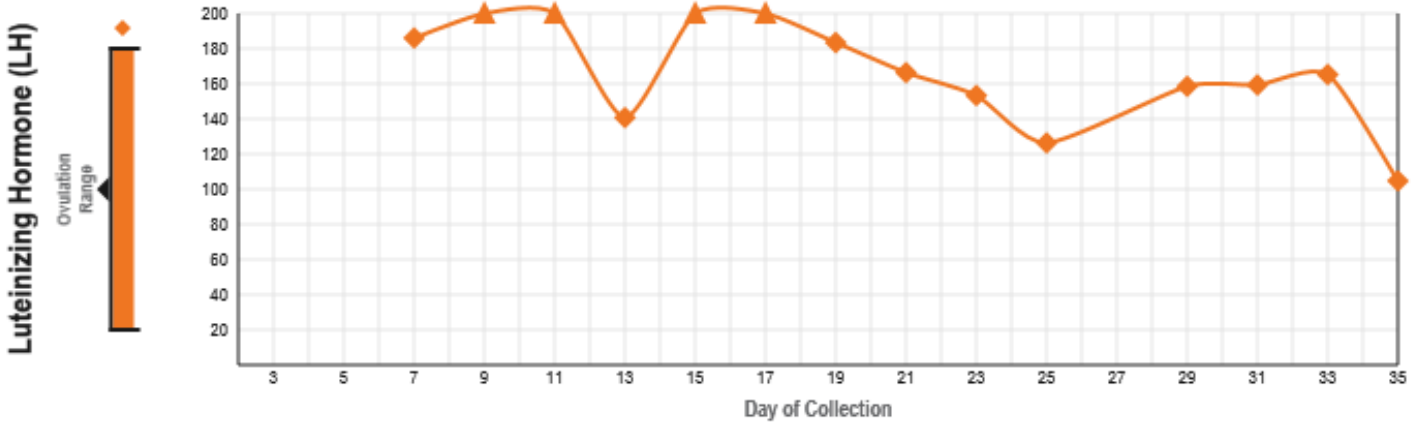

Estrogen (E1G)
Mid-Follicular Range
Luteal Range
Progesterone (PDG)
Luteal Range
23
Day of Collection
Luteinizing Hormone (LH)
Ovulation Range
Day of Collection


Estrogen (E1G)
Mid-Follicular Range
Luteal Range
Progesterone (PDG)
Luteal Range
200
180
160
140
120
100
80
60
40
20
12000
10000
8000
6000
4000
2000
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
Day of Collection
Luteinizing Hormone (LH)
Ovulation Range
200
180
160
140
120
100
80
60
40
20
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
Day of Collection

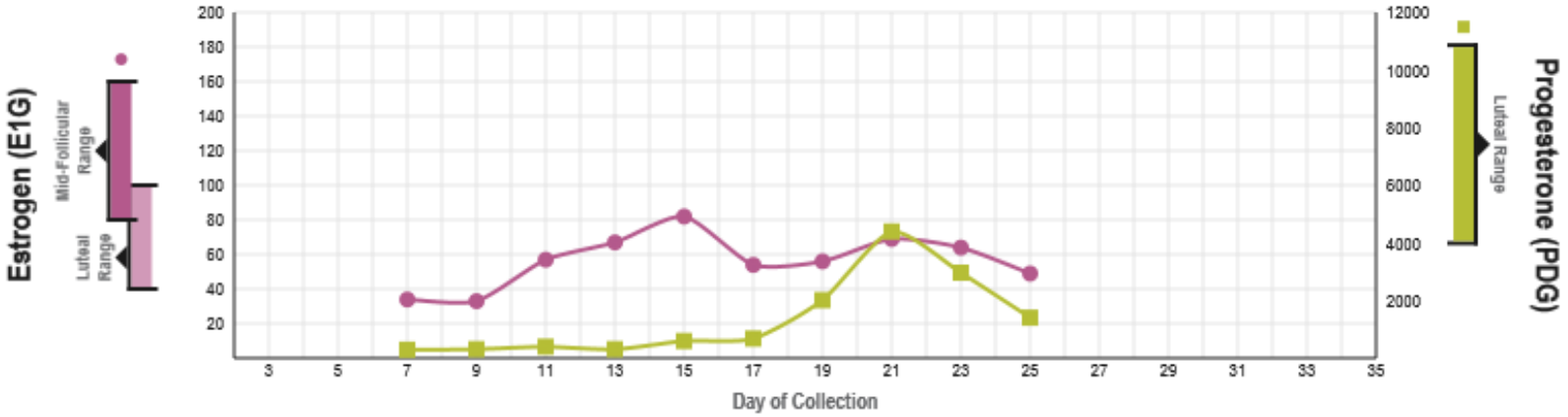

Estrogen (E1G)
Mid-Follicular Range
Luteal Range
200
180
160
140
120
100
80
60
40
20
12000
10000
8000
6000
4000
2000
Luteal Range
Progesterone (PDG)
3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Day of Collection

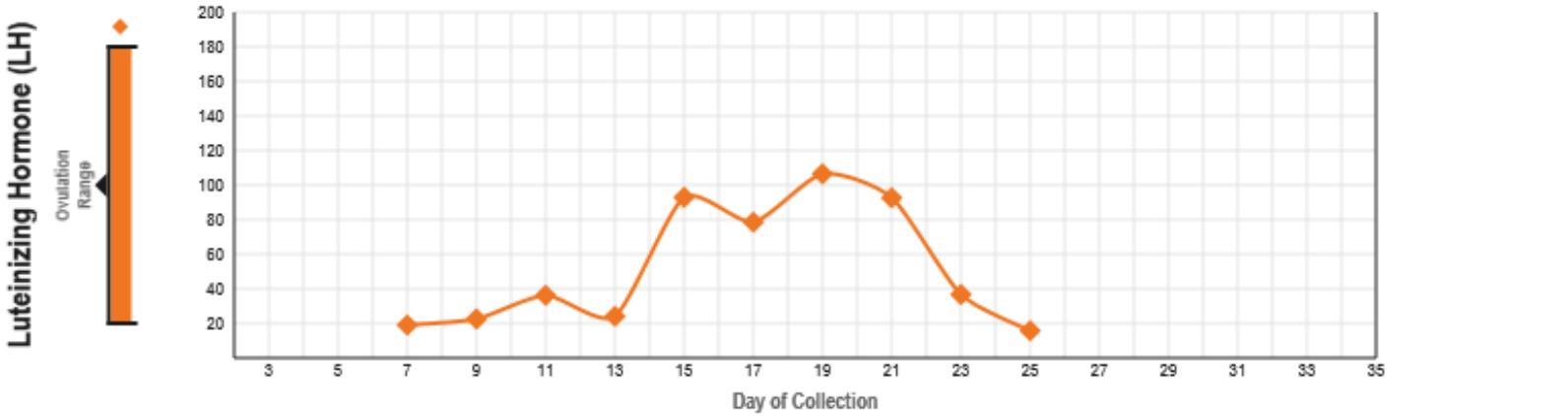

Luteinizing Hormone (LH)
Ovulation Range
200
180
160
140
120
100
80
60
40
20
3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35
Day of Collection





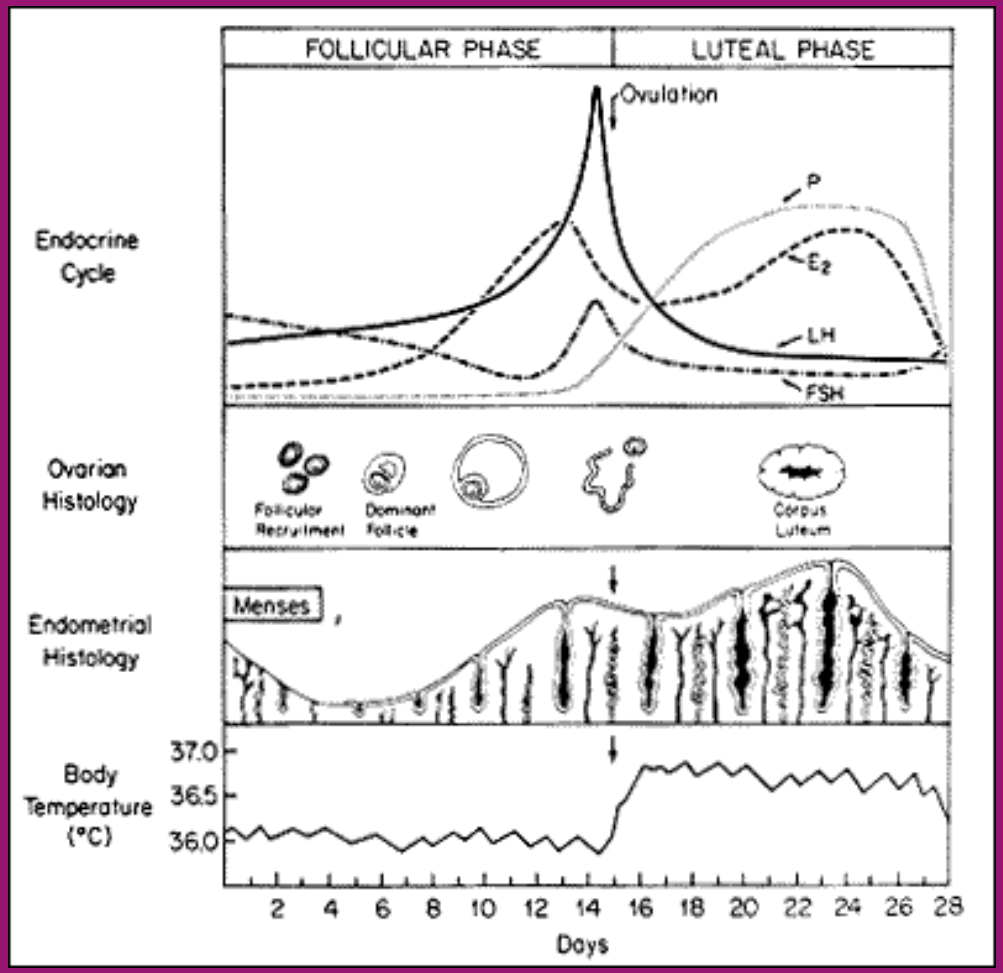
ZRT LABORATORY





ZRT LABORATORY

Whatever the problem, remember physiology



RESOURCES

- www.resolve.org
- www.fertilityfriend.com
- www.endotext.org
- www.wikipedia.com

Thank you

Alison McAllister, ND

amcallister@zrtlab.com

ZRT Clinicians are available
9-5 PST
No appointment needed

1-866-600-1636