Obesity in the Female Patient with a focus on PCOS

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ROME 2019 SOUTHEAST Savannah, GA, June 13 – 16

Conflict of Interest Disclosure

I have no conflicts and nothing to disclose

ROME 2019 SOUTHEAST Savannah, GA, June 13 – 16

Learning Objectives

- Review evidence based guidelines for the diagnosis, assessment, and treatment of PCOS in a range of patient ages
- Review obesity treatment options with patients with PCOS
- Review obesity treatment and in women planning and trying for conception and pregnancy

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Gender-specific Manifestations of Adiposopathy

Women
- Hyperandrogenemia
- Hirsutism
- Acne
- Polycystic ovarian syndrome
- Menstrual disorders
- Infertility
- Gestational diabetes mellitus
- Preeclampsia
- Thrombosis

Men
- Hypoandrogenemia
- Hyperestrogenemia
- Erectile dysfunction
- Low sperm count
- Infertility

 References/s: [43] [44] [45]

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Epidemiology : Very Common Metabolic disorder

- 4-10% of women of reproductive age suffer from PCOS (1)
- Women with PCOS may be at risk for multiple morbidities including ***OBESITY***, insulin resistance, type II diabetes mellitus, cardiovascular disease, infertility, cancer, and psychological disorders (2)
- ***4 Billion dollars*** spent annually in the U.S. to screen for the disease and treat its various morbidities, including hirsutism, infertility, diabetes (3)
- Patients with PCOS twice as likely to get admitted to hospital (3)

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https://www.gbhealthwatch.com/index.php

- PCOS is likely a complex genetic disease with at least several susceptibility genes.
- A woman has a 50% chance of getting PCOS if her mother or sibling also has the disorder.
- Studies have also shown that male siblings of women with PCOS are more likely to show signs of insulin resistance than males without a female sibling with PCOS.
- The majority of the genes linked to PCOS are involved in sex hormone production and metabolism or associated with impaired insulin function.

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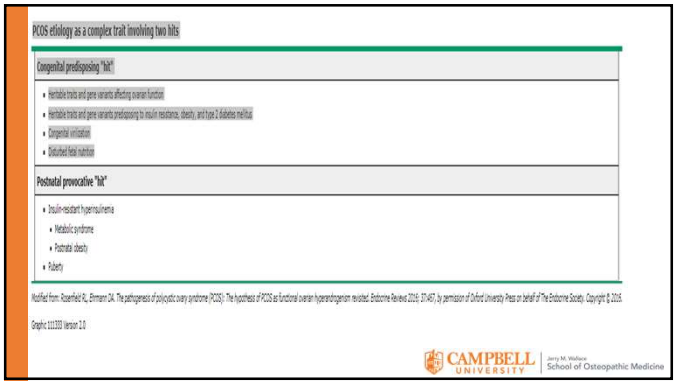

Common Genetic Variants Associated with PCOS

GENE	FUNCTION AND ROLE IN THE METABOLIC SYNDROME	SNP (RISK ALLELE)
Genes involved in sex hormone function		
CYP1A1	Enzyme involved in sex hormone production	rs4646903 (G)
DENND1A	Involved in cellular trafficking of hormone receptors	rs2479106 (G)
DENND1A	Involved in cellular trafficking of hormone receptors	rs10818854 (A)
FSHR	Receptor for the hormone FSH (follicle stimulating hormone)	rs6166 (T)
HSD17B6	Enzyme involved in the degradation of sex hormones	rs898611 (C)
LHCGR	Receptor for LH and hCG hormones	rs10495960 (A)
SHBG	carrier of sex hormones through the blood	rs6257 (C)
Genes involved in insulin function		
IGF2	Hormone that is related to insulin	rs680 (T)
INSR	Receptor for the hormone insulin	rs2252673 (C)
Relationship to PCOS is poorly understood		
SERPINE1	SERPINE1/PAI-1 levels are increased in PCOS; involved in clotting	rs1799768 (D)
THADA	Unknown mechanism but some variants associated with type 2 diabetes	rs12478601 (C)

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https://www.gbhealthwatch.com/index.php

- Obesity Comprehensive Panel
- GBDNA2020
- The GBinsight **Obesity Comprehensive Panel** is designed to analyze 99 genes important for understanding the genetic architecture of obesity. The sequence analysis includes entire protein-coding and splicing regions, selected exons, SNPs and deletions and insertions of genes implicated in both monogenic and polygenic forms of obesity. Gene groups include: body mass index-associated variants, genes involved in central nervous system regulation of appetite and satiety, emotional eating and eating disorders, and genes associated with energy level, basal metabolic rate, lipid metabolism and body fat distribution. Rare mutations associated with non-syndromic monogenic obesity are also included. Genes with limited evidence for their association with obesity can be optionally included.

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https://www.gbhealthwatch.com/index.php

- Non-Syndromic Monogenic Obesity Panel
- GBDNA2021
- The GBinsight **Non-Syndromic Monogenic Obesity Panel** is designed to analyze 16 genes related to non-syndromic monogenic obesity. The sequence analysis includes entire protein-coding and splicing regions as well as known causal variants outside of these regions that can detect single nucleotide variations and deletions and insertions that contain pathogenic and likely pathogenic mutations that cause monogenic forms of non-syndromic obesity.

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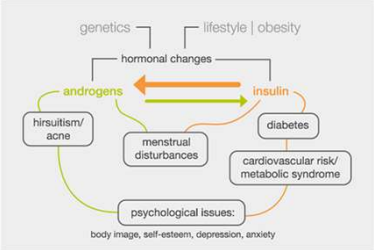
Pathophysiology: Big Picture

Figure 1. Overview of the causes, pathology and symptoms of PCOS. Adapted from Teede et al. BMC Med. 2010



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MULTIFACITED DISEASE

- Uncontrolled ovarian steroid genesis
- Aberrant insulin signaling
- Excessive oxidative stress
- Genetic-environmental factors (2)

https://www.gbhealthwatch.com/science-portal-PCOS-science.php

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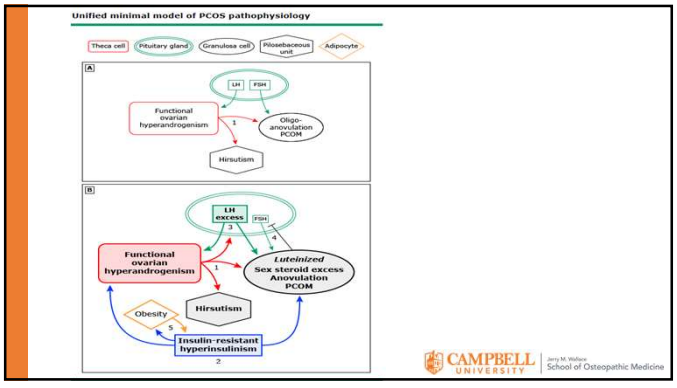
In the OVARY…

- Intrinsic defect of the theca cells of the ovary – secrete high levels of androgens (hirsutism, acne)
- Also effects granulosa cells which produce up to 4 X Antimullerian Hormone (AMH)
- This elevates the number of follicles (mostly preantral and small antral) (anovulation = infertility)
- Additionally, there is a defect in apoptotic processes in some maturing follicles

- Insulin Resistance
- Decreased insulin sensitivity caused by a postreceptor binding defect in the insulin signaling pathway is an intrinisic component of PCOS, independent of obesity
- PCOS associated with increased glycooxidative stress secondary to mitochondrial dysfunction and oxidative stress can induce insulin resistance and hyperandrogenism



1. Pituitary LH secretion is necessary to sustain the ovarian androgen excess (caused by intrinsic defect in ovary)
2. Insulin-resistant hyperinsulinism acts on theca cells to aggravate hyperandrogenism, synergizes with androgen to prematurely luteinize granulosa cells, and stimulates fact accumulation. Increased hyperandrogenemia provokes LH excess, which then acts on both theca and luteinized granulosa cells to worsen hyperandrogenism
3. LH also stimulates luteinized granulosa cells to secrete estradiol which suppresses FSH secretion which further hinders ovulation (4.)

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Diagnostic Criteria (MUST RULE OUT OTHER CAUSE)

National Institutes of Health Criteria (2 criteria)	• Hyperandrogenism • Menstrual Irregularity
Androgen Excess - PCOS Society Criteria (2 criteria)	• Hyperandrogenism • Menstrual Irregularity or Polycystic Ovaries on Ultrasonography
Rotterdam Criteria (2 out of 3 criteria)	• Hyperandrogenism • Menstrual Irregularity • Polycystic Ovaries on Ultrasonography

https://www.frontiersin.org/articles/10.3389/fphys.2016.00124/full

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Phenotypes – Rotterdam criteria

- Since PCOS tends to present as a spectrum of diseases, the Rotterdam criteria divided the disease into four phenotypes (Rotterdam, 2004):
- ➢ Frank or classic polycystic ovary PCOS (chronic anovulation, hyperandrogenism, and polycystic ovaries)
- ➢ Classic non-polycystic ovary PCOS (chronic anovulation, hyperandrogenism, and normal ovaries)
- ➢ Non-classic ovulatory PCOS (regular menstrual cycles, hyperandrogenism, and polycystic ovaries)
- ➢ Non-classic mild or normoandrogenic PCOS (chronic anovulation, normal androgens, and polycystic ovaries)

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Rule out other causes of irregular cycles/hyperandrogenism:

Condition	Labs
• Congenital Adrenal Hyperplasia	• 17 OH progesterone > 250 ng/dL
• Ovarian Tumor	• Testosterone > 200ng/dL
• Adrenal Tumor	• DHEA sulfate > 700 ug/dL
• Prolactinoma	• Prolactin > 30
• Hypothyroidism	• TSH > 4.5 mIU/mL

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14 year old female presents with one of the following: irregular periods and acne

- PMH:
  - Thelarche 12
  - Menarche 13
    - Has had 3 menses since menarche ranging in 2 -17 days
  - Acne treated with OTC products
  - FH: +PCOS/CVD/Obesity (northern European background)
  - BMI 85%
    - In children > 2 year, obesity is defined as BMI > 95%
    - BMI 85-95% overweight range

https://www.womenfitness.net/pcos-teenage-girls-early-signs/

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PCOS in Adolescents: Consider diagnosis in adolescent female who presents with menstrual irregularity/amennorhea

- 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

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PCOS in Adolescents: Consider diagnosis in adolescent female who presents with menstrual irregularity/amennorhea

- 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
- Primary amenorrhea by age 15 or > 3 years post thelarche (breast development)

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Hyperandrogenism (5)

Laboratory Evaluation

- Calculated free testosterone, free androgen index or calculated bioavailable testosterone should be used to assess biochemical hyperandrogenism
- Consider androstenedione and dehydroepiandrosterone sulface (DHEAS) if total or free not elevated
- Reliable assessment of biochemical hyperandrogenism is not possible in women on hormonal contraception (take off for 3-6 months)
- If levels marked or symptom onset sudden and progressing, consider other etiologies

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Hyperandrogenism (5)

Clinical Evaluation

- Ask about acne, alopecia, hirsutism (and current treatment), and in teens difficult to treat acne
- Ask about and address the psychosocial impact of clinical hyperandrogenism
- Use Ferriman Gallwey score (mFG) with a level of >_4-6 indicating hirsutism
- Use Ludwig visual score for degree and distribution of alopecia
- Ethnic variation of vellus hair is notable; only terminal hairs need to be considered in pathological hirsutism

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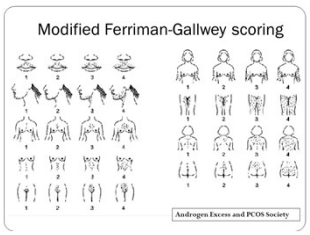
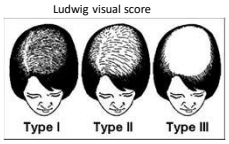
Clinical Evaluation of Hyperandrogenism



Ludwig visual score



- Vellus : fine, soft, not pigmented
- Terminal : long, coarse, pigmented

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Ultrasound and PCOM (polycystic ovarian morphology) (5)

- Do NOT use in diagnosis of PCOS in those less than 8 years since menarche due to high incidence of multi-follicular ovaries in this life stage
- Not necessary, but will diagnose complete PCOS phenotype

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Ultrasound and PCOM (polycystic ovarian morphology) (5)

- Clear protocols recommended for reporting follicule number per ovary and ovarian volume on ultrasound. Recommended minimum reporting standards:
  - Last menstrual period
  - Transducer bandwidth frequency
  - Approach/rout assessed
  - Total follicle numbers per ovary measuring 2-9 mm
  - Three dimensions and volume of each ovary
  - Reporting of endometrial thickness and appearance is preferred
  - Other ovarian and uterine pathology, as well as ovarian cysts, corpus luteum, dominant follicles > 10mm

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More clinical data on our patient…

- BP 138/90
- Waist Circumference 35
- Modified Ferriman-Galway of 5, no alopecia
- Has been overweight since 5 years of age per pediatrician
- 10th grader, gets mostly A's and B's

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More clinical data on our patient…

- Minimal exercise – likes to watch YouTube, play video games
- Family busy – fast food diet, drinks regular soda
- Doesn't feel happy and does not report any close friends
- Not sexually active
- Sleeps well 8 hours per night, no snoring, no FH OSA

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Screening for risk of OSA

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T2DM/CVD risk (5)

- All patients with PCOS should be offered regular monitoring for weight changes and excess weight, monitoring could be at each visit or minimum 6-12 months
- Weight, height, waist circumference, blood pressure should be measured annually
- Overweight and obese women with PCOS, regardless of age, should have a fasting lipid profile

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T2DM/CVD risk (5)

- Glycemic status should be assessed at baseline in all women with PCOS. Thereafter every 1-3 years.
- Perform oral glucose tolerance test, fasting plasma glucose or HbA1C. If FH + DM, h/o gestational diabetes, hypertension, PCOS with BMI > 25, OGTT recommended
- If planning pregnancy, a 75 OGTT should be offered if h/o PCOS

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Does she have PCOS?

Initial Labs:

- 17 OH progesterone, Free and Total Testosterone, Prolactin, TSH, HbA1C, Fasting Lipids
- NO sonogram
- Start low androgen combined oral contraceptive pill
- Lifestyle Intervention: Diet and Exercise
- Frequent Follow up…

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Combined oral contraceptive pills (COCPs) (5)

- COCP alone should be recommended in adult women with PCOS for the management of hyperandrogenism and/or irregular menses (OFF LABEL)
- The COCP alone should be considered in adolescents with a clear diagnosis of PCOS
- The COCP could be considered in adolescents who are deemed "at risk" but not yet diagnosed with PCOS
- Should see improvement in 6 months of COCPs of hirsuitism/irregular cycles

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Think about contraceptive needs too!

- When prescribing COCP's in adults and adolescents:
  - Use lowest effective estrogen doses (20-30 mcg of ethinlyestradiol)
  - Consider relative and absolute contraindication sand side effects of COCP's

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Lifestyle Interventions

- Lifestyle intervention should be recommended in all those with PCOS and excess weight, for reductions in weight, central obesity, and insulin resistance
- Achievable goal in 6 months is a 5-10% weight loss which yields significant clinical improvements
- Use SMART (specific, measurable, achievable, realistic, and timely) goal setting
- Psychological factors such as anxiety and depressive symptoms, body image concerns and disordered eating, need consideration and management to optimize engagement and adhearence to lifestyle interventions

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Probably…

- In an adolescent with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient, taking into account diagnostic challenges at this life stage and psychosocial and cultural factors (5)
- For adolescents who have features of PCOS but do not meet diagnostic criteria, an "increased risk" could be considered and reassessment advised at or by FULL REPRODUCTIVE MATURITY (8 years post menarche) (5)
- Testosterone levels rise during puberty and reach a peak adult level within a few years of menarche.

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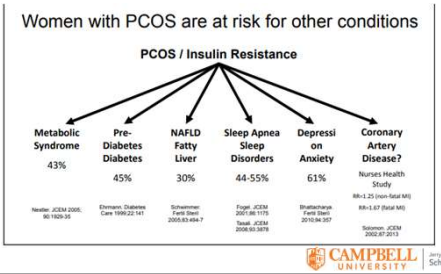

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Continue to follow patient every 6-12 months

- Lifestyle modification assessment and treatment to treat overweight and obesity
- Monitor cardiovascular Risk
- Preconceptual Counseling
- Risk for Endometrial Cancer

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https://www.researchgate.net/publication/304750222_Eng_PCOSQ-50_after_Edit

Polycystic Ovary Syndrome Questionnaire (PCOSQ-50)—Self-Administered Instructions:

The questions concern your health-related issues. Please respond to each question by checking the box with the rating that best reflects how you feel.
Choose only one option for each question. There is no right or wrong answer. Just choose the option that is closest to how you feel.

Section A: Psychosocial and emotional

In the past 4 weeks how often have you

		Never	Rarely	Some times	Often	Always
1.	Suffered from bad mood due to PCOS?	☐	☐	☐	☐	☐
2.	Experienced impatience due to PCOS?	☐	☐	☐	☐	☐
3.	Blamed yourself for having PCOS?	☐	☐	☐	☐	☐
4.	Experienced trouble dealing with others?	☐	☐	☐	☐	☐
5.	Suffered from low self-esteem due to PCOS?	☐	☐	☐	☐	☐

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Glucophage OFF LABEL

- An oral anti-diabetic biguanide drug, acts by impeding hepatic glucose production and increasing the peripheral insulin sensitivity (2)
- In obese adolescent with impaired glucose tolerance, Metformin has been shown to be beneficial in improving glucose tolerance and insulin sensitivity, in lowering insulinemia, and in reducing elevated androgen levels. (2)

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Glucophage OFF LABEL

- Where metformin is prescribed the following need to be considered:
  - Adverse effects, including gastrointestinal side-effects that are generally dose dependent and self-limiting, need to be the subject of individualized discussion
  - Starting at a low dose, with 500mg increments 1-2 weekly and extended release may minimize side effects
  - Metformin use appears to be safe long term, based on use in other populations, however ongoing requirement needs to be considered and use may be associated with low vitamin B12 levels

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Up and coming?

- Myo-inositol (MYO) and D-chiro-inositol (DCI), 2 sterioisomers of inositol, an insulin sensitizing molecule
- When combined with monacolin K (natural statin) and lipoic acid, inositol showed a dose-sependent improvement in dyslipidemia and hyperandrogenism-associated symptoms (8)
- When combined with folic acid, MYO decreased hyperstimulation syndrome to a higher extent than folic acid alone in PCOS females undergoing oocyte retrieval (s) (9)

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Up and coming?

- The combination of MYO with DCI in a physiological plasma ration of 40-1 led to a decrease risk of developing metabolic syndrome in obese women with PCOS. (10)
- Another study showed significant improvement in menstrual cycle regularity, decreased insulin resistance, better lipid profile and less acne with MYO-DCI combination (11)
- Inositol (in any form) should be considered experimental therapy in PCOS, with emerging evidence on efficacy highlighting the need for further research (5)

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Efluorithane 13.9%

- Generic: Efluorithane 13.9 %
- Inhibitor of ornithine decarboxylase (ODC) enzyme which is needed for hair follicle cell division and synthesis
- Topical for face and chin
- Not for use in patients under 12
- Works while used but hair grows back once stop

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Spironolactone OFF LABEL

- Androgen-receptor antagonist
- Add-on to OC's
- Teratogenic
- Reliable contraception mandatory
- Watch for hyperkalemia
- **Inadequate evidence in PCOS**

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Same patient well controlled on COCP's for 10 years, just got married…

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Obesity and Pregnancy

- Pregnant Obese patients are at increased risk for:
  - Gestational diabetes (early OGTT)
  - Preeclampsia
  - Cesarean delivery
  - Infections morbidity (at delivery)
  - Effects on the fetus such as increased risk of congenital anomalies, growth abnormalities, miscarriage, and stillbirth (unknown pathophysiology)

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PCOS Treatments and Pregnancy Category

Medication:	Pregnancy Category:	Definition:
Metformin (Glucophage)	B	Unlikely to harm
Pioglitazone (Actos)	C	Not known
Orlistat (Alli, Xenical)	X	Contraindicated in pregnancy
Liraglutide / Exenatide	C	Not known
Vaniqa	C	Not known
Spironolactone	D	Harmful to baby
OCP's	X	Contraindicated in pregnancy
Diet, exercise, behavior change	A	No harm to baby

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Lifestyle Modification

Diet and Exercise leading to weight loss improves ovulation and pregnancy rates

- 87 anovulatory PCOS patients (infertile > 2 years)
- BMI = 37.4
- Duration of infertility = 5.4 years
- Previous fertility treatments = 3.7 cycles

- 6 months of lifestyle modification
  - Weekly 3 hour session with the study group
    - 1st hr. doing low impact aerobic exercise
    - 2-3rd hr. attending seminars about diet, nutrition, weight loss
  - Encouraged to perform at least 2 other exercise sessions/wk.

Clark et al. Weight loss in obese infertile women results in improvement in reproductive outcomes of fertility treatment. Human Reproduction 1998;13(6):1502-1505.

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Lifestyle Modification

Diet and Exercise leading to weight loss improves ovulation and pregnancy rates

- 20 women "dropped out" → no pregnancies/ovulations

- 67 women completed the 6 month program
  - Average weight loss = **22.4 lbs.**

  - 60 (90%) resumed spontaneous ovulation
  - 52 (78%) achieved pregnancy
  - 45 (67%) had a live birth13 of 18 patients completed 6 months of lifestyle modifications and lost weight

Clark et al. Weight loss in obese infertile women results in improvement in reproductive outcomes of fertility treatment. Human Reproduction 1998;13(6):1502-1505.

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Lifestyle Modification

Effect of a low-carbohydrate, ketogenic diet on PCOS: A pilot study

- n=11 women with BMI >27 and PCOS
- Instructed on ketogenic diet and to limit carbs < 20 grams daily
- Return every 2 weeks for measurements and dietary instruction
- 6 months

- In the 5 women who completed the pilot study
  - 12% reduction in bodyweight
  - 22% reduction in free testosterone
  - 54% reduction in fasting insulin
  - 2 women became pregnant despite previously infertility

Westman et al. The effects of a low-carbohydrate, ketogenic diet on the polycystic ovary syndrome: A pilot study. Nutrition and Metabolism 2005,2:35.

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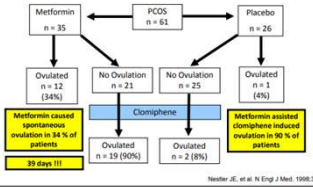
Metformin and PCOS



Nestler JE, et al. N Engl J Med. 1998;338:1876-1880.

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Bariatric Surgery and PCOS

Eid et al.	Surg for Obes and Rel Dis 2012;8(4):440	n=24, gastric bypass, 5 conceived, resolved DM, reduced HTN, lipids
Stroh et al.	Zentral-blatt fur Chirurgie 2008;133(6):608	n=3, gastric bypass, n=1 (33%) conceived, weight loss, glucose normalized
Doblado et al	Clin Endocrinol 2014;80(3):432	n=2, gastric bypass and band, both conceived
Jamal et al	Surg for Obes and Rel Dis 2012;8(4):440	n=10, gastric bypass, 100% conceived who wanted, improved glucose et al.
Talebpour et al	Obesity Surgery 2011;21(8):1119	n=69 gastric bypass or plication, 71% conceived who wanted, 47% regular menses
George et al	Obesity Surgery 2013;23(8):1043	n=156, gastric sleeve, 36% conceived who desired, 100% improved menses

Bariatric Surgery – pros!
- Improved fertility (33-100% conception rates)
- Reduce bodyweight
- Reduce insulin resistance
- Reduce testosterone levels and hirsutism
- Improve all metabolic parameters

Bariatric Surgery – cons!
- Less well studied
- All studies are retrospective chart review studies
- Potential risk of surgical complications

Limited data / references of use in PCOS
- Very effective for PCOS but invasive nature

Butterworth et al. Review Article: Bariatric Surgery, PCOS, and Infertility. Journal of Obesity 2016; published online 2016 Nov 14.

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Bariatric Surgery and Pregnancy (ACOG Practice Bulletin 105, June 2009)

- Bariatric Surgery should not be considered a treatment for infertility.
- May have decreased absorption for OCP's and unintended pregnancy.
- Can have late complications of maternal intestinal obstruction and gastrointestinal hemorrhage so keep a high index of suspicion for gastrointestinal surgical complications in pregnant patients with h/o bariatric surgery present with significant abdominal symptoms

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Bariatric Surgery and Pregnancy (ACOG Practice Bulletin 105, June 2009)

- Recommend waiting 12-24 months after surgery before conceiving so that the fetus is not exposed to rapid maternal weight loss and the patient can achieve full weight loss goals
- Consider evaluation for micronutrient deficiencies at the beginning of pregnancy (protein, iron, vitamin B12, folate, vit D, calcium)
- Patients with dumping syndrome may not tolerate the 50g GTT for gestational diabetes screening – may have to do home glucose monitoring for 1-2 weeks (fasting and 2 hour postprandial)

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Orlistat and PCOS

Graff et al.	Int J Clin Pract 2016;70(6):460-61	9 study meta-analysis of Orlistat vs. Metformin
Kumar et al.	J Hum Reprod Sci 2014;7(4):255-61	Orlistat vs. Metformin
Panidis et al	Clin Endocrinol 2014;80(3):432	Orlistat vs. Placebo
Cho et al	Clin Endocrinol 2009;70(2):233	Orlistat vs Metformin vs. Pioglitazone
Panidis et al	Fertil Steril 2008;89(4):899	Orlistat vs. Placebo
Jayagopal et al	JCEM 2005;90(2):729	Orlistat vs. Metformin

Orlistat – pros!
- Reduce bodyweight (> than metformin)
- Reduce waist circumference
- Reduce insulin resistance
- Reduce testosterone levels
- Increased spontaneous ovulation and pregnancy

Orlistat – cons!
- Less well studied than metformin
- Side effects and limited tolerability

Limited data / references of use in PCOS
- Orlistat – 12 PubMed references (as of 2/26/17)
- Might be as effective for PCOS patients

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GLP-1's Agonists and PCOS

Jensterle et al	Exper and Ther Medicine 2016;11:1194	Liraglutide vs. Liraglutide/Metformin
Jensterle et al	Endocr Res 2015;40:133	Liraglutide improves eating behavior
Jensterle et al	BMC Endo Disor 2017;17:5	Liraglutide 3.0 vs. Liraglutide 1.2/metformin
Jensterle et al	Eur J Endocr 2014;170:451	Liraglutide vs Liraglutide/Metformin
Rasmussen et al	Frontiers in Endocr 2014;5:article 140	Liraglutide
Elkind-Hirsch et al	JCEM 2008;93(7):2670	Exenatide, Metformin or Both

GLP-1's – pros!
- Reduce bodyweight (> than metformin)
- Reduce waist circumference
- Improve insulin resistance ?
- Increase spontaneous ovulation ?
- Reduce testosterone levels ?

GLP-1's – cons!
- Less well studied than metformin
- Minimal data for ovulations / pregnancy

Limited data / references of use in PCOS
- Liraglutide – 11 human PubMed references
- Exenatide – 2 human PubMed references (as of 2/26/17)

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Thiazolidinediones (TZD) and PCOS

Dunaif et al.	JCEM 1996;81:3299	Troglitazone
Ehrmann et al.	JCEM 1996;81:3299	Troglitazone
Azziz et al	JCEM 2001;86:1626	Troglitazone
Seplian et al	JCEM 2005;90:60	Rosiglitazone
Rautio et al	Hum Reprod 2006;21:1400	Rosiglitazone
Bretenthaler et al	JCEM 2004;89:3835	Pioglitazone
Ortego-Gonzalez et al	JCEM 2005;90:1360	Pioglitazone

TZD's – pros!
- Reduce insulin levels
- Increase spontaneous ovulation
- Reduce testosterone levels
- Reduce hirsutism

TZD's – cons!
- Less well studied than metformin
- May cause weight gain
- Possible association with cardiovascular adverse events / fluid

Generally not recommended to use in PCOS who do not have diabetes

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Endometrial Cancer

- No screening necessary
- Make sure your menopausal patients know to report any vaginal bleeding promptly

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Questions

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