

Challenges in Polycystic Ovary Syndrome

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“A series of seven cases is herewith reported in which amenorrhea was associated with the presence of bilateral polycystic ovaries.”

Stein IF, Leventhal MF. Am J Obstet Gynecol 1935; 29:181-191

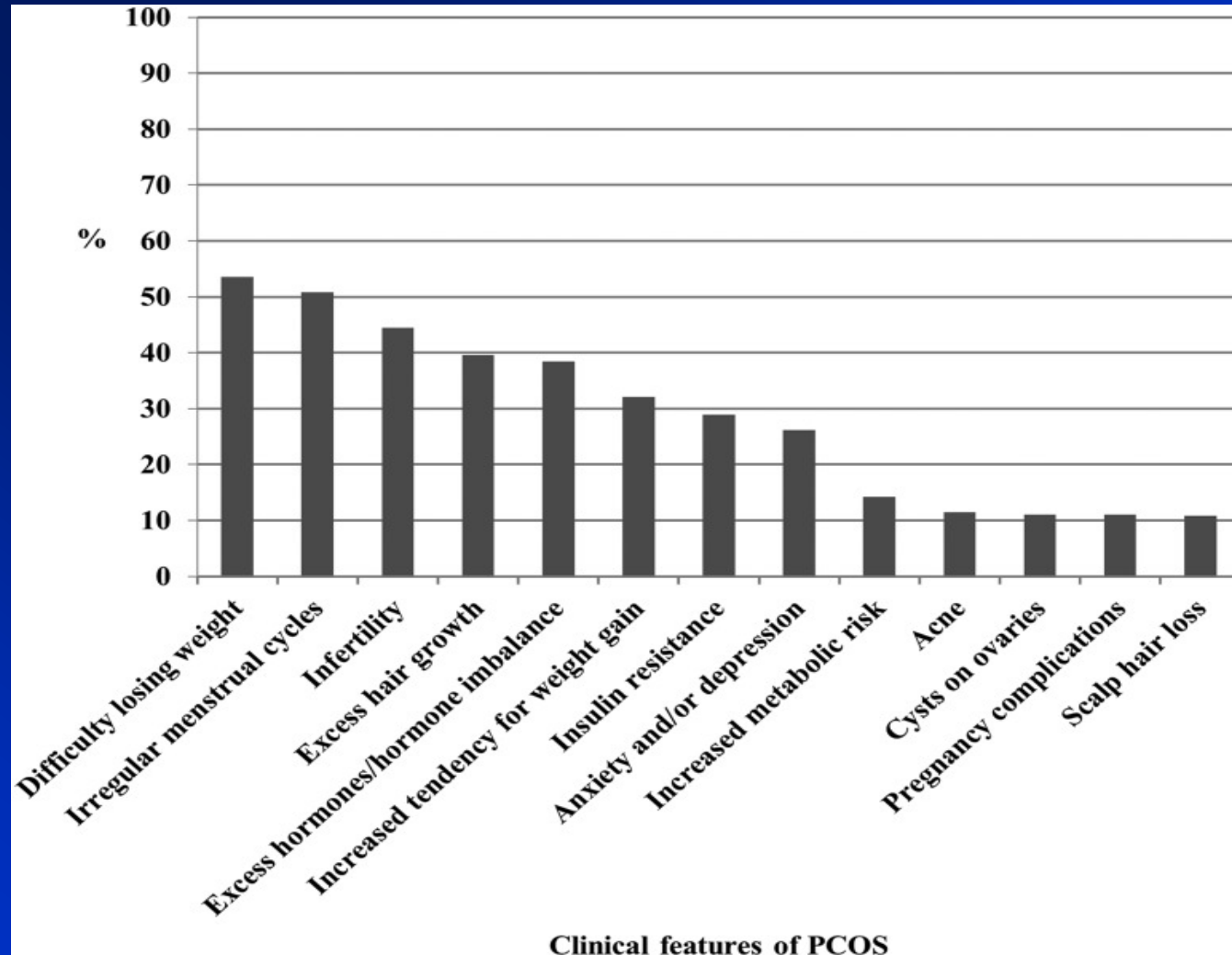
Polycystic Ovarian Syndrome (PCOS)

- Clinical heterogeneity
- Adolescent onset
- Most common feature symptoms are:
 - Mild hyperandrogenism
 - Anovulation

Epidemiology of PCOS

- Affects 6 to 10% of women in childbearing age
- Most common cause of female infertility
- May be most common endocrinopathy in young women

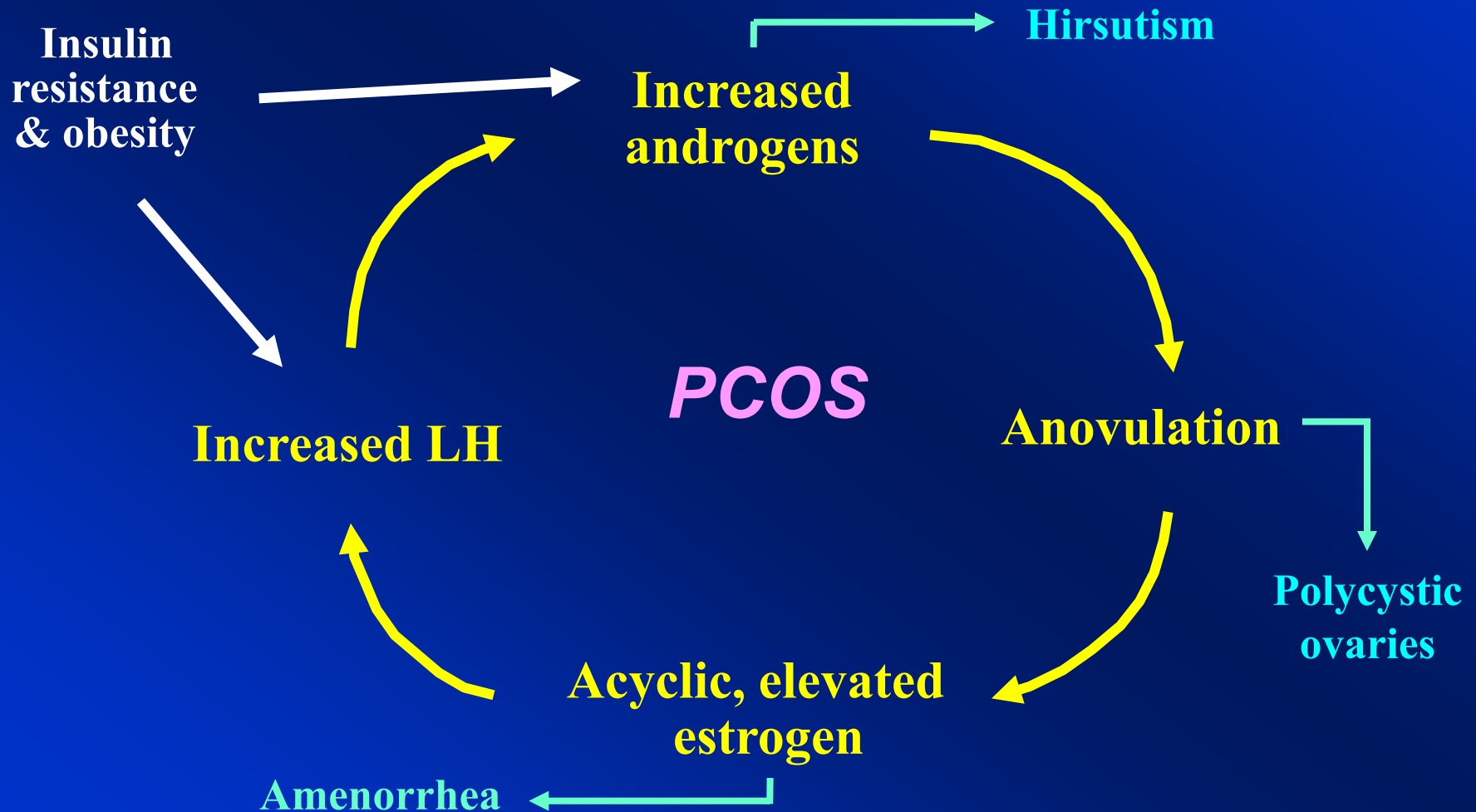
Key Patient Concerns

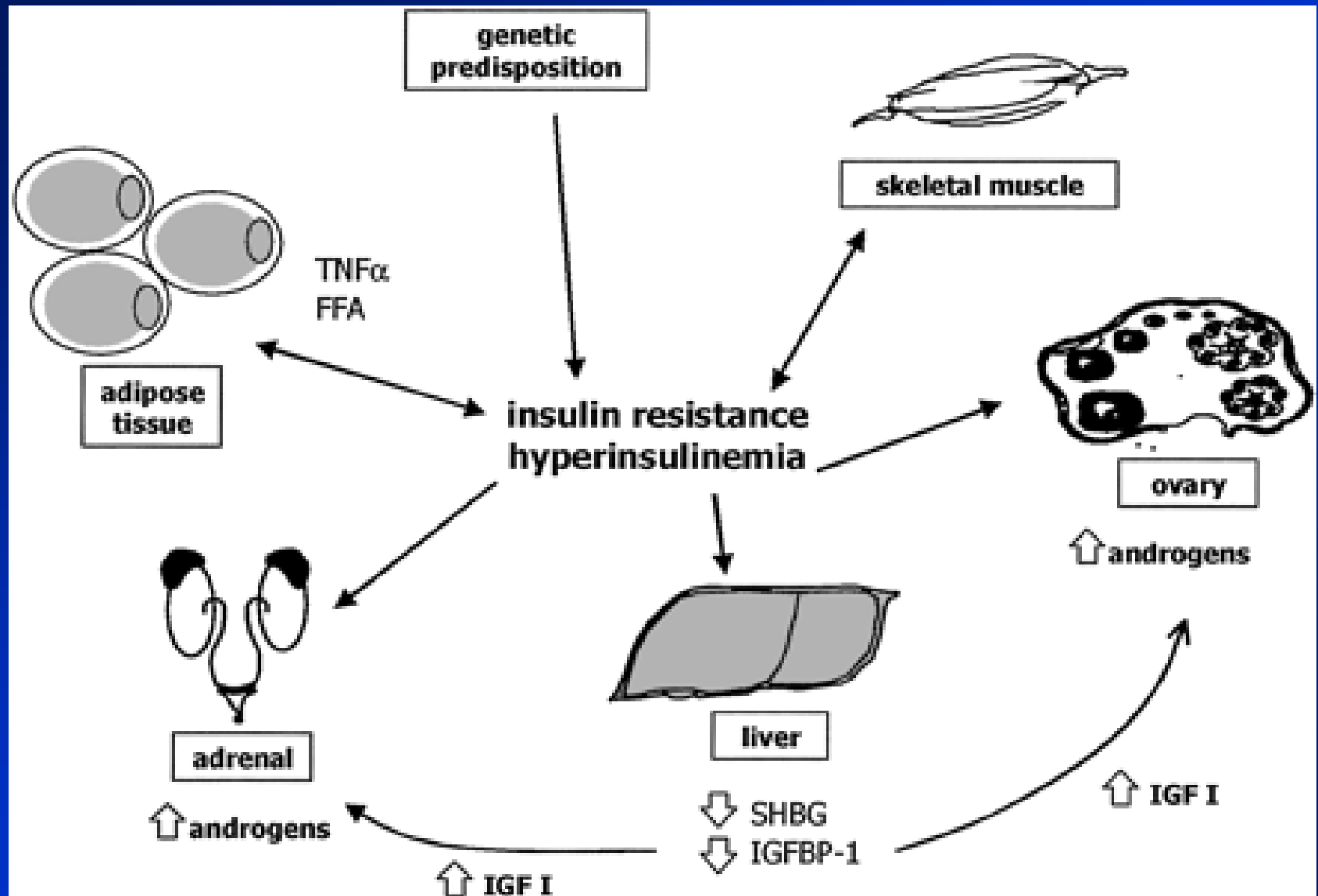


Heritability Pattern

- **Family members of PCOS women exhibit increased risk of hyperandrogenism**
- **Affected women are more likely to have daughters with PCOS**
- **Concordance in affected monozygotic twins**
 - McDonough PG et al, 1972
- **PCOS-susceptibility genes: THADA, FSHR, DENND1A, LH receptor allelic variants**
- **Most PCOS patients do not have these variants**

Pathogenesis





Diagnosis of Insulin Resistance Syndrome

One of the following:

- CVD, acanthosis nigricans, gestational DM *or* **PCOS**
- Family Hx of NIDDM or CVD
- Age > 40
- BMI > 40 kg/m²

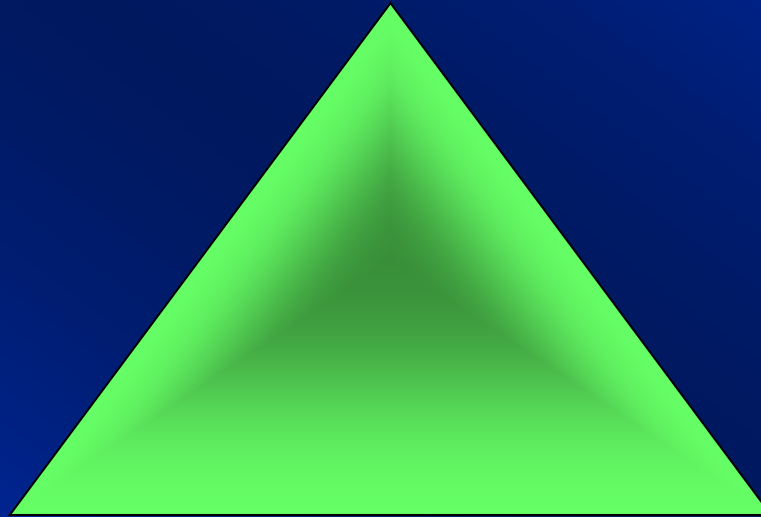
and at least two of:

- Abdominal obesity (waist > 35 inches)
- Hypertension (systolic > 130 or diastolic > 85)
- Hypertriglyceridemia (> 150 mg/dl)
- Low HDL (< 50 mg/dl)
- FG 110-125 mg/dl or 2 hr post- challenge 140-200 mg/dl

Rotterdam Criteria

Need two of three

Chronic Anovulation



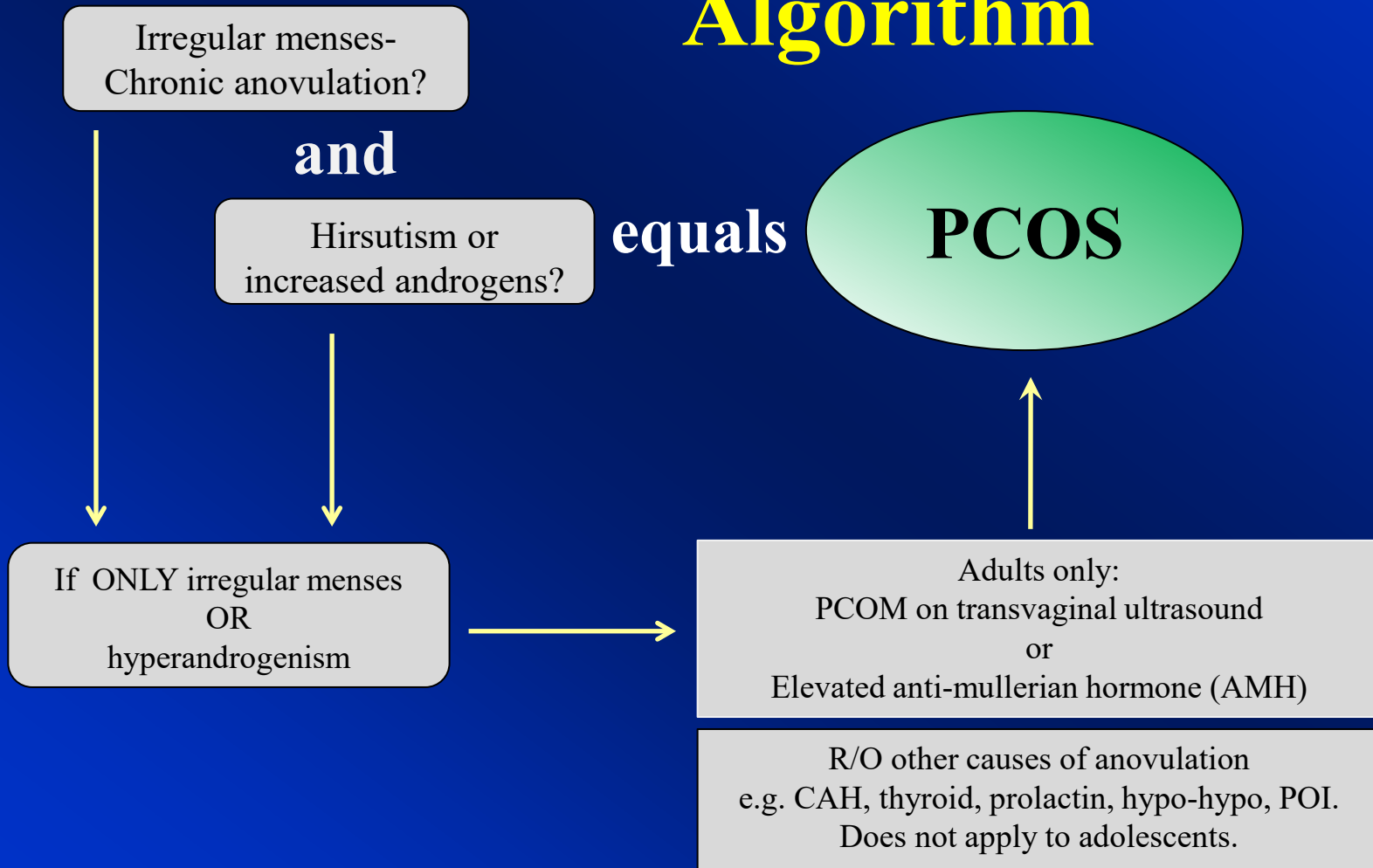
**Hyper-
Androgenism***

**Polycystic
Ovaries
Morphology***

*Rule out other causes



PCOS Diagnostic Algorithm



Helpful Diagnostic Features of PCOS

- **Classic physical appearance**
- **Clear history of anovulation**
- **Evidence of hyperandrogenism**
- **Adolescent onset**
- **Positive progestin withdrawal menses**



Management of PCOS

Long Term Goals

1. Regulate menses
 - With or without ovulation
2. Correct hyperandrogenism
3. Improve insulin sensitivity
4. Screen for long-term sequelae
 - DM
 - Hyperlipidemia
 - Hypertension

“Half of all people with type II diabetes are undiagnosed.”

“On average, type II diabetes has been present for about 10 years before diagnosis.”

Steven Gabbe, MD

PCOS and Diabetes

Both lean and obese PCOS women:

- **Have increased incidence of NIDDM**

Chang RJ et al, J Clin Endocrinol Metab 57, 1983

- **Have earlier onset of NIDDM (3rd and 4th decade)**

Dunaif A et al, J Clin Endocrinol Metab 65, 1987

PCOS and Cardiovascular Risk

Independent of weight hyperandrogenic women have:

- **higher levels of triglycerides and VLDL-C**
- **lower HDL-C and apo A-I lipoproteins**

Wild RA, Am J Obstet Gynecol 159, 1988

Barakat HA et al, Diabetes Care 16, 1999

Women with PCOS are at significant risk of CV disease and potentially of CV mortality

International Evidence-Based Guideline for PCOS, JCEM 108, 2023

Weight Loss and PCOS

Thirteen women lost at least 5% of weight over 7 months (mean $12\% \pm 5\%$)

- Increased insulin sensitivity
- Decreased free testosterone
- Increased SHBG
- 11/13 normal menses
- 5/13 pregnant

PCOS and Bariatric Surgery

In morbidly obese women with PCOS, bariatric surgery is associated with:

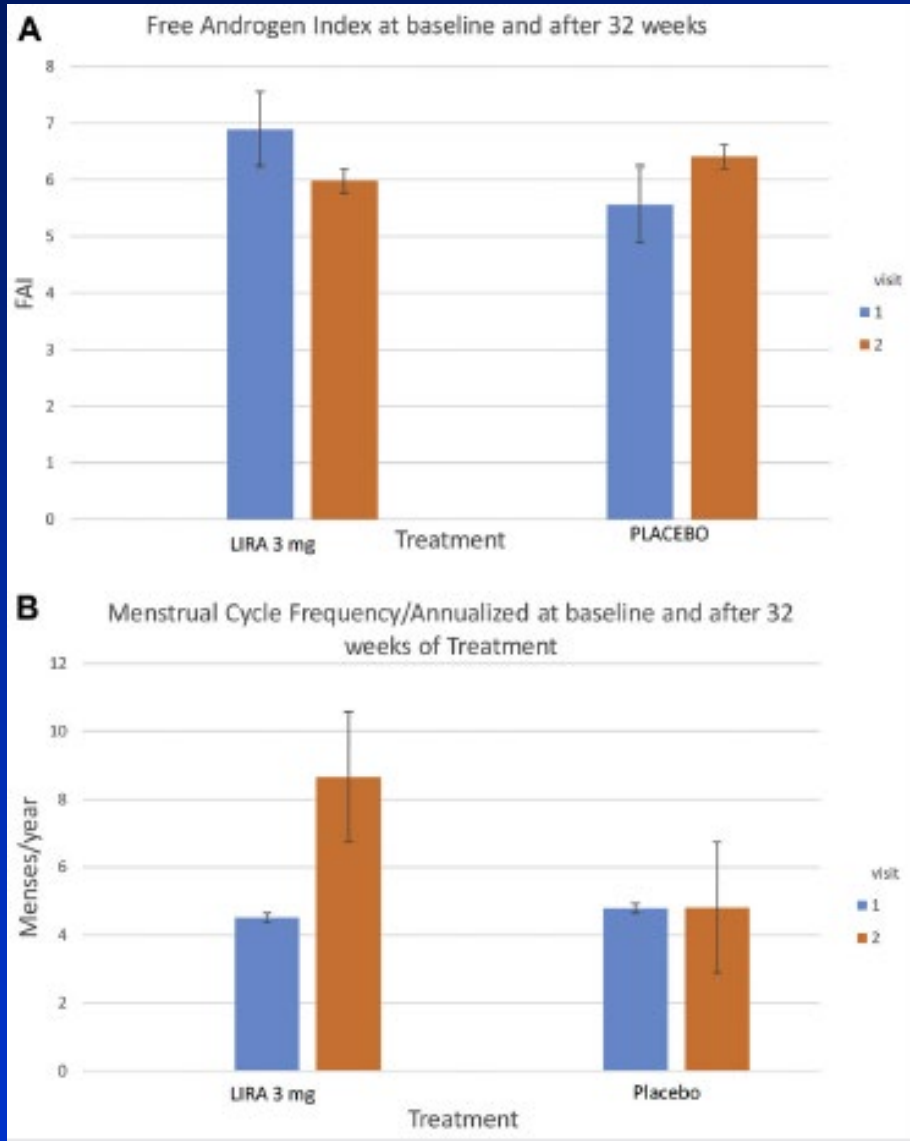
- **Decreased free T, total T, DHEAS, A, HOMA, Ferriman-Galloway score**
- **Increased SHBG**
 - **Escobar-Morreale HP, JCEM 2005**

Inositol

- **Two forms: d-chiro-inositol and myo-inositol**
- **Inositol acts as intracellular second messenger for insulin**
- **Reduce LH pulsatility and circulating androgens.**
- **Effective dosage unknown**

Szczesnowicz, AJ et al. Clin. Med. **2023**, 12, 5915
PCOS Guideline. JCEM, 108, 2023

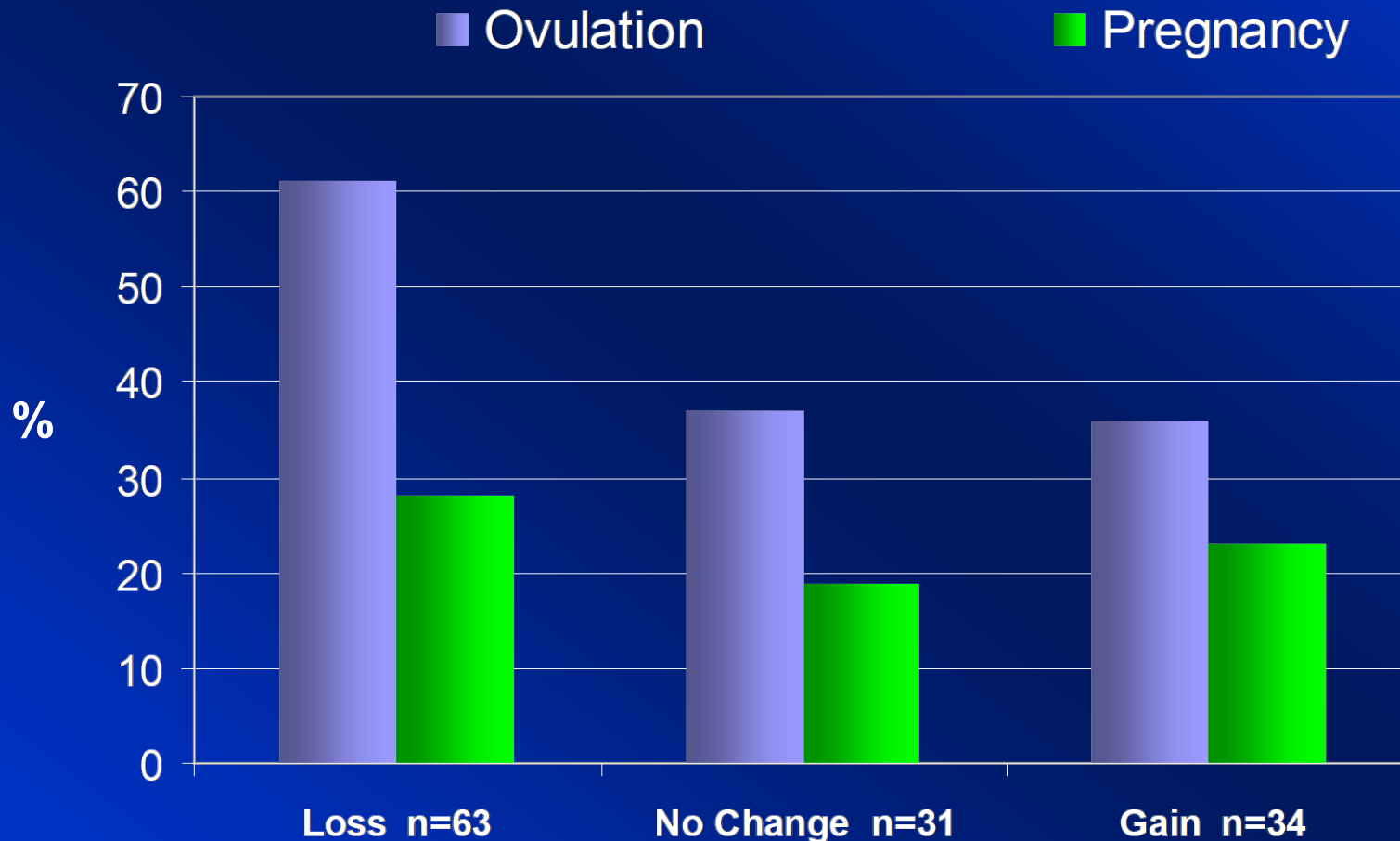
Liraglutide and PCOS



- Placebo controlled RCT
- Mean weight loss 5.7% with liraglutide (vs 1.3%, $p < 0.01$, for placebo)
- 29.5% lost $> 10\%$ starting weight (vs 8.5%, $p = 0.05$ for placebo)

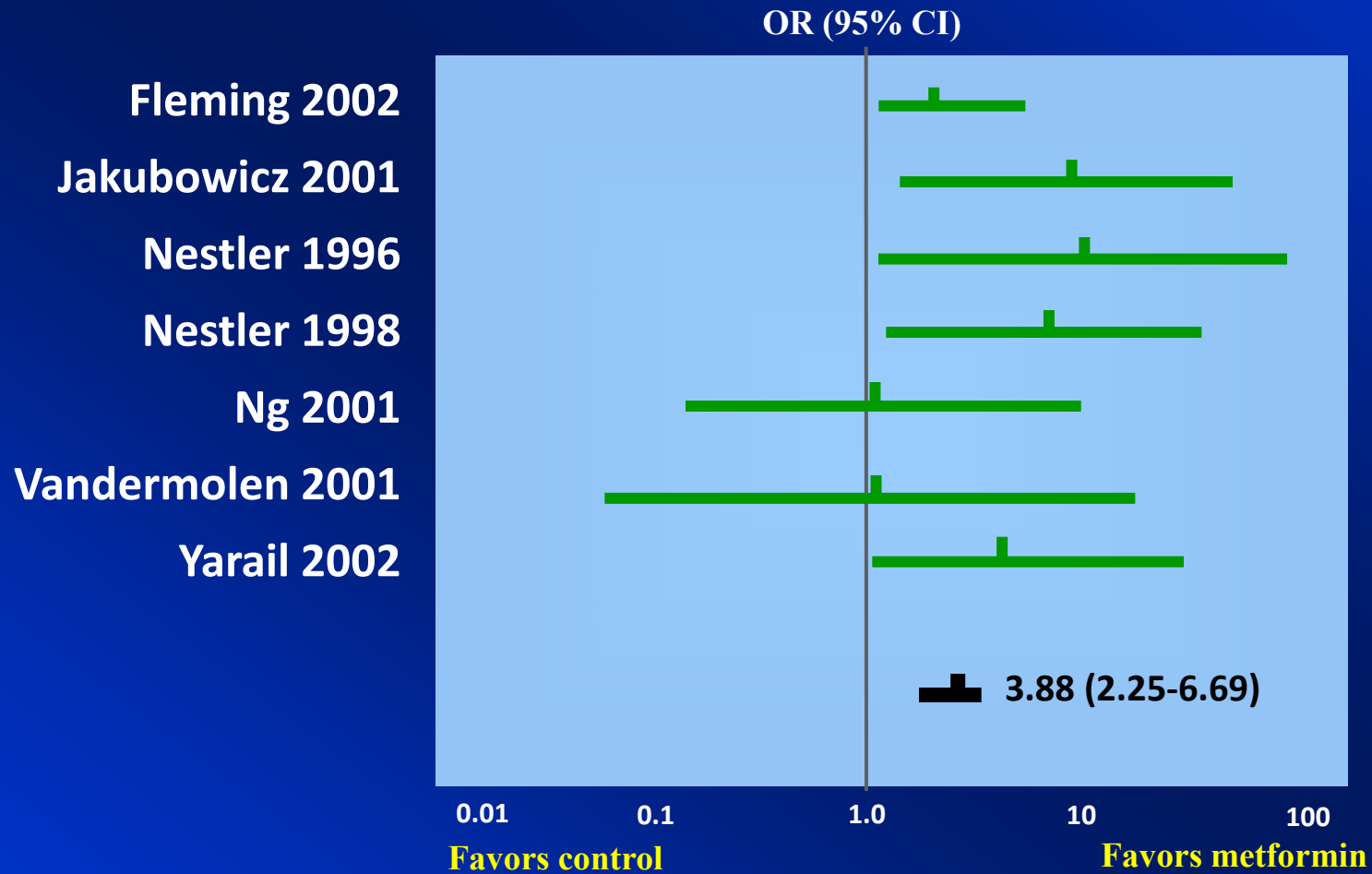
— Elkind-Hirsch KE et al. Fertil Steril 2022; 371

Effect of Weight Change on Ovulation and Pregnancy

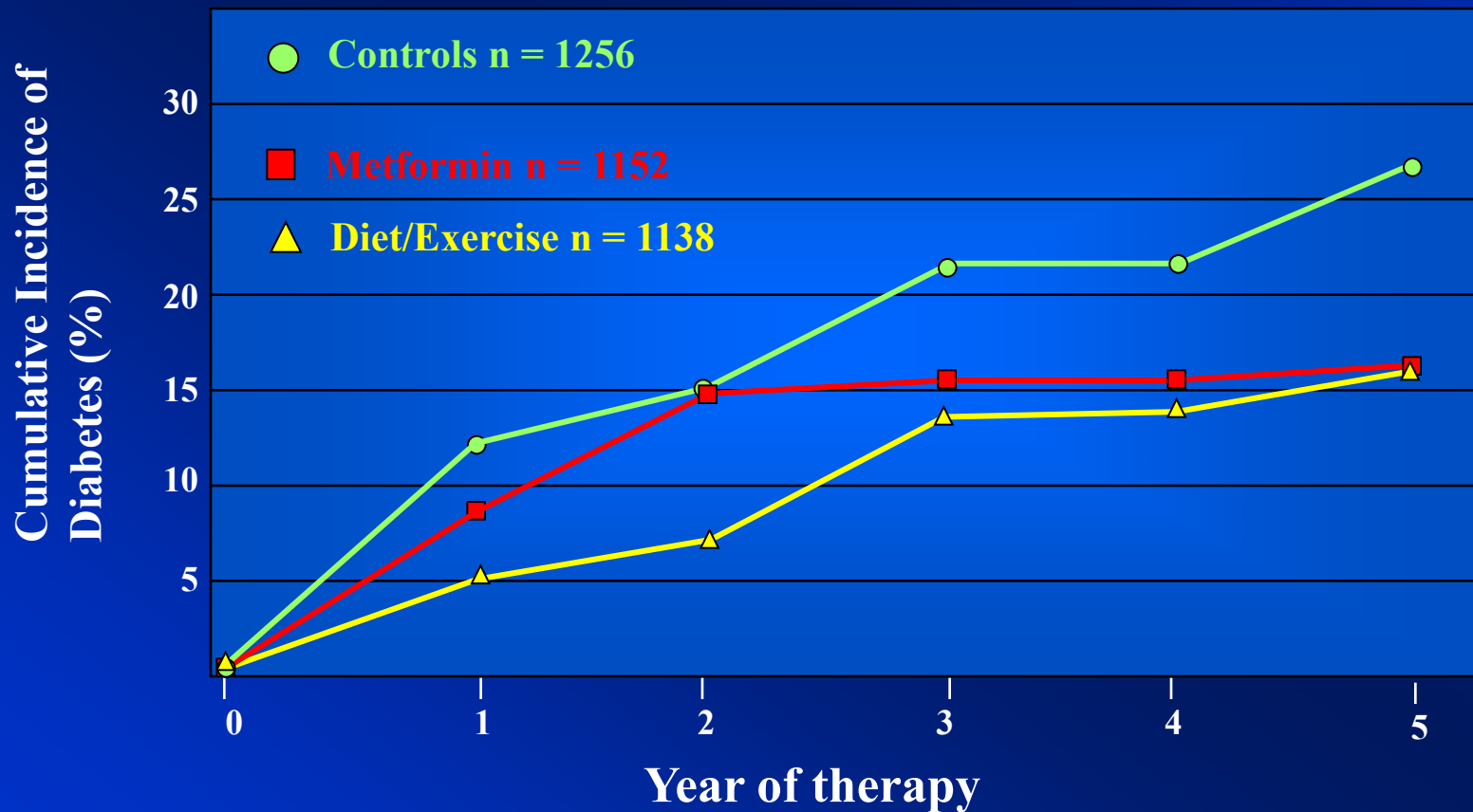


Ovulation rate Loss vs. Gain: $p=0.06$ Fisher Exact

Meta-Analysis: Metformin vs. Placebo Ovulation Rate



Prevention of Diabetes in High Risk Subjects



Diabetes Prevention Protocol NEJM, 2001

Metformin

Contraindications

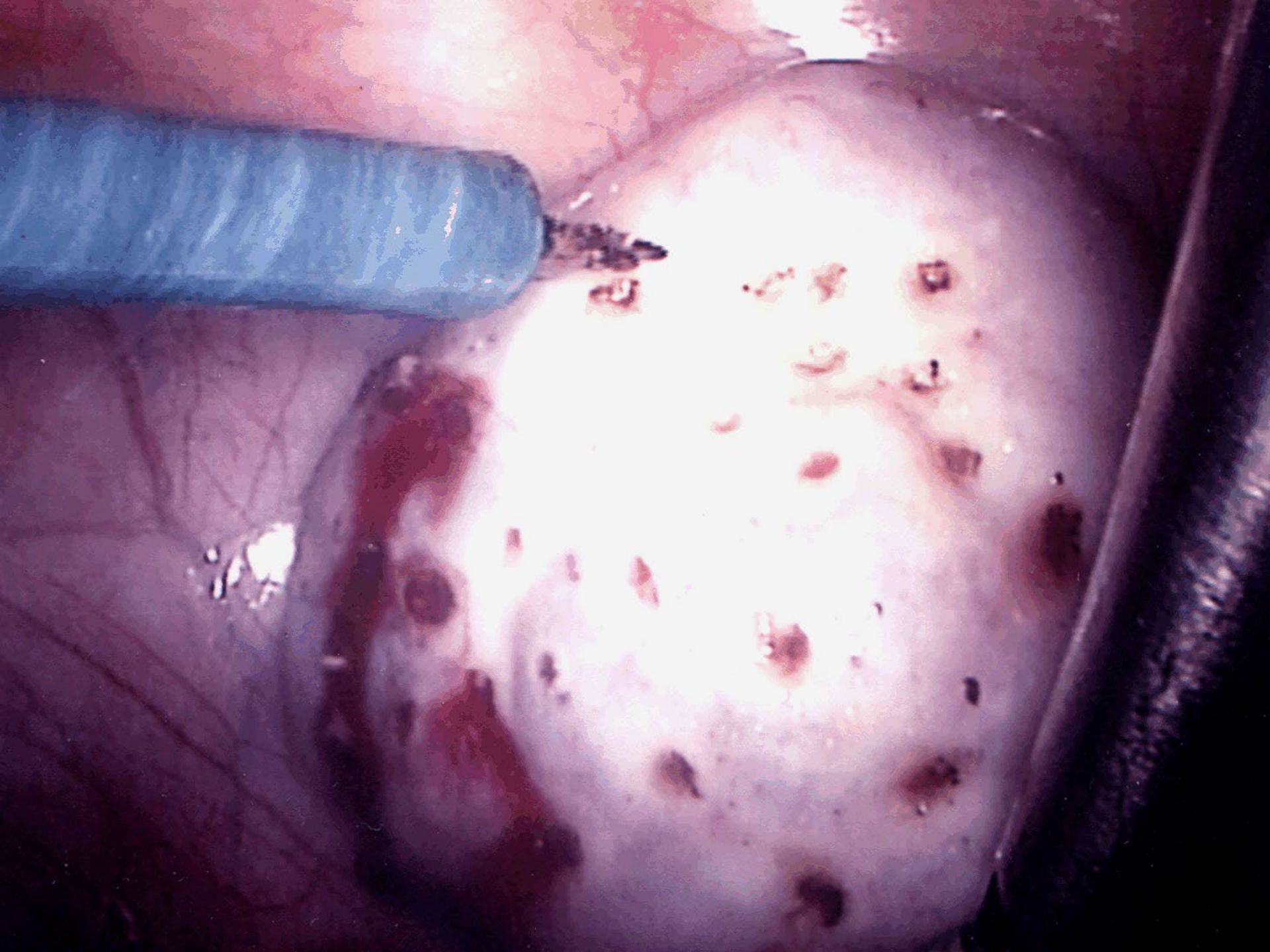
- **Hypersensitivity**
- **Renal disease**
- **Vitamin B12/folate deficiency**
- **Metabolic (lactic) acidosis**

Side effects: n&v, diarrhea

PCOS

Management of Infertility

- Complete infertility workup
- Insulin sensitization
 - Weight loss
 - Metformin
- Ovulation induction
 - Clomiphene citrate
 - Aromatase inhibitors
 - hCG trigger
 - Gonadotropins Tx



PCOS

Management in Pregnancy

- Continue metformin thru 1st trimester
- High risk for gestational diabetes and pre-eclampsia
 - 50 gm glucose screen at first prenatal visit and repeat at 24-28 wks
 - Consider 100 gm OGTT if morbidly obese
 - 75 gm glucose screen 6 wks post partum
- Regulate menses post-partum

Recurrent Pregnancy Loss and IR

74 women with recurrent pregnancy loss; 74 fertile controls

	RPL	Controls	P value
Fasting glucose (G) (mg/dl)	89.6	89.4	0.9
Fasting insulin (I) (μ U/ml)	13.8	10.2	.01
Fasting G/I ratio < 4.5 (%)	10.4	12.3	.13
HOMA-IR (%)	21.6	8.1	.04
Insulin Resistant (%)	27.0	7.0	.01

*“...the only way to keep your health is to
eat what you don’t want,
drink what you don’t like,
and do what you’d druther not.”*

Mark Twain