PCOS

The Most Common Endocrine Disorder of Reproductive Aged Women

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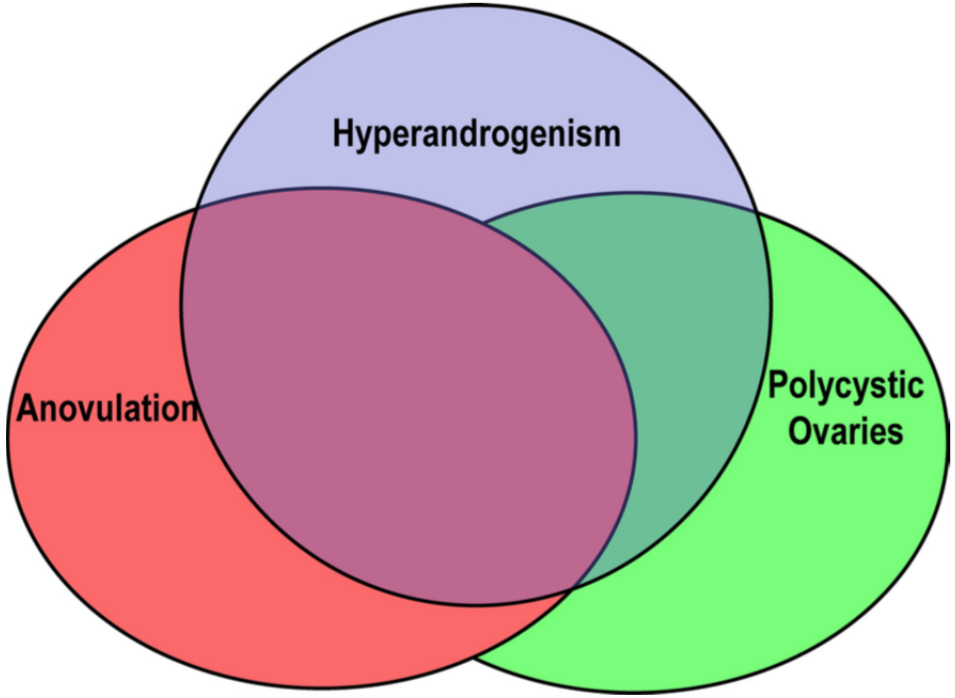
OB Grand Rounds 2/25/26

Objective

- Understand the epidemiology and inheritance of PCOS
- Discuss the pathophysiology and associated manifestations of PCOS
- Review the updated diagnostic criteria for PCOS and management recommendations (including clinical correlates re: OHSS, inositol, OSA, GLP-1, infertility)

The Most Common Endocrine Disorder of Reproductive Aged Women

- 10-13% using Rotterdam criteria
- And yet, many patients are not diagnosed accurately
- Prevalence of PCOS is remarkably similar worldwide



Genetic contribution

- Familial clustering and results from twin studies strongly support an underlying genetic basis for PCOS[1-3]
  - Having a mother or sister with PCOS conveys a 30–50% risk of developing PCOS
  - Correlation for PCOS between monozygotic twin sisters 2-fold higher compared to dizygotic twins

1 – Kahsar-Miller, Trends Endo Metab, 1998
2 – Legro, Proc Natl Acad Sci, 1998
3 – Lerchbaum, Eur J Endo, 2014

Genotype / phenotype associations

- *THADA* and *DENND1A* variants associated with
  - Endocrine and metabolic disturbances in Han Chinese women with PCOS[1]
  - Androgen excess and anovulation in European women with PCOS[2]
  - Polycystic appearing ovaries
- *C9orf3* and *rs4385527* conferred risk for all 3 manifestations of PCOS (hyperandrogenism, ovulatory dysfunction, PCOM)[3]

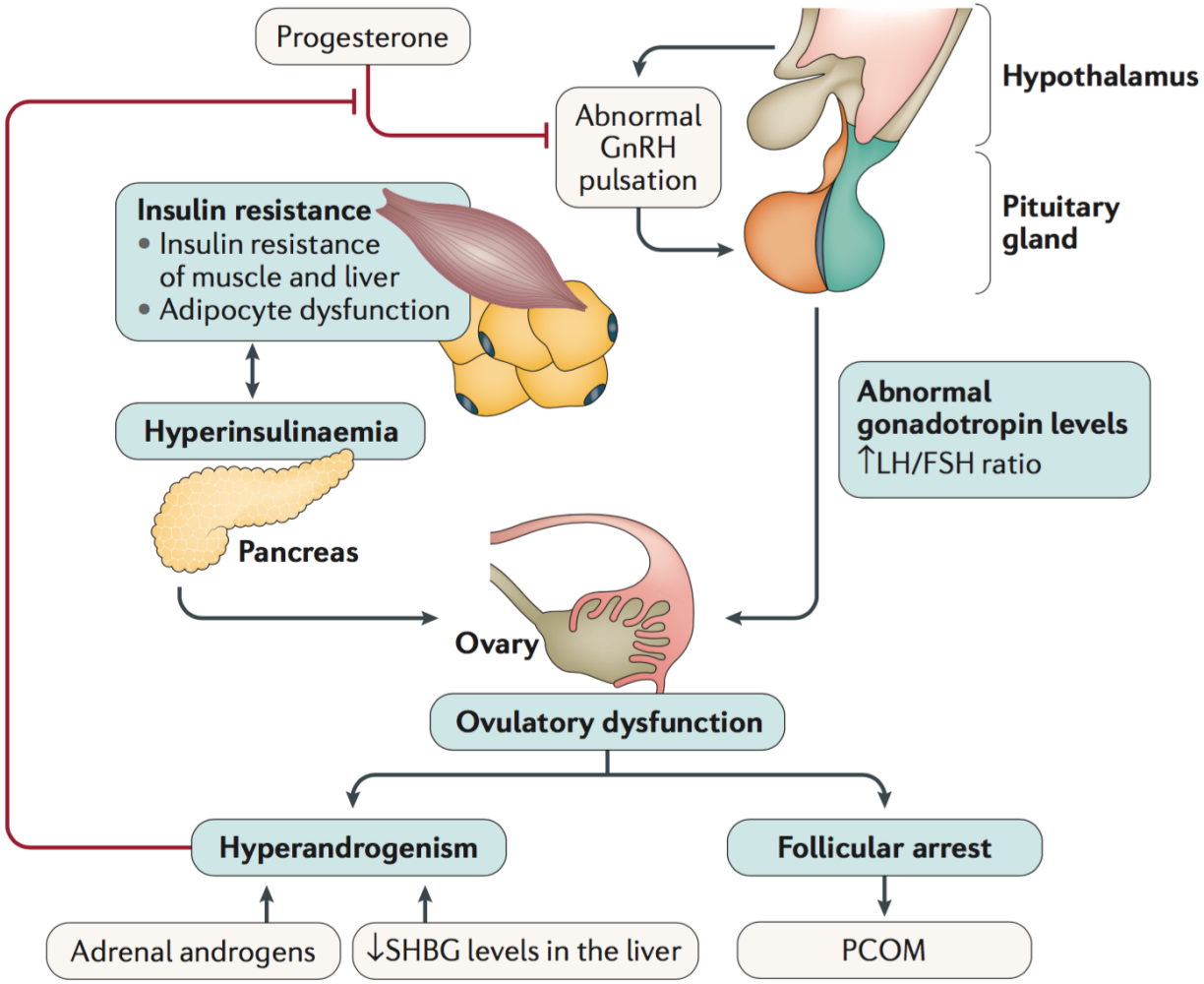
1 – Cui, Hum Reprod, 2013
2 – Welt, JCEM, 2012
3 – Cui, Hum Reprod, 2015

Genome wide association studies

- Two GWAS in Han Chinese women with PCOS identified 11 susceptibility loci[1,2]
  - *INSR, FSHR* and *C9orf3* confirmed in subsequent family based studies[3,4]
- GWAS #1 of white women of European descent confirmed *C9orf3* and identified two novel loci, *GATA4–NEIL2* and *FSHB–ARL14EP*[5]
- GWAS #2 of white women of European descent identified three susceptibility loci, *ERBB4, RAD50* and *KRR1*[6]
- **Loci identified in GWAS account for no more than 10% of the heritability of PCOS[7]**

1 – Shi, Nat Genet, 2012
2 – Chen, Nat Genet, 2011
3 – Du, Reprod Biomed Online, 2014
4 – Zhao, Sci Rep, 2015
5 – Hayes, Nat Commun, 2015
6 – Day, Nat Commun, 2015
7 – Azziz, Nat Rev Endocrinol, 2016

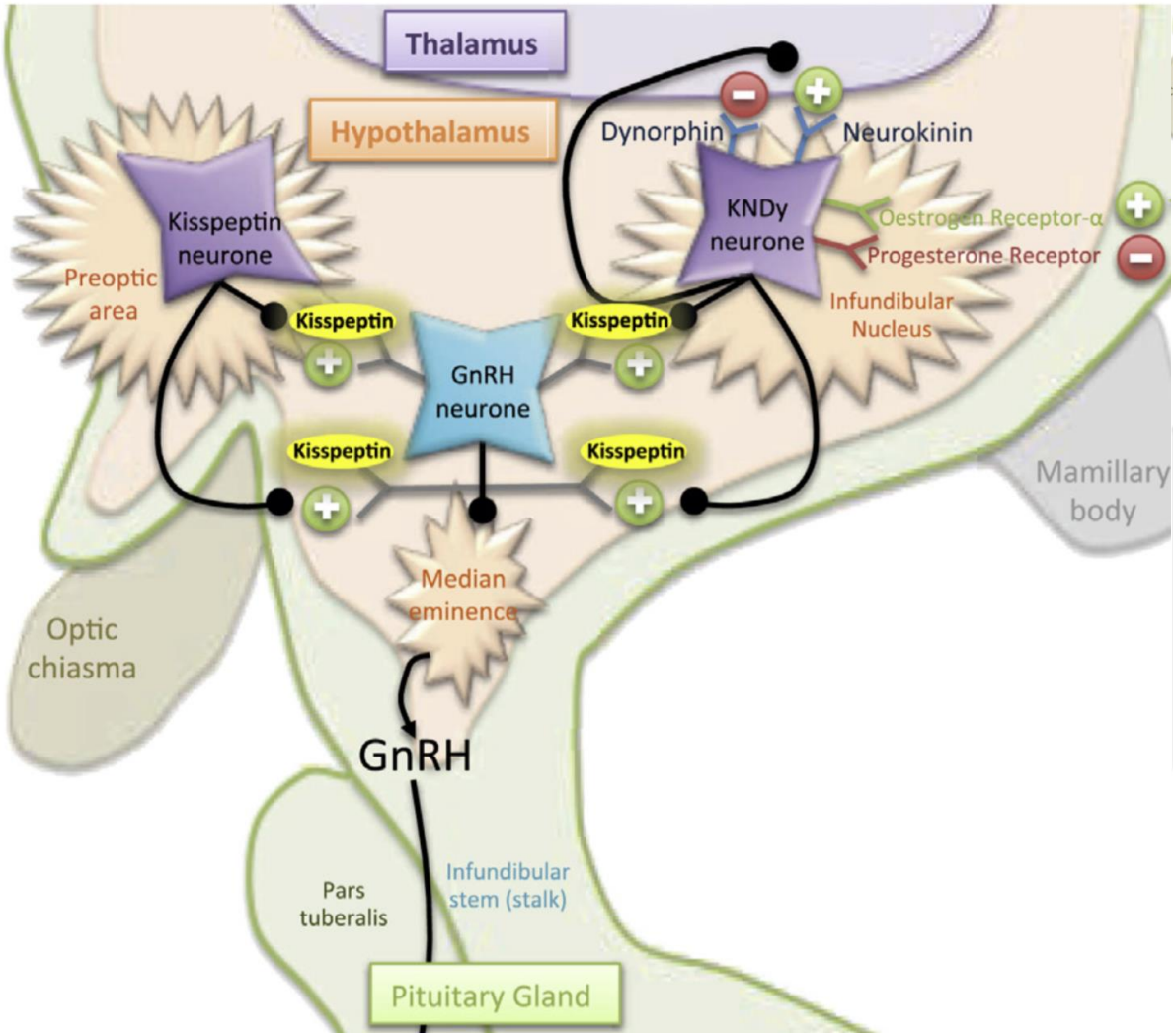
Pathophysiology

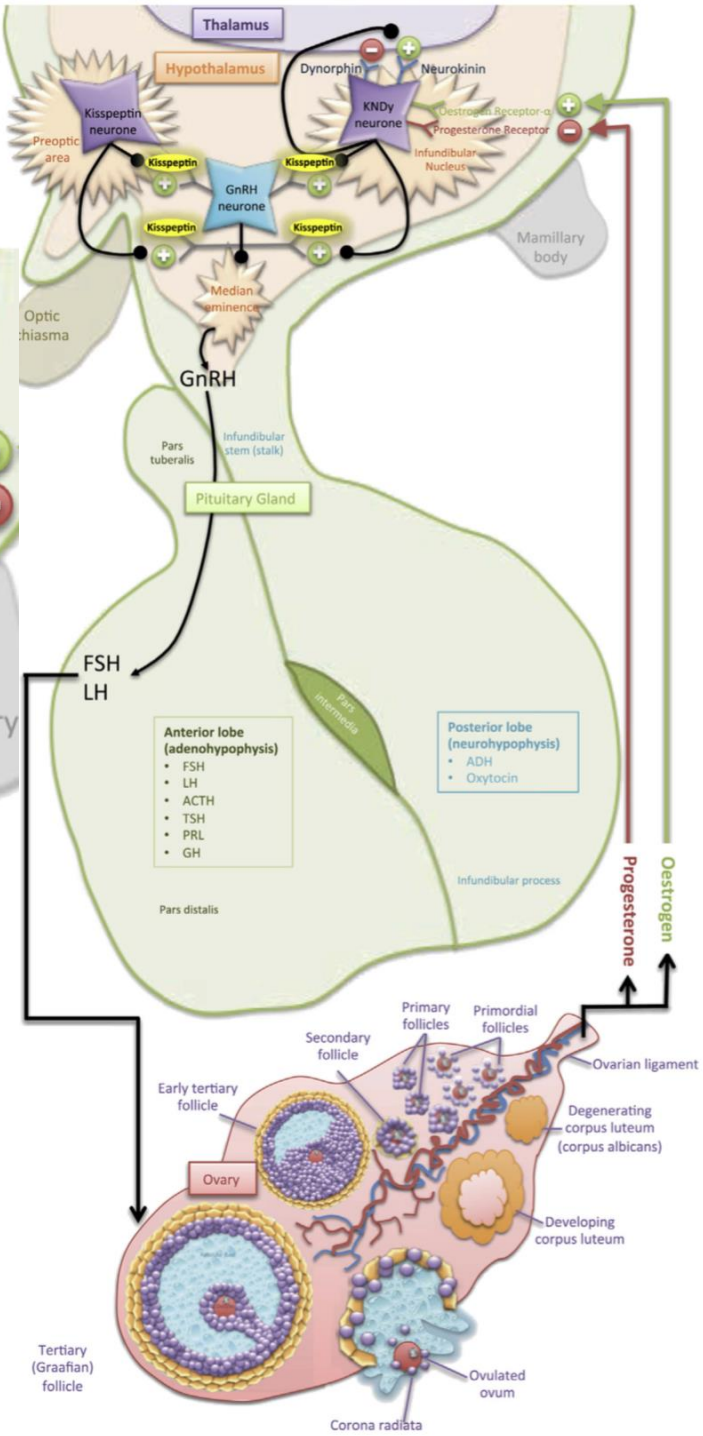


Pathophysiology: GnRH Pulse Generator

GnRH pulse generator:

- Arcuate nucleus (ARC) expresses kisspeptin, neurokinin B and dynorphin (Kiss 1 system)
- Kisspeptin signals directly to GnRH neuron to control pulsatile GnRH release





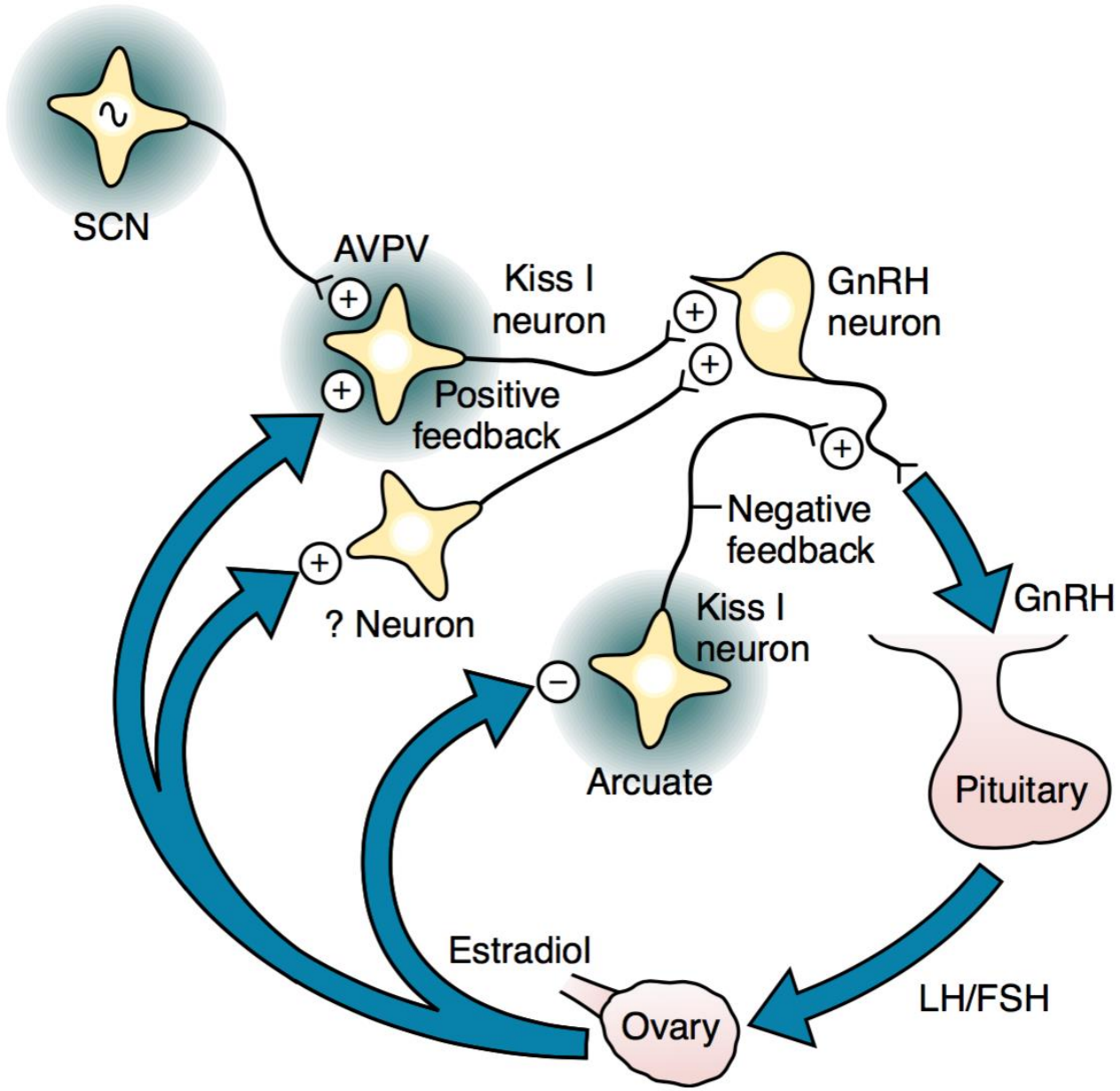
Baskind, Best Practice & Res Clin Ob/Gyn, 2016

Pathophysiology: Feedback

Kisspeptin mediated + and - feedback regulating GnRH secretion:

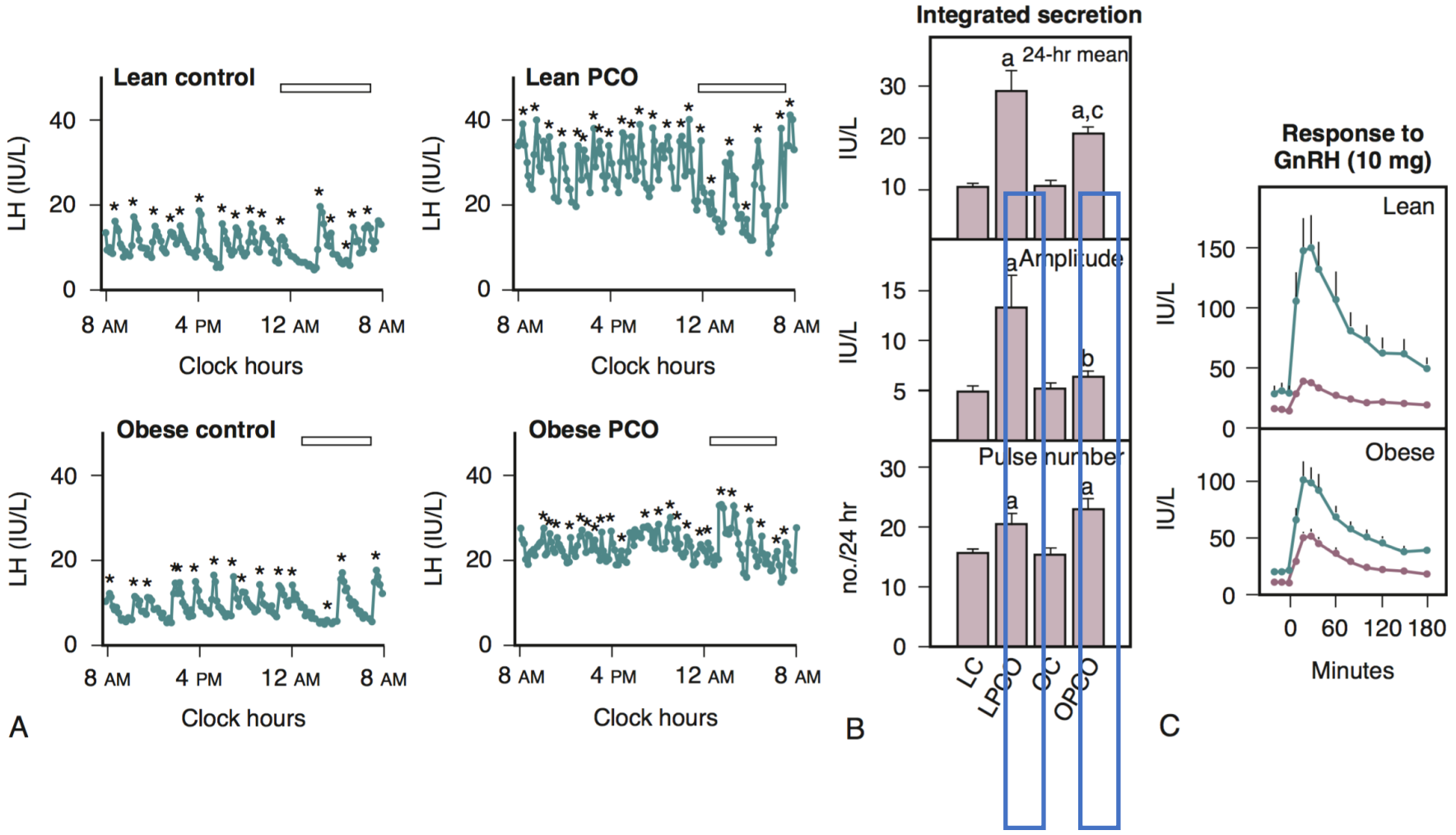
NEG feedback: Kiss1 neurons in ARC express ERα inhibited by E2

POS feedback: Kiss1 neurons AVPV express ERα stimulated by E2 → activates GnRH neurons and surge release of LH



Yen & Jaffe

LH pulsatility in PCOS



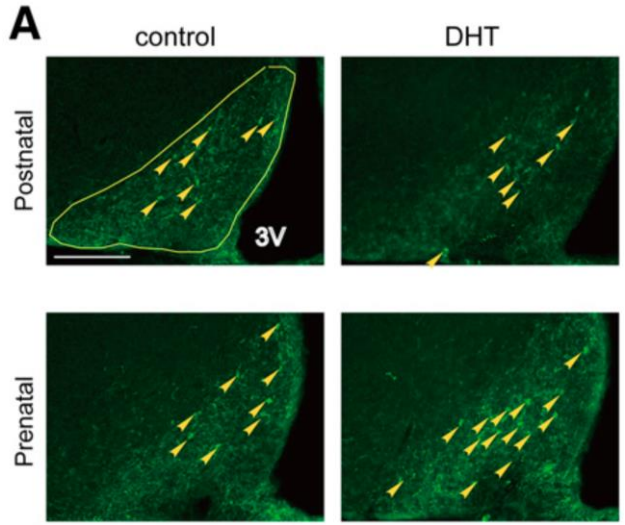
J Clin Endocrinol Metab 81:2854-2864, 1996

Role of Kisspeptin in PCOS?

- Prospective study of 157 subjects: PCOS increases serum kisspeptin levels[1]
  - Kisspeptin concentrations negatively correlated with serum FSH and positively correlated with serum T and DHEAS levels
- Prospective study of 285 PCOS cases and 162 controls: Serum levels of kisspeptin and leptin did not differ statistically between PCOS and controls[2]
  - Kisspeptin had a positive correlation with LH and leptin levels in PCOS

1 – Gorkem, Gynecol Endo, 2017
2 – Ozay, Gynecol Endo, 2016

Kisspeptin in the Hypothalamus of 2 Rat Models of Polycystic Ovary Syndrome

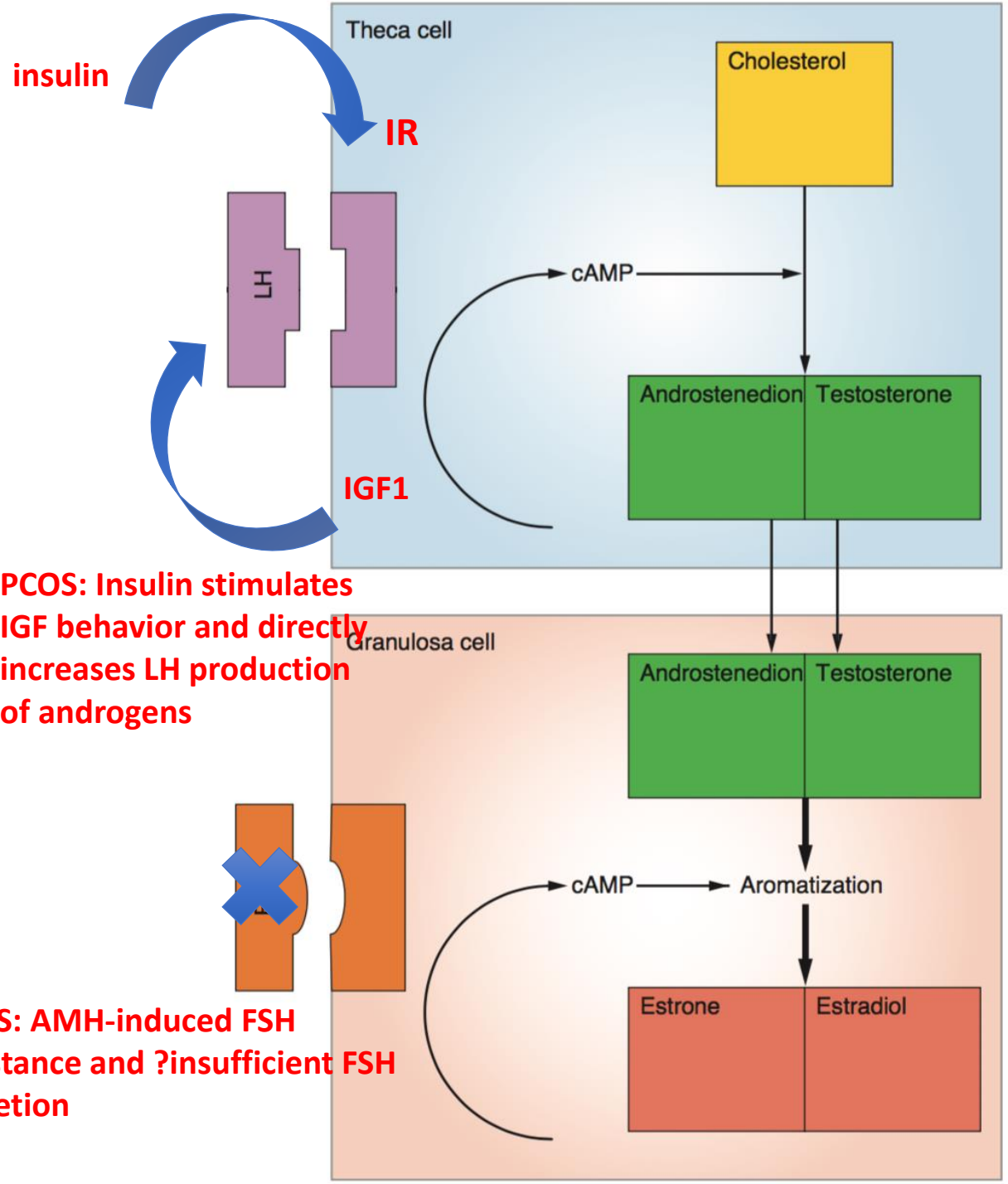


- Prenatal exposure to androgens
  - Higher kisspeptin and NKB levels in the ARC
  - Phenotype of PCOS characterized by irregular cycles, normal body weight and elevated LH secretion
- Postnatal exposure to androgens
  - Lower kisspeptin and NKB levels in the ARC
  - Phenotype of PCOS characterized by persistent diestrus, obesity, and normal LH levels

Endocrinology, February 2017, 158(2):367–377

Pathophysiology

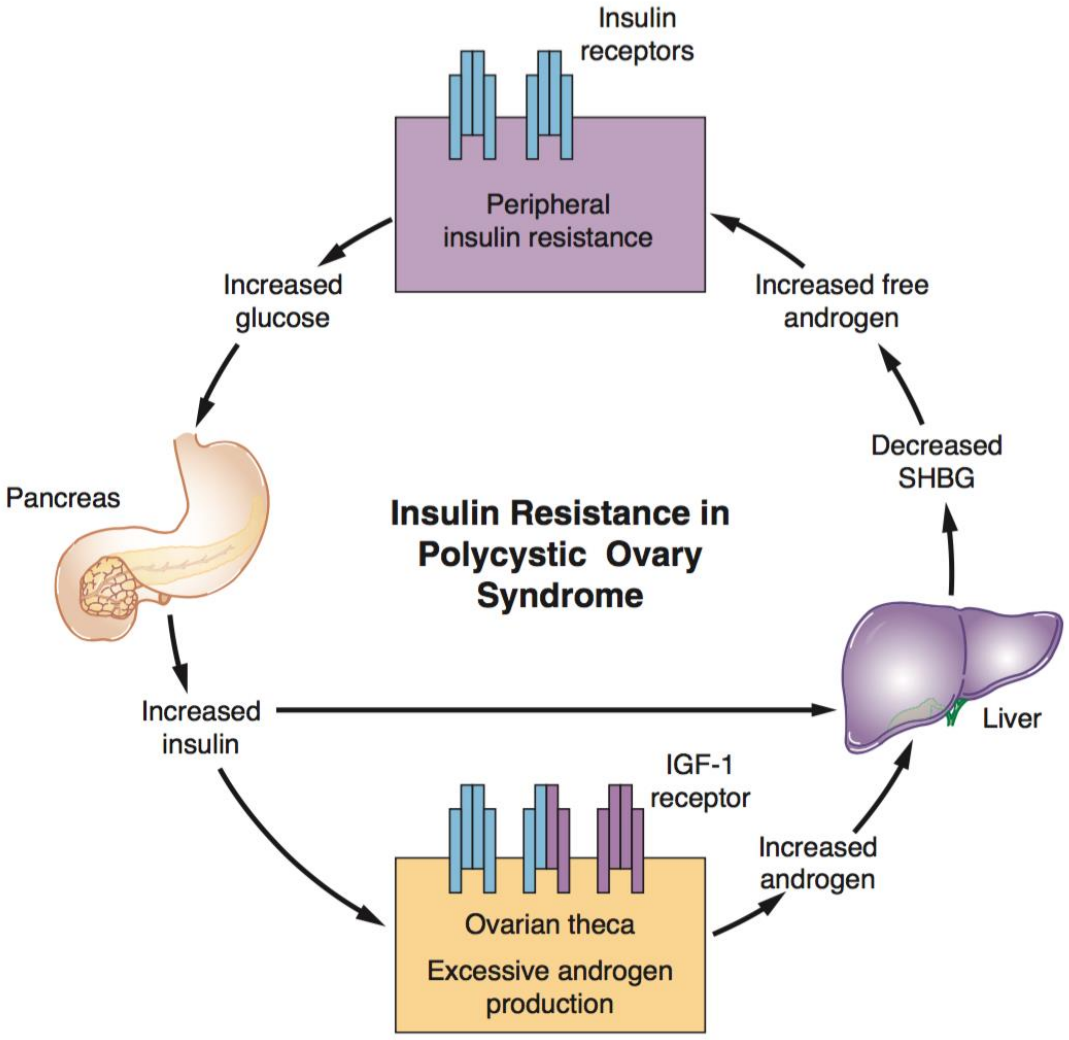
- FSH receptors are present on granulosa cells
- FSH receptors are induced by FSH
- LH receptors are present on theca cells and as the follicle grows, FSH induces LH receptors on granulosa cells
- FSH induces aromatase enzyme activity in granulosa cells
- IGF secreted by theca cells enhances LH stimulation of androgen production
- “Insulin functions as a co-gonadotropin through its cognate receptor to modulate ovarian steroidogenesis”



Nestler, Hum Reprod, 1997
Speroff, 8th edition
Dunaif, Endocrine Reviews, 2012

Insulin Resistance and PCOS

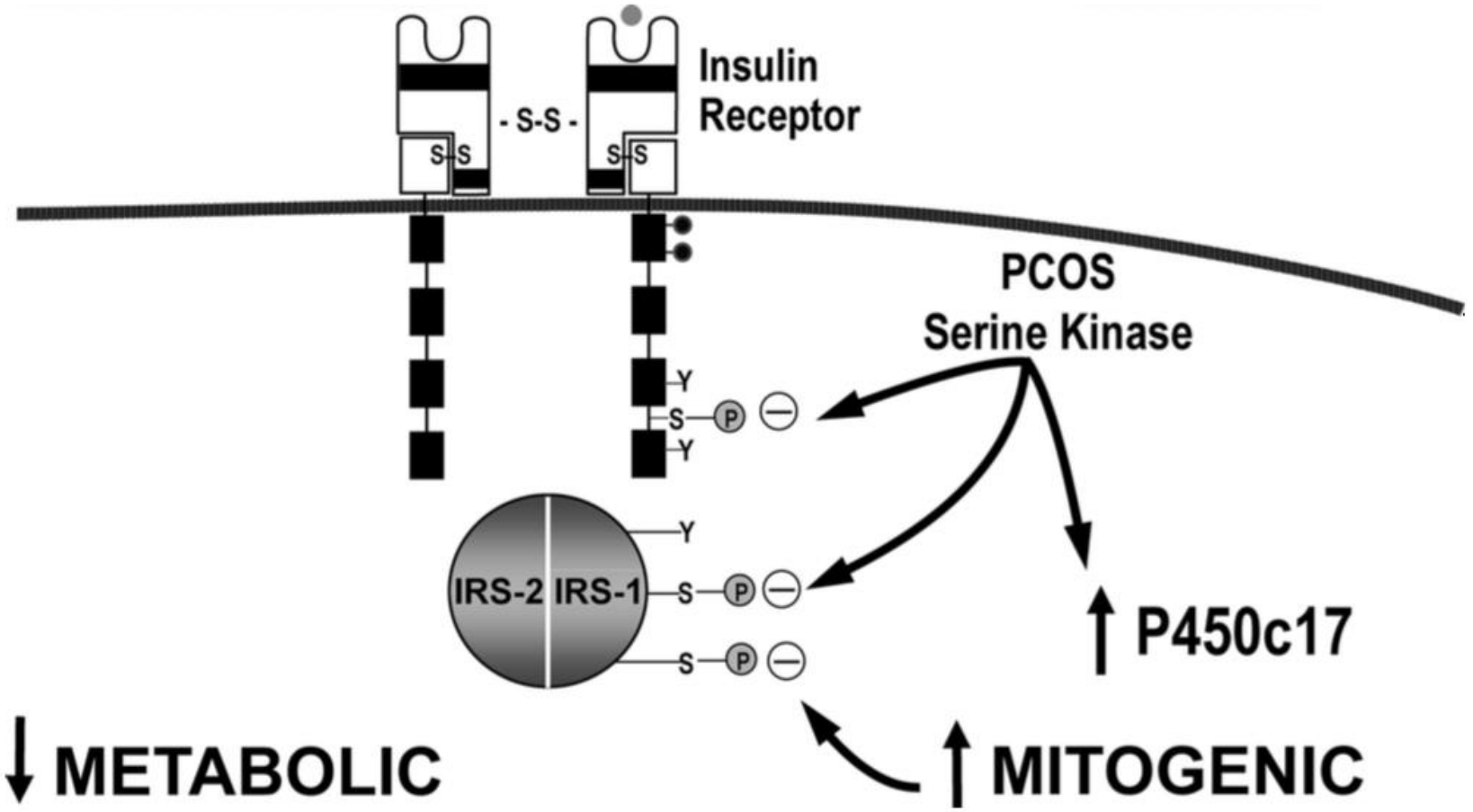
- Prevalence 50% and 75%, more common in obese vs. lean
- 7–10% of women with PCOS meet criteria for T2DM
- Hyperinsulinemia additionally inhibits hepatic SHBG production



Speroff 8th Ed

Insulin signaling defects in PCOS

- Increased Ser:Tyr phosphorylation of IR and IRS-1
- Decreased activation of PI3-K (metabolic)
- Constitutive activation of ERK/MAPK (mitogenic) pathway



Dunaif, Endocrine Reviews, 2012

AMH and PCOS

- Reduced levels of AMH in primordial and transitional follicles initially promotes recruitment of additional growing follicles[1]
- Increased AMH due to increased small antral follicles and increased production of AMH per follicle impairs further follicular growth by inhibiting FSH[2]
- Circulating FSH levels don't overcome inhibition of aromatase activity by AMH in the antral follicle[3]

1 – Laven, JCEM, 2004
2 – Stubbs, JCEM, 2005
3 – Visser, Endocrinology, 2007

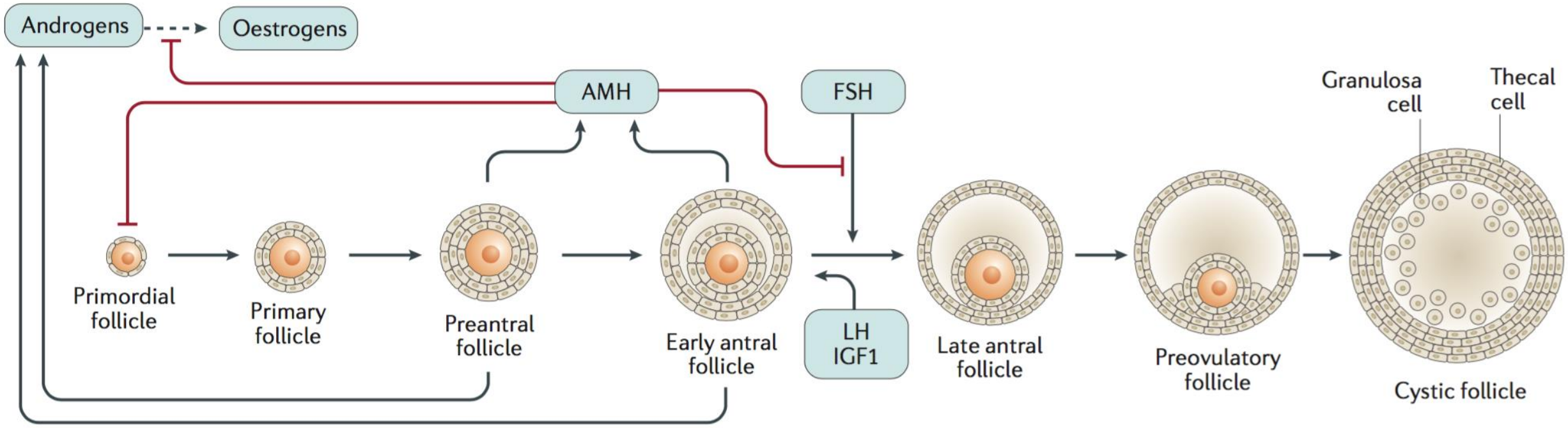
Baseline AMH Level Associated With Ovulation Following Ovulation Induction in Women With Polycystic Ovary Syndrome

- 748 women 18-40 yo with PCOS
- Lower mean AMH in ovulatory women vs anovulatory women (mean AMH, **5.54 v 7.35 ng/mL**; P=.0001) after adjusting for age, body mass index, T, and insulin level
- Each one unit increase in AMH level associated with lower odds of ovulation after adjustment for age, BMI, T, and insulin level

Mumford et al, JCEM, 2016

Mumford et al, JCEM, 2016

Ovarian follicular maturation arrest in PCOS



Azziz, Nature Reviews, 2016

Clinical Manifestations: Metabolic profile

- Many women with PCOS demonstrate basal and glucose stimulated hyperinsulinemia **independent of BMI**[1]
- 16% of women with PCOS progress from IGT to T2DM[2]
- 2% of women with PCOS develop T2DM annually[3]
- Systematic review and meta-analysis: prevalence of IGT (OR 2.4) and T2DM (OR 4.43) increased in PCOS[3]
  - subgroup analysis: increased prevalence of IGT and metabolic syndrome in lean PCOS women compared to controls

1 – Dunaif, Diabetes, 1989
2 – Legro, JCEM, 2005
3 – Moran, Hum Reprod Update, 2010

Adipocyte dysfunction in PCOS

- Inflammatory cytokines (TNF, IL6) suppress insulin mediated glucose transport more in adipocytes derived from patients with PCOS[1]
- Women with PCOS have larger adipocytes, lower lipoprotein lipase activity, and impaired catecholamine induced lipolysis[2]
- GLUT4 expression decreased in adipocytes in PCOS, similar to levels observed in adipocytes derived from patients with T2DM[3]
- Epigenetic dysregulation in PCOS: miR93 and miR223 have roles in suppressing GLUT4 content and altering glucose transport[4,5]

1 – Chazenbalk, JCEM, 2010
2 – Rosenbaum, Am J Physiol, 1993
3 – Garvey, J Clin Invest, 1991
4 – Chen, Diabetes, 2013
5 – Chuang, J Diabetes Res, 2015

Screening and Prevention

- Early treatment of obesity, hyperandrogenic symptoms and menstrual dysfunction will result in clinical improvement – unclear if this will prevent progression of PCOS
- Early treatment with metformin might reduce progression to PCOS in girls with low birth weight and precocious pubarche[1]

1 – Ibanez, JCEM, 2011
Azziz, Nature Reviews, 2016

Box 3 | **Risk factors for the development of PCOS**

Family history is the most important risk factor for developing PCOS[67–69]. Other risk factors, depending on age, include:

- Before birth
  - Small for gestational age*
- Childhood and peripuberty
  - Early-onset obesity[219–222]
  - Increased dehydroepiandrosterone sulfate levels during the onset of puberty[219–222]
  - Premature pubarche[223,224]
  - Hyperinsulinaemia[219–222]
- Adolescence[225–228]
  - Obesity, overweightness or rapid weight gain[225–228]
  - Irregular menstrual or oligo-amenorrhoea[225–228]
  - Presence of polycystic ovarian morphology[225–228]
  - High androgen levels[225–228]
  - Development of unwanted terminal hair growth on the face or body[229]

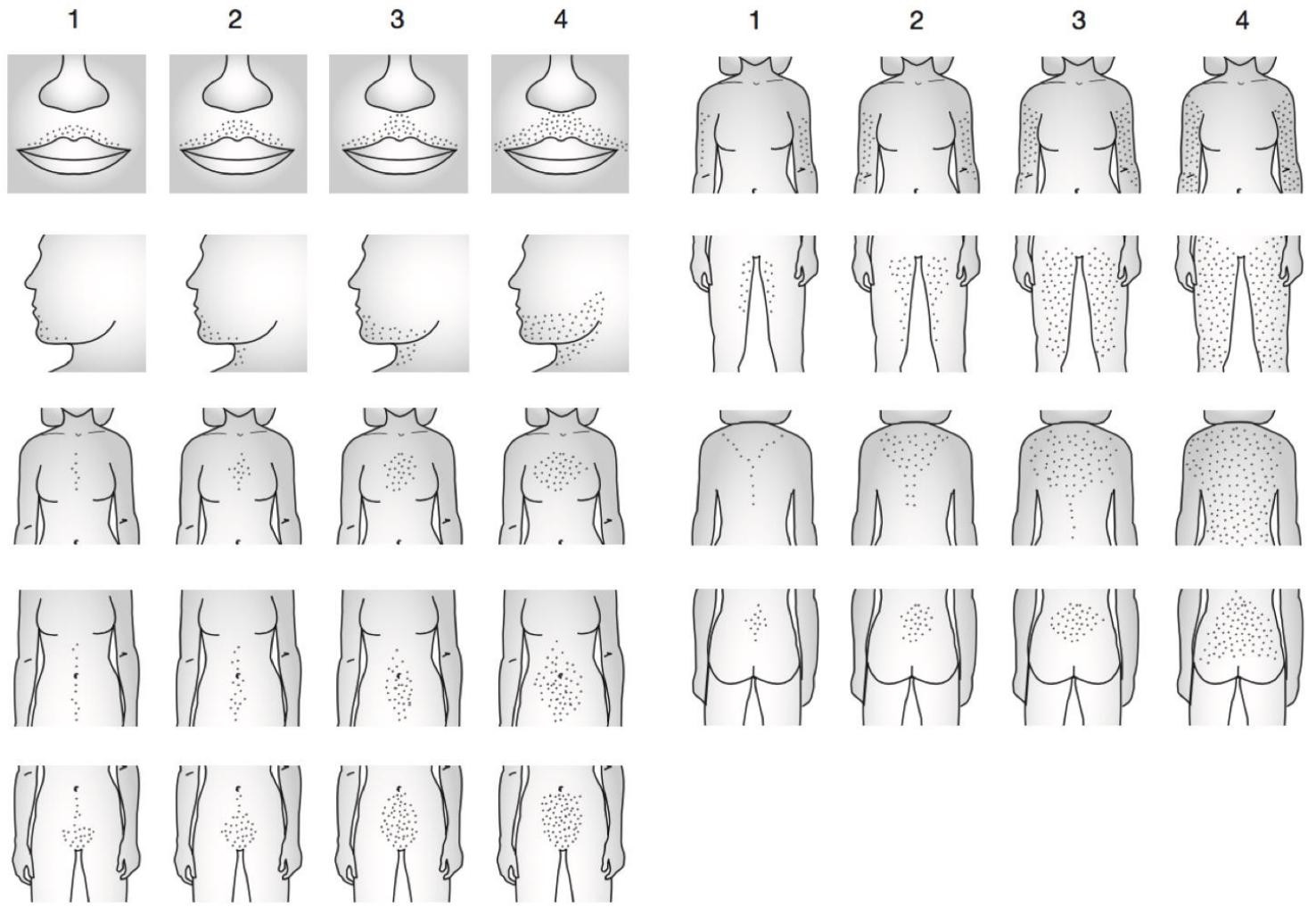
*Although some investigators have suggested that girls born small for their gestational age are at higher risk for insulin resistance and possibly PCOS[230], other studies have indicated that most women with PCOS are actually born of normal or large size for gestational age[27,231].

Hyperandrogenism

- Clinical signs: hirsutism, acne and androgenic alopecia
- Hirsutism affects 65–75% of white and AA patients with PCOS compared to the general population (0–2%)
- Acne affects 15–25% of patients with PCOS and varies with ethnicity

Hirsutism Scoring

- Modified Ferriman–Gallwey (mFG) score ≥6 (95th %), but ≥3 may be considered abnormal[1]
- 228 patients with unwanted hair growth and mFG score of ≤5, >50% demonstrated an androgen excess disorder[2]



1 - DeUgarte, JCEM, 2006.
2 - Souter, AJOG, 2004.
Azziz, Androgen Excess Disorders in Women: Polycystic Ovary Syndrome and Other Disorders, 2006

Quality of life and psychological well being in polycystic ovary syndrome

Mood and anxiety disorders in women with PCOS

- Women with PCOS have higher depression scores and higher risk of depression independent of BMI
- PCOSQ (PCOS questionnaire): most adversely affected domains **weight and infertility**
  - Body hair, emotions and acne were least affected by PCOS
  - Women with PCOS are also at risk for symptoms of generalized anxiety disorder
- Underscores need to screen and treat women with PCOS for mood and anxiety disorders

Dukras, Steroids, 2012
Jones, Hum Reprod Update, 2008
Barnard, Hum Reprod Update, 2007

Psychosocial/QOL

- Depression and anxiety are more common and more severe in women with PCOS regardless of phenotype or presence of obesity[1,2]
- Depression scores with the degree of insulin resistance[3]
- Meta-analysis of 28 studies: 2,384 patients with PCOS, 2,705 controls[4]
  - More severe emotional distress present in women with PCOS
  - Hirsutism, obesity and infertility did not fully account for high prevalence of anxiety and depression

1 – Teede, Med J Aust, 2011
2 – Dokras, Obstet Gynecol, 2011
3 – Cinar, Hum Reprod, 2011
4 – Veltman-Verhulst, Hum Reprod Update, 2012

Obstetric morbidity

- Population-based study: singleton births in 3,787 women with PCOS and >1 million without PCOS (Sweden) between 1995 and 2007
  - PCOS conferred significantly higher rates of preeclampsia (adjusted OR 1.45), very preterm birth (adjusted OR 2.21), and gestational diabetes mellitus (adjusted OR 2.23)
  - Infants born to mothers with PCOS were more prone to be large for gestational age (adjusted OR 1.39), at increased risk of meconium aspiration (adjusted OR 2.02) and having a low Apgar score (<7) at five minutes (adjusted OR 1.41)

Roos, BMJ, 2011

Cardiovascular disease

- CVD markers increased in women with PCOS (does this confer a higher risk of CVD?)
  - Coronary calcifications more prevalent in women with PCOS[1,2]
  - Thickness of intimal layer of the carotid wall > in women with PCOS[3,4]
  - Incidence of aortic calcification higher with PCOS[2]
  - Dallas heart study: arterial stenosis more prevalent in women with PCOS based on coronary angiography[5]

1 – Christian, JCEM, 2003
2 – Talbott, JCEM, 2004
3 – Luque-Ramirez, Hum Reprod, 2007
4 – Lass, JCEM, 2011
5 – Chang, Clin Endocrinol, 2011

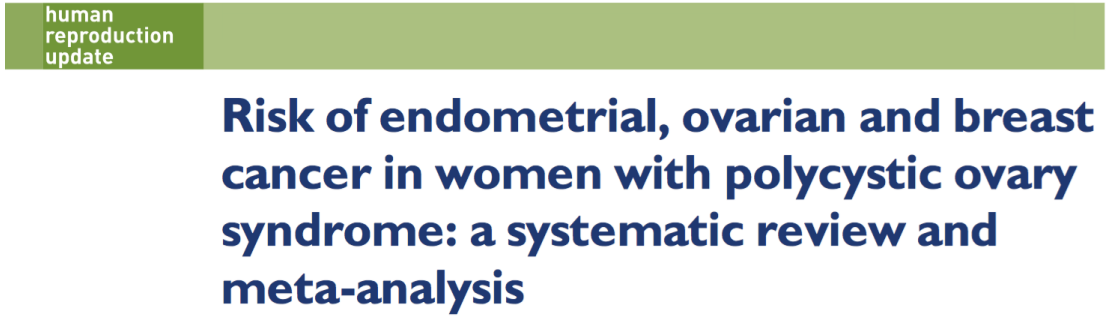
Risk of Thrombosis

- Incidence of cerebrovascular events increased in older women with PCOS[1,2]
- Risk of VTE increased (OR 1.5) compared with BMI matched controls[3]
- Risk of VTE two-fold higher in women with PCOS who take OCPs[4]

1 – Carmina, J Endocrinol Invest, 2013
2 – Bird, CMAJ, 2013
3 – Anderson, Int J Cardiol, 2014
4 – Hart, JCEM, 2015

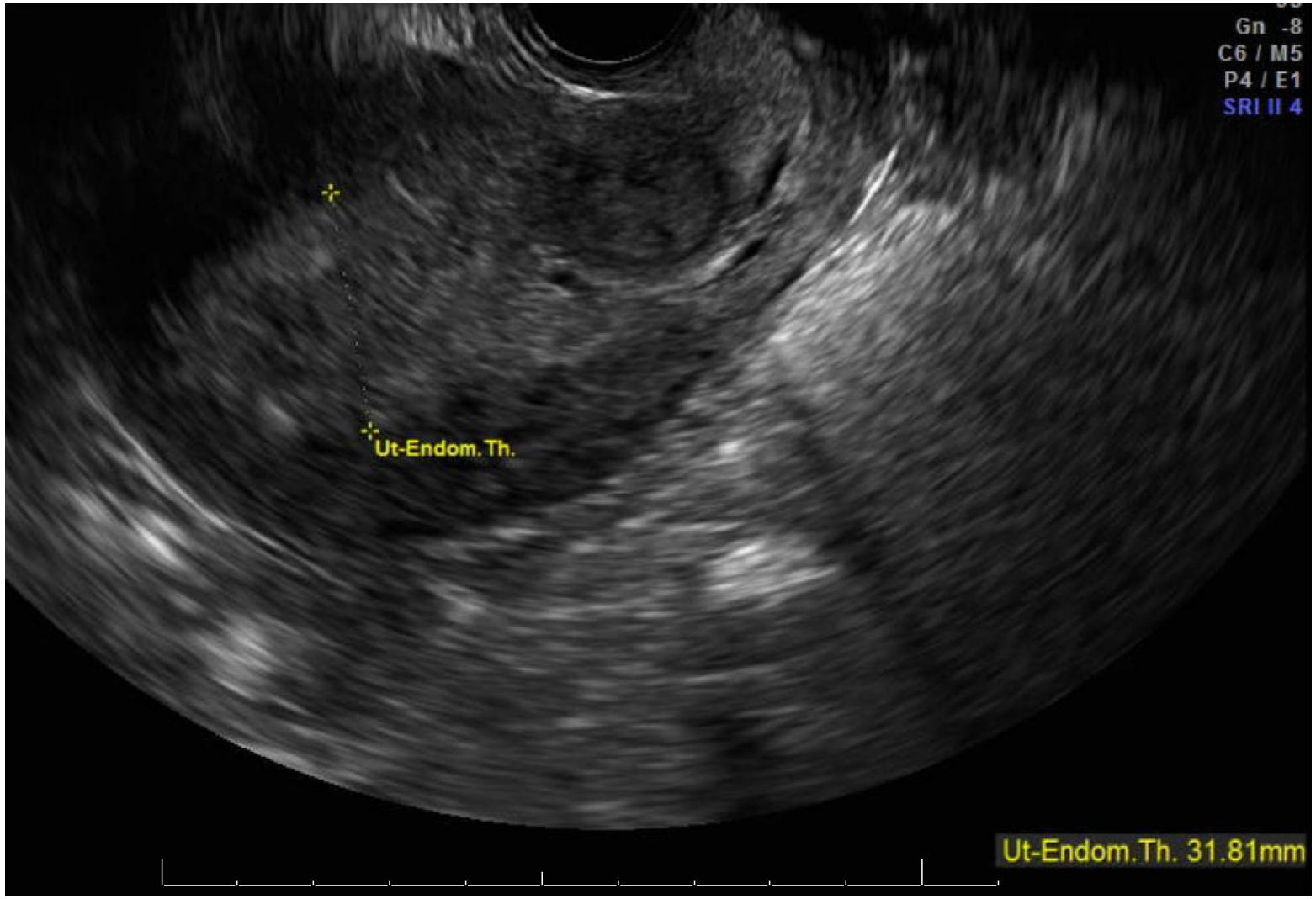
Risk of endometrial hyperplasia and cancer

- Women with PCOS are at increased risk of endometrial cancer (OR 2.79); risk of ovarian and breast cancers not increased
- When studies including women >54 years were excluded, risk for women with PCOS increased further for endometrial cancer (OR 4.05) and became significantly increased for ovarian cancer (OR 2.52), but remained non-significant for breast cancer



Barry, Human Reproduction Update, 2014

Endometrial hyperplasia and cancer



Weight Loss

- Primary treatment of metabolic dysfunction in PCOS and also improves fertility (ovulation in 40–50% of women with PCOS, 30–40% of whom are able to achieve a spontaneous pregnancy)
- Weight loss improves insulin resistance and hyperandrogenism
- At least 5% weight loss can improve ovulation, suggesting that the results depend more on energy restriction or changes in fat distribution
- Different hypocaloric diets with various macronutrient compositions have been used with no significant differences in results

Physical Exercise

- Physical exercise improves insulin resistance, promotes changes in fat distribution and reduced cardiovascular risk in women with PCOS
- Should be performed at least 30 minutes per day for at least 5 days per week
- **Associated with low adherence and sustainability**

Harrison, Clin Endo, 2012

The Impact of Bariatric Surgery on Polycystic Ovary Syndrome: a Systematic Review and Meta-analysis

- Reserved for women with PCOS with BMI >40 or with BMI >35 who have co-morbidities
- Mean age 30.8 years, mean follow-up 23.8 months
- Preoperative mean BMI 46.3 kg/m2, which improved to 34.2 kg/m2 postoperatively
- EWL% ranged from 33.0 to 75.0%, with a sample weighted mean of 57.2%
- Bariatric surgery decreased the incidence of PCOS symptoms from 45.6% to 7.1%
- 56.2% of patients reported preop menstrual irregularity, 7.1% at study endpoint
- Incidence of hirsutism preoperatively was 67.0%, 32.0% at study endpoint
- Incidence of preoperative infertility was 18.2%, 4.3% at study endpoint

Skubleny, Obes Surg, 2016

human reproduction update

Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis

- **Metformin improves body composition and insulin levels in women with PCOS who are not obese**, but has no significant effect on BMI, fasting glucose or lipid levels
- 12 RCTs, 608 women with PCOS. Lifestyle + metformin associated with lower BMI and subcutaneous adipose tissue and increased number of menstrual cycles after 6 months
- No differences in other metabolic (surrogate markers of insulin resistance, fasting and area under the curve glucose, lipids and blood pressure), reproductive (clinical and biochemical hyperandrogenism), and psychological (quality of life) outcomes after 6 months
- With metformin alone compared with lifestyle + placebo, weight and BMI were similar after 6 months, but testosterone was lower with metformin
- **Systematic review and meta-analysis suggests that lifestyle modification with metformin reduced BMI in women with PCOS to a greater degree than lifestyle modification alone**

Naderpoor, 2015

Effect of metformin on insulin levels

Hemoglobin A1C	<5.7 % of total Hgb	5.6
Resulting Agency		QUEST

Time 1		846
Glucose 0 min	65 - 99 mg/dL	91
Time 2		945
Specimen 2	mg/dL	140
Time 3		1049
Specimen 3	mg/dL	120
Time 4		1146
Specimen 4	mg/dL	44

Time 1		846
SPECIMEN 1	uIU/mL	12.4
Time 2		945
Insulin #1	uIU/mL	254.8 ←
Time 3		1049
Insulin #2	uIU/mL	196.0 ←
Time 4		1146
Insulin #3	uIU/mL	15.4
Result Header		SEE COMMENT

Comments: Reference Range

Fasting: 2.0-19.6
30 Minutes Post Glucose: 6.0-86.0
60 Minutes Post Glucose: 8.0-112.0
90 Minutes Post Glucose: 5.0-68.0
120 Minutes Post Glucose: 5.0-55.0
150 Minutes Post Glucose: 3.0-46.0
180 Minutes Post Glucose: 3.0-20.0
240 Minutes Post Glucose: <15.0

Sex Hormone Bind Glob	40	
Testosterone, Tota...	66	▲
Testosterone Free	7.0	▲
Testosterone, bioa...	12.2	▲

34 y.o. G0 with PCOS, morbid obesity (BMI 40), hirsutism, AMH 13.8, anovulatory infertility. Started on Metformin

Patient with insulin resistance

- Can also decrease serum Testosterone levels

Cochrane Library

Cochrane Database of Systematic Reviews

Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility (Review)

Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH

- 44 trials (3992 women), 38 using metformin (3495 women)
- Clomiphene more effective for obese women vs metformin alone in improving LBR (pooled OR 0.3, 2 trials, 500 women)
- Metformin associated with a significantly higher incidence of GI disturbances than placebo (pooled OR 4.27, 5 trials, 318 women)
- **Metformin did NOT improve live birth rates, alone or in combo with clomiphene**

Tang, Cochrane Database, 2012

Clinical Study
Open Access

M Jensterle Sever and others | Polycystic ovary syndrome and liraglutide | 170:3 | 451–459

Short-term combined treatment with liraglutide and metformin leads to significant weight loss in obese women with polycystic ovary syndrome and previous poor response to metformin

Mojca Jensterle Sever, Tomaz Kocjan, Marija Pfeifer, Nika Aleksandra Kravos and **Andrej Janez**

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Subjects treated with COMBI lost on average 6.5 +/- 2.8 kg compared with a 3.8 +/- 3.7 kg loss in the LIRA group and a 1.2 +/- 1.4 kg loss in the MET group ($P<0.001$)

Jensterle et al. BMC Endocrine Disorders (2017) 17:5
DOI 10.1186/s12902-017-0155-9

BMC Endocrine Disorders

RESEARCH ARTICLE Open Access

Short-term effectiveness of low dose liraglutide in combination with metformin versus high dose liraglutide alone in treatment of obese PCOS: randomized trial

Mojca Jensterle[1], Nika Aleksandra Kravos[1], Katja Goričar[2] and Andrej Janez[1*]

Abstract

Background: Liraglutide 3 mg was recently approved as an anti-obesity drug. Metformin is weight neutral, yet it could enhance the therapeutic index of GLP-1 agonist. We compared weight-lowering potential of liraglutide 1.2 mg in combination with metformin to liraglutide 3 mg monotherapy in obese PCOS.

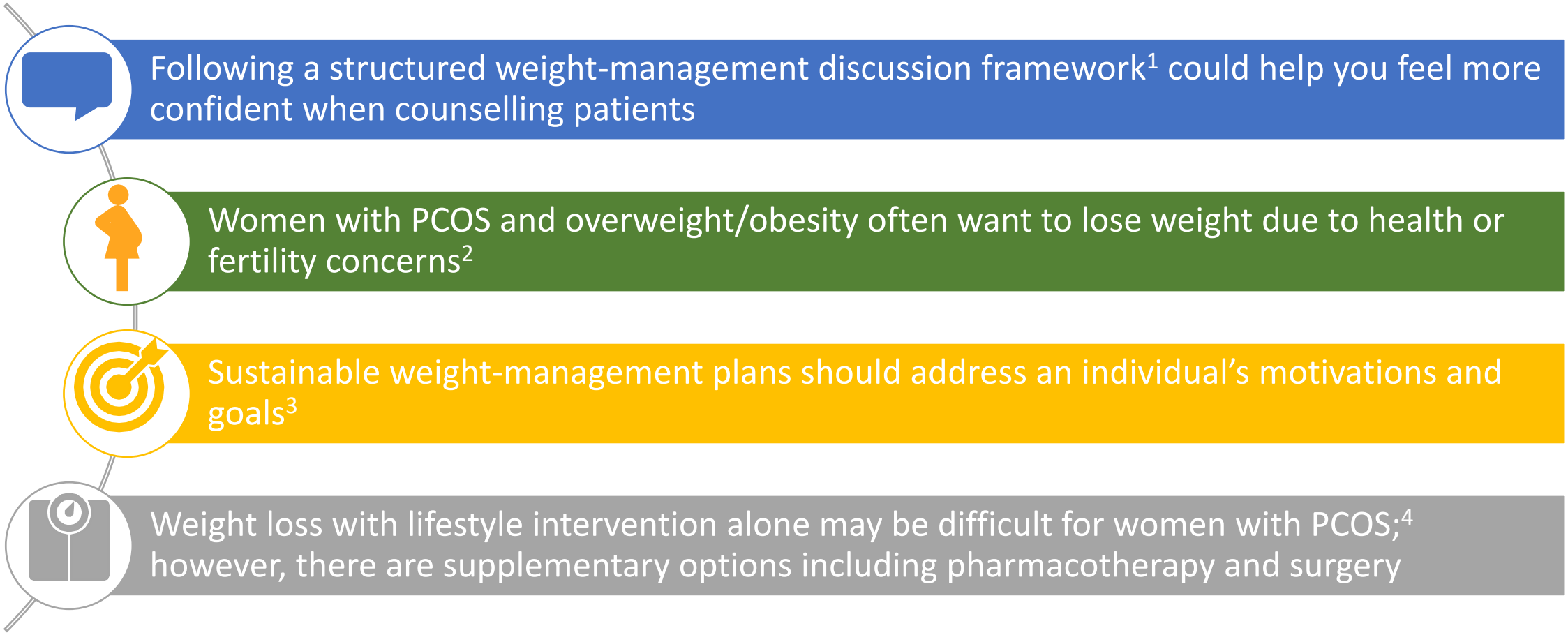
Methods: Thirty obese women with PCOS (aged 33.1 ± 6.1 years, BMI 38.3 ± 5.4 kg/m^2) were randomized to combination (COMBO) of metformin (MET) 1000 mg BID and liraglutide 1.2 mg QD ($N = 15$) or liraglutide 3 mg (LIRA3) QD alone ($N = 15$) for 12 weeks. The primary outcome was change in anthropometric measures of obesity.

Results: Both treatments led to significant weight loss (−3.6 ± 2.5 kg, $p = 0.002$ in COMBO vs −6.3 ± 3.7 kg, $p = 0.001$ in LIRA3). BMI and waist circumference reduction in LIRA3 was greater than in COMBO (−2.2 ± 1.3 vs −1.3 ± 0.9 kg/m^2, $p = 0.05$ and −4.2 ± 3.4 vs −2.2 ± 6.2 cm, $p = 0.014$, respectively). Both interventions resulted in a significant decrease of post-OGTT glucose levels. COMBO significantly reduced total testosterone and was associated with less nausea.

Conclusions: Short-term interventions with COMBO and LIRA3 both led to significant improvement of measures of obesity in obese PCOS, LIRA3 being superior to COMBO. However, COMBO further improved androgen profile beyond weight reduction and was associated with better tolerability.

Trial registration: The study was retrospectively registered with ClinicalTrials.gov (NCT02909933) on 16th of September 2016.

Approaching Weight Conversations



1. Vallis M, et al. *Can Fam Phys*. 2013;59:27-31; 2. Love JG, et al. *Int J Womens Health*. 2016;8:299-310; 3. Wharton S, et al. *CMAJ*. 2020;192:e875-e891; 4. Kim CH, et al. *Sci Rep*. 2020;10:7802.

Irregular menstrual cycles

- First-line management: combined estrogen-progestin OCPs
  - Endometrial protection
  - Decreases in LH secretion →decreases ovarian androgen production
  - Increases hepatic production of SHBG → decreases bioavailable testosterone
  - Decreases adrenal androgen secretion
- If contraindication to COCs, consider progestin only option – minipill, cyclic Provera, Mirena IUD

Anti-androgens for PCOS

Agent	Mechanism of action	US FDA-approved indication	Adverse effects	Refs
Spironolactone	Competitive inhibitor of AR binding, antimineralocorticoid, limits suppression of 5α-reductase activity and suppresses LH	Treatment of low renin hypertension, hypokalaemia and Conn syndrome	Dyspepsia; dry skin; decreased libido; hypotension; polyuria; menstrual irregularity and polymenorrhoea when not administered with an OCP; teratogenic in early pregnancy, principally on male fetuses; rare skin sensitivity to sunlight; and rare hypokalaemia	178, 179
Cyproterone acetate	Competitive inhibitor of AR binding, limits suppression of 5α-reductase activity and decreases LH-dependent androgen secretion	Palliative treatment of patients with advanced prostatic carcinoma	Breast swelling; amenorrhoea; decreased libido; teratogenic in early pregnancy, principally on male fetuses; rare liver toxicity; rare reduced adrenal response to ACTH stimulation; and rare oestrogen-related osteoporosis	180
Flutamide	Competitive antagonist of AR and reduces synthesis of DHT	Management of locally confined stage B2–stage C and stage D2 metastatic carcinoma of the prostate	Dry skin; discoloured (green) urine; decreased libido; teratogenic in early pregnancy, principally on male fetuses; and rare liver toxicity (occasionally fulminant)	176, 181
Finasteride	Competitively binds to and inhibits steroid type II 5α-reductase	Treatment of benign prostatic hyperplasia	Dry skin; headache; decreased libido; and teratogenic in early pregnancy, principally on male fetuses	182

Azziz, Nature Reviews, 2016

Infertility

- PCOS is the most common cause of anovulatory infertility
- Study: community self-reported prevalence of PCOS 5.8%[1]
  - Infertility was 15-fold higher in women reporting PCOS, independent of BMI
- Study: cohort of 786 women with PCOS diagnosed >30 years ago from hospital records[2]
  - From this selected population 66% of women reported infertility

1 – Joham, J Womens Health, 2015
2 – Wild, Hum Fert, 2000

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 8, 2007 VOL. 356 NO. 6

Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome

- Double blind multi-center trial of 626 women
- Live-birth rate 22.5% in the clomiphene group, 7.2% in the metformin group, and 26.8% in the combination therapy group
- Rate of multiple pregnancy was 6.0% in the clomiphene group, 0% in the metformin group, and 3.1% in the combination-therapy group
- First-trimester pregnancy loss did not differ significantly among the groups
- **Clomiphene superior to metformin in achieving live birth in PCOS, although multiple birth is a complication**

Legro et al, RMN, NEJM, 2007

ORIGINAL ARTICLE

Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome

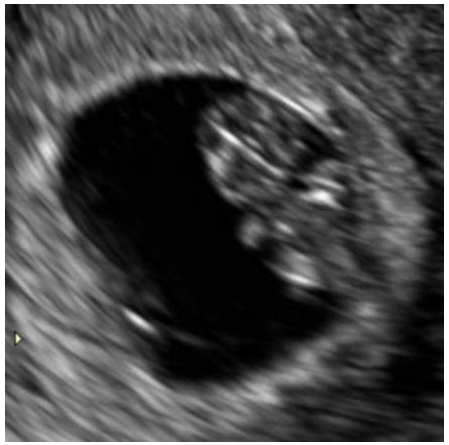
- Double blind multi-center trial of 750 women
- Women who received letrozole had more cumulative live births than those who received clomiphene (27.5% vs 19.1%, P=0.007)
- Cumulative ovulation rate higher with letrozole than with clomiphene (61.7% vs. 48.3%, P<0.001)
- No significant differences in pregnancy loss (31.8% in the letrozole group and 29.1% in the clomiphene group) or twin pregnancy (3.4% in the letrozole group and 7.4% in the clomiphene group)
- Four congenital anomalies in letrozole group versus one in the clomiphene group (P=0.65)
- **Letrozole has higher live birth and ovulation rates among women with PCOS**

Legro et al, RMN, NEJM, 2014

Back to patient with PCOS

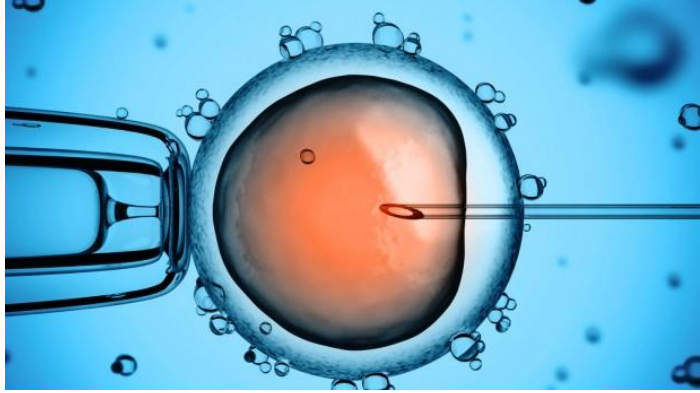
CD12	D_1				15+<7					19	15	18		1<10				11.4
Ovidrel	D_2									23	13	21		8<7				
	D3									17	27	16						
	Dav	0	0	0	###	0	0	0	0	20	18	18	0	###	0	0	0	bma

S/p letrozole 7.5 mg cycle days 3-7
Development of 3 mature ovarian follicles on cycle day 12
Triggered ovulation with hCG
Intrauterine insemination 36 hours later
Pregnant with singleton @ 9 weeks EGA



34 y.o. G0 with PCOS, morbid obesity (BMI 40), hirsutism, AMH 13.8, anovulatory infertility.

In Vitro fertilization (IVF)

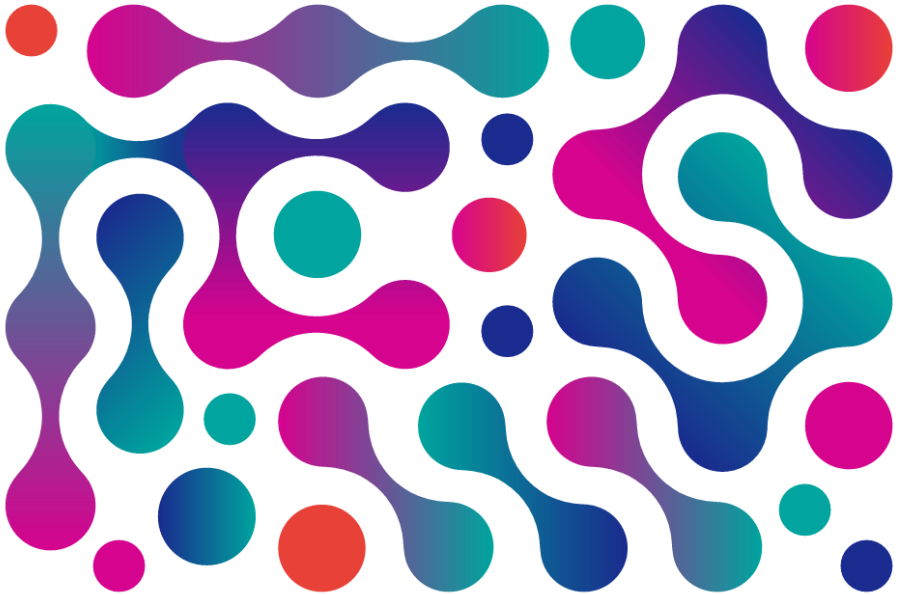


- IVF success determinants: # of oocytes, quality of oocytes
- Women with PCOS tend to have above average AMH (predicting high # of oocytes)
- Quality of oocyte: tied to age and possibly PCOS
  - PCOS: more oocytes retrieved but fewer fertilize vs age-matched controls[1]
  - PCOS: meta-analysis, increased IVF cancellation rate, more oocytes retrieved, lower fertilization rate vs age-matched controls[2]
  - Obese PCOS: lower clinical pregnancy rate vs lean PCOS[3]

1 – Homburg, F&S, 1993
2 – Heijnen, Hum Reprod Update, 2005
3 – Jungheim, F&S, 2009

Updates

International evidence-based guideline for the assessment and management of **polycystic ovary syndrome 2023** – Summary

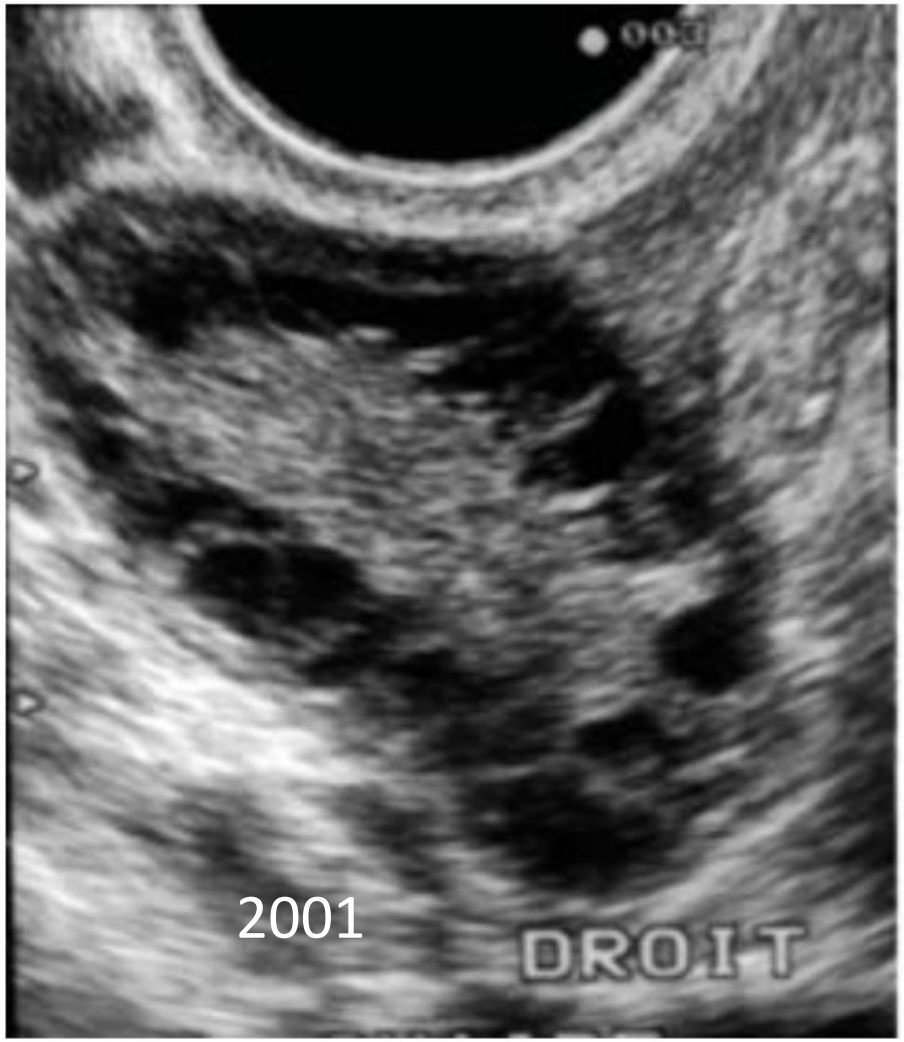


Rotterdam criteria (historical perspective)

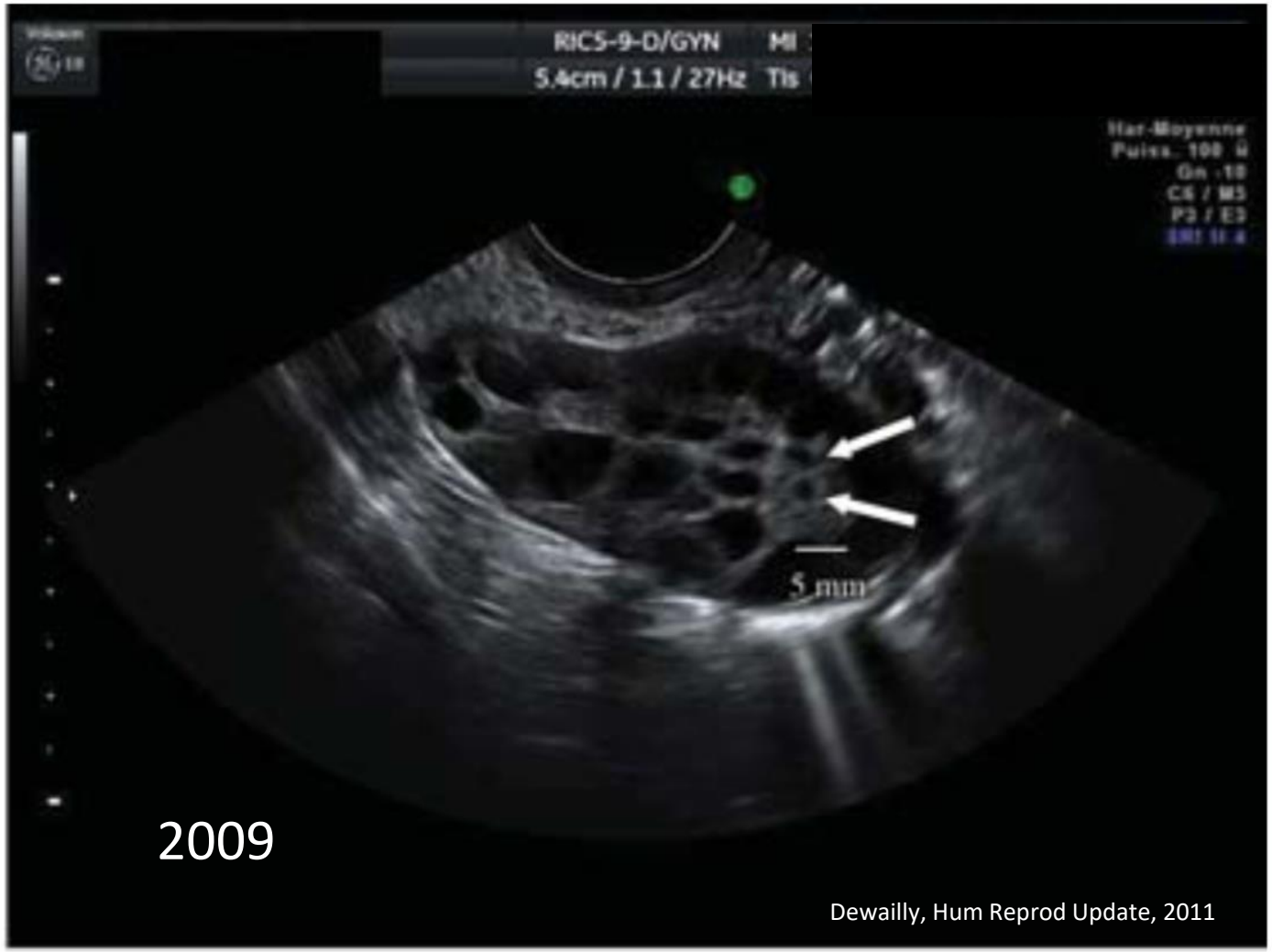
- Two of Three:
  - Disordered ovulation: Cycles > 35 days or < 10 menses/year
  - Polycystic ovaries
    - Multiple subcortical early antral follicles: >12 follicles 2-9 mm +/-ovarian volume > 10mL
    - Single ovary sufficient
  - Hyperandrogenism
    - Clinical or biochemical
  - Exclusion of other conditions
    - Cushing's, CAH, tumors

Azziz, Nature Reviews, 2016

PCOM



2001



2009

Dewailly, Hum Reprod Update, 2011

PCOM: New criteria

- FNPO (Follicle number per ovary): >20
- FNPS (Follicle number per cross section): >10 (use for older equipment or if only transabdominal view is possible
- Maintain the threshold for increased OV at ≥10 mL
  - OV has less diagnostic potential for PCOM compared with FNPO
- AMH for PCOM equal to or better than FNPO, but accuracy of available AMH assays preclude the establishment of a threshold value for its use as a surrogate marker of PCOM

Goal of the Updated Recommendations

- Reduce worldwide variation in care
- Promote high quality clinical service provision to improve health outcomes and quality of life in women with PCOS
- Empowerment

Table 1: Categories of the PCOS guideline recommendations

EBR	Evidence-based recommendations: Evidence sufficient to inform a recommendation made by the guideline development group.
CR	Consensus recommendations: In the absence of adequate evidence, a consensus recommendation has been made by the guideline development group, also informed by evidence from the general population.
PP	Practice points: Evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or consensus recommendations.

The GRADE of the recommendation is determined by the GDG from structured, transparent consideration of the GRADE framework[16] including desirable effects, undesirable effects, balance of effects, resource requirements and cost effectiveness, equity, acceptability and feasibility and includes:

❖	Conditional recommendation against the option
❖❖	Conditional recommendation for either the option or the comparison
❖❖❖	Conditional recommendation for the option
❖❖❖❖	Strong recommendation for the option

Table 2: Quality (certainty) of evidence categories (adapted from GRADE)[16]

High	⊕⊕⊕⊕	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	⊕⊕⊕◯	Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different.
Low	⊕⊕◯◯	Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect.
Very Low	⊕◯◯◯	Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Diagnosis:

Cycle irregularity

1.1		Irregular cycles and ovulatory dysfunction	
1.1.1	CR	Irregular menstrual cycles are defined as: • Normal in the first year post menarche as part of the pubertal transition • > 1 to < 3 years post menarche: < 21 or > 45 days • > 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year • > 1 year post menarche > 90 days for any one cycle	❖❖❖❖
1.1.5	PP	Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured.	

Diagnosis: Biochemical Hyperandrogenemia

1.2.1	**EBR**	Healthcare professionals should use total and free testosterone to assess biochemical hyperandrogenism in the diagnosis of PCOS; free testosterone can be estimated by the calculated free androgen index.	❖❖❖❖ ⊕○○○
1.2.2	**EBR**	If testosterone or free testosterone is not elevated, healthcare professionals could consider measuring androstenedione and dehydroepiandrosterone sulfate (DHEAS), noting their poorer specificity and greater age associated decrease in DHEAS.	❖❖❖ ⊕○○○
1.2.6	**PP**	It is very difficult to reliably assess for biochemical hyperandrogenism in women on the combined oral contraceptive pill (COCP) as the pill increases sex hormone-binding globulin and reduces gonadotrophin-dependent androgen production. If already on the COCP, yet assessment of biochemical androgens is imperative, the pill should be withdrawn for a minimum of three months and contraception should be managed otherwise during this time.	

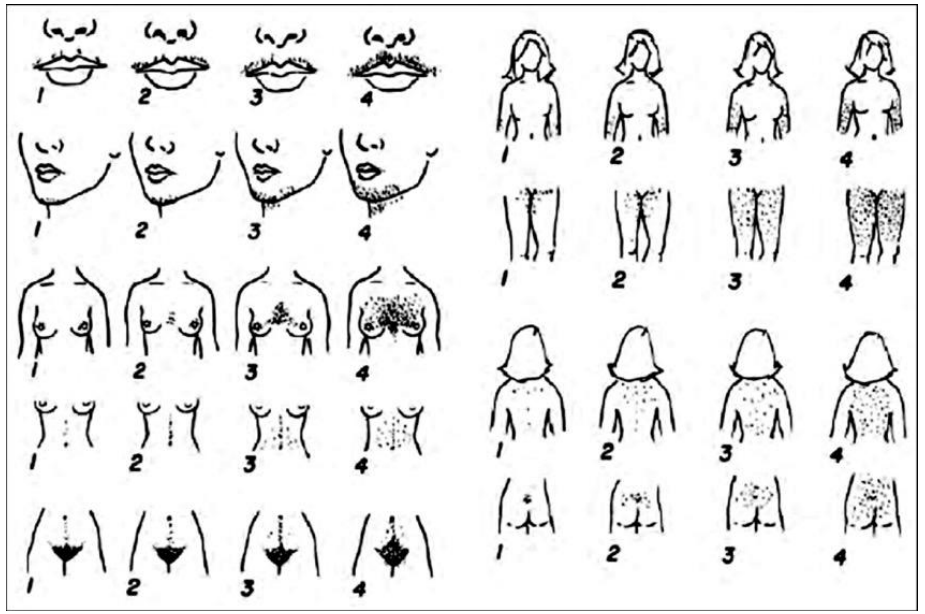
Rule out other causes of hyperandrogenism

Diagnosis: Clinical Hyperandrogenism

1.3.1	EBR	The presence of hirsutism alone should be considered predictive of biochemical hyperandrogenism and PCOS in adults.	❖❖❖ ⊕○○○
1.3.2	EBR	Healthcare professionals could recognise that female pattern hair loss and acne in isolation (without hirsutism) are relatively weak predictors of biochemical hyperandrogenism.	❖❖❖❖ ⊕○○○
1.3.3	CR	A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, female pattern hair loss and hirsutism in adults, and severe acne and hirsutism in adolescents.	❖❖❖❖

Diagnosis: Clinical Hyperandrogenism

1.3.5	CR	A modified Ferriman Gallwey score (mFG) of 4–6 should be used to detect hirsutism, depending on ethnicity, acknowledging that self-treatment is common and can limit clinical assessment.	❖❖❖❖
1.3.6	CR	Healthcare professionals should consider that the severity of hirsutism may vary by ethnicity but the prevalence of hirsutism appears similar across ethnicities.	❖❖❖



Diagnosis: Ultrasound Evaluation

1.4.3	CR	PCOM criteria should be based on follicle excess (FNPO, FNPS) and/or ovarian enlargement (OV).	❖❖❖❖
1.4.4	CR	Follicle number per ovary (FNPO) ≥ 20 in at least one ovary should be considered the threshold for PCOM in adults.	❖❖❖❖
1.4.5	CR	Ovarian volume (OV) ≥ 10 ml or follicle number per section (FNPS) ≥ 10 in at least one ovary in adults should be considered the threshold for PCOM if using older technology or image quality is insufficient to allow for an accurate assessment of follicle counts throughout the entire ovary.	❖❖❖❖

Not necessary in patients with irregular cycles and hyperandrogenism

AMH can be used as an alternative to ultrasound in adults

1.5.1	EBR	Serum anti-mullerian hormone (AMH) could be used for defining PCOM in adults.	❖❖❖ ⊕⊕⊕◯
1.5.6	PP	Laboratories and healthcare professionals need to be aware of factors that influence AMH in the general population including: • age: Serum AMH generally peaks between the ages of 20-25 years in the general population • body mass index (BMI): Serum AMH is lower in those with higher BMI in the general population • hormonal contraception and ovarian surgery: Serum AMH may be suppressed by current or recent COCP use • menstrual cycle day: Serum AMH may vary across the menstrual cycle.	

Ranges between 1.19 ng/mL and 8.26 ng/mL

Step 1: Irregular cycles + clinical hyperandrogenism

(exclude other causes)* = diagnosis

↓

Step 2: If no clinical hyperandrogenism

Test for biochemical hyperandrogenism (exclude other causes)* = diagnosis

↓

Step 3: If ONLY irregular cycles OR hyperandrogenism

Adolescents: Ultrasound or AMH is not indicated = consider at risk of PCOS and reassess later
Adults: Ultrasound for PCOM* OR Anti-Mullerian Hormone (AMH) level, if positive (exclude other causes)* = diagnosis

***Exclusion of other causes =s TSH, prolactin, 17-OH progesterone, FSH or if clinically indicated exclude other causes** (e.g. Cushing's syndrome, adrenal tumours etc) Hypogonadotrophic hypogonadism, usually due to low body fat or intensive exercise, should also be excluded clinically and with LH and FSH levels

Diagnosing PCOS in adolescents

1.1.4	**PP**	For adolescents who have features of PCOS, but do not meet diagnostic criteria, an 'increased risk' could be considered and reassessment advised at or before full reproductive maturity, 8 years post menarche. This includes those with PCOS features before combined oral contraceptive pill (COCP) commencement, those with persisting features and those with significant weight gain in adolescence.
1.4.6	**PP**	There are no definitive criteria to define polycystic ovary morphology (PCOM) on ultrasound in adolescents, hence it is not recommended in adolescents.
1.5.4	**EBR**	Serum AMH should not yet be used in adolescents.

Associated Risks:

Evaluation for cardiovascular risk

8.3	CR	All women with PCOS, regardless of age and BMI, should have a lipid profile (cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride level) at diagnosis. Thereafter, frequency of measurement should be based on the presence of hyperlipidaemia and additional risk factors or global cardiovascular risk.	❖❖❖❖
8.4	CR	All women with PCOS should have blood pressure measured annually and when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities.	❖❖❖❖

Associated Risks:

Assessment of glycemic status

1.9.2	**EBR**	Glycaemic status should be assessed at diagnosis in all adults and adolescents with PCOS.	❖❖❖❖ ⊕⊕◯◯
1.9.3	**CR**	Glycaemic status should be reassessed every one to three years, based on additional individual risk factors for diabetes.	❖❖❖❖
1.9.9	**EBR**	Healthcare professionals and women with PCOS should recommend the 75g oral glucose tolerance test (OGTT) as the most accurate test to assess glycaemic status in PCOS, regardless of BMI.	❖❖❖❖ ⊕◯◯◯
1.9.10	**EBR**	If an OGTT cannot be performed, fasting plasma glucose and/or glycated haemoglobin (HbA1c) could be considered, noting significantly reduced accuracy.	❖❖❖ ⊕◯◯◯
1.9.12	**PP**	Insulin resistance is a pathophysiological factor in PCOS, however, clinically available insulin assays are of limited clinical relevance and are not recommended in routine care (refer to 3.1.10).	

Associated risks

OSA and endometrial hyperplasia

- Obstructive sleep apnea:
  - Assess and refer

- Endometrial hyperplasia:
  - Consider biopsy if risk factors
    - Higher weight
    - T2DM
    - Persistent thickened endometrium

Associated Risks:

Anxiety, depression, and eating disorders

2.2		**Depression and anxiety**	
2.2.1	**EBR**	Healthcare professionals should be aware of the high prevalence of moderate to severe depressive symptoms and depression in adults and adolescents with PCOS and should screen for depression in all adults and adolescents with PCOS, using regionally validated screening tools.	❖❖❖❖ ⊕⊕⊕⊕
2.2.2	**EBR**	Healthcare professionals should be aware of the high prevalence of moderate to severe anxiety symptoms and anxiety disorders in adults and should screen for anxiety in all adults with PCOS, using regionally validated screening tools.	❖❖❖❖ ⊕⊕⊕⊕
2.5		**Eating disorders and disordered eating**	
2.5.1	**EBR**	Eating disorders and disordered eating should be considered in PCOS, regardless of weight, especially in the context of weight management and lifestyle interventions (see sections 2.4 and 3.6).	❖❖❖ ⊕⊕○○

Management: Weight Considerations

3.3		**Dietary interventions**	
3.3.1	**EBR**	Healthcare professionals and women should consider that there is no evidence to support any one type of diet composition over another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes.	❖❖❖ ⊕○○○
3.3.2	**CR**	Any diet composition consistent with population guidelines for healthy eating will have health benefits, and within this, healthcare professionals should advise sustainable healthy eating tailored to individual preferences and goals.	❖❖❖❖
3.4		**Exercise interventions**	
3.4.1	**EBR**	Healthcare professionals and women could consider that there is a lack of evidence supporting any one type and intensity of exercise being better than another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes.	❖❖❖ ⊕○○○
3.4.2	**CR**	Any physical activity consistent with population guidelines will have health benefits and within this, healthcare professionals should advise sustainable physical activity based on individual preferences and goals.	❖❖❖❖

Management: Weight Considerations

Prevention of weight gain / health maintenance:
- 150-300 minutes of moderate intensity activity OR
- 75-150 minutes of vigorous intensity activity

Modest weight loss / prevention of weight regain:
- Minimum of 250 minutes/week of moderate intensity activity OR
- 150 minutes/week of vigorous intensity activity

Adolescents:
- 60 minutes of moderate to vigorous activity at least 3x/week

Weight-inclusive practices

- Acknowledge that weight is only one indicator of health
- Explain how weight information will be used
- Use strategies to minimize discomfort:
  - Ask permission to discuss weight
  - Blind weighing
  - Alternatives to “obese” or “overweight” (e.g. “higher weight”)
- Offer weight-centric or weight-inclusive care
  - Intentional weight loss **versus**
  - Healthy lifestyle change without a focus on weight loss

Management:
Non-fertility features

4.2.1	**EBR**	The combined oral contraceptive pill (COCP) could be recommended in reproductive age adults with PCOS for management of hirsutism and/or irregular menstrual cycles.	❖❖❖ ⊕○○○
4.2.2	**EBR**	The COCP could be considered in adolescents at risk or with a clear diagnosis of PCOS for management of hirsutism and/or irregular menstrual cycles.	❖❖❖ ⊕○○○

No specific COC regimen recommended

Management: Indications for metformin

4.3.1	EBR	Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m² for anthropometric, and metabolic outcomes including insulin resistance, glucose, and lipid profiles.	❖❖❖ ⊕○○○
4.3.2	EBR	Metformin alone could be considered in adolescents at risk of or with PCOS for cycle regulation, acknowledging limited evidence.	❖❖❖ ⊕○○○
4.3.3	CR	Metformin alone may be considered in adults with PCOS and BMI < 25 kg/m², acknowledging limited evidence.	❖❖❖

Counsel about return of ovulation

Management: Metformin + COCs

4.4		Metformin and combined oral contraceptive pills	
4.4.1	**EBR**	COCP could be used over metformin for management of hirsutism in irregular menstrual cycles in PCOS.	❖❖❖ ⊕○○○
4.4.2	**EBR**	Metformin could be used over COCP for metabolic indications in PCOS.	❖❖❖ ⊕○○○
4.4.3	**EBR**	The combination of COCP and metformin could be considered to offer little additional clinical benefit over COCP or metformin alone, in adults with PCOS with a BMI ≤30 kg/m².	❖❖❖ ⊕○○○
4.4.4.	**PP**	In combination with the COCP, metformin may be most beneficial in high metabolic risk groups including those with a BMI > 30 kg/m², diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.	
4.4.5	**PP**	Where COCP is contraindicated, not accepted or not tolerated, metformin may be considered for irregular menstrual cycles. For hirsutism, other interventions may be needed.	

Management: Anti-obesity agents

4.5		Anti-obesity pharmacological agents	
4.5.1	**CR**	Anti-obesity medications including liraglutide, semaglutide, both glucagon-like peptide-1 (GLP-1) receptor agonists and orlistat, could be considered, in addition to active lifestyle intervention, for the management of higher weight in adults with PCOS as per general population guidelines.	❖❖❖
4.5.2	**PP**	Healthcare professionals should ensure concurrent effective contraception when pregnancy is possible, for women who take GLP-1 receptor agonists, as pregnancy safety data are lacking.	

Management: Anti-androgens for hirsutism

4.6.1	EBR	In combination with effective contraception, anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of six months of COCP and/or cosmetic therapy.
4.6.4	PP	Anti-androgens could be considered to treat hirsutism, in the presence of another effective form of contraception, for women with contraindications for COCP therapy or when COCPs are poorly tolerated.

- Counsel on risks of undervirilization of male fetus
- Strongly counsel for effective contraceptive use

Management:

Selection of anti-androgen regimen mechanism

Medication	Mechanism	Dose	Notes
Oral contraceptive pills	Inhibits gonadotropins Increases SHBG -> decreases free T	variable	Consider adding another antiandrogen after 6m
Spironolactone	Aldosterone and androgen receptor antagonist	25-200 mg/d	Hyperkalemia -> consider measuring K after 1 month Irregular menstrual bleeding
Cyproterone	Competes with DHT for AR binding Decreases LH	up to 10 mg/d	Not available in US Risk of hepatotoxicity
Finasteride	Inhibits 5-alpha reductase (T->DHT)	1-5 mg/d	No clinical trials for hirsutism Risk of undervirilization
Flutamide/ Bicalutamide	Androgen receptor antagonist	62.5 – 125 mg/d	Use not advised – liver toxicity even at low doses

All similar efficacy

Can also consider mechanical or laser light therapy or eflornithine (Vaniqua)

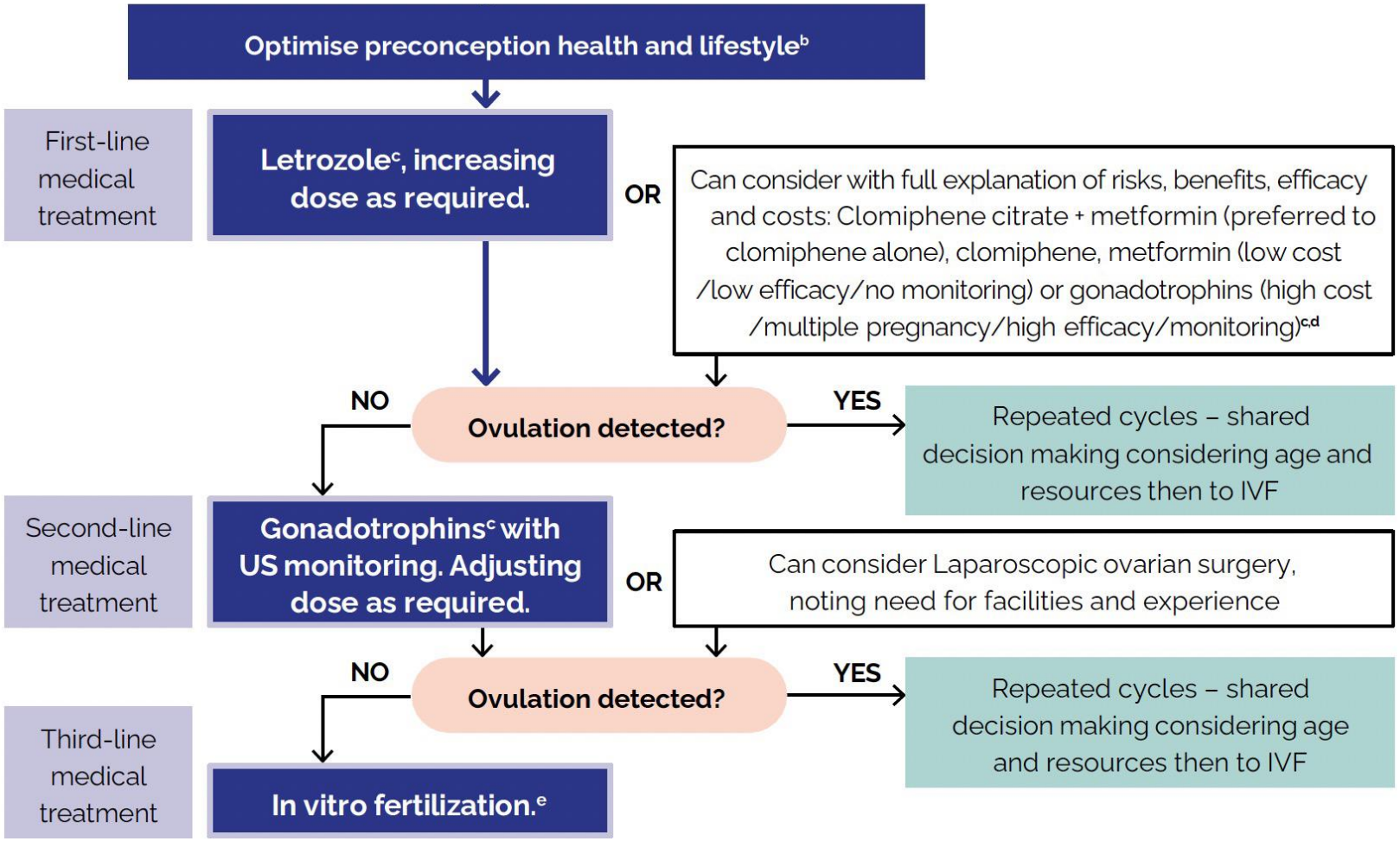
Management:

Inositol

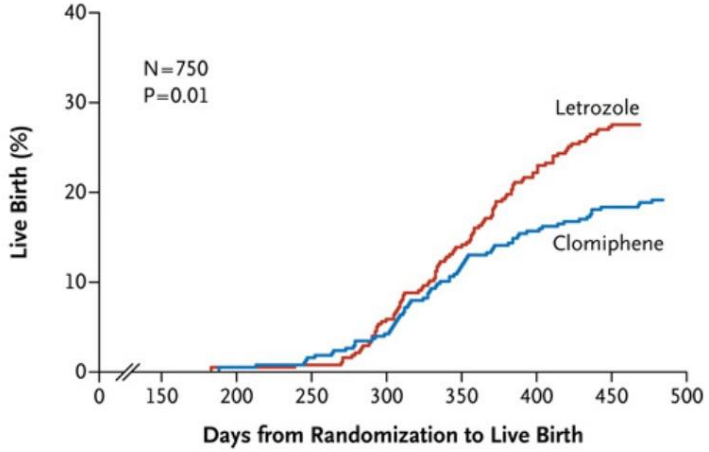
4.7		Inositol	
4.7.1	EBR	Inositol (in any form) could be considered in women with PCOS based on individual preferences and values, noting limited harm, potential for improvement in metabolic measures, yet with limited clinical benefits including in ovulation, hirsutism or weight.	❖❖❖ ⊕○○○
4.7.2	EBR	Metformin should be considered over inositol for hirsutism and central adiposity, noting that metformin has more gastrointestinal side-effects than inositol.	❖❖❖ ⊕○○○

- Best dose and duration, side effects and safety not known
- Consider experimental

Management: Fertility considerations



Ovulation induction:
Letrozole vs. clomiphene citrate



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Cochrane Library

Trusted evidence.
Informed decisions.
Better health.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with SERMs with or without adjuncts	Risk with letrozole with or without adjuncts				
Live birth rate	204 per 1000	307 per 1000 (265 to 352)	OR 1.72 (1.40 to 2.11)	2060 (11 RCTs)	⊕⊕⊕⊕ High	

Legro *et al,* NEJM 2014.

Summary of Updates

- Further refinement of individual diagnostic criteria, a simplified diagnostic algorithm and inclusion of anti-Mullerian hormone (AMH) levels as an alternative to ultrasound in adults only
- Strengthening recognition of broader features of PCOS including metabolic risk factors, cardiovascular disease, sleep apnea, very high prevalence of psychological features, and high risk status for adverse outcomes during pregnancy
- Emphasizing the poorly recognized, diverse burden of disease and the need for greater healthcare professional education, evidence-based patient information, improved models of care and shared decision making to improve patient experience, alongside greater research
- Maintained emphasis on healthy lifestyle, emotional wellbeing and quality of life, with awareness and consideration of weight stigma
- Emphasizing evidence-based medical therapy and cheaper and safer fertility management.

Summary

- PCOS is a common syndrome with different phenotypes and complex genetics
- The etiology involves both regulation at the hypothalamic and ovarian levels, negative feedback, and positive feedback cycles
- There are reproductive aspects and metabolic aspects. Treatment depends on the symptoms affecting QOL.
- Follow the updated guidelines!