Insulin Resistance & Effects on Fertility

GRETCHEN V MARSH DO

AOSRD CONGRESS OF MEDICAL EXCELLENCE 4.0

MARCH 26 2022

Disclosure

Gretchen V. Marsh, D.O.

has listed no financial interest/arrangement that would be considered a conflict of interest.

Objectives

By the end of this presentation the participants will be able to:

1) Define & diagnose insulin resistance
2) Describe the effects of insulin resistance especially on fertility
3) Formulate treatments for insulin resistance

Background

DEFINITION, MEASUREMENT, EFFECT

Definition: Insulin Resistance

An attenuated effect of insulin on blood glucose homeostasis, primarily by less efficient export of glucose from the blood into skeletal muscle, adipose, and liver tissue.

Kolb et al. Insulin: too much of a good thing is bad. *BMC Medicine* 2020

A state or condition in which a person's body tissues have a subnormal level of glucose response to endogenous or exogenous insulin.

Spoto et al. Insulin resistance in chronic kidney disease: a systemic review *AmJPhysiolog Renal Phsiology* 2016

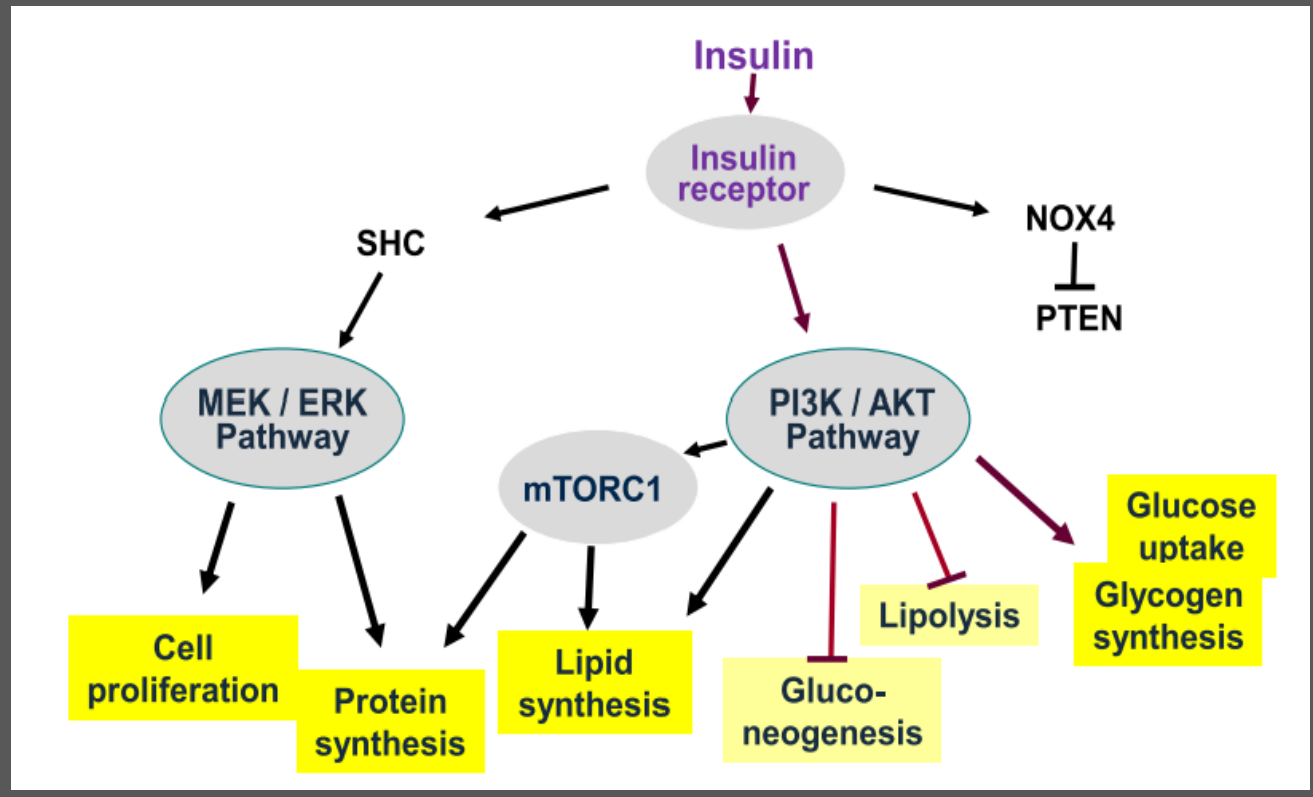
Normal function

Mitogen Activated protein kinase (MAP): cell growth & steroidogenic effects

Phosphatidylinositol 3kinase(P13K): metabolic effects including glucose disposal into skeletal muscle

NOX4: NADPH oxidase family of proteins. Oxygen sensing, vasomotor control, cell proliferation

Kolb et al
Insulin: too much of a good thing is bad.
BMC Medicine 2020

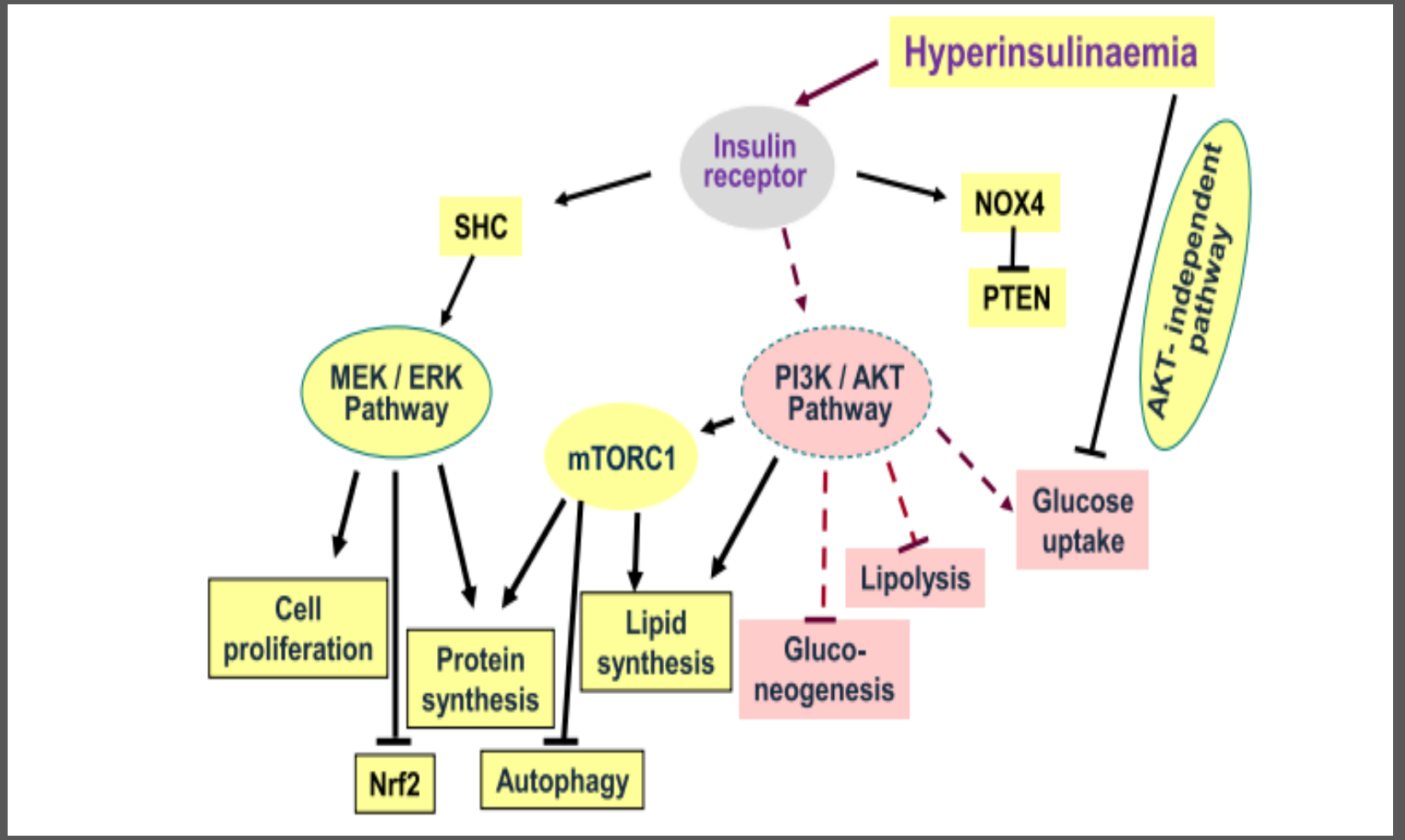


IR & hyperinsulinemia

Chronic exposure to high ambient insulin causes an imbalance of cellular responses because of the downregulation of some signaling pathways resulting in unbalanced anabolic activity of insulin favoring protein synthesis while suppressing autophagy.

Suppression of Nrf2 increases susceptibility of cells due to oxidative or other environmental insults.

Kolb et al 2020



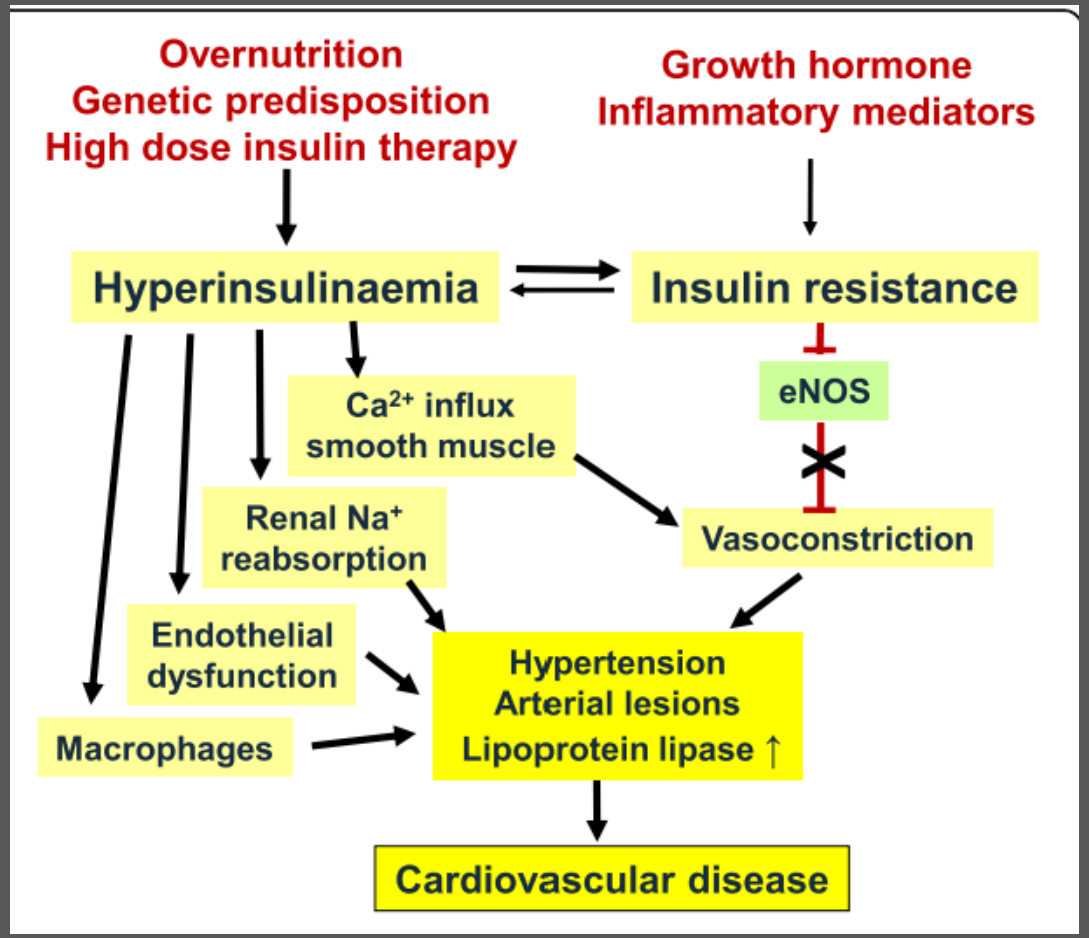
Hyperinsulinemia

Induction of IR by genetic disruption of signaling, increased GH, inflammatory status results in hyperinsulinemia.

Permanently elevated insulin concentrations are considered an attempt to overcome insulin resistance.

Other causes: insulinoma, congential hyperinsulinsim

Kolb et al 2020



Impairment of bodily functions

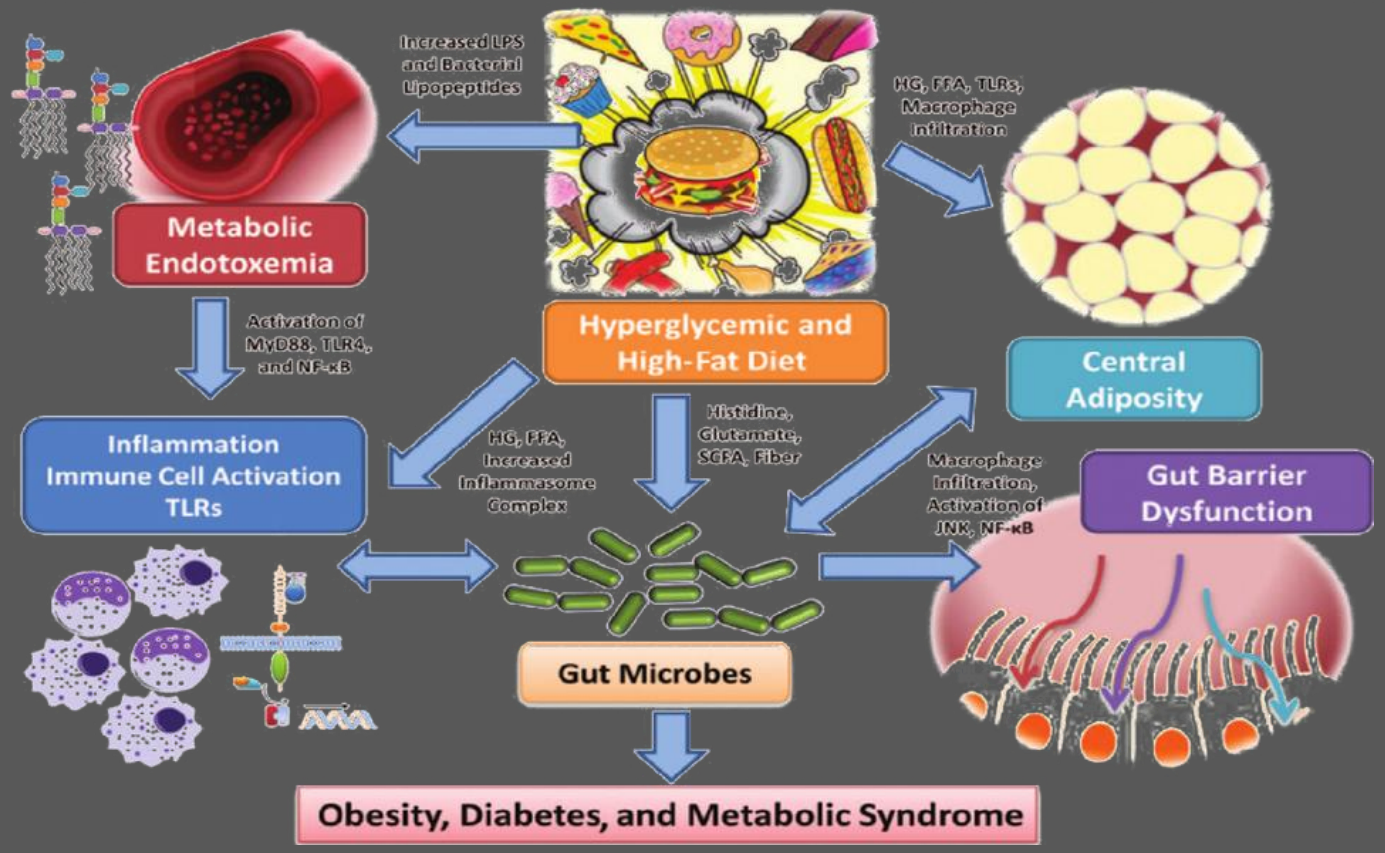
Longevity: lowered insulin associated with healthy aging

Sustained insulin levels and IR promote atherogenesis

Upregulates PAI-1 adhesion molecules & pro-inflammatory cytokines through MAP kinase pathway

Increases risk of hypertension by enhancing renal reabsorption of sodium ions.

Kolb et al, *BMC Medicine*, 2020



Measurement techniques

Gold standard: Euglycemic, hyperinsulinemic clamp

Similar: Insulin mediated glucose disposal

Fasting plasma glucose concentration (mg/dL = FPG)

Fasting plasma insulin concentration (uIU/mL = FPI)

Ratio of above: (FPG/FPI)

Oral GTT with insulin response

IOG60:

HOMA-IR: FPI x FPG/ 22.5

QUICKI: 1/(log FPI + log FPG)

Measurement techniques

Gold standard: Euglycemic, hyperinsulinemic clamp

Similar: Insulin mediated glucose disposal

Fasting plasma glucose concentration (mg/dL = FPG)
Can be deceptive

Fasting plasma insulin concentration (uIU/mL = FPI)
High correlation, practical

Ratio of above: (FPG/FPI)
Only as good as above

Oral GTT with insulin response
More data, can be practical

IOG60: 60 min insulin & glucose levels (Contreras JES 2019)

HOMA-IR: FPI x FPG/ 22.5
Homeostatic model assessment of insulin resistance;

QUICKI: 1/(log FPI + log FPG) Quantitative insulin sensitivity check index; Equivalent to OGTT Matsuda indices for insulin sensitivity

Surrogate markers

There are a lot.

Polak et al
New markers of insulin resistance in PCOS
JEndocrinolInvest 2017

Adiponectin: secreted by mature adipocytes.

Resistin: adipose derived peptide

Leptin: regulates energy homeostasis & mediator of inflammation in setting of obesity

Visfatin: adipocytokine

Vaspin: visceral adipose tissue derived serine protease inhibitor

Apelin: peptide from bovine stomachs

Kisspeptin: key stimulating factor of GnRH pulsatile secretion

Copeptin: C-terminal pro-vasopressin fragment

Irisin: myokine with brown fat like development

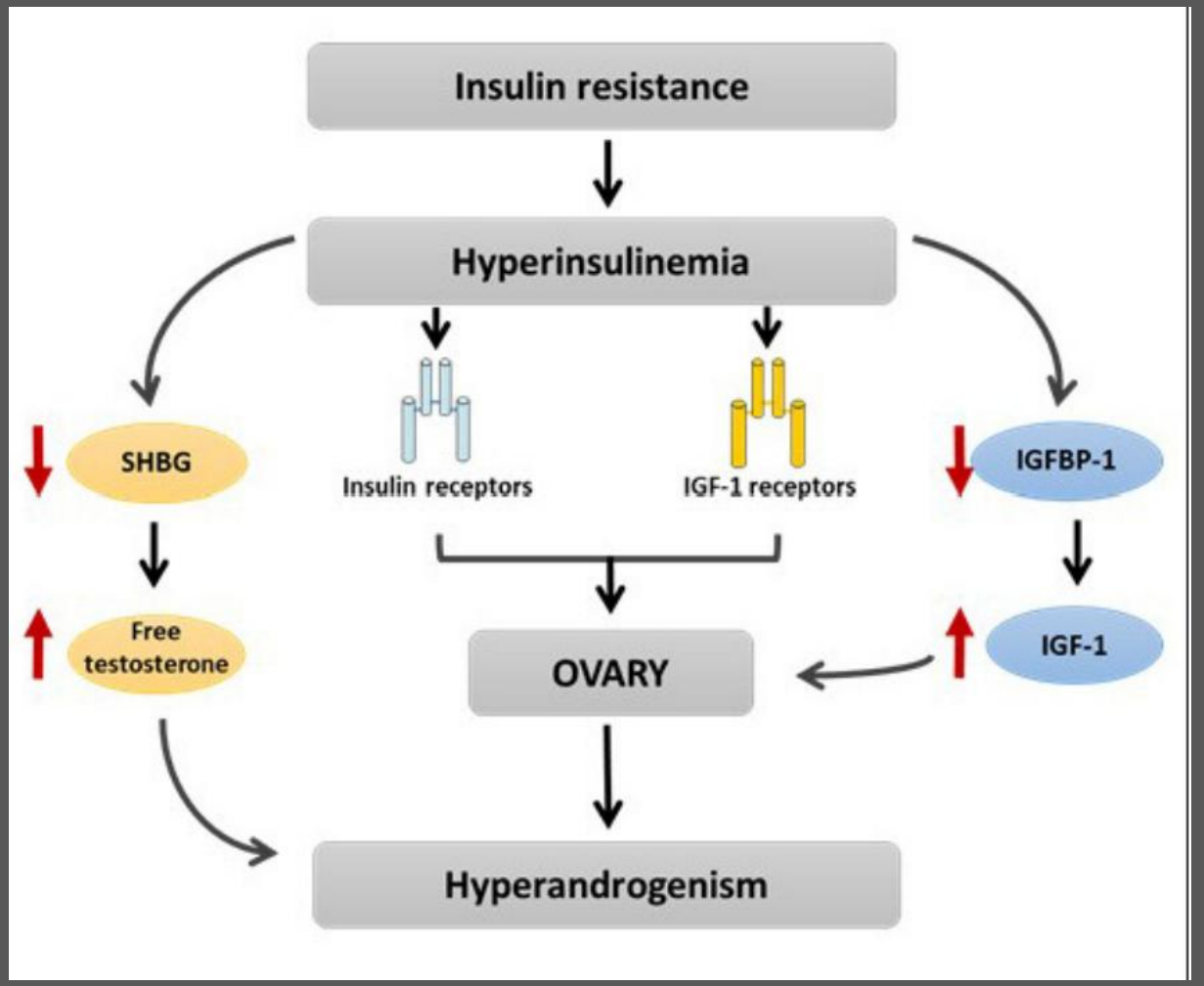
Ghrelin: peptide hormone primarily from stomach

Zonulin: eukaryotic protein regulates gut permeability

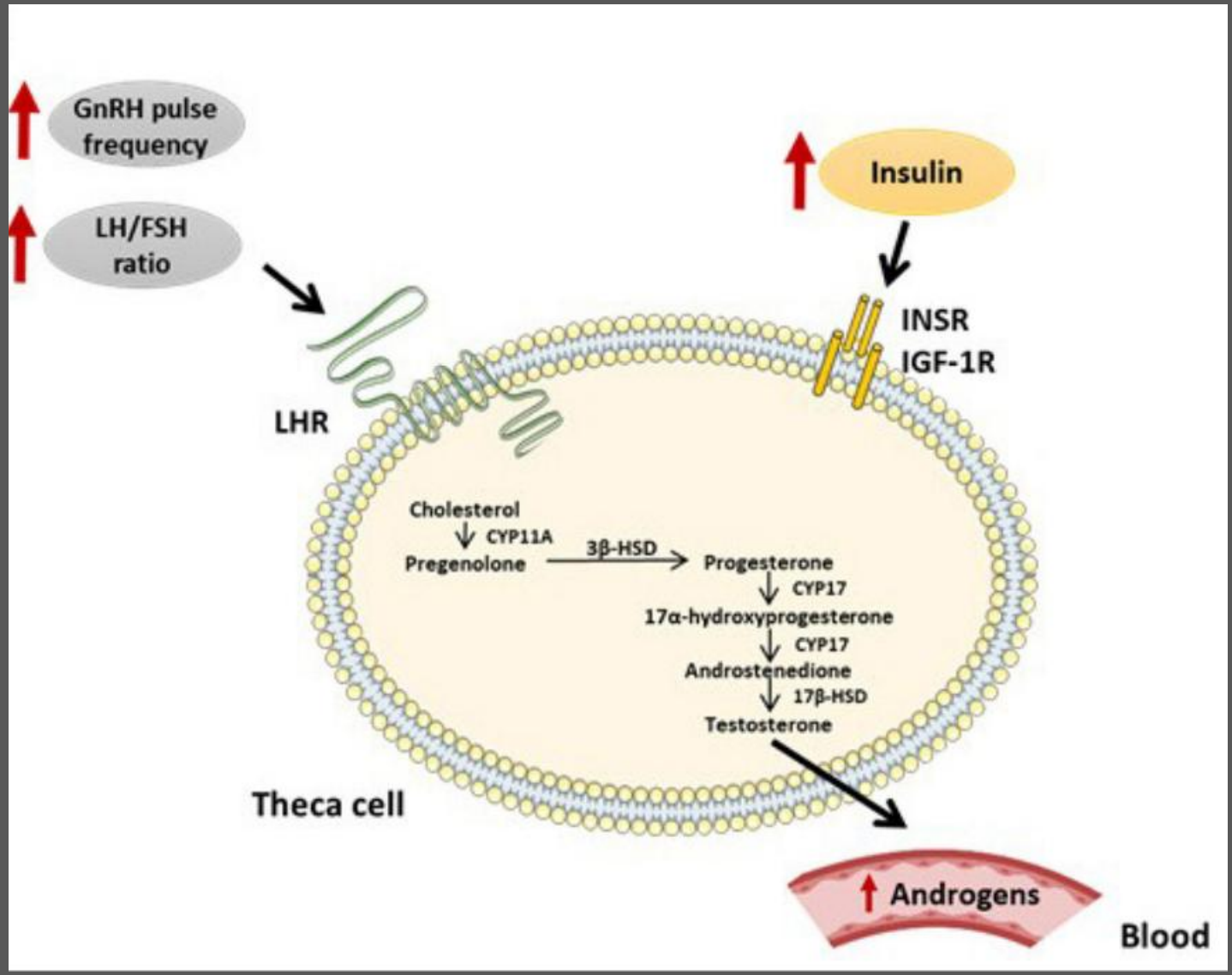
Female fertility

Insulin like Growth Factor (IGF-1) or somatomedin-C has role in proliferation, differentiation and apoptosis & is produced in liver in response to GH.

IGF-1 is one of the most potent natural activators of the AKT pathway, a stimulator of cell growth and proliferation, and a potent inhibitor of programmed cell death.



Female Fertility

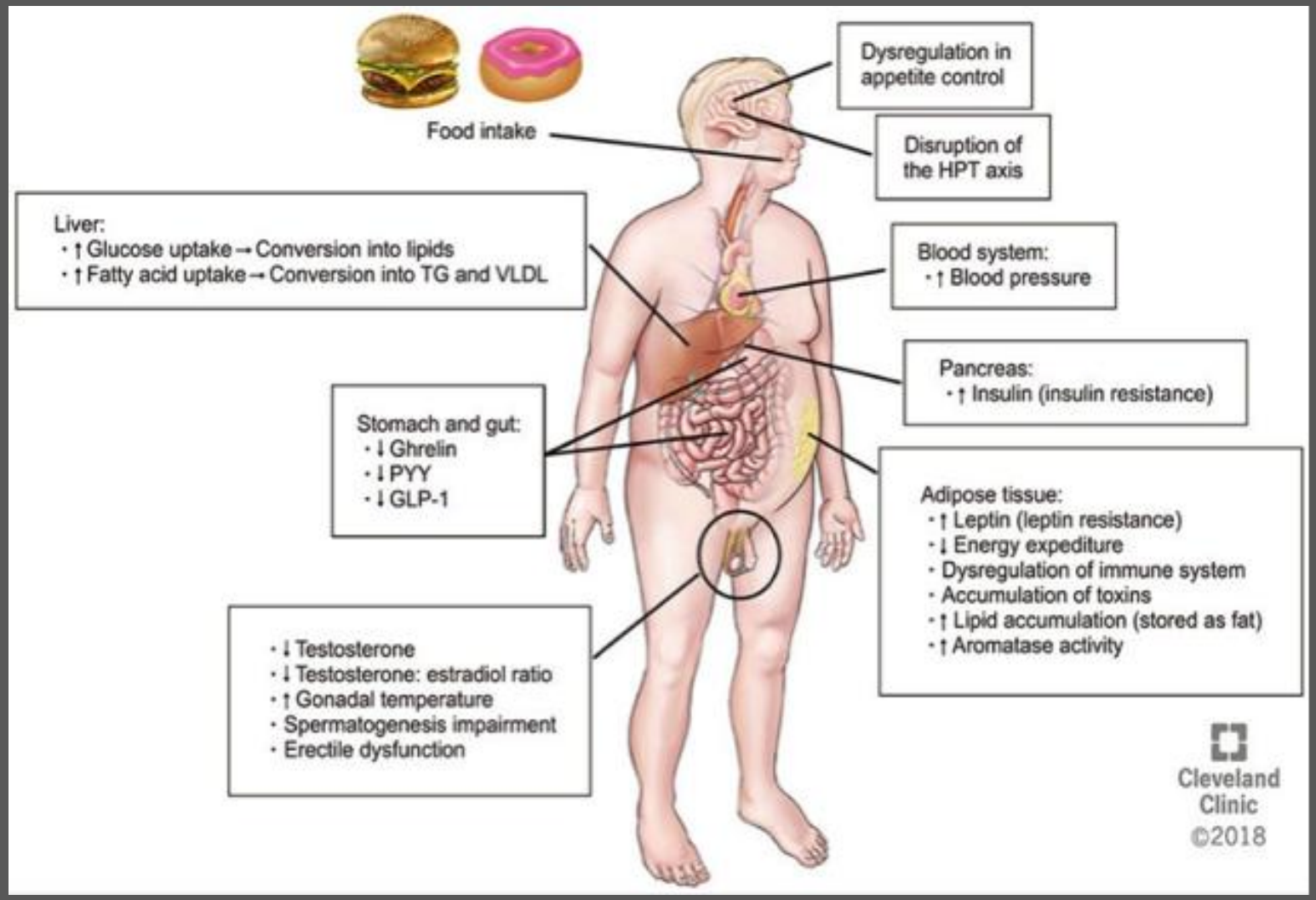


Male Fertility

Sex linked differences in IGF-1 sensitivity and at different levels either too high or too low.

HOMA-IR and IGF-1 linked.

Friedrich et al The Association between IGF-1 and Insulin Resistance *Diabetes Care* April 2012



Practical applications

FOCUSING ON FERTILITY

Seminal Fluid

Obesity is associated with increased seminal insulin & leptin

Leisgang et al
Reprod Biol Endocrinol 2014

Obesity associated with:

*increased serum and seminal insulin and leptin but no difference in seminal glucose.

*lower QUICKI test (more insulin resistance), decreased sperm concentration.

*increased mitochondrial membrane potential (MMP) and DNA fragmentation index.

*non-significant impact on motility and morphology.

PCOS

Affects 8-15% of women of reproductive age.

Type A: higher BMI, androgens, insulin, lipid derangement

Type D: least severe

Androgen Excess & PCOS Society

European Society for Human Reproduction & Embryology (ESHRE)

Monash University, AU PCOS program

	Phenotypes			
Characteristics	***A***	***B***	***C***	***D***
Hirsutism/HA	√	√	√	
Ovulatory Dysfunction	√	√		√
Polycystic ovaries	√		√	√
NIH 1990	√	√		
Rotterdam 2003	√	√	√	√
AE-PCOS 2006	√	√	√	

IR & PCOS

PCOS: Insight into pathogenesis & association with insulin resistance

Barber et al
Clinical Med 2015

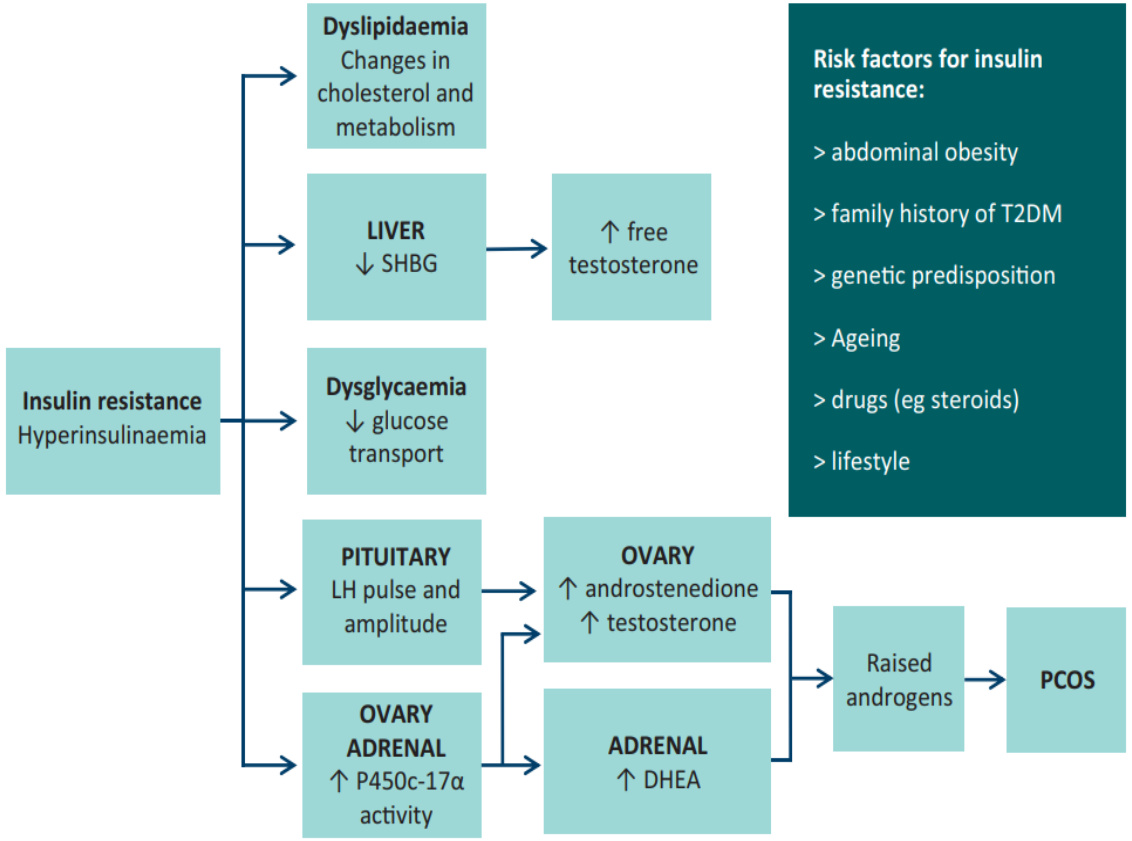


Fig 1. Overview of peripheral insulin resistance in PCOS.
DHEA = dehydroepiandrosterone; LH = luteinising hormone; PCOS = polycystic ovary syndrome; SHBG = sex hormone binding globulin; T2DM = type-2 diabetes mellitus.

18 yo G0

HPI: 18 yo with abnormal labs on pre-college physical

OB/Gyn: Menarche 13 yo Menses 3-4 day flow q 3 weeks. No charting

FHx: Father-"pre-diabetes"

Physical: BMI 32.7 Grade 1-2 facial acne, neg hirsutism

Labs: (7.5 hour fast) Insulin 28

Hgb A1C 5.6%

AST 29 ALT 49

Testosterone 15 ng/dL

18 yo G0

RECHECK

Oral GTT	Glucose ug/dL	Insulin uIu/mL
Fasting	78	12 28
1hr	133	67
2hr	95	131

17-OH Progesterone: 65 ng/dL

TGL: 145 mg/dL

Hgb A1C%: 5.6

AST 29/ALT 49

Testosterone 15 ng/dL

4 MONTH FU

Fasting insulin: 20 uIu/mL

17-OH Progesterone: 92 ng/dL

T Chol: 166; TGL 105; HDL 60; LDL 85

Hgb A1C: 5.5%

AST 24/ ALT 27

Testosterone 32 ng/dL fTestosterone 7.1

Androstendione 209

AM Cortisol: 19.4 ug/dL

Insulin resistance

A simple and improved predictor extracted from the oral glucose tolerance test.

Contreras et al
Journal of the Endocrine Society
April 2019

Oral Glucose Tolerance 75gm (mg/dL serum)

	Contreras et al	Quest Lab		
Fasting	90.3	<100		
1 hr	127.3	Not est.		
2hr	108.4	<140		

Insulin Response to Glucose 75gm (uIU/mL)

	Contreras et al	Quest Lab		
Fasting	6.8	19.6		
1hr	66.3	112		
2hr	45.8	55		

Insulin resistance

A simple and improved predictor extracted from the oral glucose tolerance test.

Contreras P et al JES 2019

Fasting	78	12
1hr	133	67
2hr	95	131

Oral Glucose Tolerance 75gm (mg/dL serum)

	Contreras et al	Quest Lab
Fasting	90.3	<100
1 hr	127.3	Not est.
2hr	108.4	<140

Insulin Response to Glucose 75gm (uIU/mL)

	Contreras et al	Quest Lab
Fasting	6.8	19.6
1hr	66.3	112
2hr	45.8	55

29 yo G2P2020

Menarche: 12 yo

BMI: 35

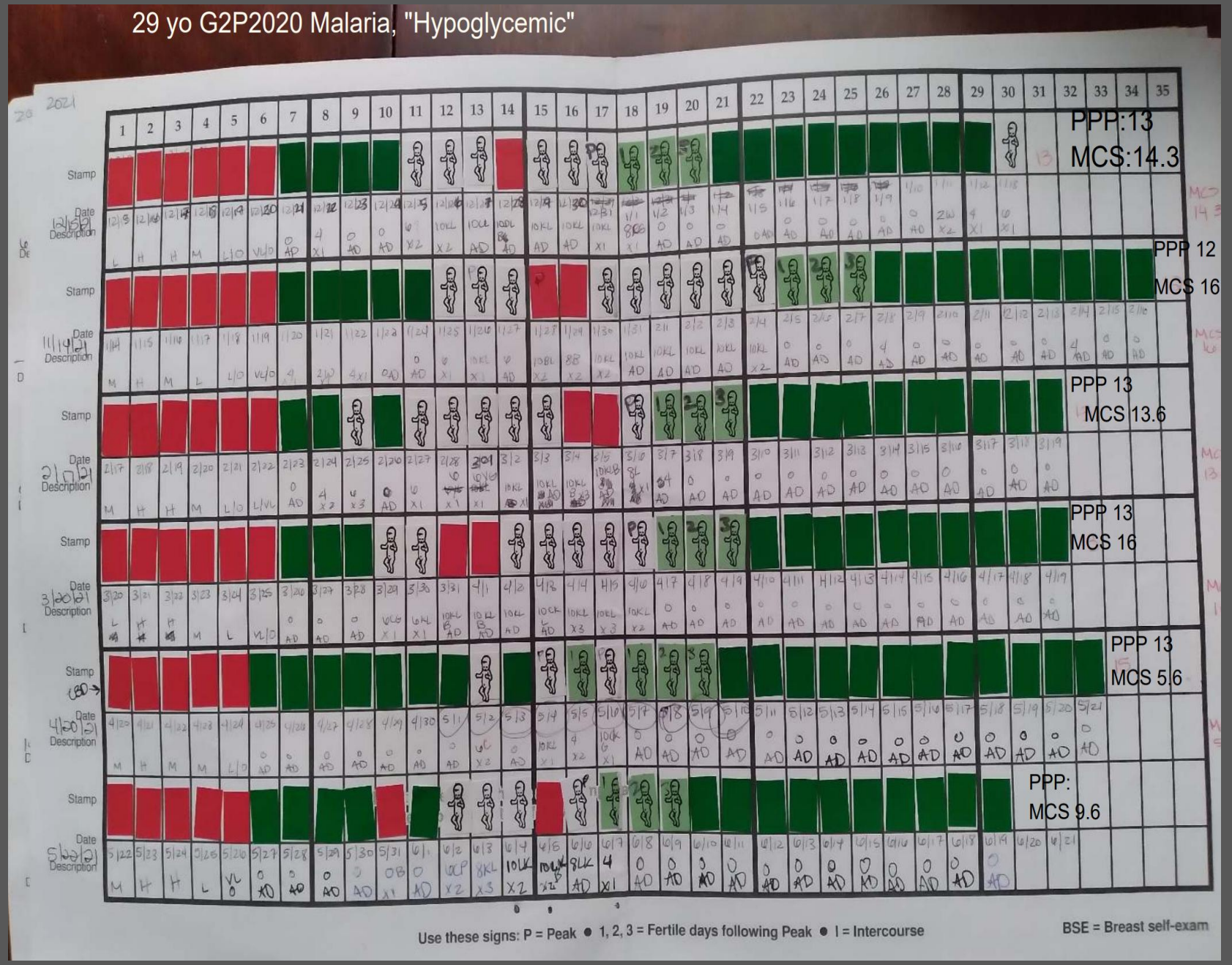
PMH: “Hypoglycemia”, malaria

TSH: 4.97 mIU/L fT4 1.5 ng/dL

Vit D 16 ug/mL Prolactin 27.3 ng/mL

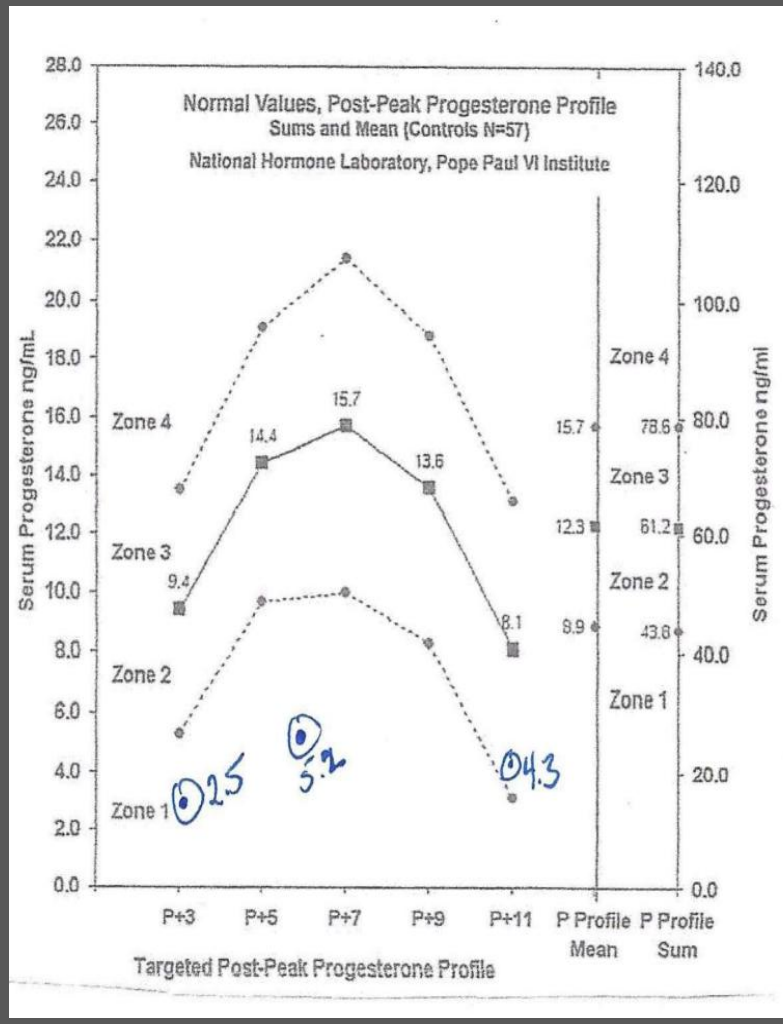
Testosterone 26 ug/dL fTest 3.3 pg/mL

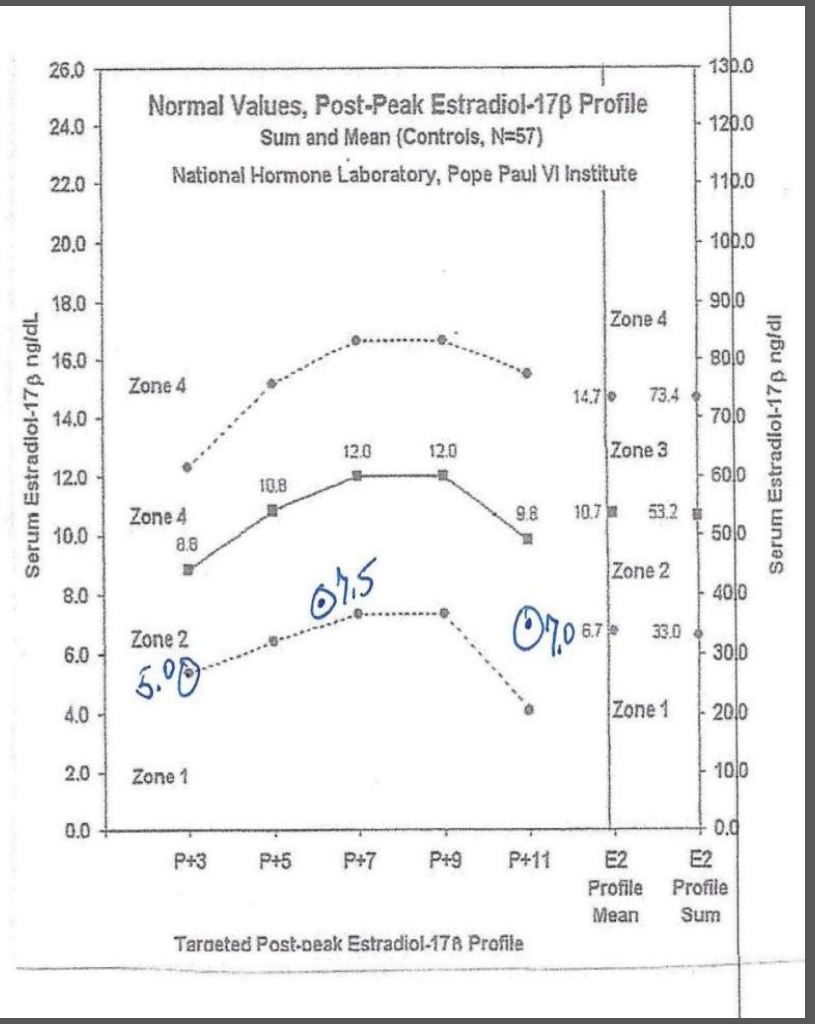
DHEA-S 213 mcg/dL



29 yo G2P2020

Luteal phase deficiency Type II





29 yo G2P2020

Oral Glucose Tolerance 75gm (mg/dL serum)

	Contreras et al	Quest Lab
Fasting	90.3	<100
1 hr	127.3	Not est.
2hr	108.4	<140

Insulin Response to Glucose 75gm (uIU/mL)

	Contreras et al	Quest Lab
Fasting	6.8	19.6
1hr	66.3	112
2hr	45.8	55

29 yo G2P2020

Oral Glucose Tolerance 75gm (mg/dL serum)

	Contreras et al	Quest Lab		
Fasting	90.3	<100	56	
1 hr	127.3	Not est.		
2hr	108.4	<140	69	

Insulin Response to Glucose 75gm (uIU/mL)

	Contreras et al	Quest Lab		
Fasting	6.8	19.6	24	
1hr	66.3	112	99	
2hr	45.8	55	33	

Treatments

RESTORE TO OPTIMAL HEALTH BY ADDRESSING UNDERLYING CAUSE

Nutrition & Activity

ZERO CARB DINNER & NIGHTLY INTERMITTENT FASTING

DAILY BRISK WALKS & IMPROVED SKELETAL MUSCLE FITNESS

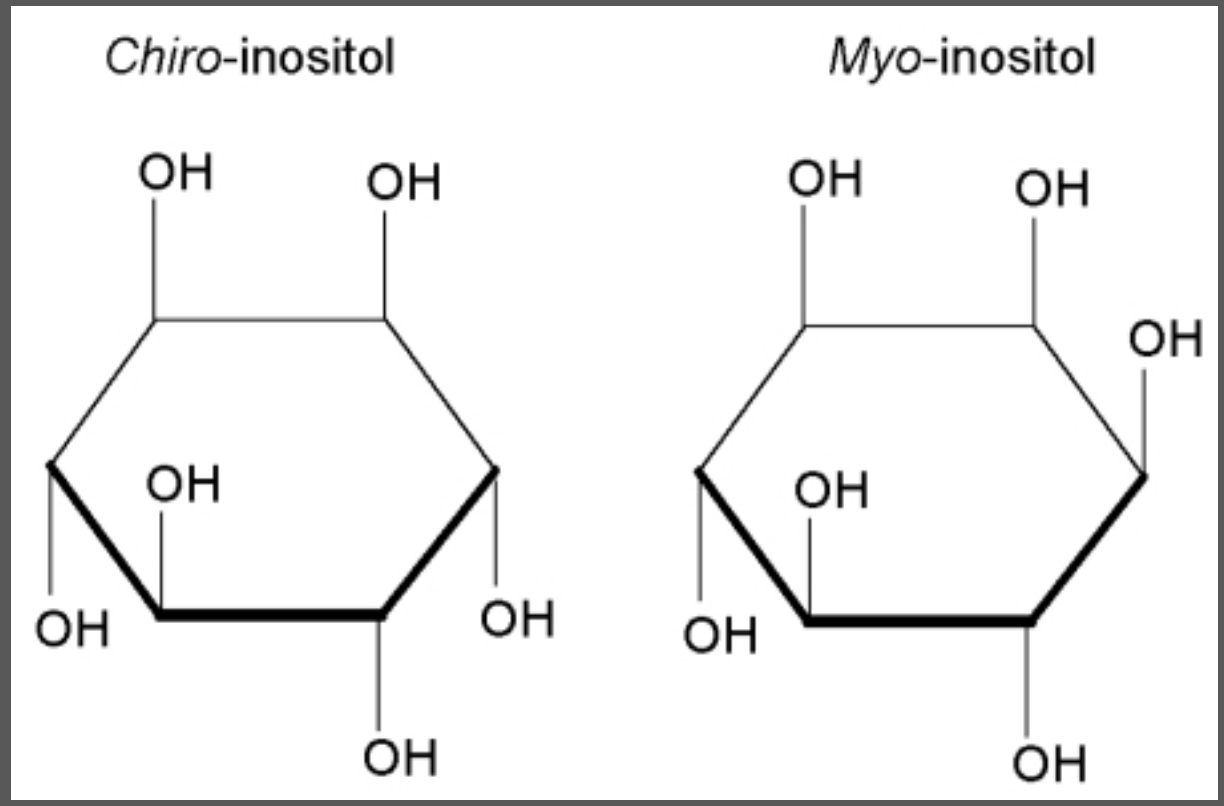
Inositols: PCOS

Inositolphosphoglycan (IPG) mediators: Deficiencies in D-chiro and myo-inositols may contribute to insulin resistance

Women with PCOS, increased glucose stimulated DCI-IPG release is significantly correlated with improved insulin sensitivity.

Significant testosterone decrease

Cheang et al,
Insulin stimulated releasee of D-Chiro-Inositol IPG mediator correlates with insulin sensitivity in Women with PCOS *Metabolism* 2008



Inositols: Sperm

Effect of Myoinositol & antioxidants on sperm quality in Men with metabolic syndrome

Oliva et al
InterJ Endocrin Sept 2016

Men with metabolic syndrome were given a supplement twice daily of: Myoinositol 1 gm; L-carnitine 30mg; L-arginine & Vit E; 55 ug selenium, 200 ug folic acid.

HOMA index: sig decrease

E2: sig decrease

SHBG: sig decrease

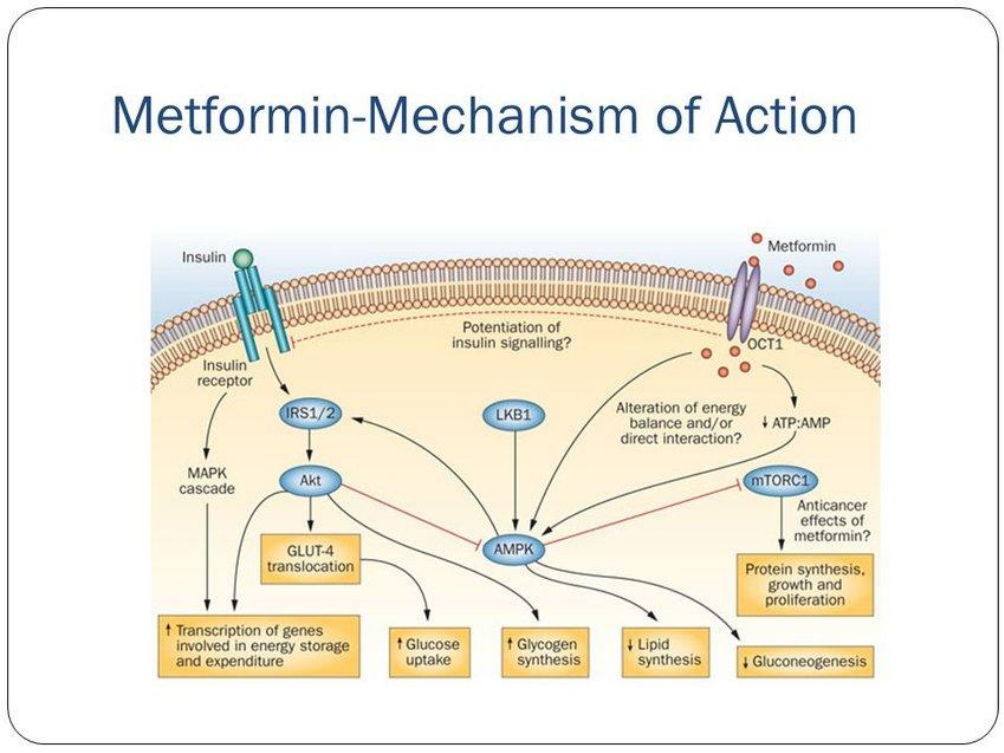
Testosterone and Free T: sig increase

Semen concentration, motility, morphology: sig increase

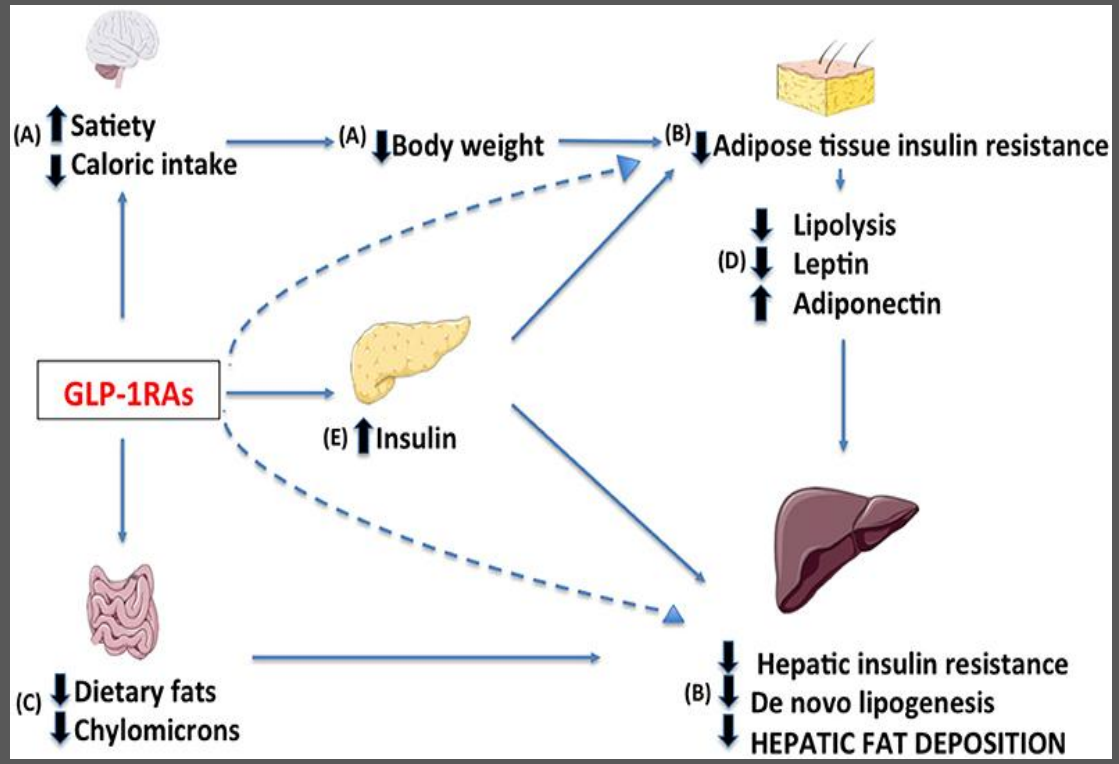
Antioxidant role of selenium and role of L-carnitine (sperm formation & membrane stabilization, vasodilation via NO) are noted.

Insulin sensitizers

METFORMIN



GLP-1 AGONISTS



Vitamin D3

The relationship between Vitamin D3 and insulin in PCOS-a critical review

Kaminska et al *JPhysioPharm* 2021

*Vit D3 deficiency primarily in obese vs lean PCOS.

*Ovary seems to be an additional source of Vit D3 and its production is disrupted in PCOS

*Reduction of AMH (produced by granulosa cella of early antral follicles) which is usually high in PCOS

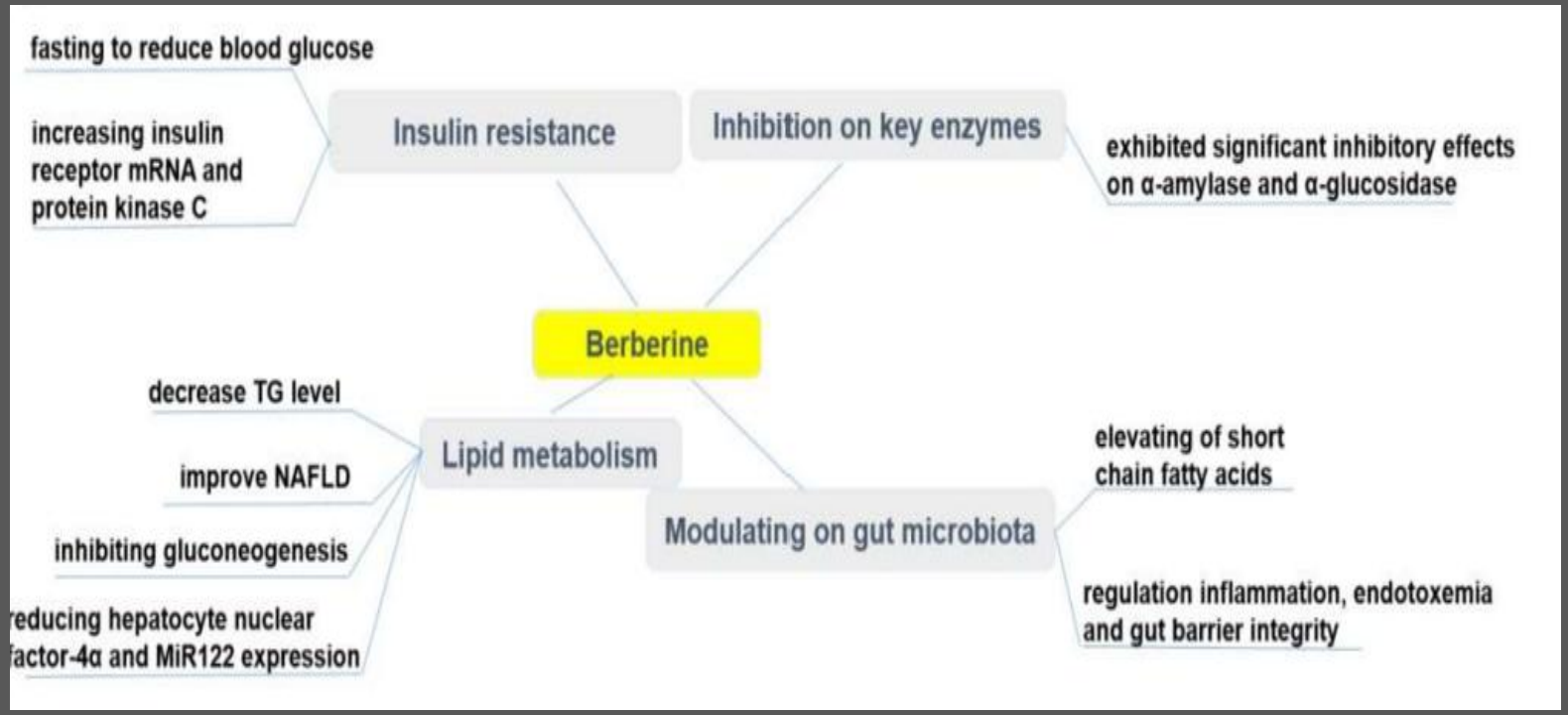
*Normalization or improvement in menses with Vit D3

*Vit D3 deficiency associated with impaired glucose clearnce and insulin secretion.

*Vit D3 supplementation significantly reduced HOMA-I, Total Cholesterol, LDL, & insulin levels and increased QUICKI

Berberine

Principal bioactive ingredient of *Rhizoma coptidis* (Huang Lian)



Berberine

500mg twice daily

Safety in pregnancy not established

Links between chronic inflammation and insulin resistance due to increased activity of IKKBeta kinase.

IKKBeta kinase induces insulin resistance via free fatty acid increase.

Yi et al
Berberine reverses free-fatty-acid-induced insulin resistance in 3T3-L1 adipocytes through targeting IKKB. *World J Gastroenter* Feb 2008

Lowers glucose in Type 2 DM by increasing insulin receptor expression

Feng et al
Berberine in CV and Metabolic Dz *Theranostics* 2019

What about…

SPIRONOLACTONE

Does not fix the underlying cause

Can help to preserve hair follicles

Pregnancy Category D

CHEMICAL CONTRACEPTIVES

Does not fix the underlying cause

Associated with impaired glucose tolerance, elevated bp, and depression

Conclusion

gvmarshdo@gmail.com

Most of insulin resistance but not all is due to obesity from overeating.

Insulin resistance is on a continuum stretching to DM.

Effects of insulin resistance are on all organs including reproductive organs.