Liraglutide for Obese Women with Polycystic Ovary Syndrome

Alyssa Lagasca, PharmD

Learning Objectives

01 Describe the disease state, diagnosis and treatment of PCOS.

02 Understand how liraglutide is currently utilized and its role in PCOS.

03 Analyze a phase 3 trial of subcutaneous liraglutide for obese women with PCOS.

04 Propose UM criteria for use of liraglutide in obese women with PCOS.

PCOS = Polycystic Ovary Syndrome
UM = Utilization Management

What is PCOS?

A condition where the ovaries produce more androgen than usual which result in numerous small cysts in the ovaries.

- **Psychological Features**

Anxiety, depression and body image

- **Reproductive Features**

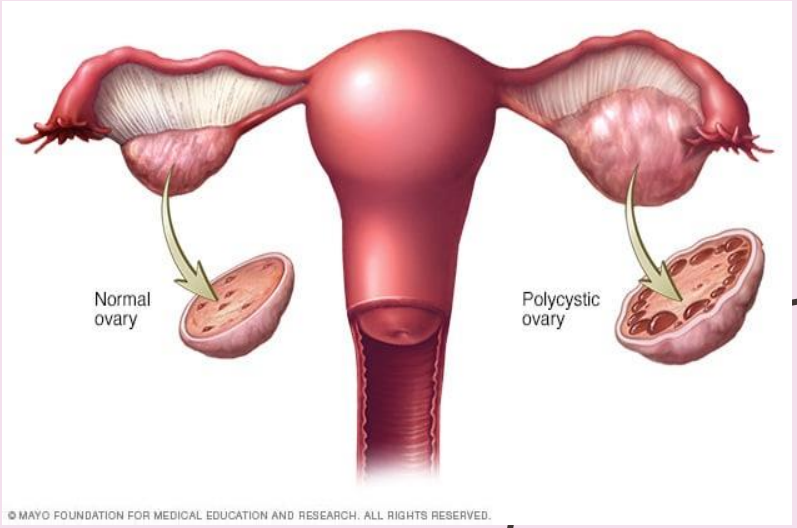
Irregular menstrual cycle, hirsutism, infertility and pregnancy complications

- **Metabolic Features**

Insulin resistance, prediabetes, type 2 diabetes, metabolic syndrome, and cardiovascular risk factors

- **Other symptoms**

Acne, oily skin, skin tags, and dark patches on back of neck and/or armpits



Polycystic Ovary Syndrome (PCOS). Johns Hopkins Medicine. 2023.
Teede HJ et al. Fertil Steril. 2018

PCOS = Polycystic Ovary Syndrome

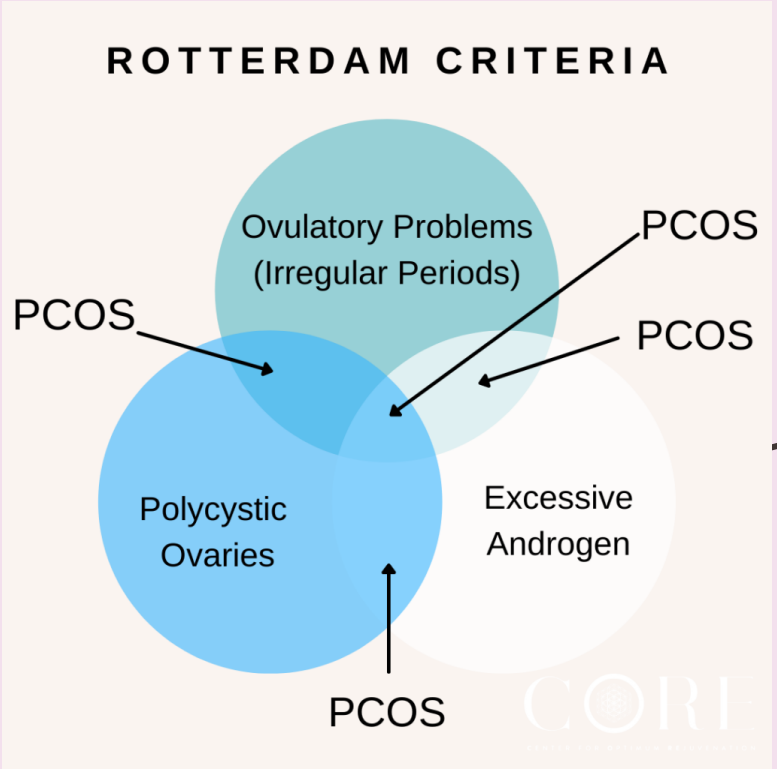
Diagnosis of PCOS

- Rotterdam criteria – 2 out of 3 criteria required:

1) Irregular ovulation
2) Clinical and/or biochemical signs of hyperandrogenism like thyroid disease
3) Polycystic ovaries via ultrasound

Diagnosis is only <u>confirmed</u> when other conditions that mimic PCOS are excluded:

1) Disorders that cause irregular ovulation
2) Disorders that cause hyperandrogenism like thyroid disease
3) Hyperprolactinemia
4) Androgen-secreting tumors



Barbieri RL, Ehrmann DA. UpToDate. 2023.

PCOS = Polycystic Ovary Syndrome

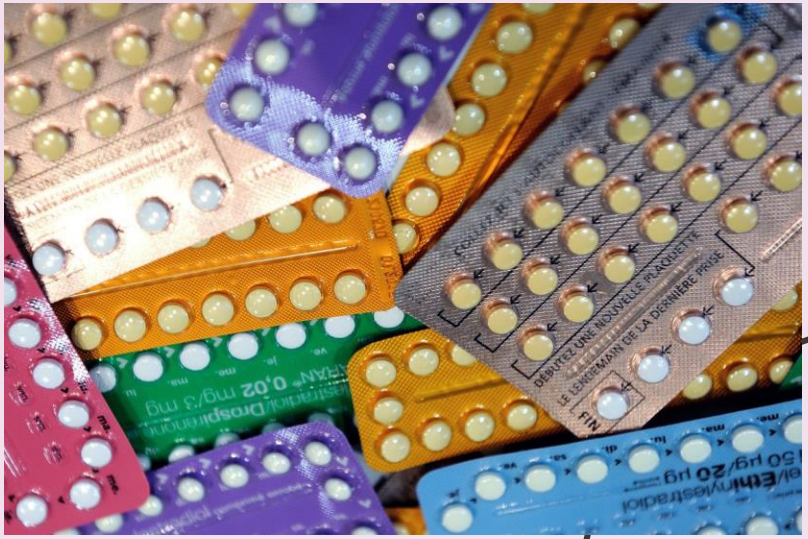
Treatment of PCOS

- **<u>Non-pharmacological</u>**

Diet and exercise for weight loss
Psychological therapy for anxiety and depression

- **<u>Pharmacological</u>**

1st line: Combined estrogen-progestin oral contraceptives



Barbieri RL, Ehrmann DA. UpToDate. 2023.

PCOS = Polycystic Ovary Syndrome

Liraglutide (Saxenda, Victoza)

FDA Approval

Approved in 2010 for Type 2 Diabetes and established cardiovascular disease
Note: Only **Saxenda** is approved for weight loss

Mechanism of Action

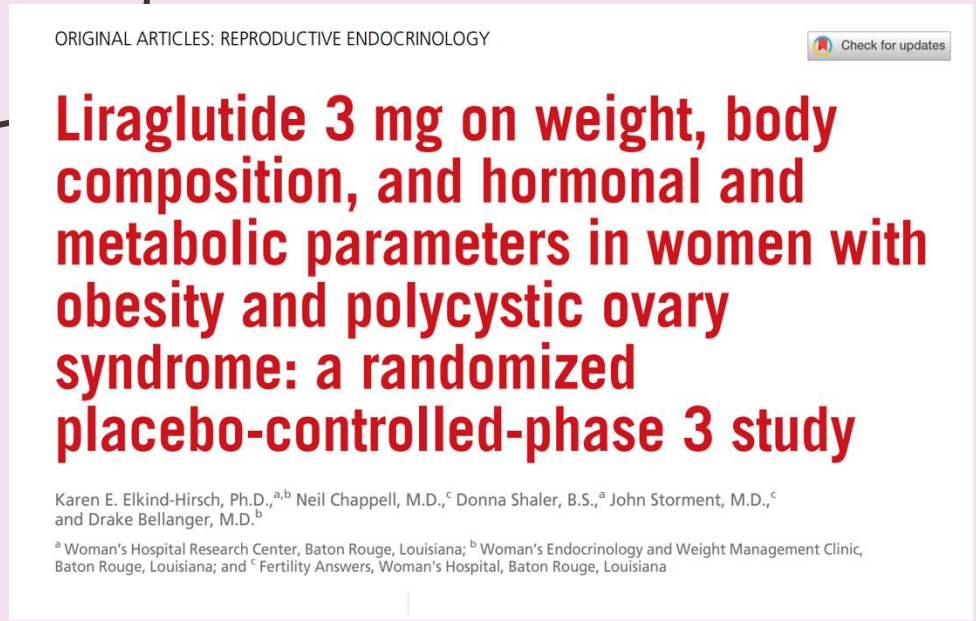
Activates GLP-1 receptor to increase insulin release in presence of elevated sugar

Role in PCOS

Although it is not FDA approved for PCOS, evidence based studies for obesity in women with PCOS have greater results with liraglutide versus placebo

Victoza [package insert]. Novo nordisk A/S. 2023.
Saxenda [package insert]. Novo nordisk A/S. 2023.
Barbieri RL, Ehrmann DA. UpToDate. 2023.
Obesity appears to increase the risk of developing polycystic ovary syndrome. Endocrine Society. 2023.

PCOS = Polycystic Ovary Syndrome
FDA = Food and Drug Administration
GLP-1 = Glucagon-like peptide 1



ORIGINAL ARTICLES: REPRODUCTIVE ENDOCRINOLOGY

Check for updates

Liraglutide 3 mg on weight, body composition, and hormonal and metabolic parameters in women with obesity and polycystic ovary syndrome: a randomized placebo-controlled-phase 3 study

Karen E. Elkind-Hirsch, Ph.D.,[a,b] Neil Chappell, M.D.,[c] Donna Shaler, B.S.,[a] John Storment, M.D.,[c] and Drake Bellanger, M.D.[b]

[a] Woman's Hospital Research Center, Baton Rouge, Louisiana; [b] Woman's Endocrinology and Weight Management Clinic, Baton Rouge, Louisiana; and [c] Fertility Answers, Woman's Hospital, Baton Rouge, Louisiana

✓Double blinded, randomized control trial
☒ Single center study (Hospital-based outpatient endocrine and metabolic center)
☒ Sponsored by the drug company (Novo Nordisk)

Trial Design

Phase 3, single-center, double-blinded, placebo-controlled, randomized control trial

Randomized via 2:1 ratio (Liraglutide: Placebo)

Sponsored by Novo Nordisk, the manufacturer

Elkind-Hirsch, et al. 2023.

Inclusion Criteria

- Diagnosed with PCOS with a body mass index of at least 30 kg/m^2
- Nondiabetic, premenopausal
  - Participants were required to recall frequency of their menses in the previous 12 months
  - Eligibility: **Irregular periods together with hyperandrogenism**
- Aged 18-45 years
- Agreement to use effective contraceptive consistently during study

✓Included specific criteria that ensured irregular menstrual cycle, hyperandrogenism and obesity as a factor
✓ Age cut off as most affected (premenopausal)

Elkind-Hirsch, et al. 2023.

PCOS = Polycystic Ovary Syndrome

Exclusion Criteria

- Diabetic
- Menopausal or postmenopausal
- Smoking within 6 months
- Pregnancy or Lactation
- Clinically significant systematic disease
- Uncontrolled hypertension
- Acute pancreatitis
- Injectable hormonal contraceptive use within 6 months
- Use of oral contraceptives
- Other steroid hormones
- Drugs that affect GI motility or carbohydrate metabolism
- Anti-obesity drugs within 3 months before study entry

✓Appropriate to exclude patients with acute pancreatitis and pregnancy
☒ Exclusion of diabetes population makes it less generalizable to greater population

Elkind-Hirsch, et al. 2023.
PCOS and Diabetes. CDC. 2023.

Parameter	Liraglutide 3mg (n=44)	Placebo Liraglutide 3mg (n=23)
Subject number		
Age (years)	31 +/- 0.9	32 +/- 1.2
Anthropometric		
BW (kg)	111 +/- 2.8	119 +/- 4.7
BMI (kg/m^2)	41.6 +/- 1.1	43.9 +/- 1.7
WC (cm)	111 +/- 2.2	116 +/- 3.3
WHR	0.85 +/- .01	0.84 +/- 0.02
DXA		
TBF (%)	47.6 +/- 0.82	48.2 +/- 0.77
AND/GYN R	1.08 +/-0.01	1.09 +/- 0.02
Lean BM	55 +/- 1.05	58.5 +/- 1.8
Hormonal		
TT (ng/dL)	49 +/- 2.9	45 +/- 3.3
FAI	6.9 +/- 0.6	5.6 +/-0.4
DHEA-S (mcg/dL)	176 +/- 13	152 +/- 11
TSH	2.5 +/- 0.16	2.7 +/-0.33
Prolactin	22 +/- 1.3 +/-	22 +/- 1.6
Cycles/Year	4.5 +/- 0.3	4.8 +/-0.5
Glycemic		
HbA1C (%)	5.5 +/- 0.06	5.5 +/- 0.08
FBG (mg/dL)	96 +/- 1.7	95 +/- 2.4
MBG (mg/dL)	129 +/- 4.9	127 +/- 4.9
HOMA-IR	4.8 +/-0.6	5.1 +/-1.03
IS $_{OGTT}$	3.25 +/- 0.46	2.8 +/- 0.42
IGI/HOMA	0.69 +/- 0.09	0.61 +/- 1.2
Cardiometabolic		
CHOL (mg/dL)	181 +/- 4.9	183 +/- 8.7
HDL-C (mg/dL)	42.5 +/- 17	42.2 +/- 1.5
LDL-C (mg/dL)	113.5 +/- 4.5	117.7 +/- 7.2
TRG (mg/dL)	131 +/- 10	117 +/- 12
TRG/HDL-C R	3.3 +/- 0.3	2.9 +/- 0.4
SBP (mmHg)	122 +/- 1.7	126 +/- 2.0
DBP (mmHg)	82 +/- 0.96	83 +/- 1.5

Baseline Characteristics

- 55 non-Hispanic White **(67%)** and 27 non-Hispanic Black women **(33%)** started on treatment
  - Race was **equally distributed** between treatment arms
- Baseline anthropometric, hormonal, glycemic and cardiometabolic characteristics **did not differ**

✓No difference in characteristics relevant to PCOS like anthropometrics and glycemic between treatment groups
☒ 67% of the study population is White

Elkind-Hirsch, et al. 2023.
Engmann, et al. 2017

PCOS = Polycystic Ovary Syndrome

Blinding & Randomization

- Double-blind design
- Randomized to 2:1 ratio for subcutaneous injection of Liraglutide 3 mg or visually matching placebo once daily for 32 weeks
- Block randomization using computer-generated random numbers

✓Investigators and outcome assessors were blinded
✓Participants were blinded, randomized, and stratified
✓Independent unblinded research assistant instructed investigator as to which serial numbers of the drug to supply to each participant

Elkind-Hirsch, et al. 2023.

Statistical Analysis

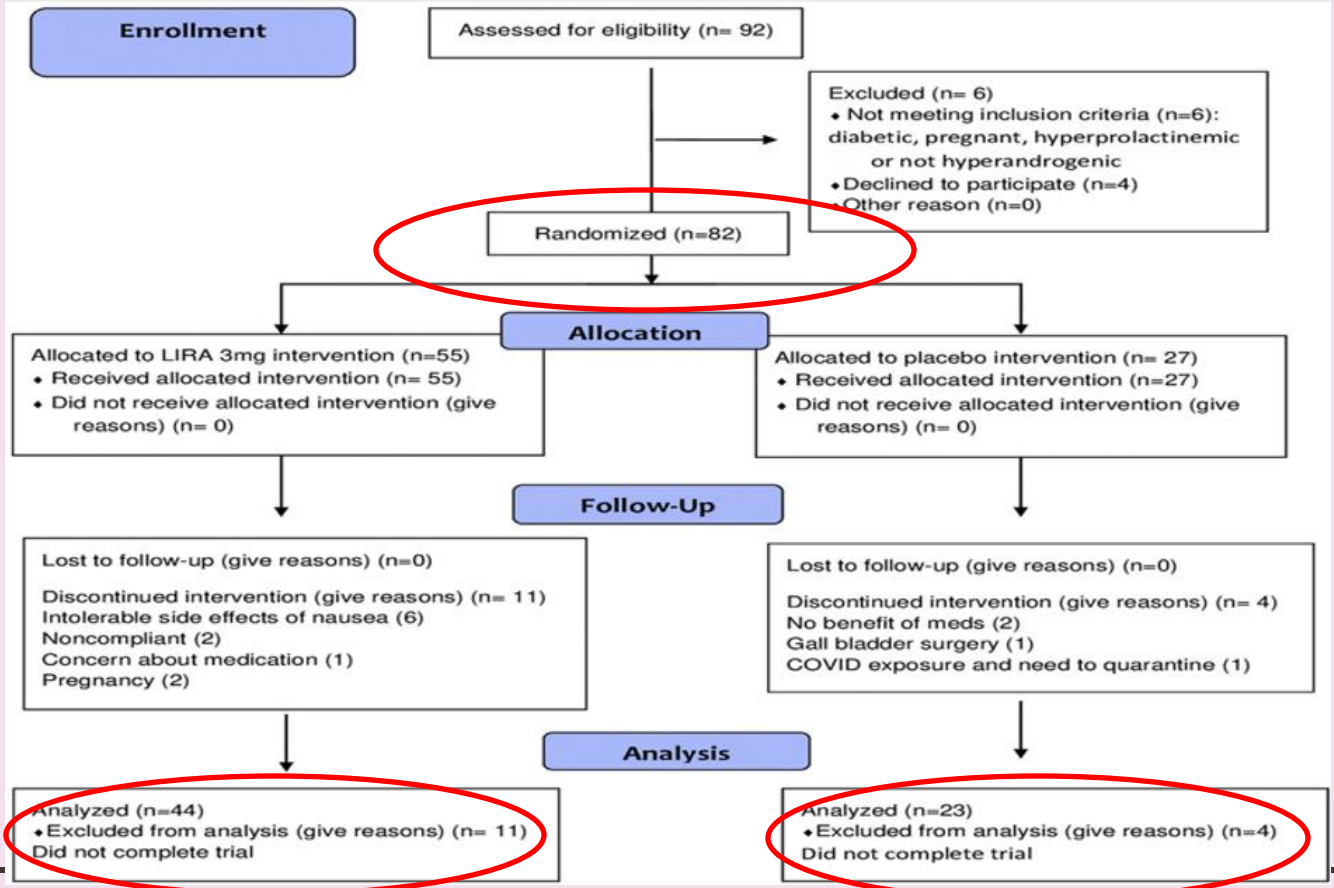
- A sample size of 82 were randomized with 80% power.
- Liraglutide 3 mg was tested for superiority to placebo
- PP analysis utilized for efficacy endpoints, ITT analysis for safety
- Multiple imputation with "missing-at-random" assumption

✓80% Power is appropriate
✓Multiple imputation is beneficial to account for attrition
☒ Per-protocol analysis not ideal for a superiority trial

PP = Per-protocol
ITT = Intention-to-Treat

Elkind-Hirsch, et al. 2023.

Subject Disposition



✓Met power at 67 participants (needed 57)
☒18.3% overall attrition
☒ 7.6% differential attrition of liraglutide vs. placebo

Elkind-Hirsch, et al. 2023.

Co-primary Endpoints

- **First primary endpoint:** Changes in body weight (kg) from baseline to week 32
- **Second primary endpoint:** Proportion of participants losing ≥ 5% of baseline body weight from baseline to week 32
- **Third primary endpoint:** Change in free androgen index (FAI) from baseline to week 32

✓Clinically significant co-primary endpoints that highlight patient outcomes that matter to them
✓Endpoint is validated, objective and related to the disease of interest

Elkind-Hirsch, et al. 2023.

Table 1:

Co-primary endpoint	LIRA 3 mg (n = 44)	Placebo (n=23)	P-value
Change in body weight (kg) from baseline to week 32 P-value of ≤ 0.01	Before: 111 (+/-) 2.8 After: 104.7 (+/-) 2.9 **-5.7% weight loss**	Before: 119 (+/-) 4.7 After: 117.9 (+/-) 5 **-1.4% Weight loss**	.002
Change in FAI from baseline to week 32 P-value of ≤ 0.01	Before: 6.9 (+/-) 0.6 After: 5.98 (+/-) 2.9 **Significant FAI decrease**	Before: 5.6 (+/-) 0.4 After: 6.4 (+/-) 0.75 **Slight FAI increase**	.006

TABLE 2

Change in weight from baseline to study completion.

Parameter	LIRA 3 mg	Placebo-LIRA 3 mg	*P* value
No. of subjects	44	23	
Weight loss from baseline			
Mean percent weight loss	5.7 ± 0.75	1.4 ± 1.09	.002
Frequency of ≥5% weight loss	**25 (57%)**	**5 (22%)**	**.009**
Frequency of ≥10% weight loss	13 (29.5%)	2 (8.7%)	.046

Note: Values are presented as mean ± SEM. *P* value reflects LIRA 3 mg vs. placebo-LIRA 3 mg. Main outcome is bolded. Mean percent weight loss is calculated from week 32 ([weight − baseline weight]/baseline weight). LIRA = liraglutide.

Elkind-Hirsch. LIRA 3 mg on weight and androgens in PCOS. Fertil Steril 2022.

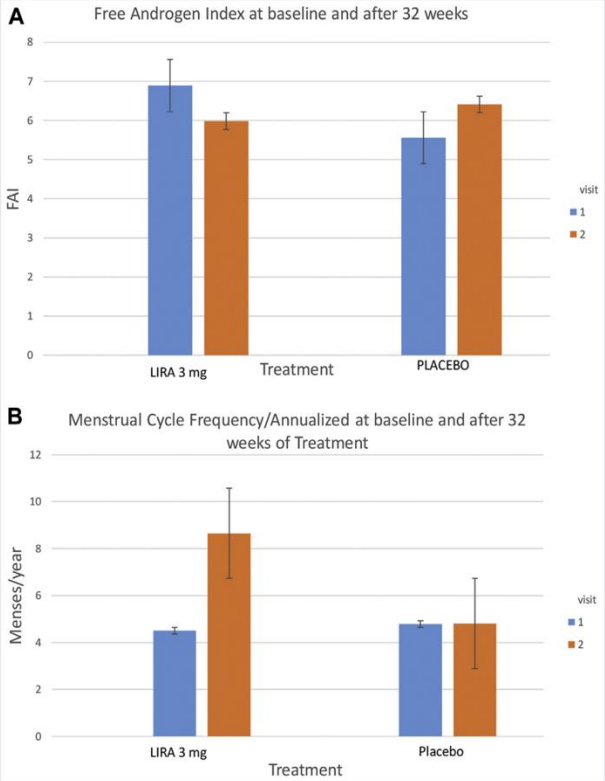
FAI: Free Androgen Index

Results

- ✓Results are statistically significant (P<0.01)
- ✓Clinically meaningful response as 57% of the patients in LIRA group had ≥ 5% weight loss
- ✓FAI decreased in LIRA group while it increased in placebo

Elkind-Hirsch, et al. 2023.

FIGURE 2



(**A**) Changes in free androgen index (FAI) at baseline (visit 1) and after 32 weeks of treatment (visit 2). FAI was significantly decreased in subjects with PCOS and obesity and without diabetes with LIRA 3 mg wherein no change in FAI was found with PL LIRA 3 mg therapy (P=.006). Data shown are mean ± SEM. (**B**) Changes in menstrual cycle at baseline (visit 1) and after 32 weeks of treatment (visit 2). Return of menses to a normal monthly pattern was significantly better with LIRA 3 mg therapy in participants with PCOS and obesity and without diabetes compared with treatment with PL LIRA 3 mg which showed little improvement (P=.0001). Data shown are mean ± SEM.

Elkind-Hirsch. LIRA 3 mg on weight and androgens in PCOS. Fertil Steril 2022.

Elkind-Hirsch, et al. 2023.

Safety

Summary of Adverse Events during Trial

Adverse event	Liraglutide 3mg (n=55)	Placebo Liraglutide (n=27)
Nausea	14 (25.5%)	3 (11%)
Vomiting	5 (9%)	0
Diarrhea	4 (7.3%)	0
Constipation	3 (5.5%)	1(3.7%)
Heartburn	2(3.6%)	1(3.7%)
Reflux	2(3.6%)	0
Indigestion	2(3.6%)	0
Injection site reaction (bruising redness, itching	3(5.5%)	0
Prolong menstrual bleeding	3(5.5%)	1(3.7%)
No menstrual cycles	0	1(3.7%)
COVID 19	0	1(3.7%)

☒ Over 25% of Liraglutide group could not tolerate due to nausea.

Elkind-Hirsch, et al. 2023.

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Thank you!

Do you have any questions?

Alyssa Lagasca, PharmD