35 Woman with Hirsutism, Acne and Weight Gain

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Learning Objectives

- Understand the relationship between epilepsy, valproic acid and PCOS
- Review metformin treatment in PCOS
- Recognized GLP-1 receptor agonist as a potential treatment of PCOS

HPI

- 35 y Caucasian woman referred for PCOS/weight management
- Diagnosis at age 26 by OB-GYN when she presented with infertility
  - Had features of hyperandrogenism (facial hair, acne)
  - Irregular menstruation
  - Confirmed polycystic ovaries by ultrasound

HPI

- At diagnosis: metformin and clomiphene initiated
- Has two children after clomiphene treatment
- Now metformin 500 mg bid
- Never been on OCP (history of migraine)

HPI

- Weight gain from 180 to 266 lbs over 4 years
- Tries diet control (carb counting 1200 Kcal/day) and exercise (treadmills 1.30 hrs/day) with 10 lbs weight loss in 6 months duration
- PCP prescribe phentermine/topiramate (qsymia) in 2016
- Now her weight is 226 lbs

HPI

- Ob/gyn history
  - Menarche: 11 years old
  - Menstrual cycles were initially regular
  - Subsequently at age 16, menses became irregular with a frequency of approximately 6 times per year
  - LMP: 1 month prior to her visit in clinic, her previous period was 4 months before
  - G10 P2 AB8
  - History of HELLP, pre-eclampsia
  - No gestational diabetes

Past Medical History

- Depression
- Anxiety
- HTN
- PCOS
- Migraine
- Dyslipidemia

Past Surgical History

- Back surgery (Fractures L 5-S1)

Social History

- Live with her husband
- Work as a pediatric nurse
- Former smoker, stopped in 2009
- No EtOH
- No Illicit drugs
- No problem with sexual function

Family History

- Caucasian
- Denies family history of endocrinopathies, DM or thyroid disease
- PCOS: sister, aunt
- Father had CAD s/p stent at age 54

Allergy

- Penicillin
- Sulfamethoxazole-Trimethoprim

Medication Prior Visit

- Cholecalciferol (Vitamin D3) 1,000 unit 1 tab qd
- Fenofibrate 145 mg 1 tab qd
- Lorazepam 2 mg/mL 1 mg prn
- Metformin 500 mg 1 tab bid
- Metoprolol 50 mg 1 tab bid
- Naproxen 1 tab prn
- Phentermine/Topiramate (QSYMIA) 7.5-46 mg 1 tab od
- Valsartan-Hydrochlorothiazide 80-12.5 mg 1 tab od
- Venlafaxine 150 mg 1 tab od

ROS

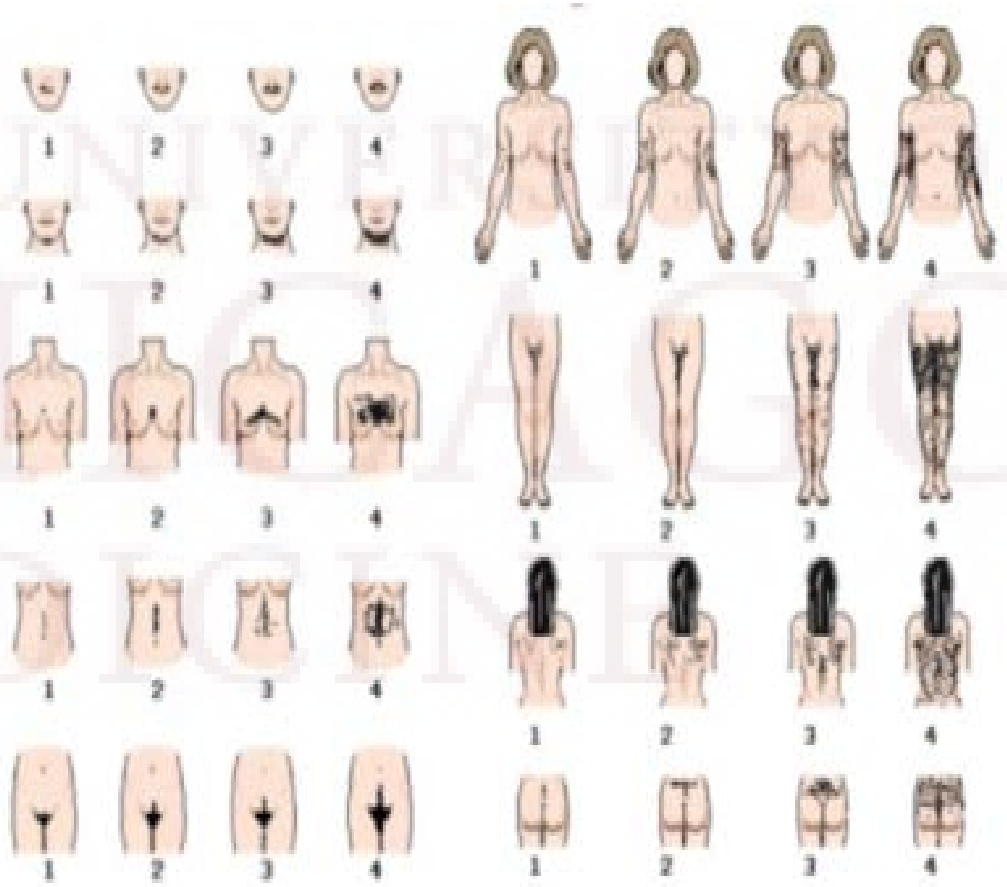
- + Acne, anxiety and depression
- Prior treatment with anti-epileptics for seizure disorder, taken valproic acid from age 13-18 (last seizure was at age 16)
- Denies galactorrhea, headaches, vision changes
- No neck mass or goiter, symptoms of hypothyroidism
- No evidence to suggest lipodystrophy
- Never been on steroids
- No eating disorders
- Other systems are negative

Physical Exam

- Vitals: BP 95/63 | Pulse 87 | Ht 160 cm (5' 3") | Wt 102.7 kg (226 lb 6.4 oz) | BMI 40.1 kg/m2
- General: No apparent distress. Appears stated age. Obese female
- HEENT: No pharyngeal erythema. PERRL, EOMI
- Neck: No neck pain. No thyromegaly or thyroid nodules appreciated. No thyroid bruit
- Cardiovascular: regular rate and rhythm. Peripheral pulses 2+ symmetric, no edema
- Pulmonary/Chest: clear to auscultation bilaterally
- Gastrointestinal: soft, non-tender, non-distended abdomen. No rebound or guarding
- Musculoskeletal: normal strength, range of motion of joints, normal tone
- Neurological: AOx3, no focal deficits. No proximal muscle weakness, normal DTRs
- Lymph: No cervical, supraclavicular, axillary or inguinal lymphadenopathy
- Derm: No rash. No thinning of the hair or hairline recession. + acne at left eyebrow. No buffalo hump, no moon faces, no violaceous striae, + facial hair
- Psychiatric: Normal mood. Appropriate thought content.

Ferriman-Gallwey Score

- Upper Lip:2
- Chin: 2
- Chest:0
- Upper Abdomen: 0
- Lower Abdomen: 0
- Upper Back: 0
- Lower Back: 0
- Upper Arm: 0
- Inner Thigh:0
- Total: 4



Legro et al. (2013). JCEM; 12:4565-92

Labs

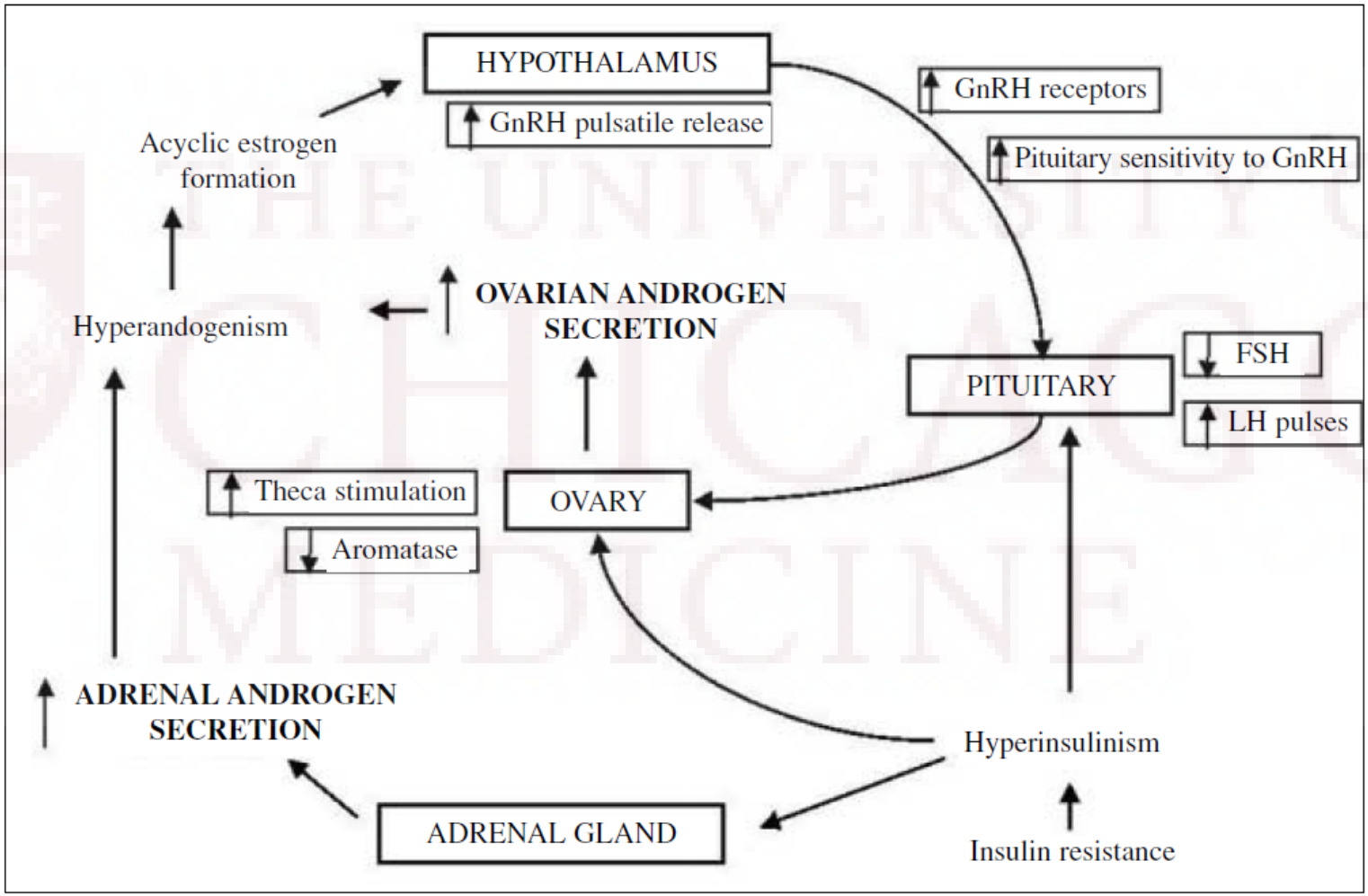
- A1C 5.6(2015)->5.3%(2017)
- Urine pregnancy test : negative

Lipid panel	11/30/13	4/5/16	8/19/17
Total Cholesterol		197	70
HDL	27	25	27
LDL		97	29
TG	302	476	70

Clinical Questions

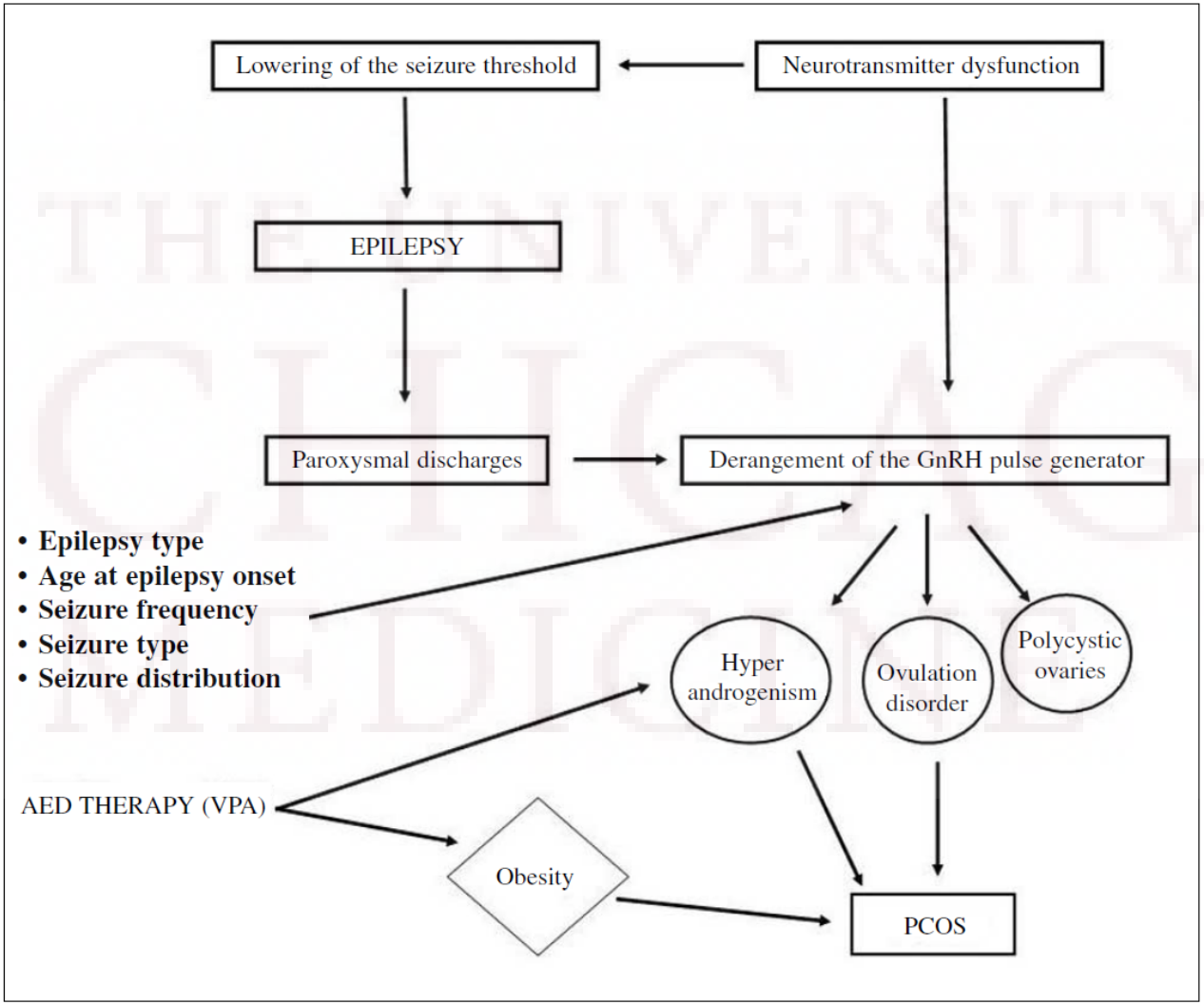
- Epilepsy and abnormalities in the HPO axis?
- Any relationship between valproic acid and PCOS? What mechanisms?

Pathogenesis of PCOS



Bilo & Meo. (2006).Neurol Sci;27:221–230

Epilepsy and PCOS



Bilo & Meo. (2006).Neurol Sci;27:221–230

Epilepsy and PCOS

- Observational study
- Objective: To determine the incidence and risk factors of PCOS in Chinese women with epilepsy
- N=102 women with epilepsy
- Results: PCOS was found in 12.7% of women with epilepsy comparing to 6.8% of women in general population
- Their average age at the start of seizure was 13.8±6.5 years

Zhou et al. (2012). Seizure;21:729–733

Epilepsy and PCOS

Table 2
Incidence and risk factor analysis of PCOS and its isolated components in Chinese WWE ($n = 102$).

AEDs	Polycystic ovaries		A/oligomenorrhoea		Hyperandrogenism		PCOS	
	–	+ N=29	–	+ N=20	–	+ N=7	–	+ N=13
Number of cases (%)	73 (71.6)	29 (28.4)	82 (80.4)	20 (19.6)	95 (93.1)	7 (6.9)	89 (87.3)	13 (12.7)
Age of seizure start (mean ± SD years)	17.2 ± 8.6	14.0 ± 4.9	16.7 ± 8.5	14.6 ± 7.1	16.6 ± 8.4	11.0 ± 3.4*	16.7 ± 8.4	13.0 ± 7.2*
Duration of seizure (mean ± SD years)	6.3 ± 5.9	5.7 ± 4.6	6.1 ± 5.8	6.3 ± 4.5	6.0 ± 5.6	8.1 ± 3.7	6.0 ± 5.6	.3 ± 4.9
Type of seizure [n (%)]								
SPS/CPS ($n = 17$)	11 (64.7)	6 (35.2)	15 (88.2)	2 (11.8)	16 (94.1)	1 (5.9)	16 (94.1)	1 (5.9)
PG/PSG ($n = 60$)	46 (76.7)	14 (23.3)	48 (80.0)	12 (20.0)	55 (91.7)	5 (8.3)	52 (86.7)	8 (13.3)
Unclassified ($n = 25$)	16 (64.0)	9 (36.0)	19 (76.0)	6 (24.0)	24 (96.0)	1 (4.0)	21 (84.0)	4 (16.0)
Frequency of seizure								
Free in 3 months ($n = 52$)	36 (69.2)	16 (30.8)	40 (76.9)	12 (23.1)	46 (88.5)	6 (11.6)	49 (98.0)	1 (2.0)
Experience in 3 months ($n = 50$)	37 (74.0)	13 (26.0)	42 (84.0)	8 (16.0)	49 (98.0)	1 (2.0)	46 (92.0)	4 (8.0)
AEDs therapy [n (%)]								
No therapy ($n = 30$)	25 (83.3)	5 (16.7)	27 (90.0)	3 (10.0)	30 (100)	0 (0.0)	30 (100)	0 (0.0)
AEDs therapy ($n = 72$)	48 (66.7)	24 (33.3)##	55 (76.4)	17 (23.6)##	65 (90.3)	7 (9.7)#	59 (81.9)	13 (18.1)##
Duration of AEDs therapy (mean ± SD years)	2.5 ± 3.1	3.7 ± 3.7	2.6 ± 3.2	3.6 ± 3.6	2.6 ± 3.2	5.0 ± 3.9*	2.5 ± 3.1	4.6 ± 3.9*

* $p < 0.05$, vs. negative (–) patients, in an unpaired t-test.
\# $p < 0.05$, vs. no AEDs therapy, in a Chi-square test.
\## $p < 0.01$, vs. no AEDs therapy, in a Chi-square test.

No AED / AED: 0 vs 13

Zhou et al. (2012). Seizure;21:729–733

Valproic Acid and PCOS

Table 3
Analysis of PCOS and its isolated components in 72 Chinese WWE used AEDs.

AEDs	Polycystic ovaries		A/Oligomenorrhoea		Hyperandrogenism		PCOS	
	–	+	–	+	–	+	–	+
Signal AED [*n* (%)]								
VPA (*n* = 21)	11 (52.4)	10 (47.6)*	13 (61.9)	8 (38.1)*	17 (80.9)	4 (19.0)	13 (61.9)	8 (38.1)*
Another AED (*n* = 28[a])	22 (78.6)	6 (21.4)	26 (92.9)	2 (7.1)	26 (92.9)	2 (7.1)	26 (92.9)	2 (7.1)
≥2 AEDs [*n* (%)]								
Non-VPA AEDs (*n* = 12)	10 (83.3)	2 (16.7)	10 (83.3)	2 (16.7)	12 (100)	0 (0.0)	12 (100)	0 (0.0)
VPA + other AEDs (*n* = 11)	5 (45.5)	6 (54.5)*	6 (54.5)	5 (45.5)*	10 (90.9)	1 (9.1)	8 (72.7)	3 (27.3)*
AEDs therapy [*n* (%)]								
Non-VPA AEDs (*n* = 40)	32 (80.0)	8 (20.0)	36 (90.0)	4 (10.0)	38 (95.0)	2 (5.0)	38 (95.0)	2 (5.0)
VPA (*n* = 32)	16 (50.0)	16 (50.0)#	19 (59.4)	13 (40.6)#	27 (84.4)	5 (15.6)*	21 (65.5)	11 (34.4)#

[a] Among them 13 patients used CBZ, 6 LTG, 5 TPM, and 4 OXC.
* $p < 0.05$, vs. non-VPA AEDs therapy, in a Chi-square test.
# $p < 0.01$, vs. non-VPA AEDs therapy, in a Chi-square test.

No VPA / VPA: 2 vs 11

Zhou et al. (2012). Seizure;21:729–733

Valproic Acid and PCOS

- Cross-sectional study
- Objective: To study an association of long-term effects of valproic acid on reproductive endocrine functions in women with epilepsy in Turkey
- N=71 (VPA: 40 and other AED: 31)

Gorkemli et al. (2009). Gynecol Obstet Invest;67:223–227

Valproic Acid and PCOS

Table 1. Main results of the study

	WWE on VA monotherapy	WWE on non-VA therapy	p
Number	40 (56.3%)	31 (43.7%)	–
Menstrual disorders	29 (72.5%)	13 (41.9%)	0.009
PCO	22 (55%)	14 (45.2%)	NS
Hyperandrogenism	15 (37.5%)	7 (22.6%)	NS
PCOS	25 (62.5%)	10 (32.3%)	0.011

NS = Not significant.

Table 2. Demonstration of dose- and duration-related PCOS and menstrual disturbance

	PCOS (+) (n = 25)	PCOS (–) (n = 15)	p
Mean VPA doses, mg	926 ± 412	953 ± 190	NS
Duration of therapy			
<34 months	n = 14	n = 5	NS
≥34 months	n = 11	n = 10	
	Menstrual irregularity (+) (n = 29)	**Menstrual irregularity (–) (n = 11)**	**p**
Mean VPA doses, mg	976 ± 376	832 ± 213	NS
Duration of therapy			
<34 months	n = 16	n = 3	NS
≥34 months	n = 13	n = 8	

NS = Not significant.

Gorkemli et al. (2009). Gynecol Obstet Invest;67:223–227

Valproic Acid and PCOS

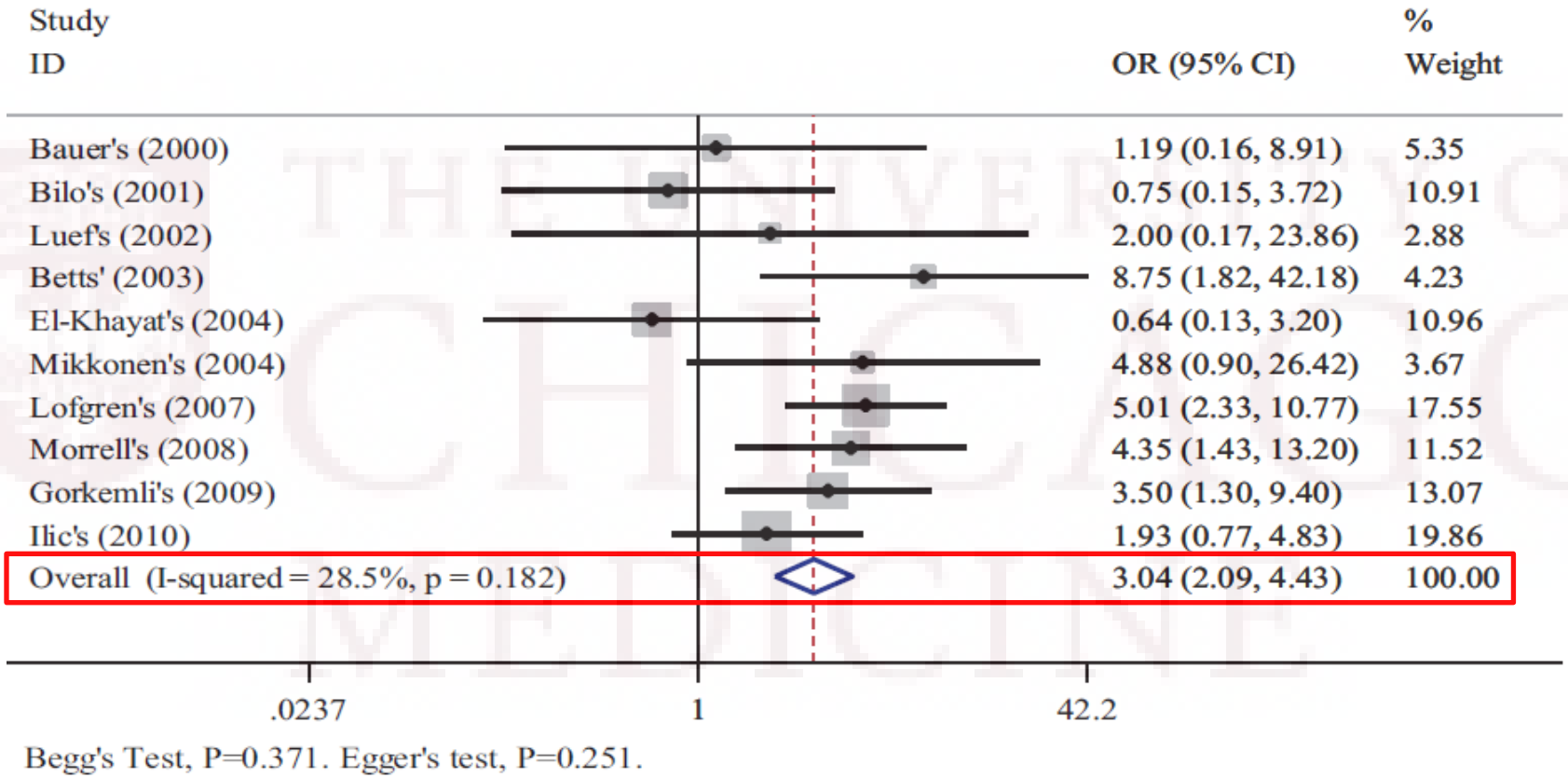
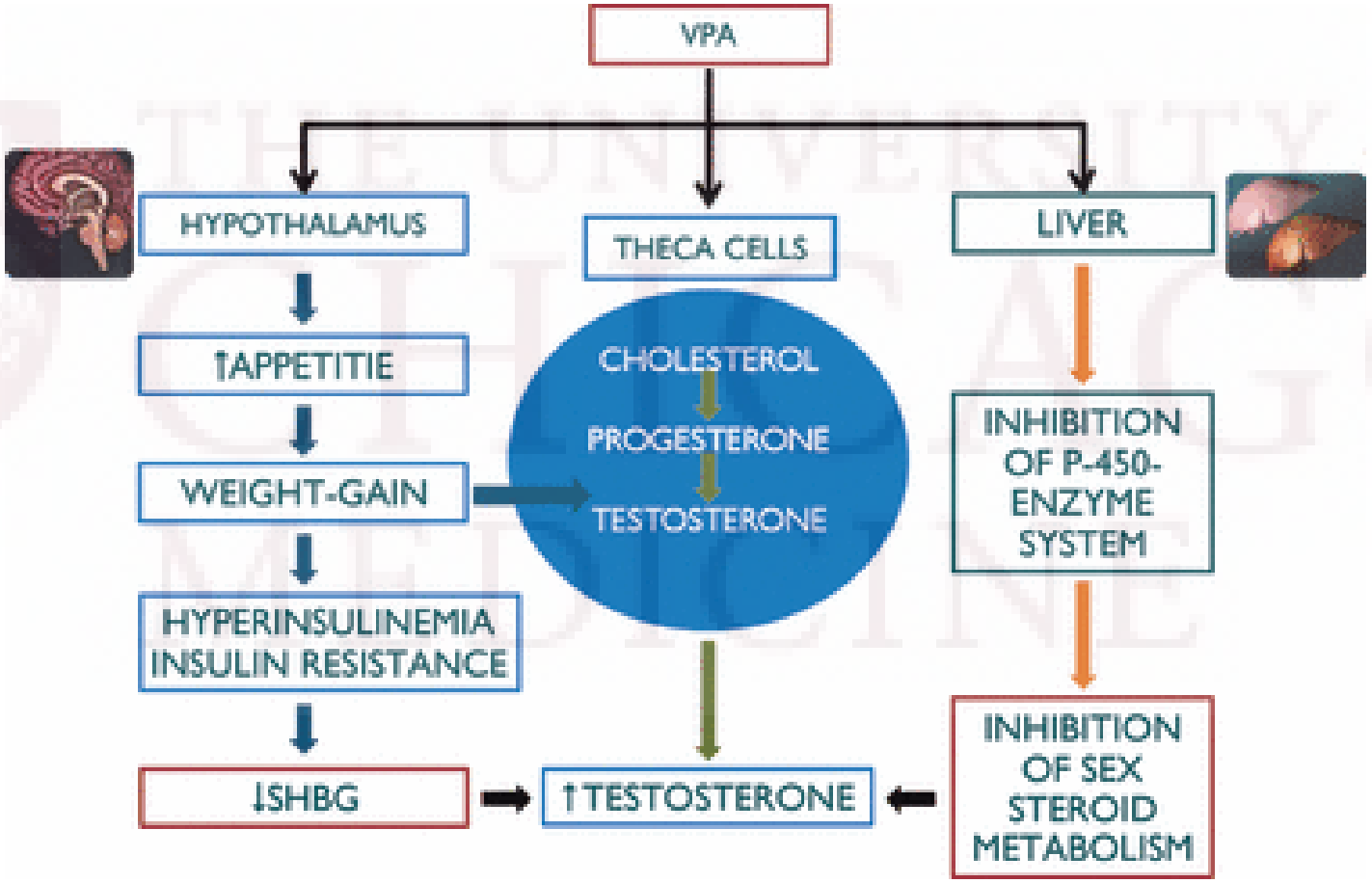


Fig. 1 PCOS of VPA vs other AEDs, accepting different definitions of PCOS.

Hu et al. (2011). Epilepsy Res;97:73-82

Mechanisms of Proposed Hyperandrogenism by Valproic Acid



Verrotti et al. (2011). Epilepsia; 52:199–211

Valproic Acid and PCOS

- Polycystic ovarian morphology or an elevated testosterone level found in 80% of women who started taken valproate before age 20
- Reproductive endocrine effects of VPA may be reversible after the medication discontinuation
- In a follow-up study of 5 years, 60% of the patients who were on VPA during the follow-up study had PCOS as compared to 5.5% of women whose medication had been discontinued

Isojärvi et al. (1993). N Engl J Med.;329:1383-8
Hu et al. (2011). Epilepsy Res;97:73-82

Clinical Questions

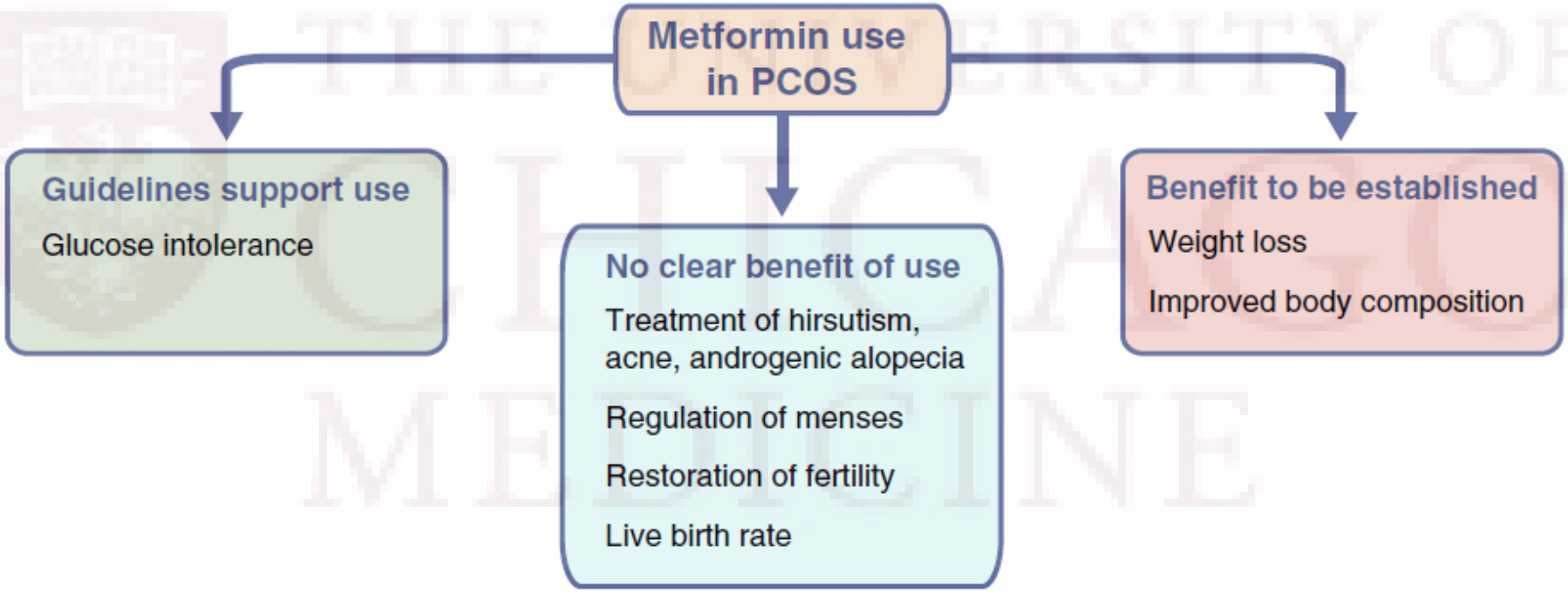
- Recommendation on metformin use in non-diabetic PCOS?
- Any evidence on weight loss treatment in PCOS with Qsymia?
- Role of GLP-1 receptor agonist in PCOS

Metformin Use in PCOS

- Strong recommendation:
  - Recommend metformin in women with PCOS who have T2DM or IGT who fail lifestyle modification
- Weak recommendation:
  - The use of metformin as a first-line treatment of cutaneous manifestations, for prevention of pregnancy complications, or for the treatment of obesity.
  - For women with PCOS with menstrual irregularity who cannot take or do not tolerate HCs, suggest metformin as second-line therapy

Legro et al. (2013). JCEM; 12:4565-92

Metformin Use in PCOS



Sam & Ehrmann. (2017). Diabetologia

Qsymia (Phentermine/Topiramate)

- PHEN/TPM combined with lifestyle modification may be an effective and well-tolerated treatment for obesity and weight-related metabolic complications
- Long-term efficacy and safety have yet to be defined
- Frequent side-effects: paresthesia, dry mouth, constipation and insomnia

Kiortsis et al. (2013).Hormones;12:507-16

Qsymia (Phentermine/Topiramate)

- Phentermine: sympathomimetic amine which acts as an appetite suppressant
- Topiramate: anticonvulsant that has weight loss side effects
- FDA approved in 2012
- Endocrine society: do not use in patient with Hx of heart disease, uncontrolled HTN
- No study in PCOS subgroup

Kiortsis et al. (2013).Hormones;12:507-16

Qsymia (Phentermine/Topiramate)

PHENTERMINE/TOPIRAMATE for weight loss in adults who are overweight (with weight-related health problems) or obese				
Patient population	3,754 adults age 18-65 (mean age 48) who were either: -**overweight** (Body Mass Index [BMI] of 27 to 29.9) with weight related problems-high blood pressure, high cholesterol, heart disease, type 2 diabetes or sleep apnea -or **obese** (BMI of 30 or higher) 74% women, mean weight 236 pounds, mean BMI 39			
Design	Double blind, superiority (40% drop out)			
Duration	1 year			
Weight loss counseling for all groups	**Reduced-calorie diet** (**500** calories less) **Nutritional and lifestyle counseling offered**			
Results	**PHENTERMINE/ TOPIRAMATE** 15mg/92mg qd	**PHENTERMINE/ TOPIRAMATE** 7.5mg/46mg qd	**PLACEBO**	**Absolute Difference** [95% CI] (7.5mg/46mg *minus* placebo)
How did the drug help?				
Mean % of body weight lost at 1 year	Lost **11%** of weight	Lost **9%** of weight	Lost **2%** of weight	**7%** [6%-8%] **more weight lost**
Percent of people who lost various amounts of weight				
Lost 5%-9% of their weight	21%	25%	12%	**13%** [8%-17%] **more people**
Lost 10%-14% of their weight	18%	18%	4%	**14%** [10%-17%] **more**

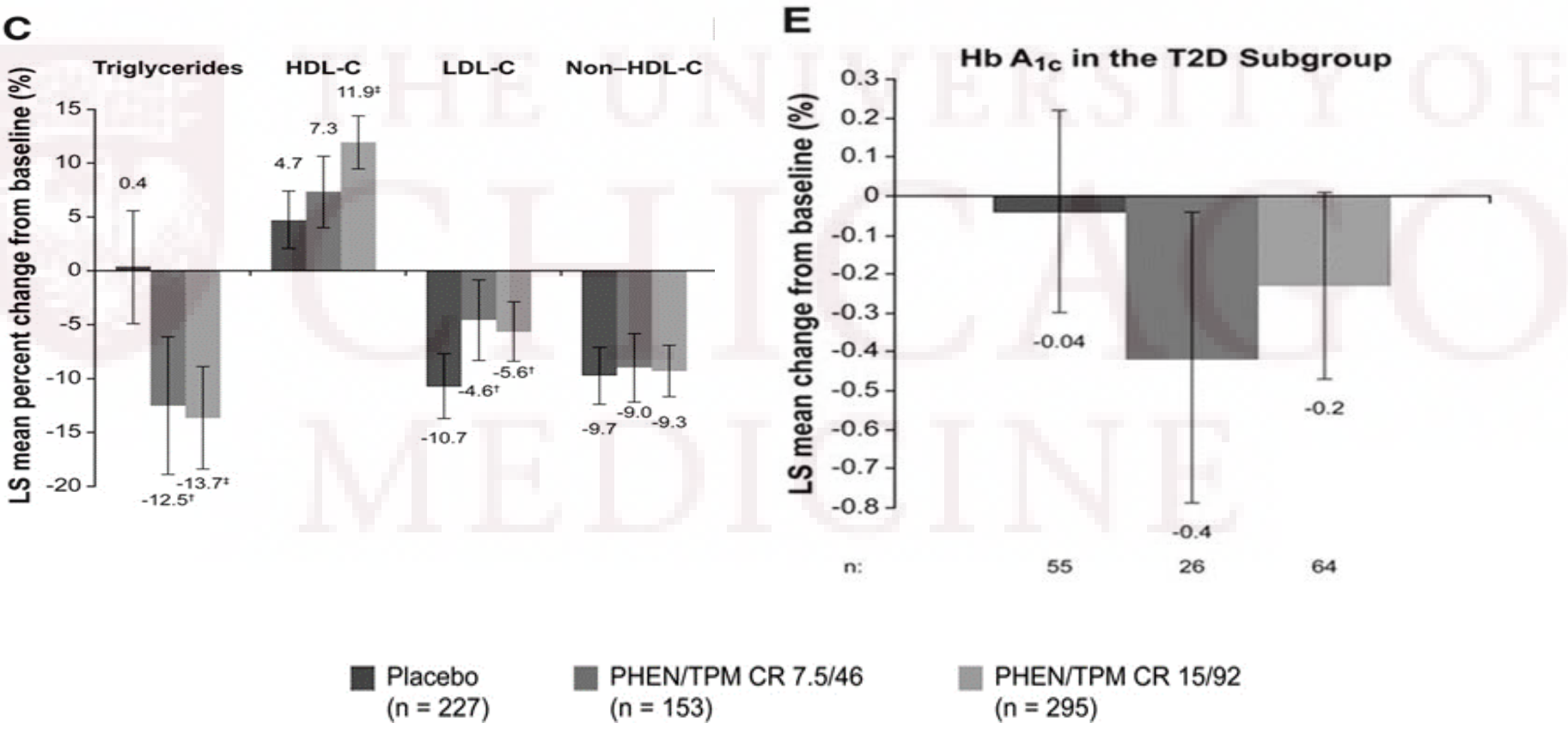
Woloshin S et al. (2014).JAMA. 74(4):615-9.

Qsymia on Cardiometabolic Variables

- SEQUEL trial
- Two-year sustained weight loss and metabolic benefits with qsymia in obese and overweight adults : a randomized, placebo-controlled extension study
- N=676
- Placebo vs qsymia (7.5/46) vs qsymia (15/92)

Garvey et al. (2012).Am J Clin Nutr;95:297–308

Qsymia on Cardiometabolic Variables



Garvey et al. (2012).Am J Clin Nutr;95:297–308

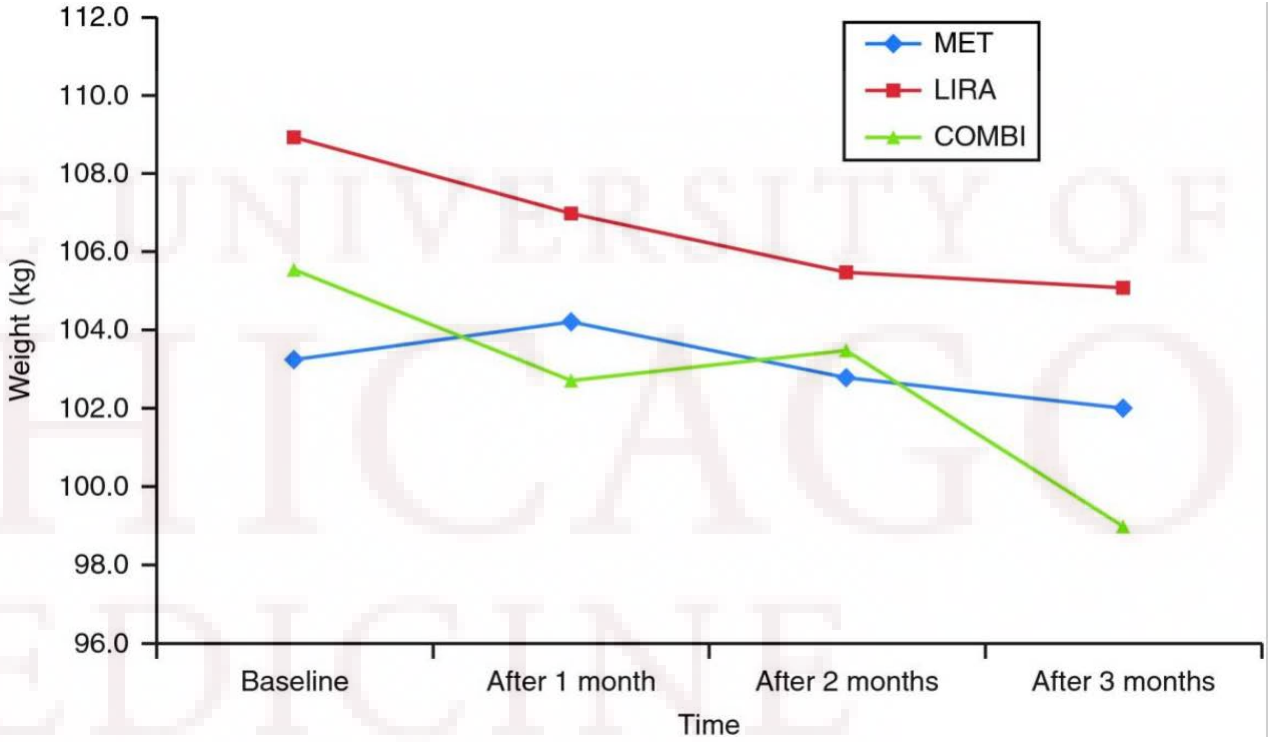
Liraglutide and PCOS

- 12-week open-label, prospective study
- N=40 (nondiabetes, pretreated with metformin for at least 6 months)
- Metformin 1000 mg BID : liraglutide (LIRA) 1.2 mg QD : combined MET 1000 mg BID and LIRA (COMBI) 1.2 mg QD
- Primary outcome: change in body weight

Jensterle Sever et al. (2014). Eur J Endocrinol;170:451-9

Liraglutide and PCOS

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 1.2±1.4 kg loss in the MET group ($P<0.001$ for the differences between the COMBI and MET therapy arms)



Jensterle Sever et al. (2014). Eur J Endocrinol;170:451-9

Liraglutide and PCOS

- 26-week double blind, randomized trial
- N=72
- Liraglutide 1.8 mg QD : placebo
- Outcome: bleeding pattern, sex hormones and gonadotrophins

Nylander et al. (2017). Reprod Biomed Online;35:121-127

Liraglutide and PCOS

Table 2 – Baseline values and changes, from baseline to week 26, in markers of ovarian function.

	Liraglutide			Placebo			Difference between groups	
	Baseline (n = 48)	Difference at six months (n = 44)	*P*	Baseline (n = 24)	Difference at six months (n = 21)	*P*	Mixed model (crude)	*P*
Bleeding ratio	0.67 (0.33 to 0.83)	0.28 (0.20 to 0.36)[b]	<0.001	0.58 (0.33 to 0.83)	0.14 (0.02 to 0.26)[c]	<0.05	0.14 (0.03 to 0.24)	<0.05
Ovarian volume (ml)	12.8 (3.5)[a]	−2.0 (−3.1 to −0.9)[a]	<0.001	12.1 (4.9)[a]	−0.2 (−1.7 to 1.4)[a]	NS	−1.6 (−3.3 to 0.1)	NS
Antral follicle count	29.0 (22.5 to 44.0)[d]	−2.0 (−6.0 to 2.0)[b]	NS	28.0 (16.0 to 43.0)[b]	2.5 (−2.0 to 7.0)	NS	0.88 (0.74 to 1.06)[e]	NS
Stroma volume (ml)	11.4 (2.9)[d]	−1.9 (−3.1 to −0.8)[b]	<0.01	10.7 (4.5)[b]	−0.2 (−1.7 to 1.2)[a]	NS	0.86 (0.71 to 1.03)[e]	NS
AMH (pmol/ml)	70.5 (39.7 to 113.4)	−8.4 (−17.4 to 0.6)	NS	72.3 (27.5 to 104.7)[a]	3.5 (−13.9 to 21.0)[a]	NS	0.87 (0.72 to 1.04)[e]	NS
LH (IU/L)	8.0 (5.1 to 12.9)	−1.7 (−5.9 to 2.6)	NS	8.7 (4.5 to 14.2)	1.0 (−2.7 to 4.6)	NS	1.08 (0.73 to 1.59)[e]	NS
FSH (IU/L)	6.1 (3.8 to 7.9)	−0.3 (−1.3 to 0.8)	NS	5.8 (4.6 to 6.6)	0.2 (−1.3 to 1.7)	NS	0.95 (0.74 to 1.21)[e]	NS
Oestradiol (nmol/L)	0.25 (0.17 to 0.58)	−0.04 (−0.07 to 0.14)	NS	0.24 (0.19 to 0.39)	0.02 (−0.14 to 0.11)	NS	1.01 (0.74 to 1.39)[e]	NS
Total testosterone (nmol/L)	1.23 (0.91 to 1.63)	−0.07 (−0.25 to 0.10)	NS	1.35 (0.95 to 1.93)	0.15 (−0.10 to 0.39)	NS	0.88 (0.71 to 1.09)[e]	NS
Free testosterone (nmol/L)	0.026 (0.021 to 0.038)	−0.005 (−0.009 to −0.001)	<0.01	0.033 (0.023 to 0.040)	0.004 (−0.003 to 0.011)	NS	0.81 (0.65 to 1.00)[e]	0.05
Free androgen index	3.84 (2.78 to 6.54)	−1.34 (−2.19 to −0.48)	<0.01	4.95 (3.08 to 6.32)	0.80 (−0.42 to 2.01)	NS	0.74 (0.58 to 0.95)[e]	<0.05
Androstenedione (nmol/L)	6.31 (4.39 to 7.93)[a]	−0.69 (−1.44 to 0.06)	NS	6.29 (4.63 to 8.84)	0.76 (−0.39 to 1.92)	NS	0.85 (0.70 to 1.04)[e]	NS
SHBG (nmol/L)	31.0 (22.0 to 44.5)	7.4 (4.1 to 10.7)	<0.001	30.5 (23.0 to 37.5)	2.0 (−2.9 to 7.0)	NS	1.19 (1.02 to 1.39)[e]	<0.05

Data presented as mean (SD), median (p25–p75) and differences as mean (95% CI).
Missing: [a], one; [b], two; [c], three; [d], four; [e], presented as a ratio.
Exclusion of the 16 women with regular menstruation at baseline did not significantly alter the results.
AMH, anti-Müllerian hormone; NS, not statistically significant; SHBG, sex hormone binding globulin.
Adjusting the mixed model for age, BMI and smoking status at baseline did not alter the results.

Nylander et al. (2017). Reprod Biomed Online;35:121-127

Exenatide and PCOS

- 24-week double blind, randomized trial
- N=176
- Exenatide 10 µg BID : metformin (MET) 1000 mg BID first 12 weeks then MET alone during the second 12 weeks
- Outcome: body weight, rate of pregnancy

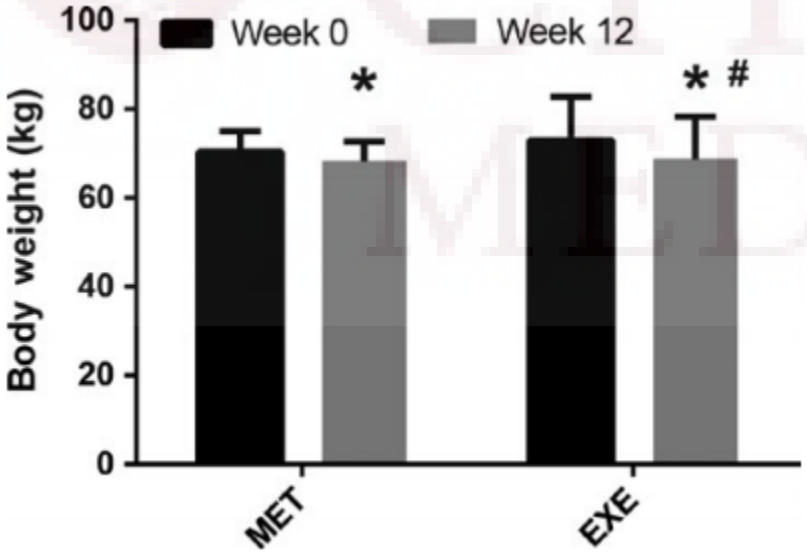
Liu et al. (2017). Clin Endocrinol

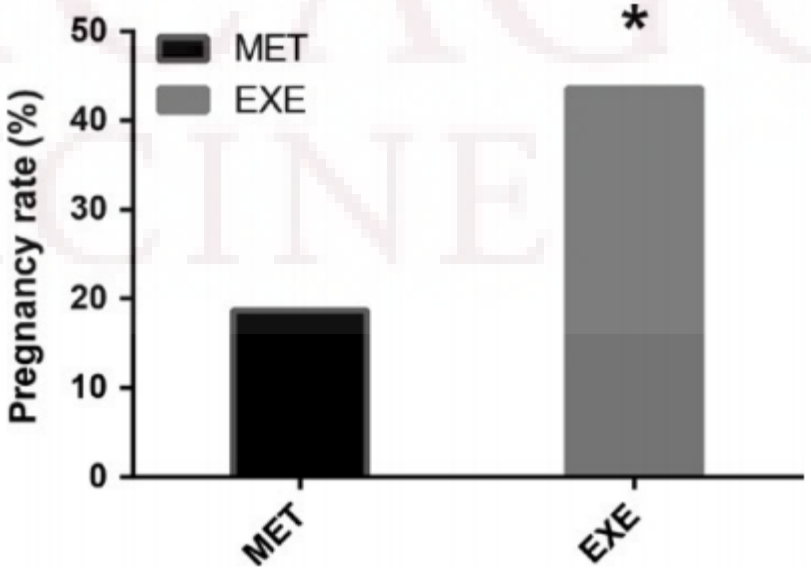
Exenatide and PCOS

TABLE 3 Natural pregnancy rate in two groups during the second 12 weeks

Groups	n	Natural pregnancy
EXE	78	34 (43.6%)
MET	80	15 (18.7%)
$\chi 2$		11.39*

*$P < .05$.





Liu et al. (2017). Clin Endocrinol

This Patient

- Metformin increased to metformin XR 1000 mg bid
- Started on progesterone(provera) 12 days to regulate her cycle
- Monitor HTN, lipid abnormalities
- Referred to dermatology for laser hair removal
- Encouraged therapeutic lifestyle modifications of diet and exercise to promote weight loss
- Stop qsymia
- Consider GLP-1 receptor agonist

References

- Farhi DC, Nosanchuk J, Silverberg SG.Endometrial adenocarcinoma in women under 25 years of age.Obstet Gynecol. 1986 Dec;68(6):741-5.
- Hu X, Wang J, Dong W, Fang Q, Hu L, Liu C.A meta-analysis of polycystic ovary syndrome in women taking valproate for epilepsy.Epilepsy Res. 2011 Nov;97(1-2):73-82.
- Isojärvi JI, Laatikainen TJ, Pakarinen AJ, Juntunen KT, Myllylä VV. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. N Engl JMed. 1993 Nov 4;329(19):1383-8.
- Hu X, Wang J, Dong W, Fang Q, Hu L, Liu C.A meta-analysis of polycystic ovary syndrome in women taking valproate for epilepsy.Epilepsy Res. 2011 Nov;97(1-2):73-82.
- Blay SL, Aguiar JV, Passos IC. Polycystic ovary syndrome and mental disorders: a systematic review and exploratory meta-analysis.Neuropsychiatr Dis Treat. 2016 Nov 8;12:2895-2903.
- Richard S. Legro Silva A. Arslanian David A. Ehrmann Kathleen M. Hoeger M. Hassan Murad Renato Pasquali Corrine K. Welt. Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline The Journal of Clinical Endocrinology & Metabolism, Volume 98, Issue 12, 1 December 2013, Pages 4565–4592
- Sam S, Ehrmann DA.Metformin therapy for the reproductive and metabolic consequences of polycystic ovary syndrome.Diabetologia. 2017 Aug 3.
- Kiortsis DN. A review of the metabolic effects of controlled-release Phentermine/Topiramate.Hormones (Athens). 2013 Oct-Dec;12(4):507-16.
- Jensterle Sever M, Kocjan T, Pfeifer M, Kravos NA, Janez A.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.Eur J Endocrinol. 2014 Feb 7;170(3):451-9.
- Nylander M, Frøssing S, Clausen HV, Kistorp C, Faber J, Skouby SO. Effects of liraglutide on ovarian dysfunction in polycystic ovary syndrome: a randomized clinical trial. Reprod Biomed Online. 2017 Jul;35(1):121-127.

35 Woman with Hirsutism, Acne and Weight Gain

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