Obesity and Polycystic Ovary Syndrome

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Agenda

- Introduction
- What is PCOS?
- Diagnosis of PCOS
- PCOS and obesity
- Insulin Action in PCOS & Obesity
- Glucose Tolerance in PCOS & Obesity
- Can Obesity Cause PCOS?
- Does PCOS Cause Obesity?
- Hormonal Regulations of Weight and Appetite
- Pathogenesis of PCOS
- Management of PCOS with obesity

Introduction

- 1935 by Stein and Leventhal
- Obesity is a common feature
- U.S prevalence of obesity with PCOS 80%. Outside the U.S 20%.
- Different diagnostic criteria for PCOS
- Environmental factors' role in obesity and PCOS
- Biologic basis
- Obesity exacerbates abnormalities associated with PCOS

What is PCOS?

- The most common hormonal abnormality in reproductive-age women
- Reproductive features of PCOS:
  - increased androgen production
  - disordered gonadotropin secretion
  - menstrual irregularity
  - hirsutism,
  - infertility.
- Metabolic characteristics of PCOS:
  - prominent defects in insulin action and β-cell function
  - increased risk for glucose intolerance and type 2 diabetes.
  - Obesity (40–80% overweight or obese)
- Genetic susceptibility :
  - To date, the genes responsible for PCOS have not been clearly identified.

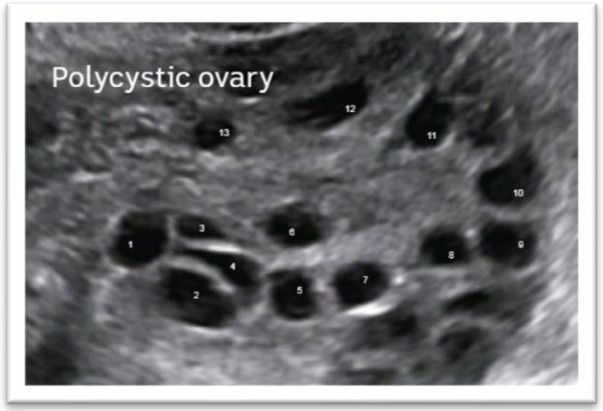
Diagnosis of PCOS

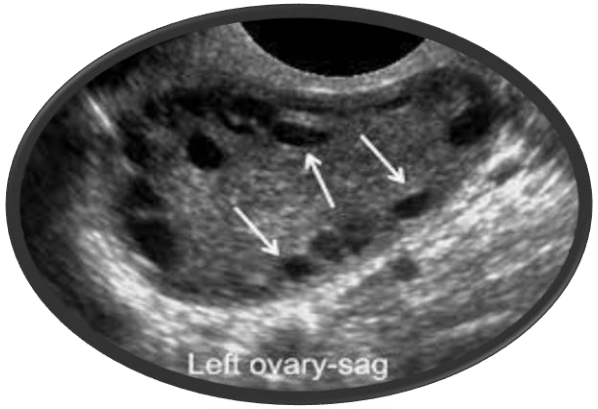
NIH/NICHD Criteria* 1990	Rotterdam Criteria* 2003
Diagnosis requires both features:	Diagnosis requires 2 of 3 features:
1. Oligo and/or anovulation	1. Oligo and/or anovulation
2. Hyperandrogenism Clinical or biochemical	2. Hyperandrogenism Clinical or biochemical
	3. PCO morphology**

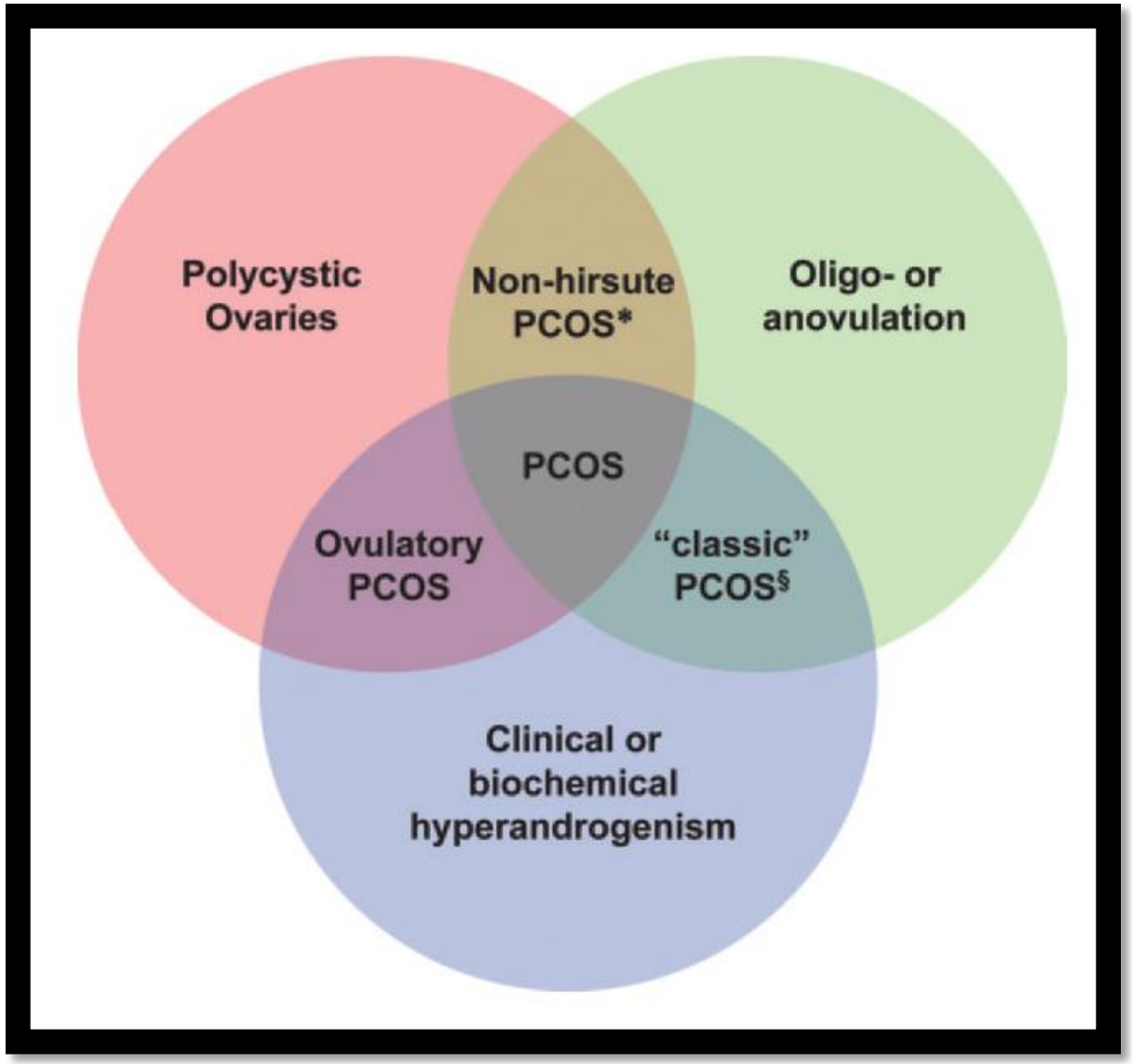
- **Controversial**
  - Minority have No PCO morphology.
  - 25% have PCO morphology
  - insulin resistant or increased risk for type 2 diabetes .

- **Diagnostic Criteria for PCOS**
- *Other androgen excess or related disorders have to be excluded prior to diagnosis of PCOS.
- **Defined by at least one ovary demonstrating an ovarian volume>10 ml or presence of 12 or more follicles measuring 2-9 mm in size.

Diagnosis, types of PCOS

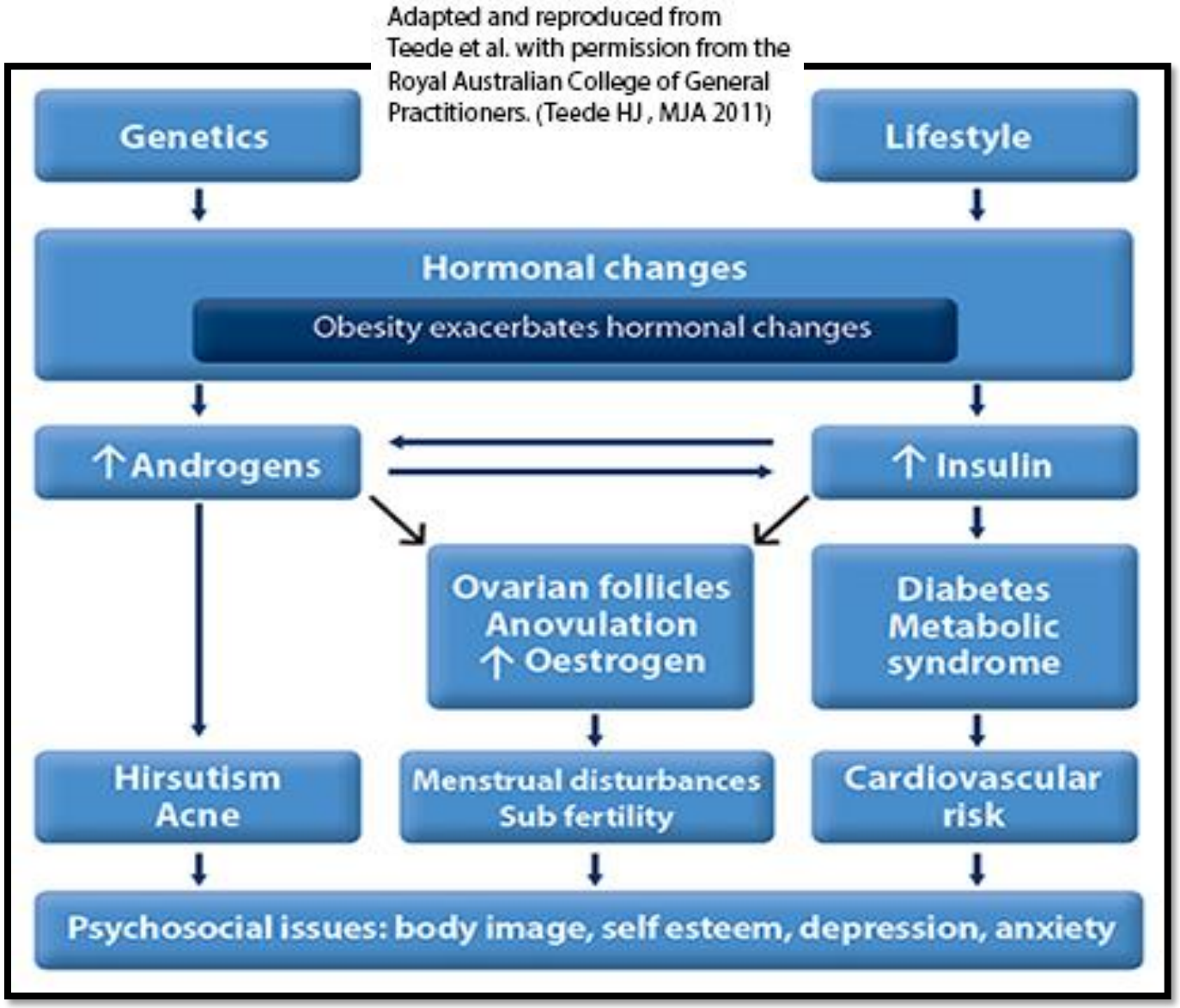






PCOS and obesity

- Genetic predisposition
- Environmental factors (high-caloric diets and reduced exercise)



Insulin Action in PCOS: Relation with Obesity

- Insulin resistance is common in PCOS worsened by obesity.
- insulin action on skeletal muscle is decreased by 35–40%
- Hepatic insulin resistance in obese women with PCOS.
- Synergistic effect of obesity and PCOS →glucose intolerance.

- Fasting insulin levels increased in PCOS
- In PCOS, basal insulin secretion is increased
- insulin responses to glucose are low.
- Women with PCOS (obese and nonobese) have a lower disposition index compared to normal women.

- Disposition index: Relation between insulin secretion and sensitivity is constant so that changes in insulin sensitivity are accompanied by reciprocal changes in insulin secretion that maintain normal glucose tolerance

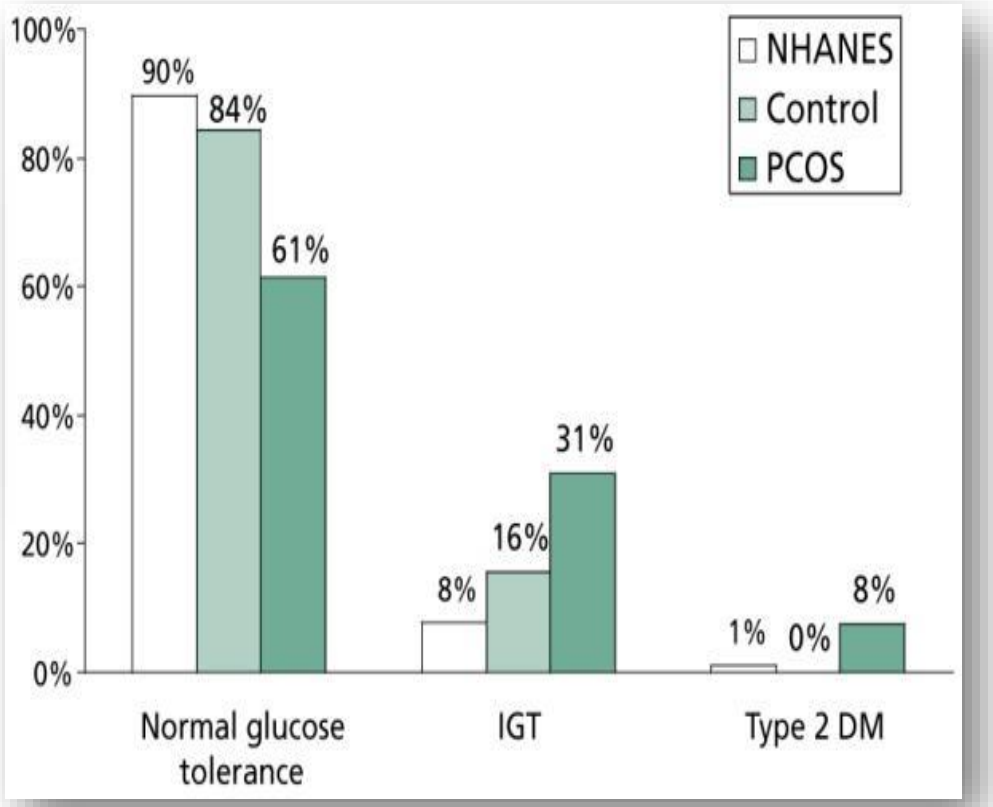
Glucose Tolerance in PCOS: Relation with Obesity

- Women with PCOS have a high prevalence of IGT and type 2 DM.
- Prevalence of IGT & type 2 DM is higher in obese women with PCOS.
- Glucose intolerance risk increased with increasing BMI
- PCOS is associated with defects in insulin action and β-cell function, exacerbated by obesity.

Obes Manag. 2007 April ; 3(2): 69–73. doi:10.1089/obe.2007.0019.

Obesity and Polycystic Ovary Syndrome

Susan Sam, MD
Assistant Professor of Medicine, Section of Endocrinology, Diabetes and Metabolism University of Illinois Medical Center, Chicago, IL



- **Women with PCOS had much higher prevalence of abnormal glucose tolerance**

(NHANES) National Health and Nutrition Examination Survey

0021-972X/99/$03.00/0
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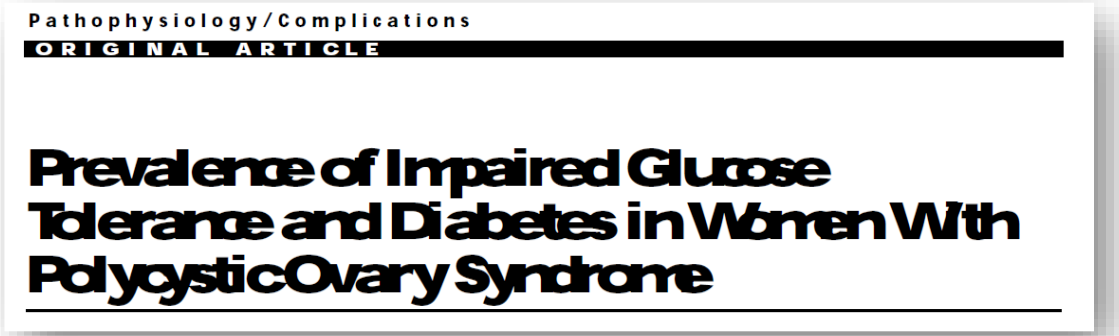
Prevalence and Predictors of Risk for Type 2 Diabetes Mellitus and Impaired Glucose Tolerance in Polycystic Ovary Syndrome: A Prospective, Controlled Study in 254 Affected Women*

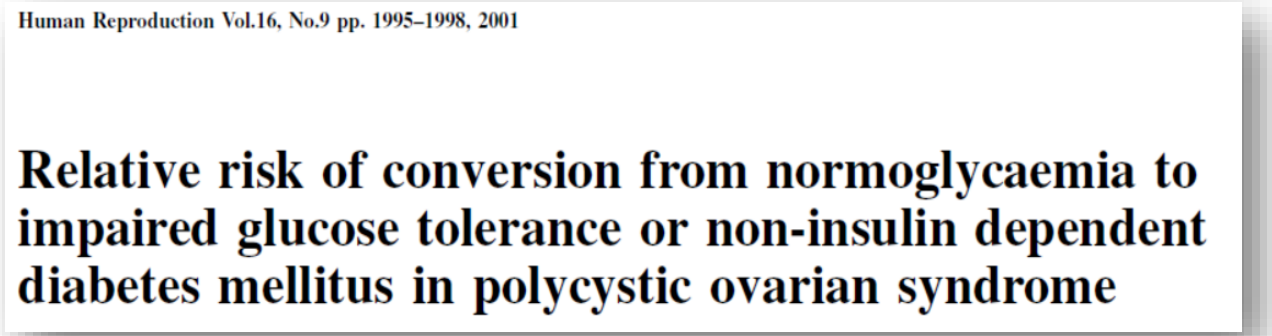
- 254 reproductive-age PCOS
- 80 control
- Matched ethnicity, age, and weight
- Prevalence of IGT and type 2 diabetes

- Risk for developing IGT increased with increasing BMI

- Prevalence of IGT and type 2 DM were much lower in nonobese women with PCOS (10.3% and 1.5%, respectively) compared to the obese

RICHARD S. , et al :Prevalence and Predictors of Risk for Type 2 Diabetes Mellitus and Impaired Glucose Tolerance in Polycystic Ovary Syndrome: A Prospective, Controlled Study in 254 Affected Women, Journal of Clinical Endocrinology and Metabolism, Vol. 84, No. 1





- Women with PCOS had 45% prevalence of IGT & DM
- Women with PCOS and type 2 DM were significantly obese

- Studies from Australia : high prevalence of IGT in women with PCOS in association with obesity
- Overweight women with PCOS had a 7-fold increase in the risk of abnormal glucose tolerance

- Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care. 1999;22:141–146.
- Norman RJ, Masters L, Milner CR, Wang JX, Davies MJ. Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. Hum Reprod. 2001;16:1995–1998.

- In summary, PCOS is associated with high rates of glucose intolerance resulting from defects in insulin action and β-cell function.
- Detection of glucose abnormalities in women with PCOS is best performed by means of glucose tolerance testing, since fasting glucose levels may be normal

Susan Sam, Obesity and Polycystic Ovary Syndrome :Obes Manag. 2007 April ; 3(2): 69–73. doi:10.1089/obe.2007.0019

Can Obesity Cause PCOS?

- Reproductive disturbances are common in obese women regardless of the diagnosis of PCOS.
- Women with obesity are more likely to have menstrual irregularity and anvolatory infertility.
- The risk of anovulatory infertility increases with increasing BMI.
- Weight reduction can restore regular menstrual cycles.

Comparative Study > Arch Intern Med. 2006 Oct 23;166(19):2081-6.
doi: 10.1001/archinte.166.19.2081.

Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women

Francisco Alvarez-Blasco [1], José I Botella-Carretero, José L San Millán, Héctor F Escobar-Morreale

- Majority of obese women do not develop hyperandrogenemia and do not have PCOS
- In PCOS bioavailable androgen levels are increased and worsened by central obesity,
- Sex hormone binding globulin are reduced due to hyperinsulinemia.
- PCOS was 5-fold more common among premenopausal overweight or obese women.

Alvarez-Blasco F, Botella-Carretero JI, San Millan JL, Escobar-Morreale HF. Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. Arch Intern Med. 2006;166:2081–2086.

Does PCOS Cause Obesity?

- Androgens & body composition
- android compared to gynoid
- Women with central obesity have IR and risk for CVD and DM
- Women with PCOS have a high prevalence of upper-body obesity
- Dual-energy X-ray absorptiometry (central fat in women with PCOS)

- Higher testosterone in women with PCOS role in fat distribution
- Studies of isolated abdominal fat cells from women with PCOS have revealed larger-sized cells in both obese and nonobese women with PCOS
- Hyperandrogenemia in PCOS women enhances android body fat distribution

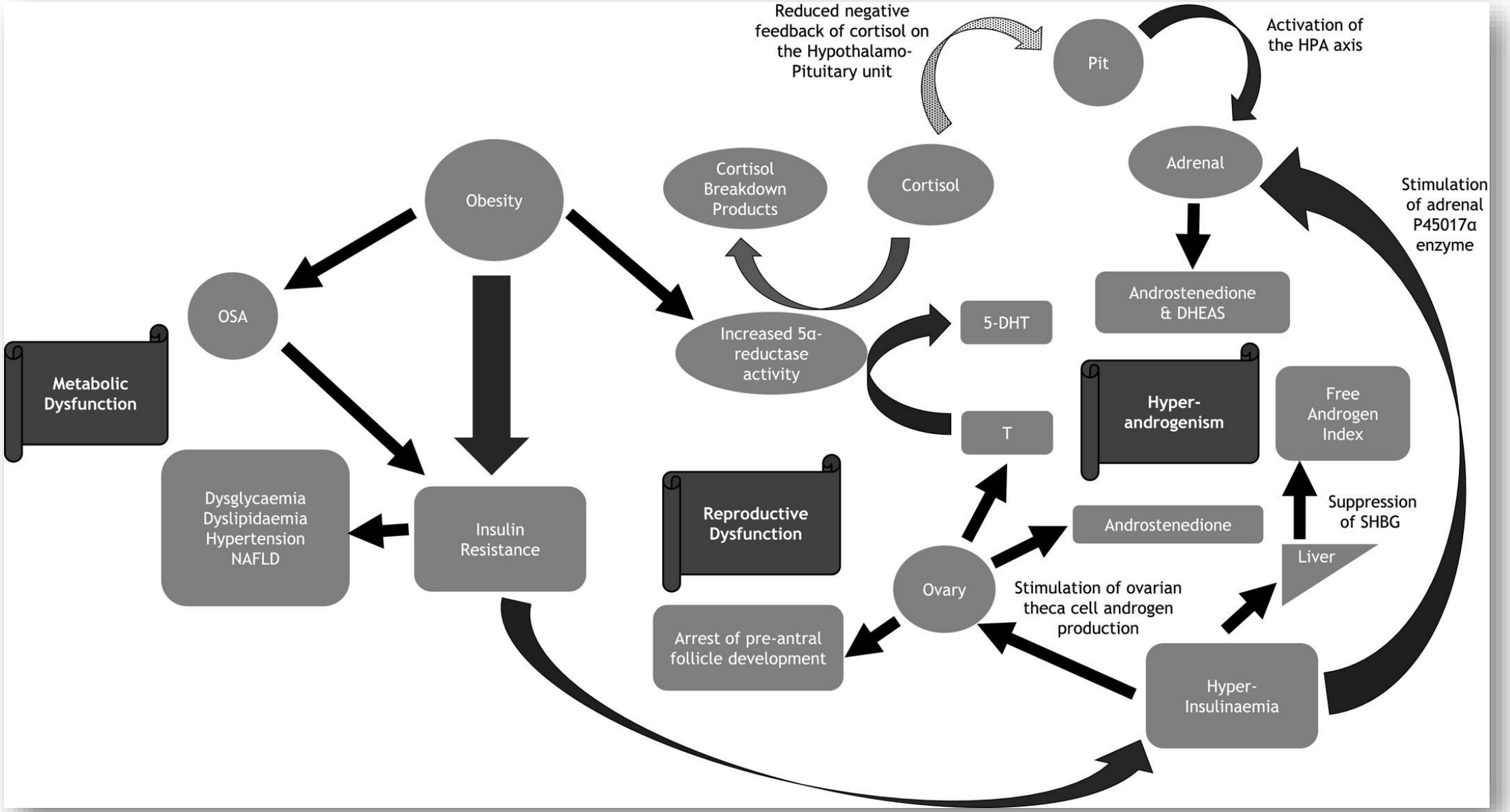
Hormonal Regulations of Weight and Appetite

- Lower levels of ghrelin reported in women with PCOS
- Fasting ghrelin levels are reported to be lower in obese
- Evidence of dysregulated Ghrelin homeostasis in PCOS
- Women with PCOS have less marked post-prandial reduction in Ghrelin thus less satiety

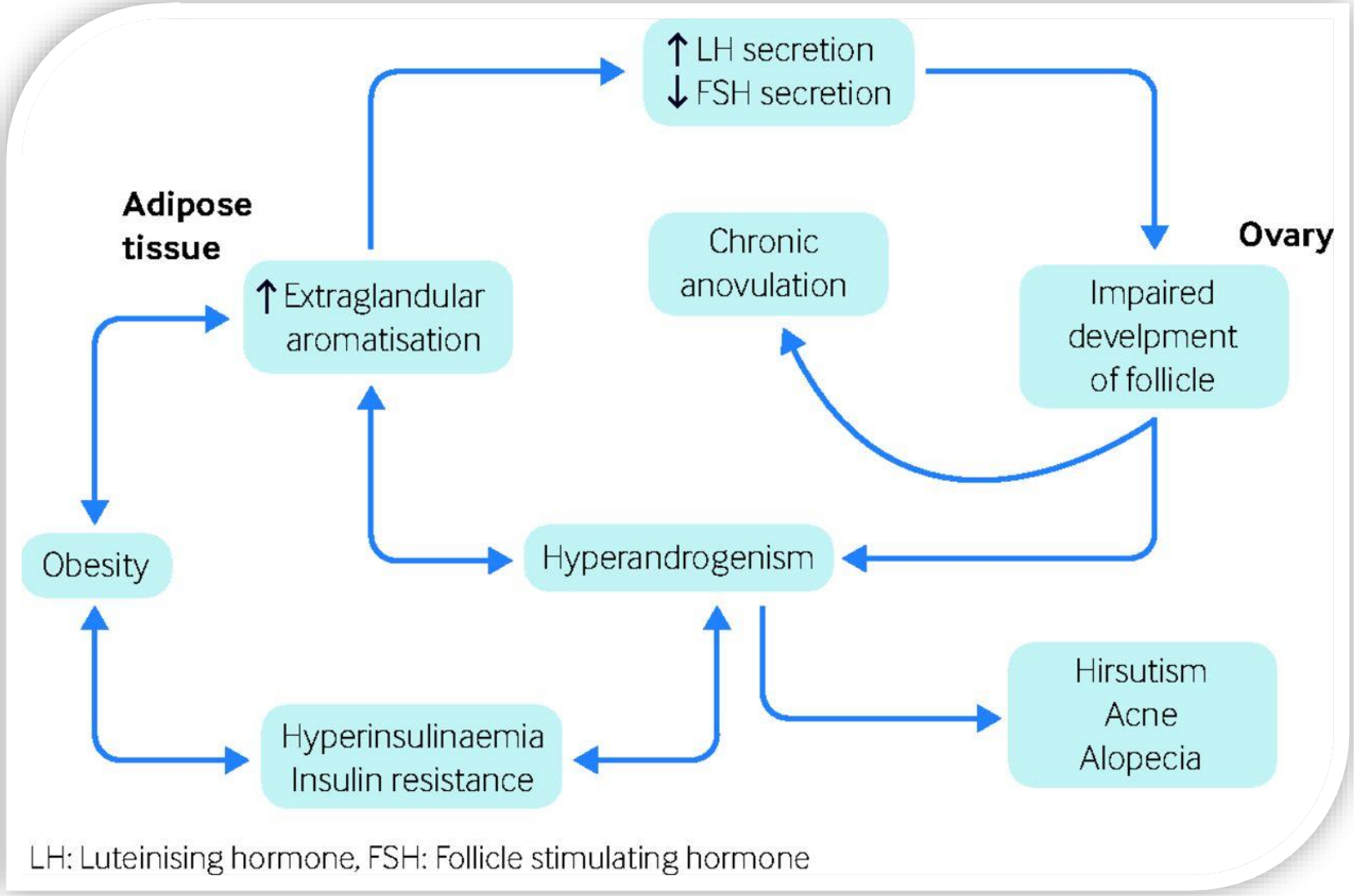
Pathogenesis of PCOS

- Insulin resistance in PCOS
- weight gain in the pathogenesis of metabolic dysfunction in PCOS
  - Adipokines
  - Obstructive sleep apnoea (OSA)
  - Visceral and hepatic fat
- weight gain in the pathogenesis of hyperandrogenism in PCOS
  - Figure

Thomas M. Barber, Stephen Franks: Obesity and polycystic ovary syndrome, Clinical Endocrinology. 2021;95:531-541
https://doi.org/10.1111/cen.14421


Reduced negative feedback of cortisol on the Hypothalamo-Pituitary unit
Pit
Activation of the HPA axis
Adrenal
Stimulation of adrenal P45017α enzyme
Obesity
Cortisol Breakdown Products
Cortisol
OSA
Androstenedione & DHEAS
Increased 5α-reductase activity
5-DHT
T
Metabolic Dysfunction
Hyper-androgenism
Free Androgen Index
Dysglycaemia Dyslipidaemia Hypertension NAFLD
Insulin Resistance
Reproductive Dysfunction
Androstenedione
Suppression of SHBG
Liver
Ovary
Stimulation of ovarian theca cell androgen production
Arrest of pre-antral follicle development
Hyper-Insulinaemia

A diagram showing the interaction between obesity, the hormonal profile and metabolic features of polycystic ovary syndrome.



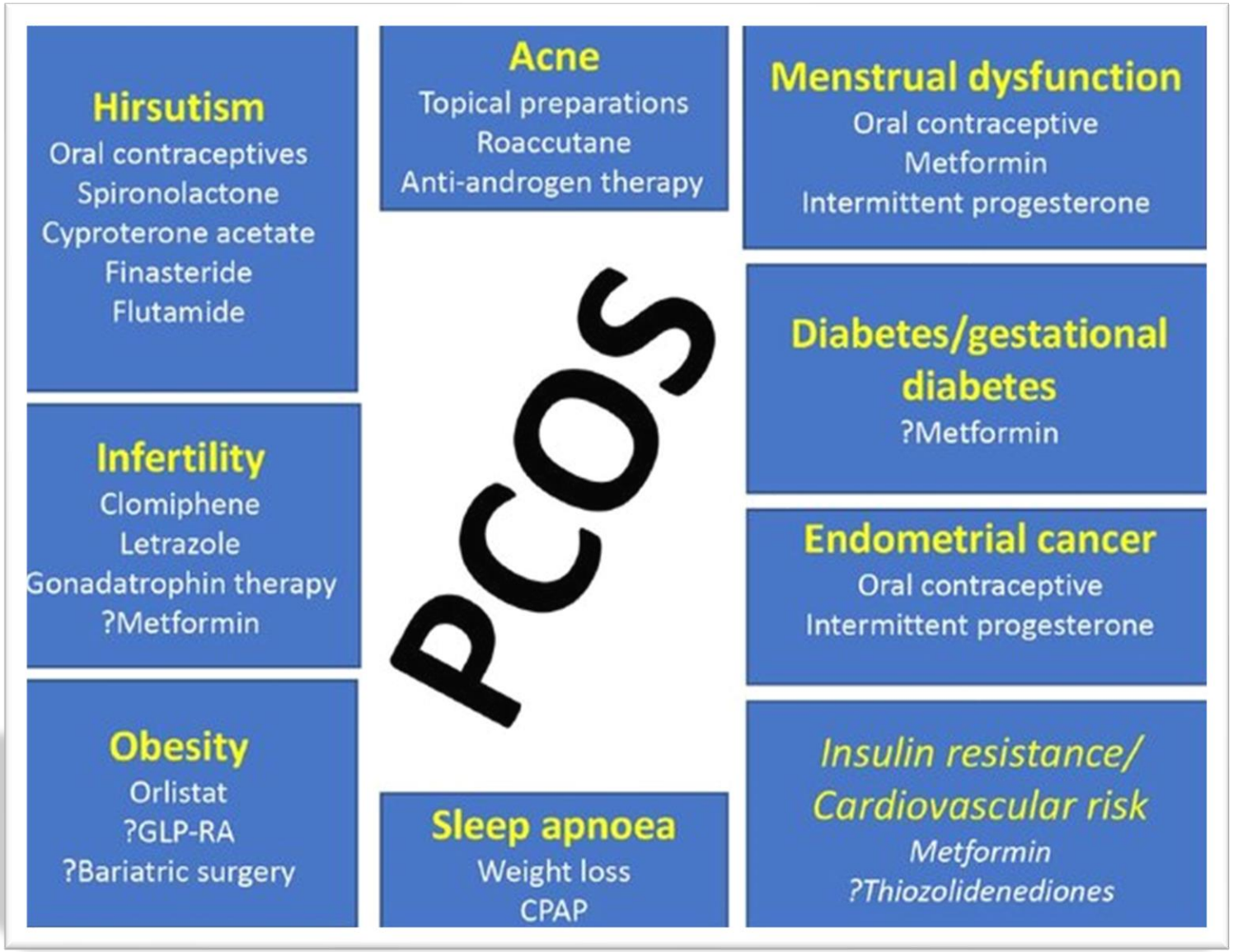
Isabel McLuskie, and Aisha Newth BMJ 2017;356:bmj.i6456

thebmj

Management of PCOS with obesity

- Lifestyle
- Calorie restriction & weight loss result in a reduction of hyper-insulinaemia
- Pharmacotherapy
- Weight loss
- Physical activity
- Aerobic exercise improve reproductive function and ovulation
- Optimization of sleep, duration

Therapeutic Management of PCOS



Therapeutic Advances in Endocrinology and Metabolism

Cardiovascular profile of pharmacological agents used for the management of polycystic ovary syndrome

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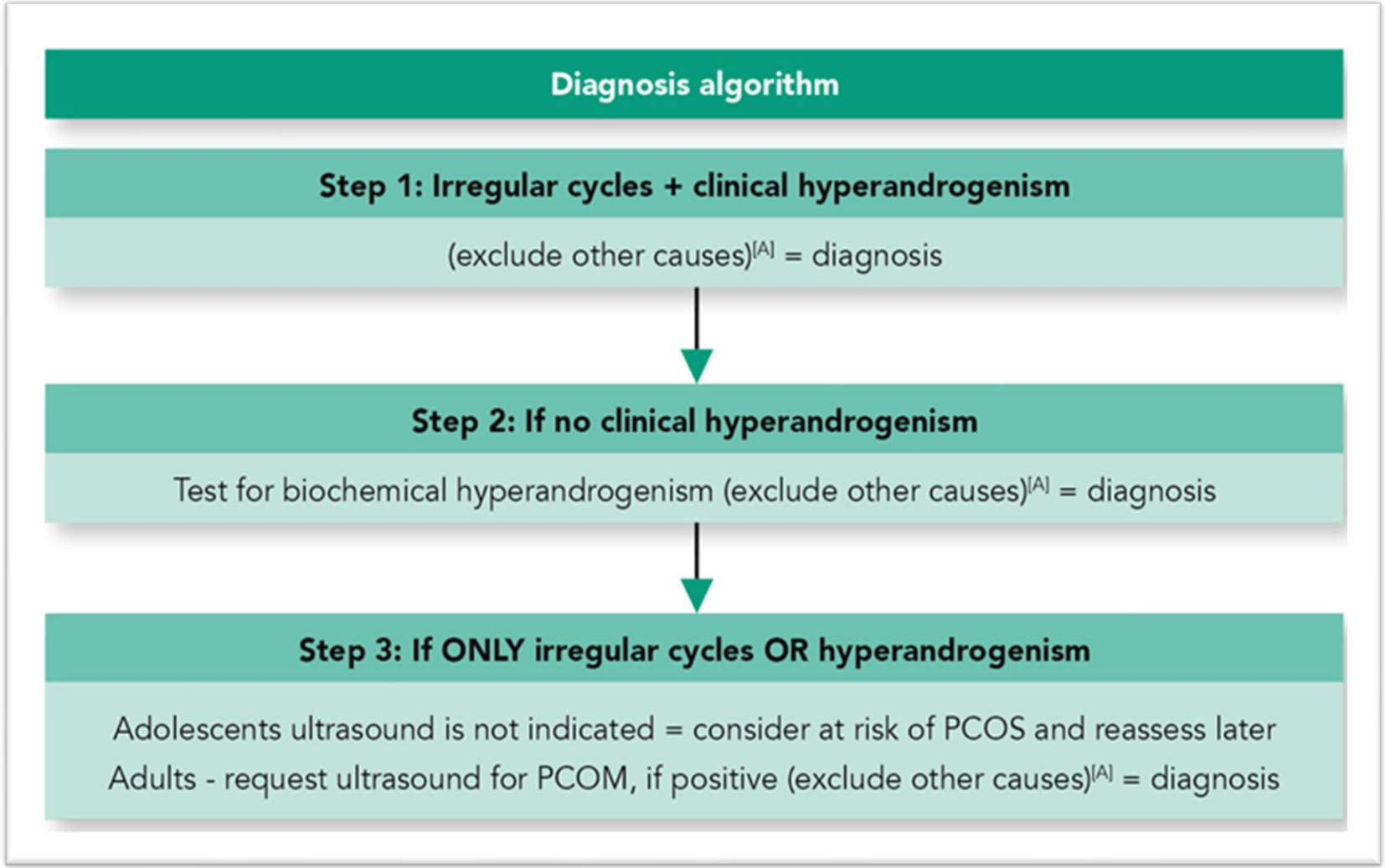
Table 1. Therapy used in PCOS and possible cardiovascular impact.

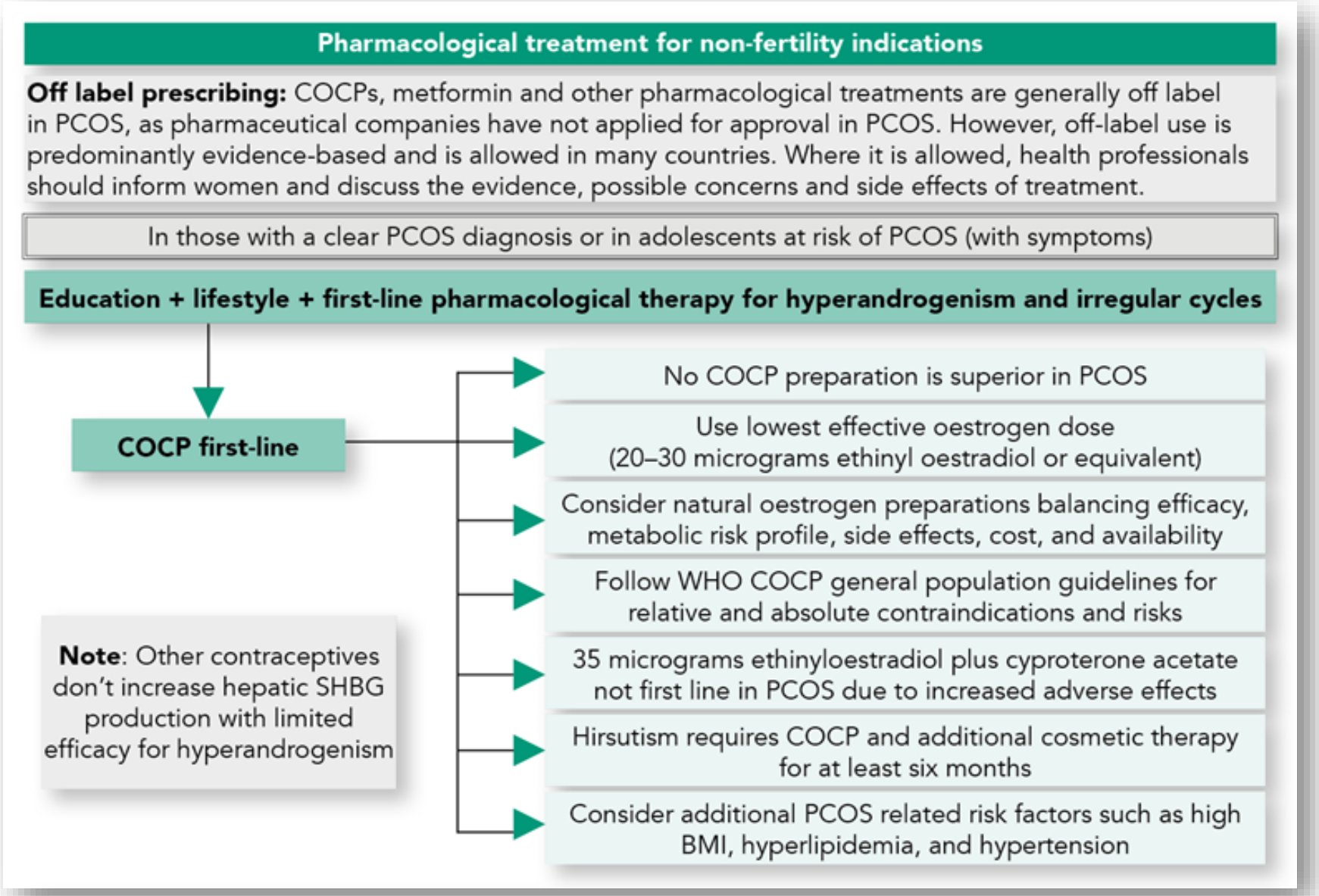
Classes of antidiabetic agents	Possible cardiovascular impact	References
Hormone contraception	Estrogen-containing OCPs may potentially have an adverse cardiovascular risk, increased risk of hypertension and dyslipidemia, elevated inflammatory markers, decreased insulin sensitivity	Sathyapalan and Atkin;[17] Randeva and colleagues;[18] Solomon and colleagues;[20] de Bastos and colleagues[21]
Spironolactone	Decrease in triglycerides, increase in HDL and decreased insulin resistance. Cardiovascular benefits in patients with established cardiovascular disease	Christakou and colleagues;[22] Lidegaard and colleagues;[23] Okoroh and colleagues[24]
Finasteride	No data on the benefits or detriments of this treatment on cardiovascular risk, only studies in men	Anand and colleagues[25]
Flutamide	Decreases in the LDL/HDL ratio, total cholesterol and triglycerides	Zulian and colleagues[26]

Metformin	Decrease in oxidative damage, inflammation and improvement in endothelial dysfunction. Cardiovascular benefit shown in diabetes; prevention of diabetes	Velazquez and colleagues;[27] Legro and colleagues;[28] Insel and colleagues[29]
Thiazolidinediones (glitazones):	Reduction in insulin resistance, alteration in visceral to subcutaneous fat ratio, improved endothelial function	Day;[30] Ferwana and colleagues;[31] Cho and colleagues[32]
DPP IV inhibitors/ GLP-1 receptor agonists	Very few studies. Weight loss with GLP-1RAs and potential cardiovascular benefit in diabetes	Ahren;[33] Gautier and colleagues;[34] Jensterle and colleagues[35]
SGLT2 inhibitor	Studies awaited in PCOS to determine if the cardiovascular benefit seen in diabetes translates to PCOS	Pi-Sunyer and colleagues[36]
Clomiphene	ECG QT interval decrease that may be protective for cardiovascular events	Dickey and colleagues[37]

International evidence-based guideline for the assessment and management of polycystic ovary syndrome

By International PCOS Network | 21 September 2020




Pharmacological treatment for non-fertility indications
Off label prescribing: COCPs, metformin and other pharmacological treatments are generally off label in PCOS, as pharmaceutical companies have not applied for approval in PCOS. However, off-label use is predominantly evidence-based and is allowed in many countries. Where it is allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects of treatment.
In those with a clear PCOS diagnosis or in adolescents at risk of PCOS (with symptoms)
Education + lifestyle + first-line pharmacological therapy for hyperandrogenism and irregular cycles
COCP first-line
No COCP preparation is superior in PCOS
Use lowest effective oestrogen dose (20–30 micrograms ethinyl oestradiol or equivalent)
Consider natural oestrogen preparations balancing efficacy, metabolic risk profile, side effects, cost, and availability
Follow WHO COCP general population guidelines for relative and absolute contraindications and risks
35 micrograms ethinyloestradiol plus cyproterone acetate not first line in PCOS due to increased adverse effects
Hirsutism requires COCP and additional cosmetic therapy for at least six months
Consider additional PCOS related risk factors such as high BMI, hyperlipidemia, and hypertension
Note: Other contraceptives don't increase hepatic SHBG production with limited efficacy for hyperandrogenism

Second-line pharmacological therapies

COCP + lifestyle + metformin

Should be considered in women with PCOS for management of metabolic features, where COCP + lifestyle does not achieve goals.

Could be considered in adolescents with PCOS and BMI ≥ 25 kg/m^2 where COCP and lifestyle changes do not achieve desired goals.

Most beneficial in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.

COCP + anti-androgens

Evidence in PCOS relatively limited.

Anti-androgens must be used with contraception to prevent male fetal virilisation.

Can be considered after 6/12 cosmetic treatment + COCP if they fail to reach hirsutism goals.

Can be considered with androgenic alopecia.

Metformin + lifestyle

With lifestyle, in adults should be considered for weight, hormonal and metabolic outcomes and could be considered in adolescents.

Most useful with BMI ≥ 25 kg/m^2 and in high risk ethnic groups.

Side-effects, including GI effects, are dose related and self-limiting.

Consider starting low dose, with 500 mg increments 1-2 weekly.

Metformin appears safe long-term. Ongoing monitoring

Anti-obesity medications can be considered with lifestyle as per general population guidelines, considering cost, contraindications, side effects, availability and regulatory status and avoiding pregnancy when on therapy.

Inositol (in any form) should currently be considered experimental in PCOS, with emerging evidence of efficacy highlighting the need for further research.

REFERRAL

Box 2
When to refer a patient to an obesity medicine specialist or a multidisciplinary weight loss clinic

Consider referral to multidisciplinary weight management centers[a] or obesity medicine specialists for the following:

1. Patients with medically complex obesity who are resistant to lifestyle modification after 6 to 12 months and/or have not had an adequate response to 1 or 2 medication trials
2. Patients requiring more intensive weight loss treatments (eg, very low calorie diets, combination pharmacotherapy, weight loss surgery, or weight loss devices)
3. Weight loss before surgery (eg, general, orthopedic, or transplant surgeries)
4. Weight loss before pregnancy or in vitro fertilization
5. Patients with medication-induced weight gain
6. Patients with a BMI greater than 50 kg/m^2

[a] Multidisciplinary (eg, exercise trainer, dietitian, psychologist, physician, surgeon).

CONCLUSION

- PCOS as a complex metabolic disorder.
- Obesity is a common finding in PCOS and aggravates many of its reproductive and metabolic features.
- Weight gain and obesity are involved in the pathogenesis of PCOS
- The relationship between PCOS and obesity is complex, not well understood, and most likely involves interaction of genetic and environmental factors.
- Hyperinsulinaemia, provides an explanation for the subsequent hyperandrogenism and reproductive dysfunction.
- Obesity is highly stigmatized in our society. Hirsutism, acne and sub-fertility challenge key attributes of womanhood.
- Women with obesity and PCOS require careful management, offered with a compassionate and empathic approach by a multi-disciplinary team, and with the patient centered.

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