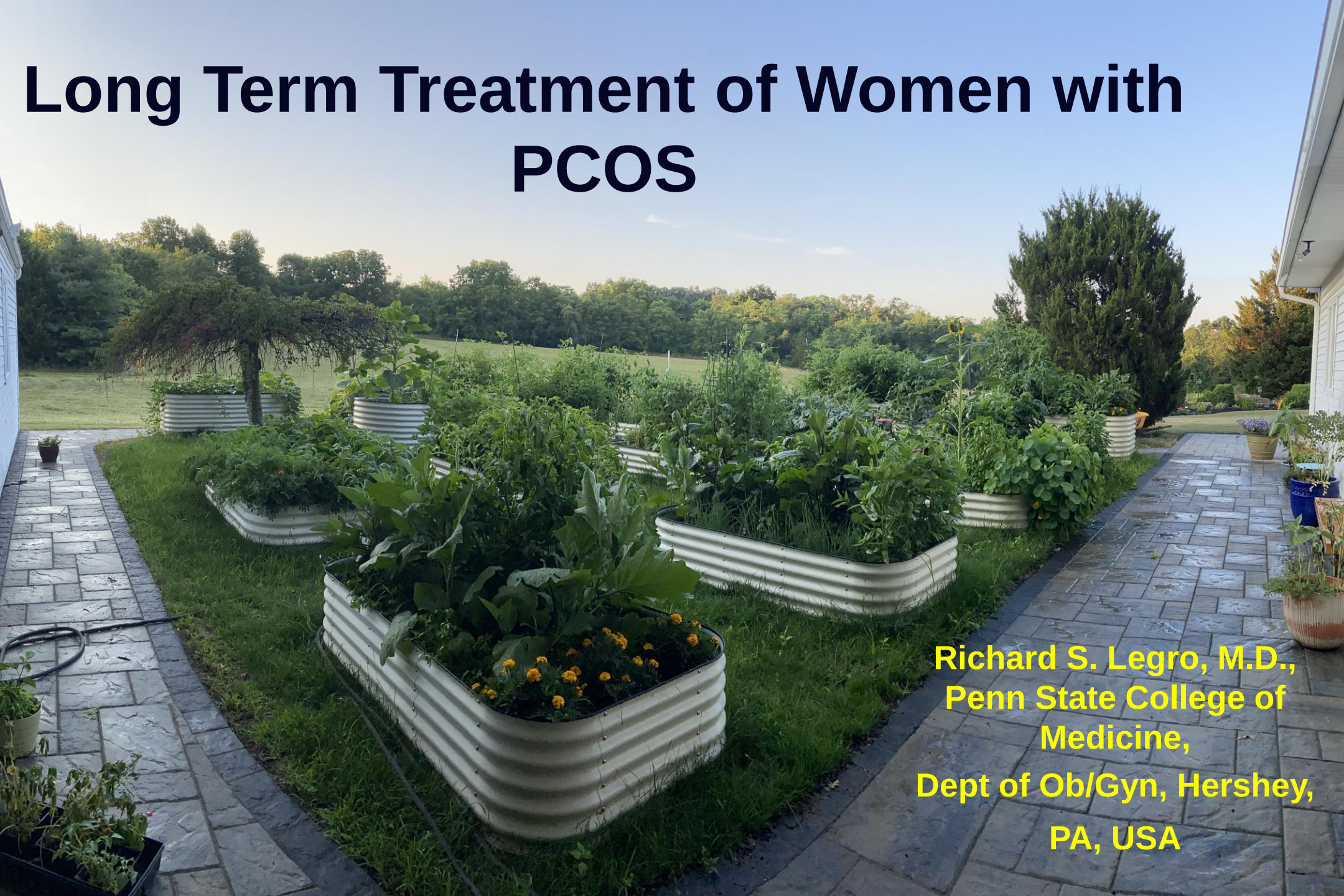
Long Term Treatment of Women with PCOS



Richard S. Legro, M.D.,
Penn State College of Medicine,
Dept of Ob/Gyn, Hershey,
PA, USA

Conflicts

- **Consultant:** Novo Nordisk, NIH
- **Funding**: Guerbet, NIH, PA DOH

Off Label Uses

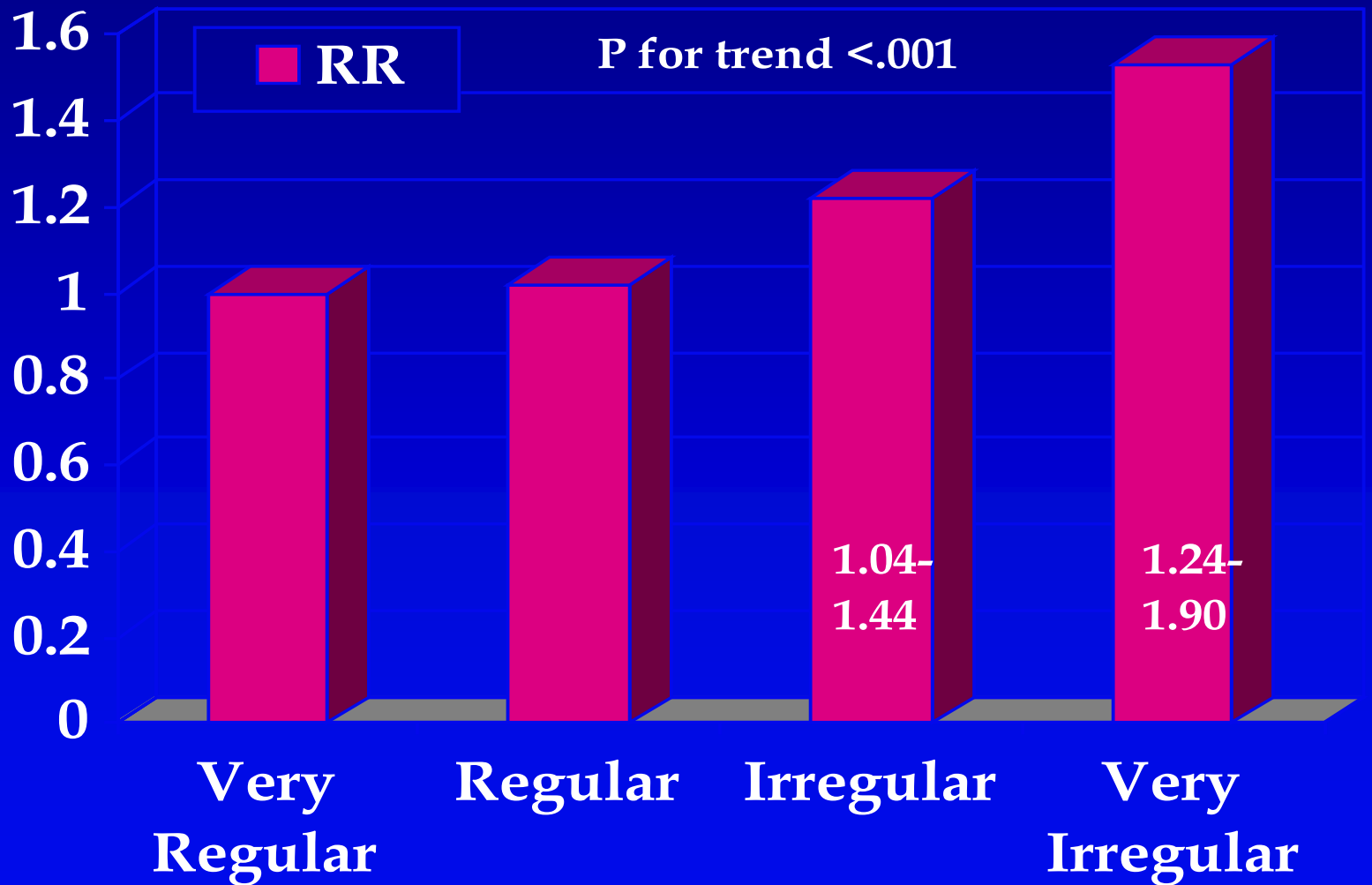
- Metformin, Thiazolidinediones, Other Anti-Diabetic and Anti-Obesity. drugs, and Aromatase Inhibitors are not FDA approved to treat infertility and / or PCOS

Learning Objectives

- Review Evidence for CVD Events in Women with PCOS
- Assess Risk/Benefit Ratios of common metabolic and reproductive treatments
- Identify future treatment options

What about CVD Mortality and Events in Women with PCOS?

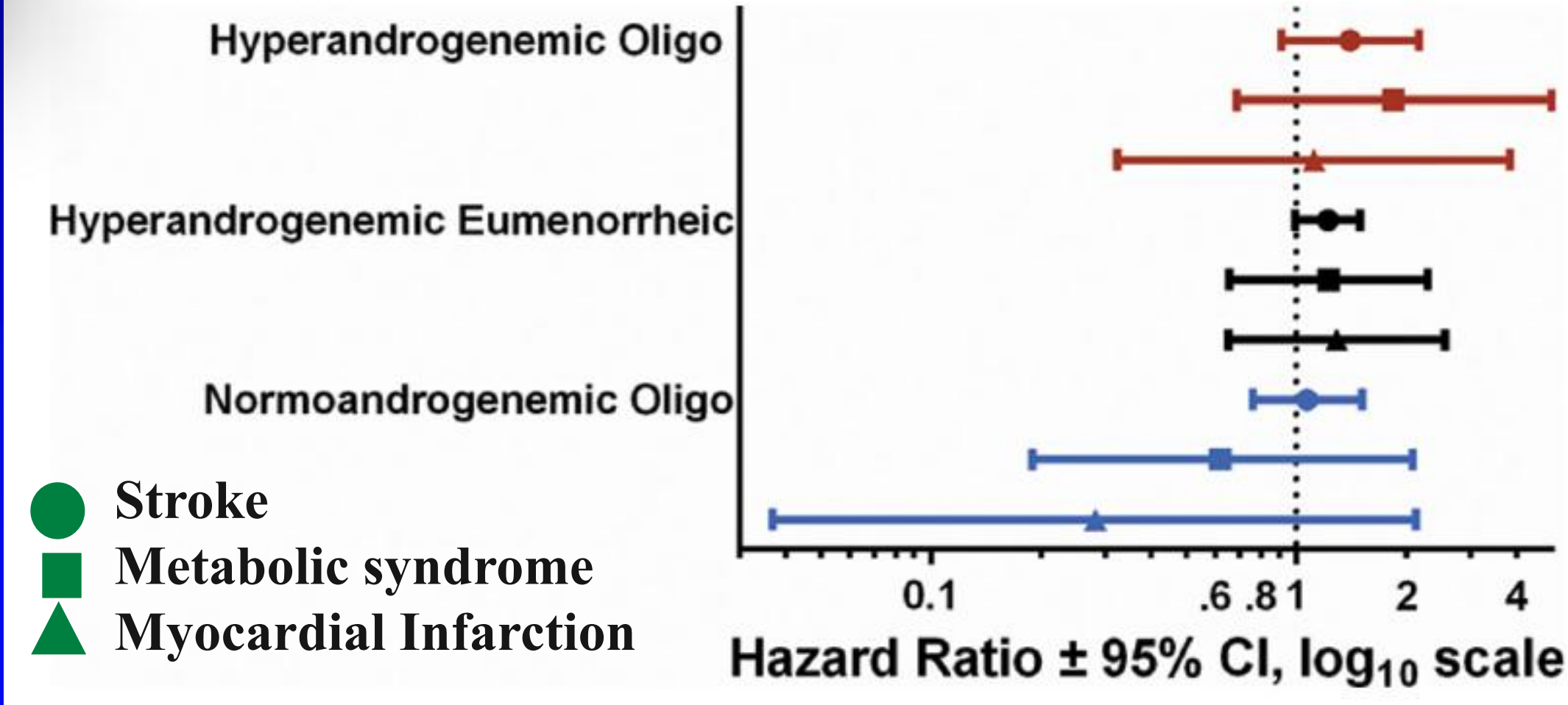
Relative Risk of Total Coronary Heart Disease by Menstrual Cycle



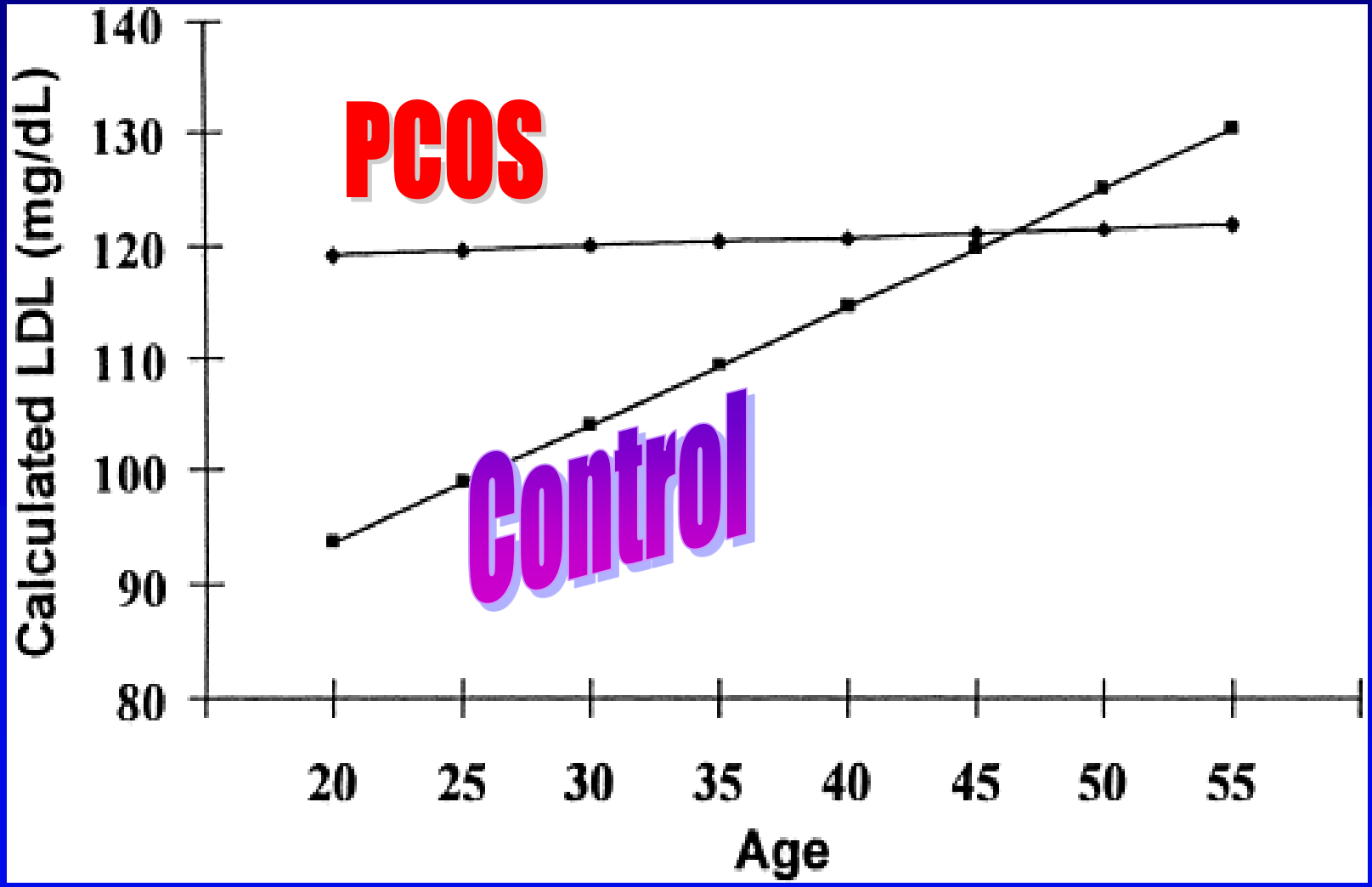
Solomon CG et al, JCEM, 2002

Lack of Increased CVD Hazard Ratio According to PCOS Phenotypes (compared to normal controls) in SWAN Cohort

Polotsky et al, JCEM, 2014



Effect of Age on LDL-C: Worse in Controls

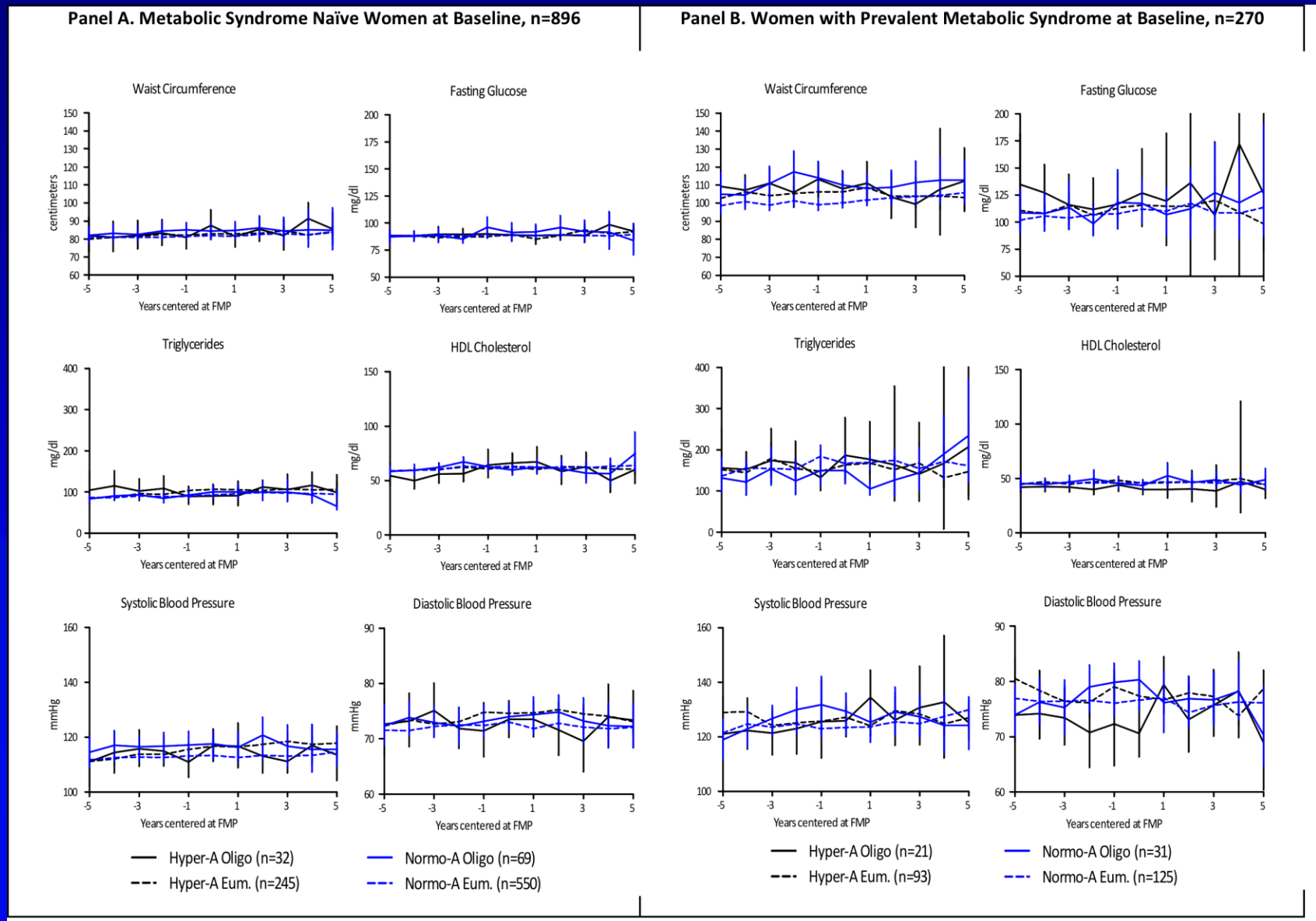


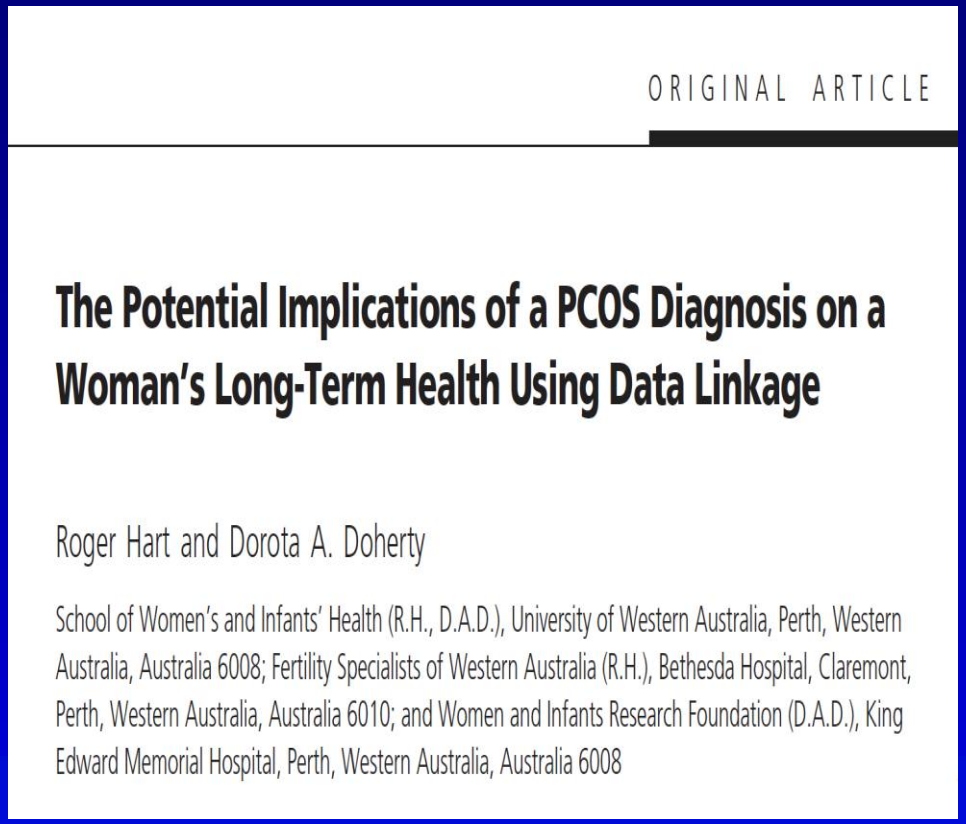
Talbott EO et al, J Clin Epidemiol, 1998

No Change in CVD Risk Factors over 10 years in Women with and without PCOS in SWAN Cohort

N = 1166 women

Polotsky et al, JCEM, 2014





ORIGINAL ARTICLE

The Potential Implications of a PCOS Diagnosis on a Woman's Long-Term Health Using Data Linkage

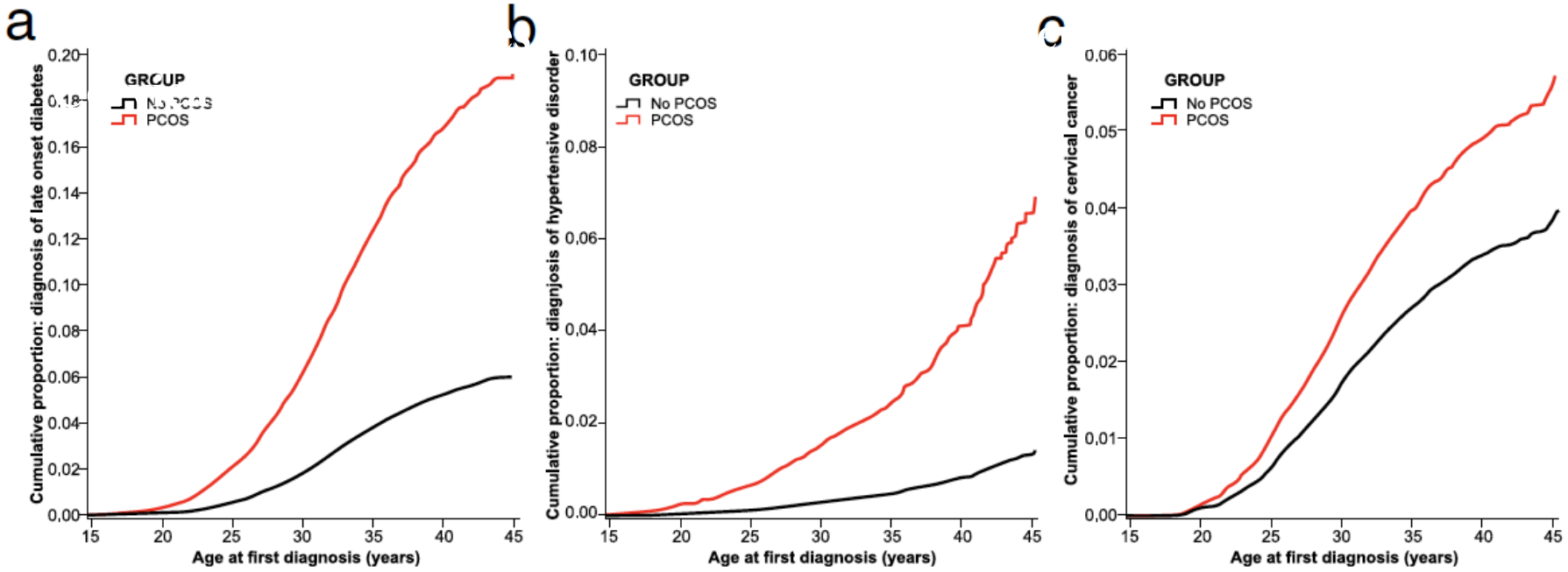
Roger Hart and Dorota A. Doherty

School of Women's and Infants' Health (R.H., D.A.D.), University of Western Australia, Perth, Western Australia, Australia 6008; Fertility Specialists of Western Australia (R.H.), Bethesda Hospital, Claremont, Perth, Western Australia, Australia 6010; and Women and Infants Research Foundation (D.A.D.), King Edward Memorial Hospital, Perth, Western Australia, Australia 6008

JCEM, 2015

- A population-based retrospective cohort study using data linkage from all hospitals within Western Australia.
- Participants: A total of 2566 women with PCOS hospitalized from 1997–2011 and 25 660 randomly selected age-matched women without a PCOS diagnosis derived from the electoral roll.

Cumulative Age of First Hospitalization by Diagnosis



Hart et al, JCEM 2015

Admissions in Women with PCOS

Disorder	PCOS	Controls
Ischemic Heart Disease	0.8%	0.2%
Cerebrovascular Disease	0.6%	0.2%
Arterial Disease	0.5%	0.2%
Venous Disease	10.4%	5.4%
Hypertensive Disorders	3.8%	0.7%

Hart et al, JCEM 2015

Other Morbidities Resulting in Hospitalizations also More Common in Women with PCOS

- Reproductive
  - Heavy menstrual periods, miscarriage, infertility, utilization of IVF
- Accidental/Self-inflicted
  - Land transport accidents, self-harm, drug related incidents
- Medical
  - Asthma, obesity, stress/anxiety, depression

Hart et al, JCEM 2015

PCOS Treatment Considerations

Reproductive

- Treat Hyperandrogenism
  - Hirsutism, Acne, Androgenic Alopecia
- Control Anovulatory Uterine Bleeding
- Prevent Endometrial Cancer

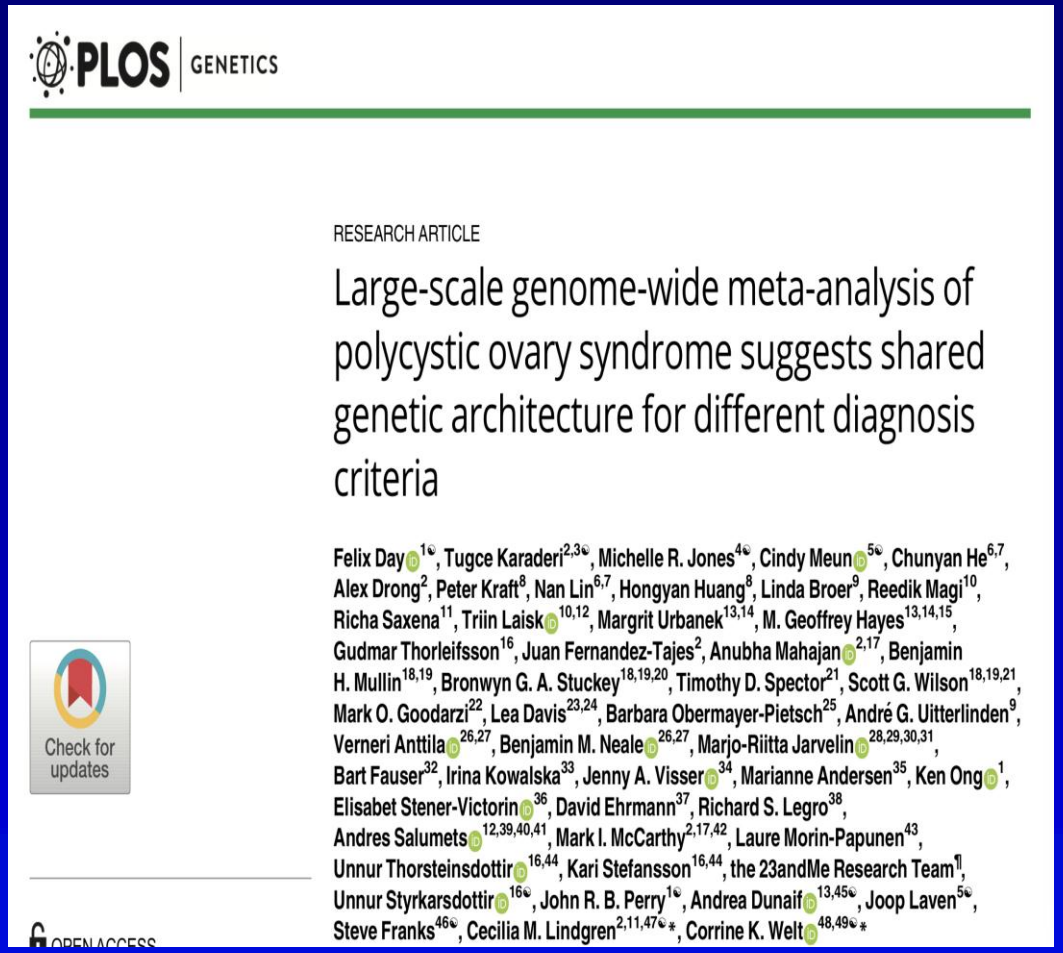
Metabolic

- Weight loss if obese
- Prevent Diabetes
- Correct Dyslipidemia
- Treat Hypertension
- Avoid treatments that exacerbate insulin resistance

Polycystic Ovary Syndrome: Chronic Anovulation with Androgen Excess

A Metabolic Disorder of Insulin Resistance

A Reproductive Disorder of Hypothalmic/Ovarian Dysfunction



PLOS GENETICS

RESEARCH ARTICLE

Large-scale genome-wide meta-analysis of polycystic ovary syndrome suggests shared genetic architecture for different diagnosis criteria

Felix Day[1☯], Tugce Karaderi[2,3☯], Michelle R. Jones[4☯], Cindy Meun[5☯], Chunyan He[6,7], Alex Drong[2], Peter Kraft[8], Nan Lin[6,7], Hongyan Huang[8], Linda Broer[9], Reedik Magi[10], Richa Saxena[11], Triin Laisk[10,12], Margrit Urbanek[13,14], M. Geoffrey Hayes[13,14,15], Gudmar Thorleifsson[16], Juan Fernandez-Tajes[2], Anubha Mahajan[2,17], Benjamin H. Mullin[18,19], Bronwyn G. A. Stuckey[18,19,20], Timothy D. Spector[21], Scott G. Wilson[18,19,21], Mark O. Goodarzi[22], Lea Davis[23,24], Barbara Obermayer-Pietsch[25], André G. Uitterlinden[9], Verneri Anttila[26,27], Benjamin M. Neale[26,27], Marjo-Riitta Jarvelin[28,29,30,31], Bart Fauser[32], Irina Kowalska[33], Jenny A. Visser[34], Marianne Andersen[35], Ken Ong[1], Elisabet Stener-Victorin[36], David Ehrmann[37], Richard S. Legro[38], Andres Salumets[12,39,40,41], Mark I. McCarthy[2,17,42], Laure Morin-Papunen[43], Unnur Thorsteinsdottir[16,44], Kari Stefansson[16,44], the 23andMe Research Team[¶], Unnur Styrkarsdottir[16☯], John R. B. Perry[1☯], Andrea Dunaif[13,45☯], Joop Laven[5☯], Steve Franks[46☯], Cecilia M. Lindgren[2,11,47☯*], Corrine K. Welt[48,49☯*]

Check for updates

OPEN ACCESS

2018

- Identified 3 novel loci and replicated 11 others
- PCOS by self report and by physician phenotyping identified the same loci
- Genetic correlations with obesity, fasting insulin, type 2 diabetes, lipid levels and coronary artery disease
- Identified a male phenotype: metabolic dysfunction and male pattern balding

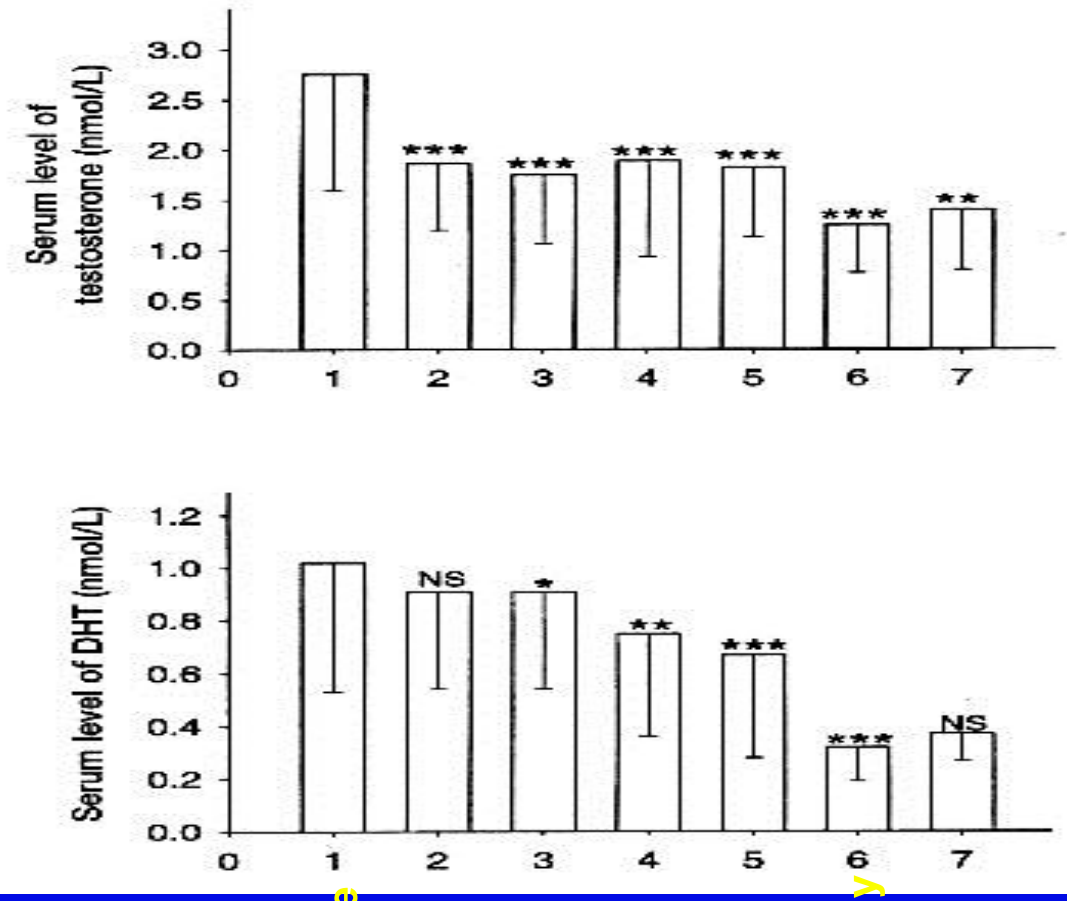
But….

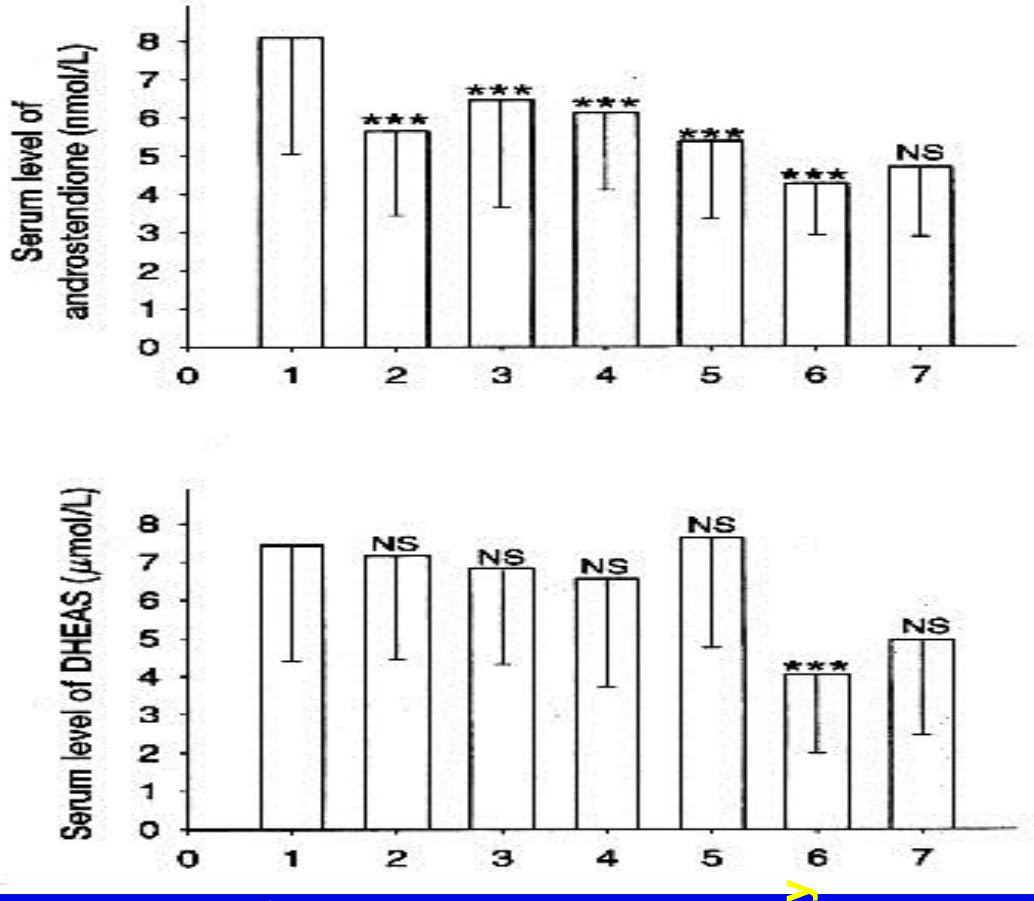
- No single variant explains PCOS, the mechanisms behind the development of PCOS based on a genetic locus are poorly understood
- Despite the extensive study of PCOS, the genetic loci identified to date only explain a small portion of the genetic underpinnings of PCOS (<10%).

Stein-Leventhal Syndrome
(Am J Obstet Gynecol 1935;24:181-91)

- Original description of disorder in 7 women
  - Amenorrhea (usually secondary) or occasional menometrorrhagia
  - Hirsutism
  - Sterility
  - Large, pale polycystic ovaries with thickened capsules
- "Adequate" wedge resection of ovaries resulted in regular menstrual periods and fertility in "all" cases

Long Term Improvement in Androgen Levels After Ovarian Diathermy in PCOS





Before 3 m 1 y 3 y 10 y 10-18 y >18 y

Before 3 m 1 y 3 y 10 y 10-18 y >18 y

Gjonnaess H. Fertil Steril 69: 697-701, 1998

Reproductive Treatments for PCOS

Anti-Androgens are highly teratogenic and lead to incomplete formation of the male external genitalia of exposure in early pregnancy

- Pro ser
  - Antago
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  - alpha e
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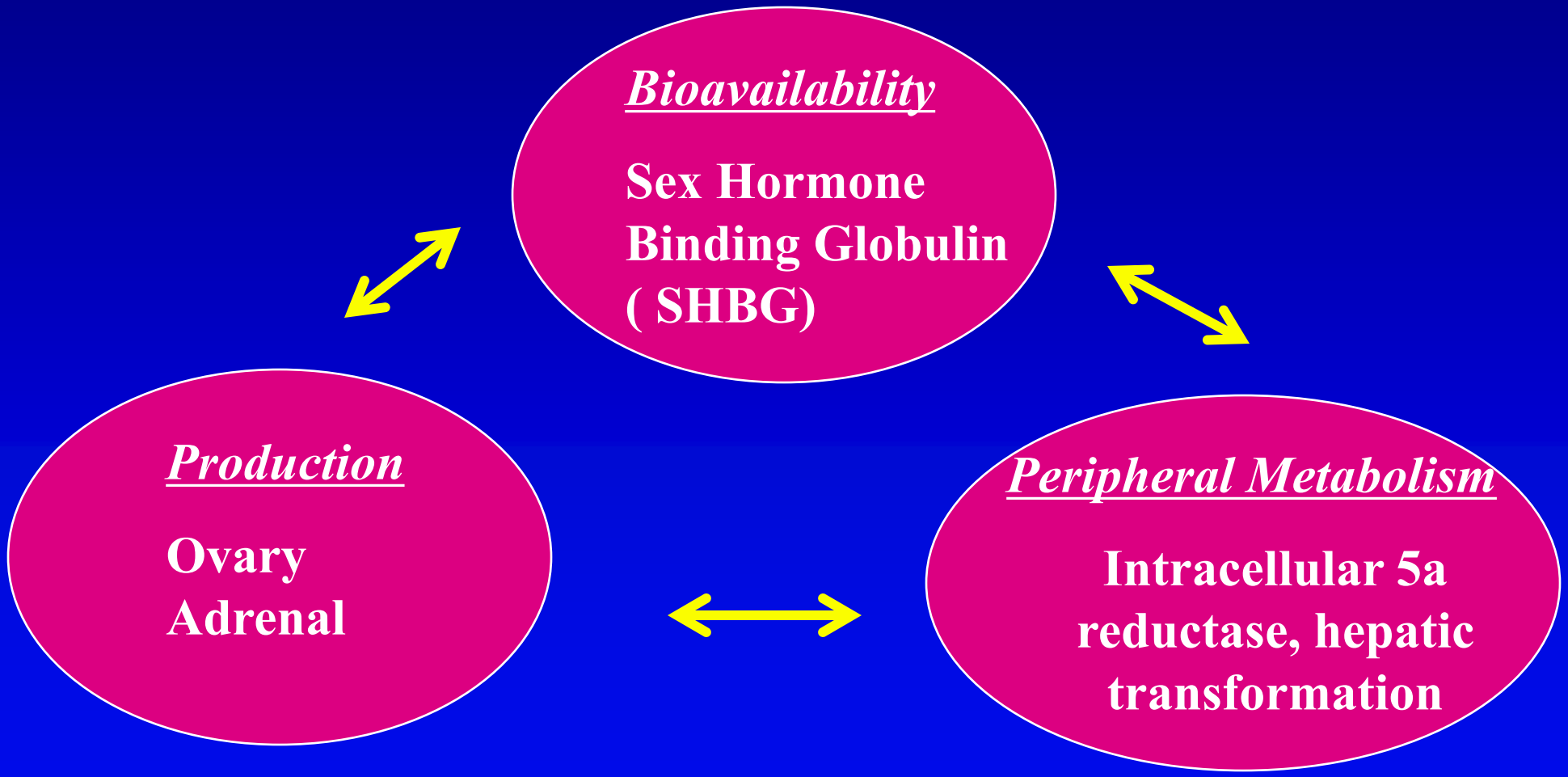
  - –Dutasteride

Triumvirate of Androgen Action



Oral Contraceptives (OCPs) in Treatment of Hirsutism/Acne

- Suppress pituitary and ovarian androgen production
- Increase sex hormone binding globulin
- Potential androgen receptor antagonism with synthetic progestin (i.e drospirenone)
- No US FDA indications for hirsutism but some formulations have indication for the treatment of acne

ABSOLUTE CONTRAINDICATIONS (relevant to PCOS)

Smoker over the age of 35 (≥ 15 cigarettes per day)

Hypertension (systolic ≥ 160mm Hg or diastolic ≥ 100mm Hg)

Current or past history of venous thromboembolism (VTE)

Migraine headache with focal neurological symptoms

Diabetes with retinopathy/nephropathy/neuropathy

RELATIVE CONTRAINDICATIONS (to PCOS)

Smoker over the age of 35 (< 15 cigarettes per day)

Adequately controlled hypertension

Hypertension (systolic 140–159mm Hg,diastolic 90–99mm Hg)

Migraine headache over the age of 35

Currently symptomatic gallbladder disease

Mild cirrhosis

History of combined OC-related cholestasis

Users of medications that may interfere with combined OC metabolism

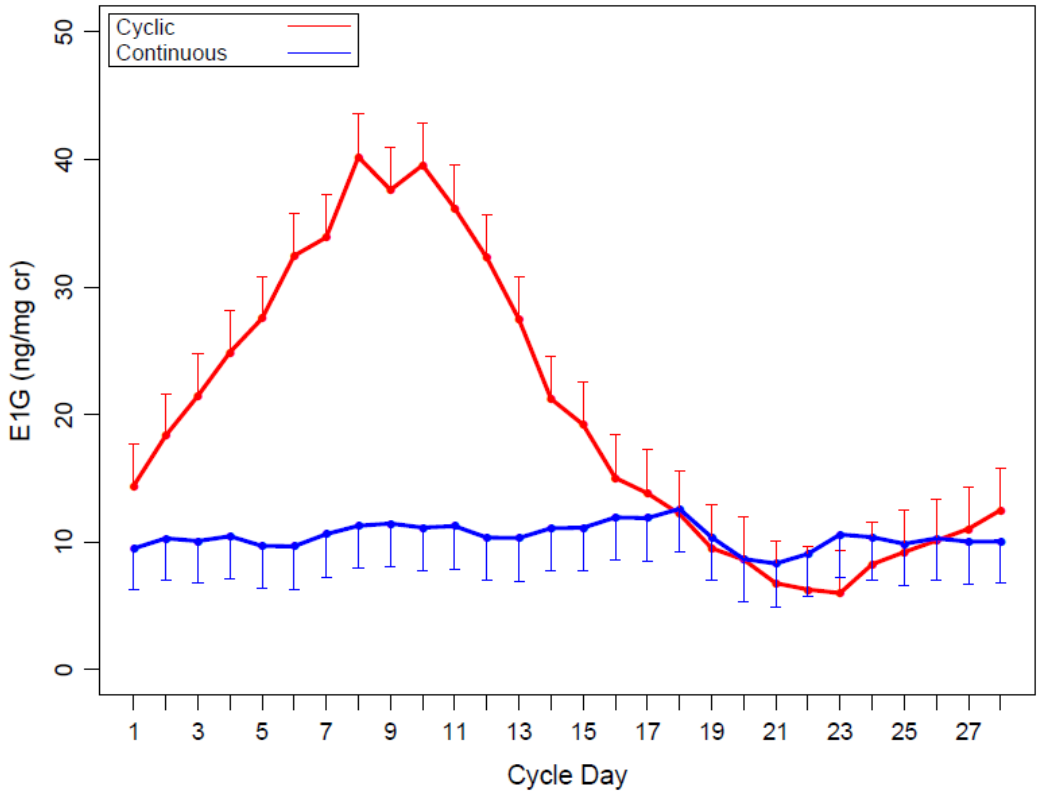
NOTE: Hyperlipidemias not included

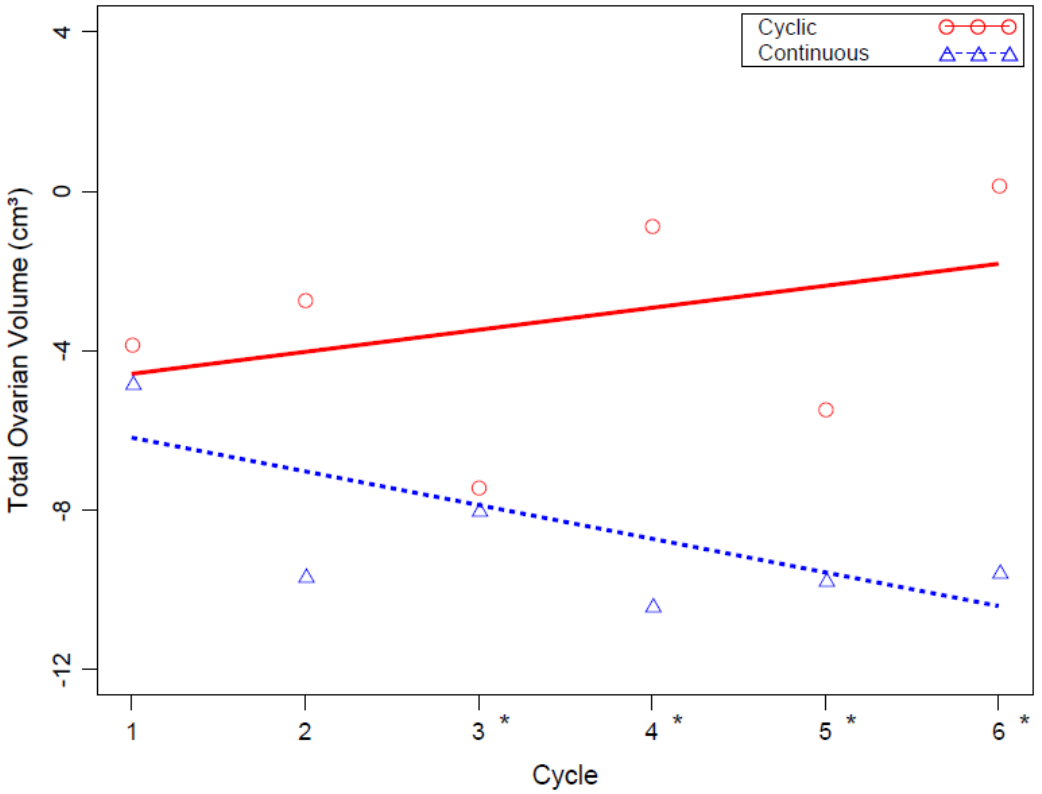
! Consider carefully before prescribing to PCOS

No OCP formulation has been found to be superior to another in treating hirsutism or acne

Should the Pill be given continuously (extended cycle) to treat Hirsutism?

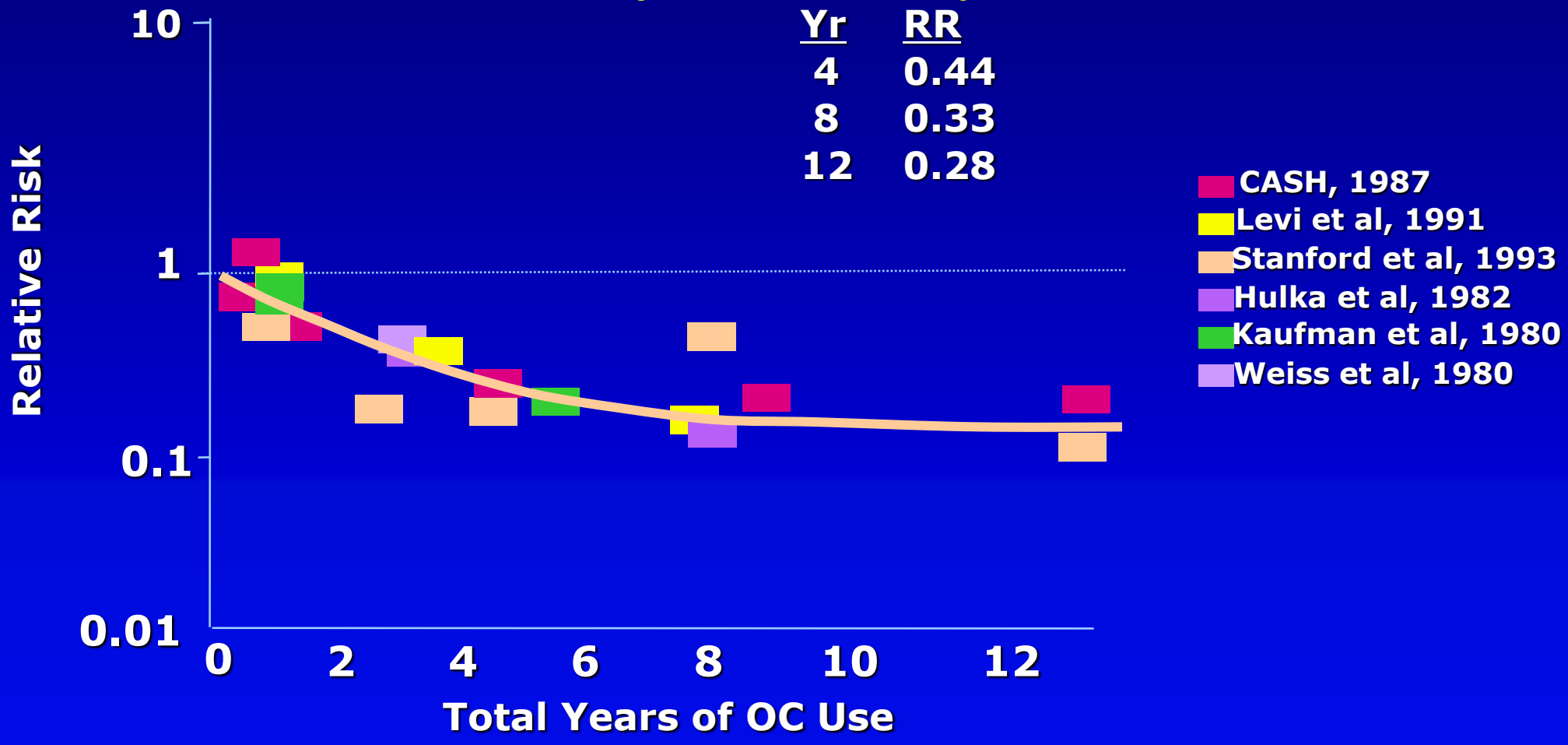
Extended Cycle OCP Better Ovarian Suppression and No Cycle Rebound in Ovarian Function.





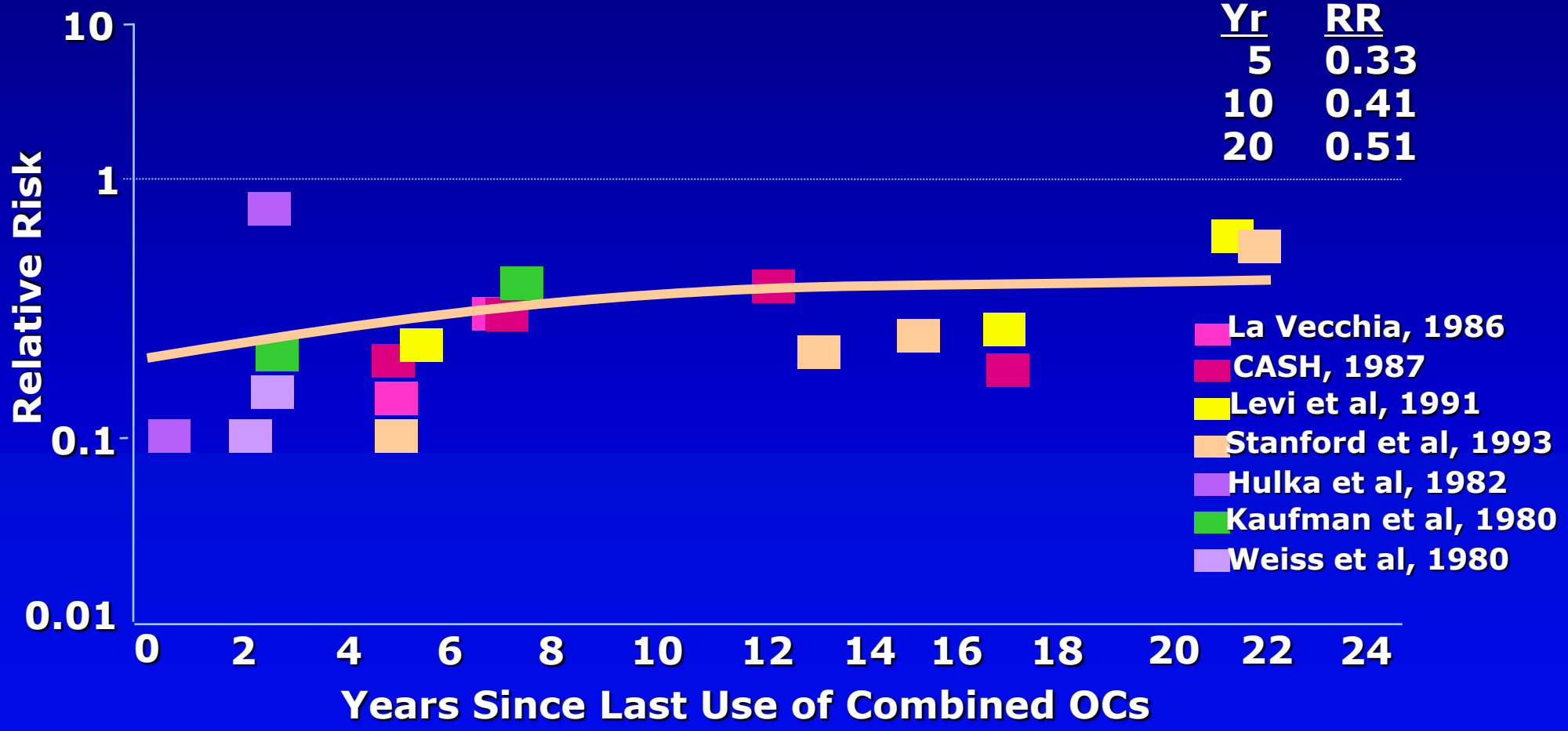
Legro et al, JCEM, 2008

OCs Reduce Risk of Endometrial Cancer *By Years of Use*



Adapted from Schlesselman JJ. *Hum Reprod*. 1997;12:1851-1863.

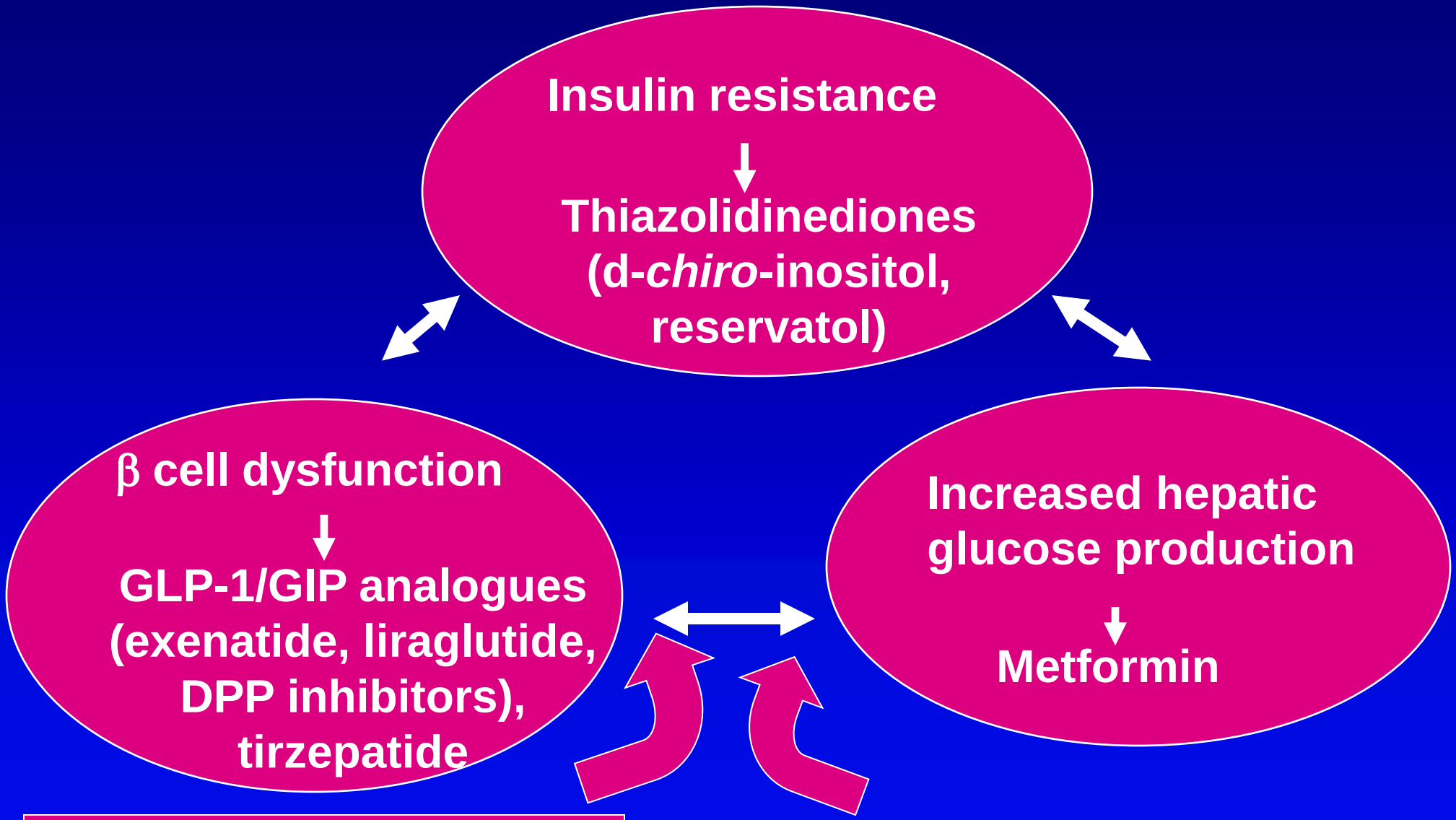
OCs Protect Against Endometrial Cancer After Discontinuation



Adapted from Schlesselman JJ. *Hum Reprod*. 1997;12:1851-1863.

What is the evidence that treating insulin resistance treats reproductive symptoms of PCOS?

Drug Treatments for Type 2 Diabetes

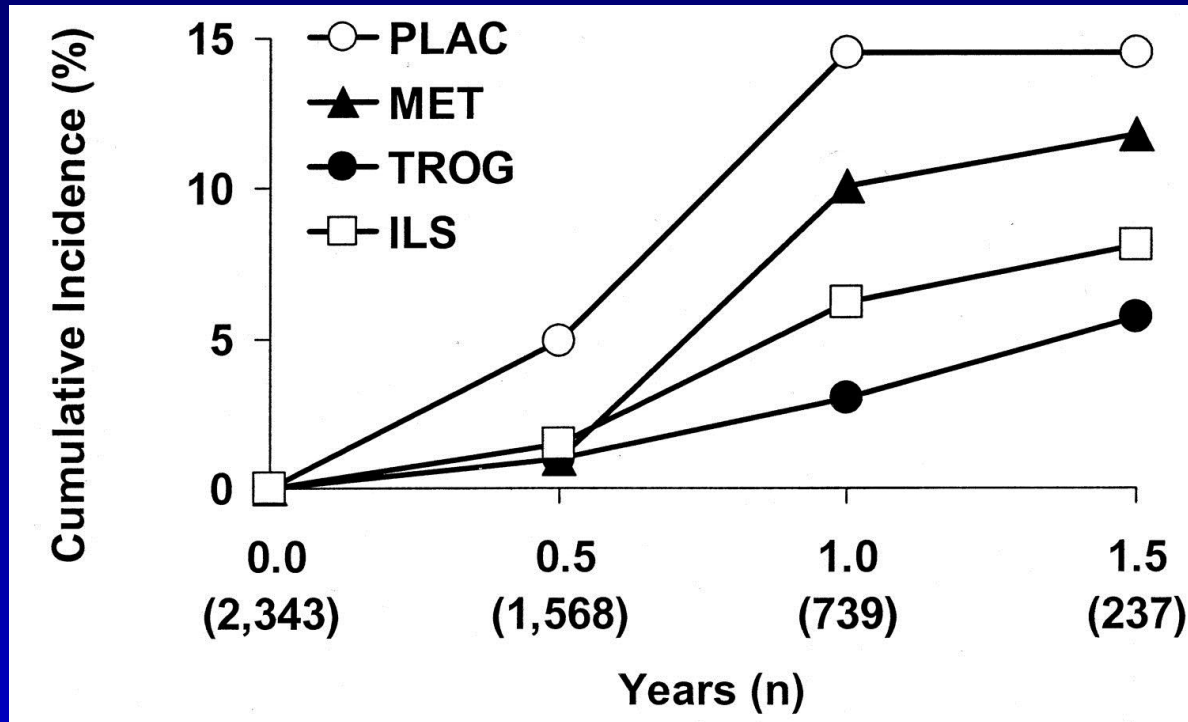


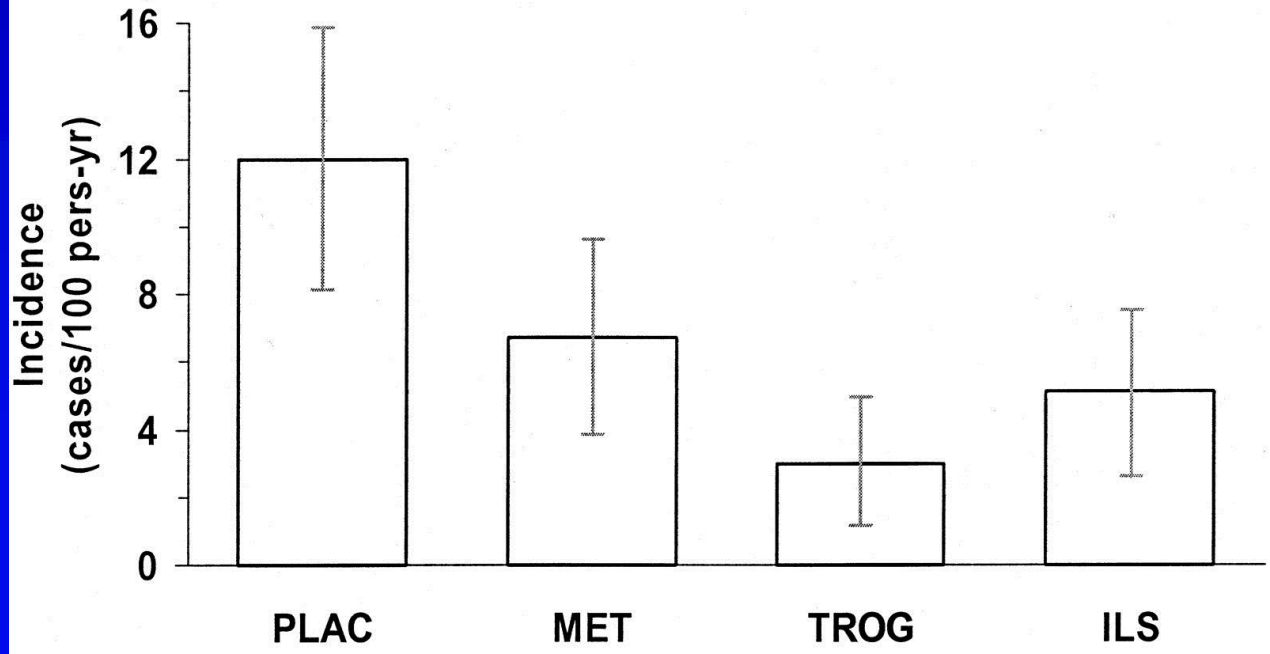
Metformin, TZDs, d-chiro Inositol, Exenatide and PCOS

No approved indication to treat PCOS, anovulation, or hirsutism in the U.S.

Thiazolidine-diones (TZD) Better than Intensive Lifestyle (ILS) and Metformin in Preventing Diabetes

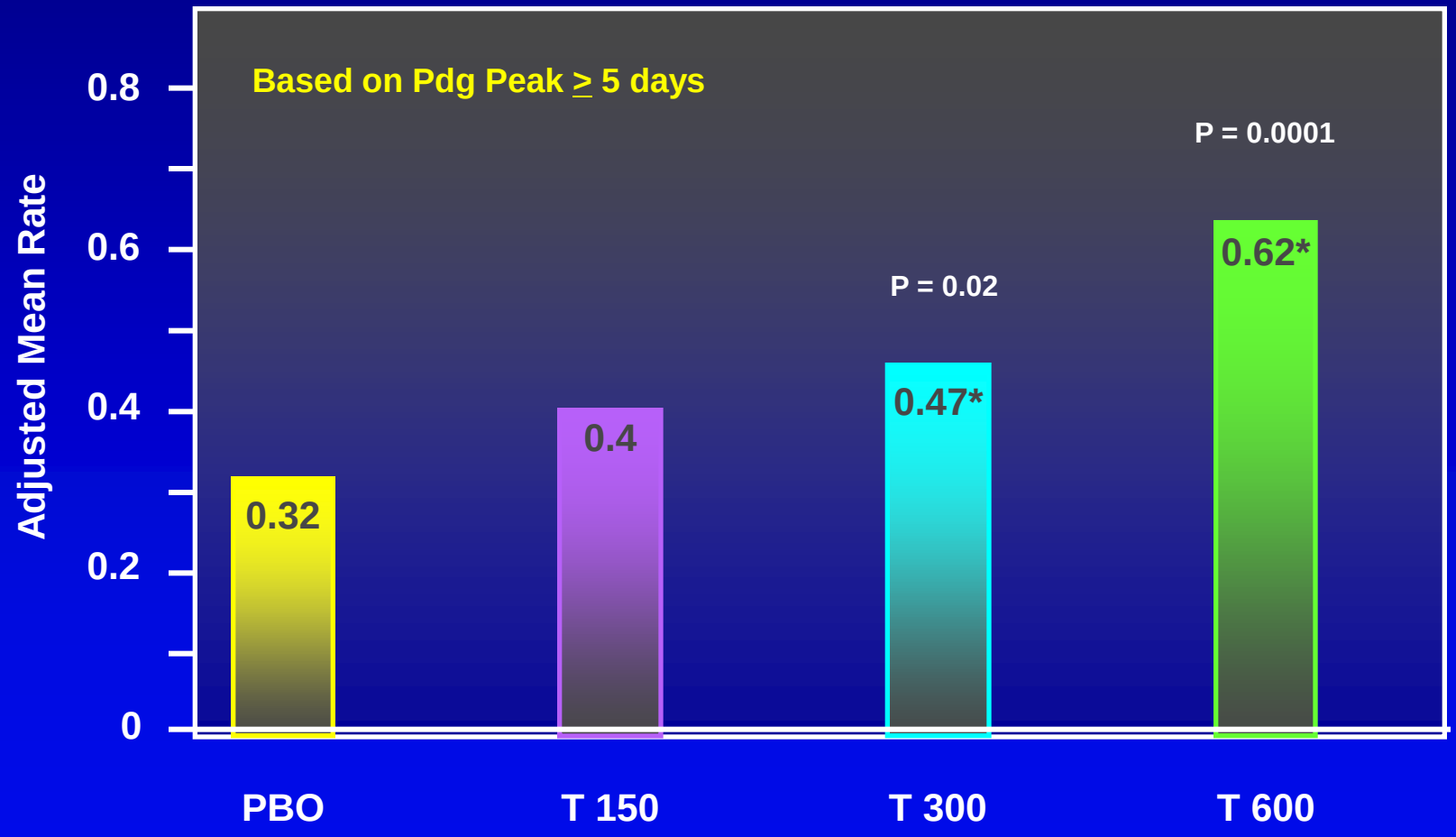
Knowler et al, Diabetes, 2005





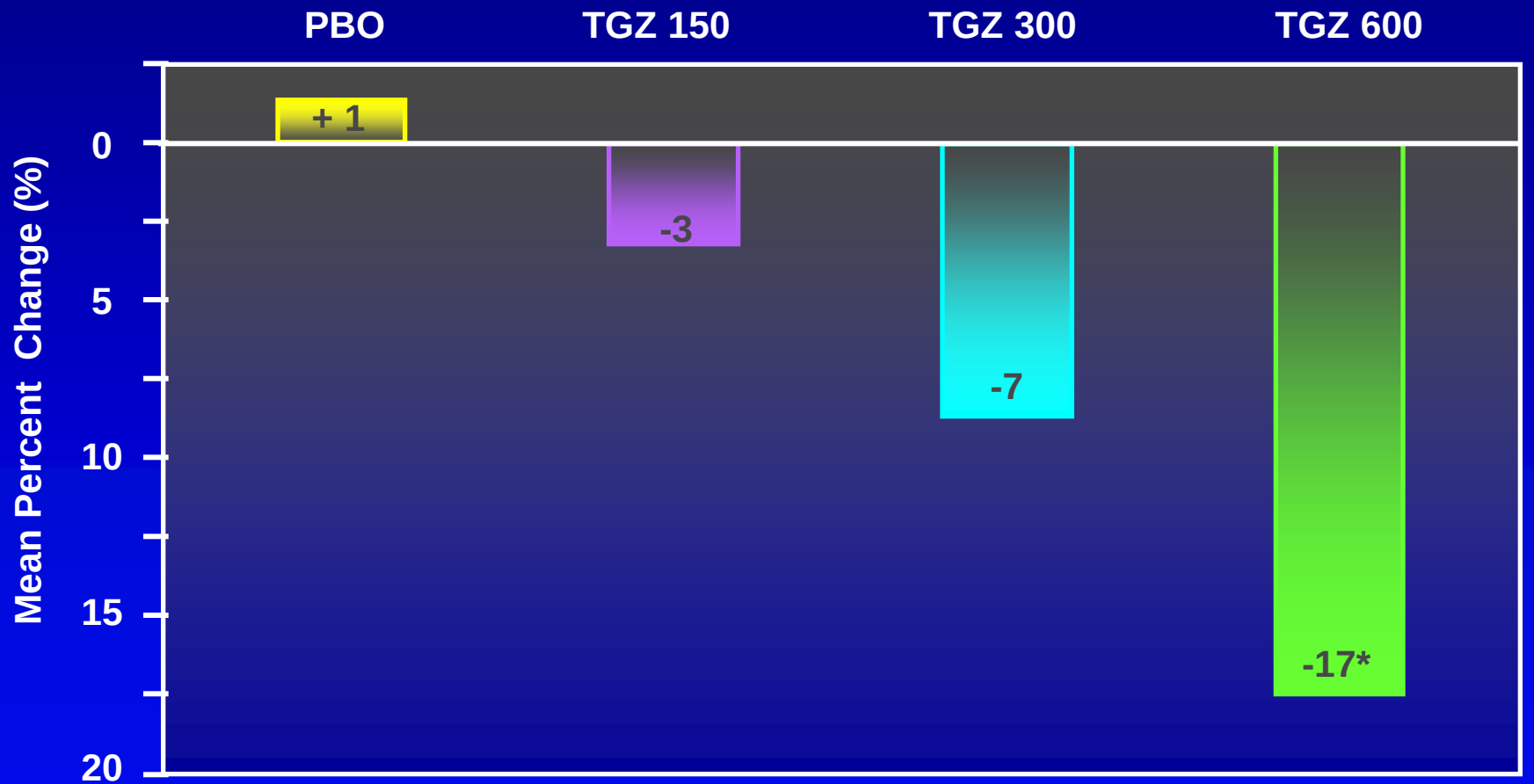
Incidence Rate of Ovulation with Troglitazone

Number of (observed/expected) ovulations averaged for each treatment group



Azziz et al, JCEM, 2001

Modified Ferriman - Gallwey Scores According to Troglitazone Dose



* P < 0.05

Azziz et al, JCEM, 2001

Thiazolidinediones in PCOS- Unfavorable risk/benefit ratio

- Troglitazone-
  - Removed from the market due to hepatoxicity
- Rosiglitazone-
  - Concerns about increased risk of myocardial infarction
  - ADA recommends against its use except for refractory type 2 DM
- Pioglitazone
  - Bladder Cancer

- Class Effects
  - Pregnancy Category C
    - ? Fetal toxicity
  - Weight gain
  - Increased adiposity

Metformin- Favorable Pharmacology

- Circulates unbound
- Excreted unchanged from the kidney

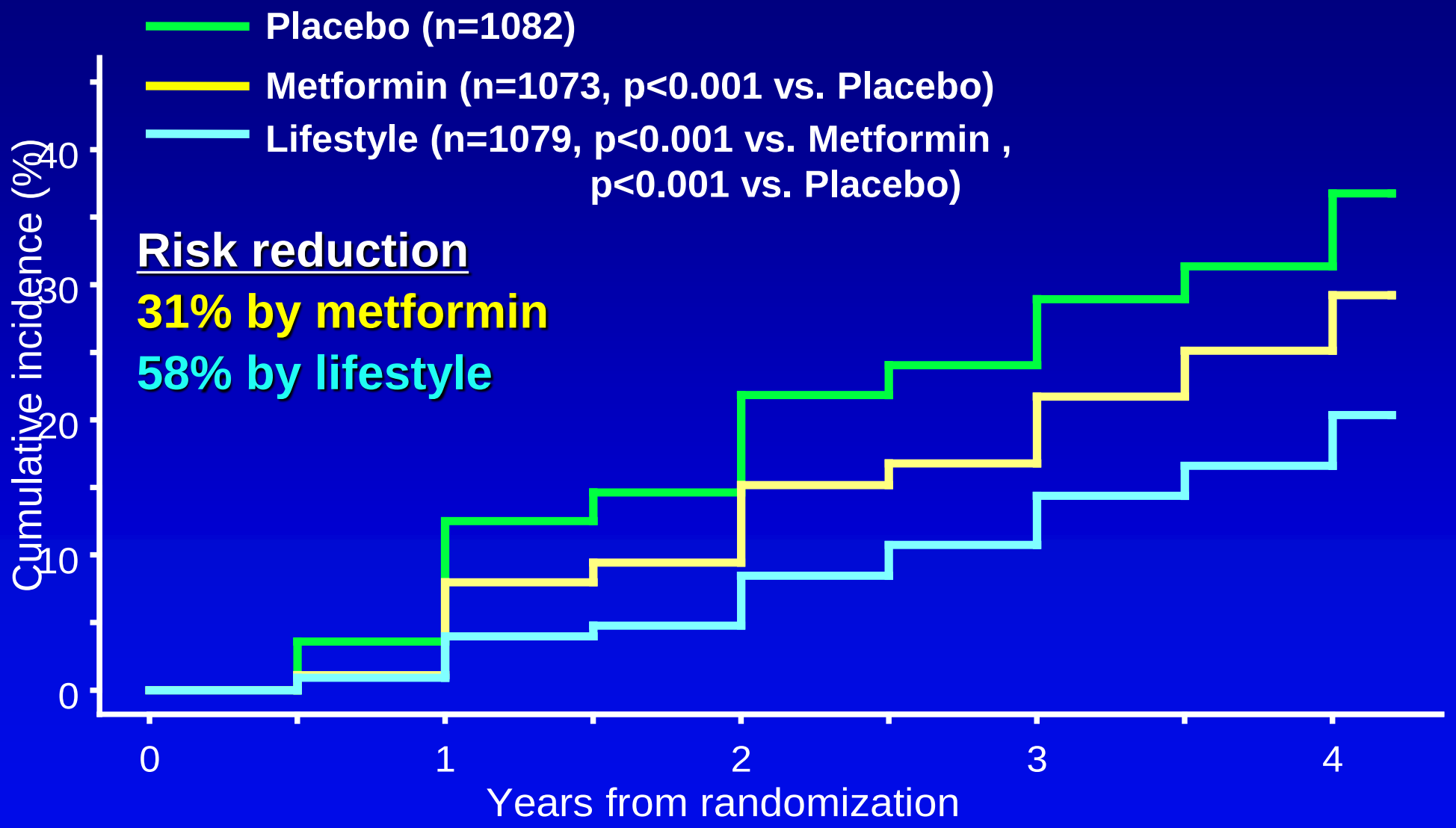
  Avoid with renal impairment
- Short Half-life of 1.3-4.5 hour
- Rarely induces hypoglycemia
- Relatively safe and well tolerated

  20% GI side effects- Nausea/diarrhea

  Weight neutral or weight loss

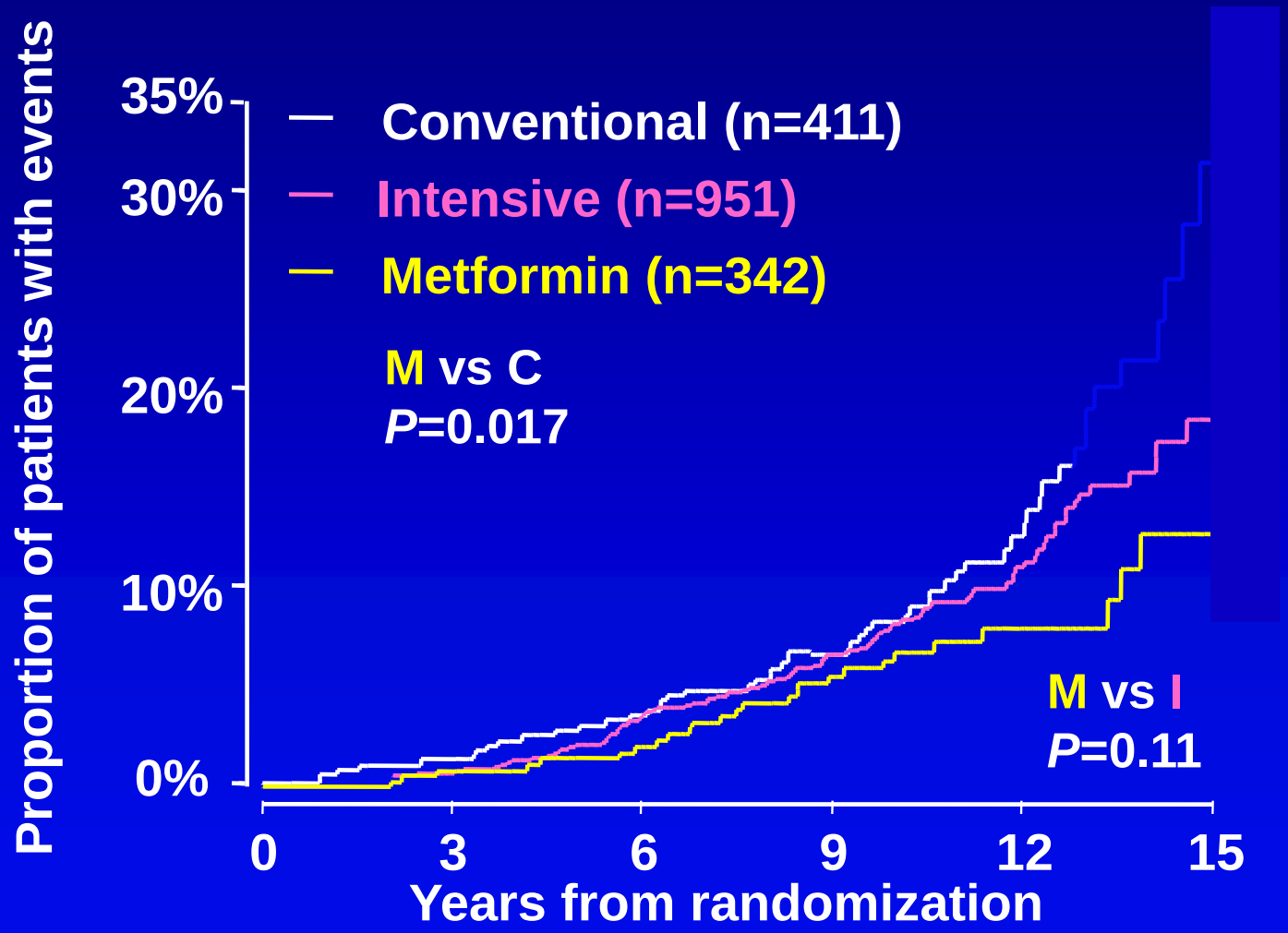
Safe during pregnancy

Incidence of Diabetes



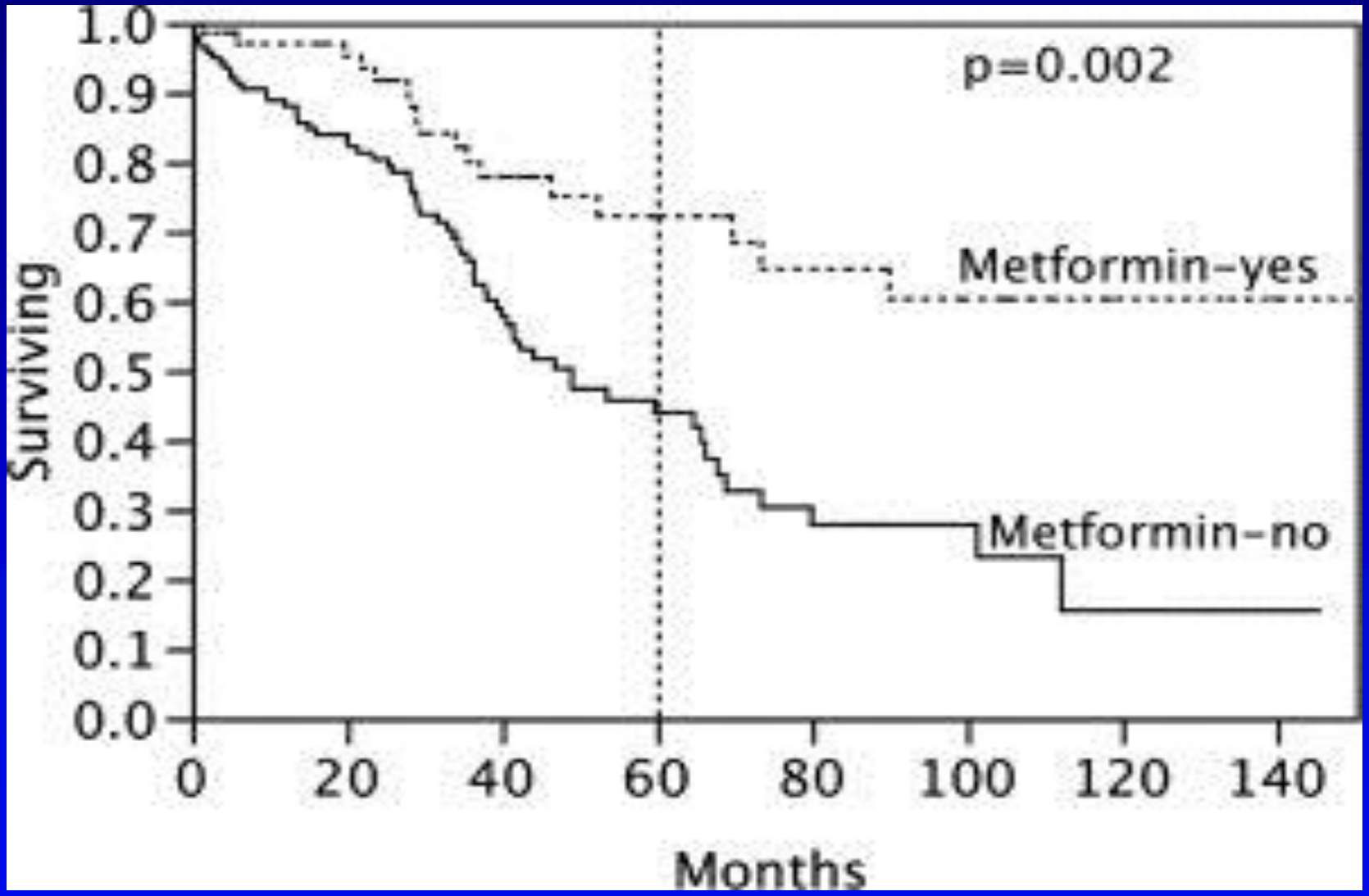
The DPP Research Group, *NEJM 346*:393-403, 2002

UKPDS: Diabetes-Related Deaths Reduced 42% with Metformin



UKPDS Group. *Lancet*. 1998;352:854-865.

Metformin intake is associated with better survival in ovarian cancer



Cancer
Volume 119, Issue 3, pages 555-562, 3 DEC 2012 DOI: 10.1002/cncr.27706

J Clin Endocrin Metab. First published ahead of print December 29, 2010 as doi:10.1210/jc.2010-1803

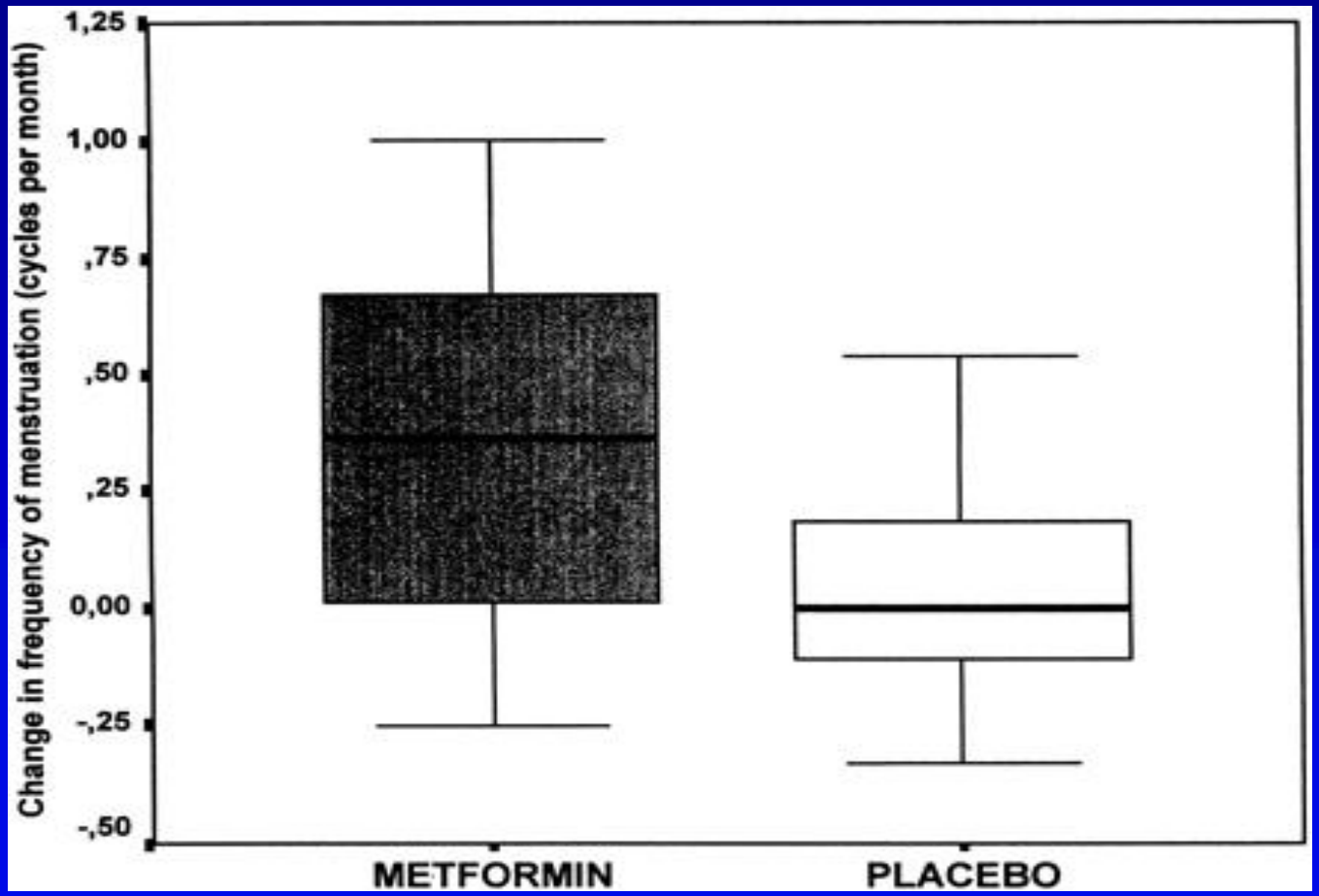
ORIGINAL ARTICLE

Endocrine Research

Metformin Treatment Exerts Antiinvasive and Antimetastatic Effects in Human Endometrial Carcinoma Cells

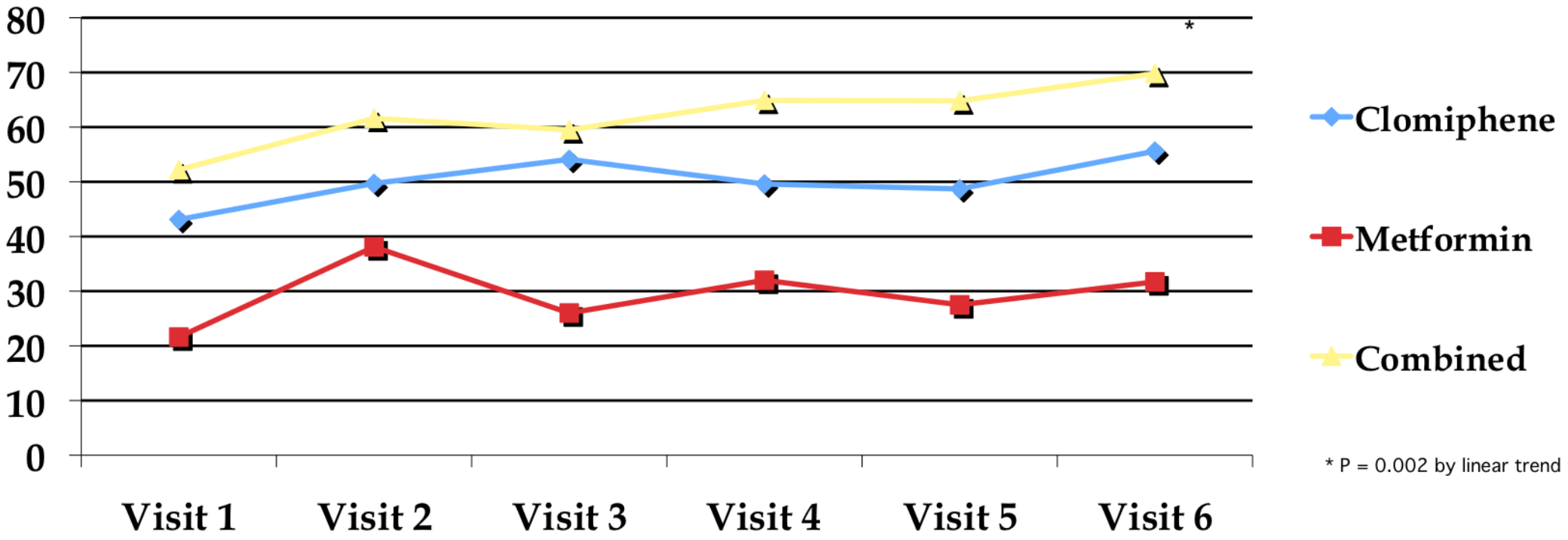
Bee K. Tan, Raghu Adya, Jing Chen, Hendrik Lehnert, Louis J. Sant Cassia, and Harpal S. Randeva

Menstrual Frequency Increases on Metformin in PCOS

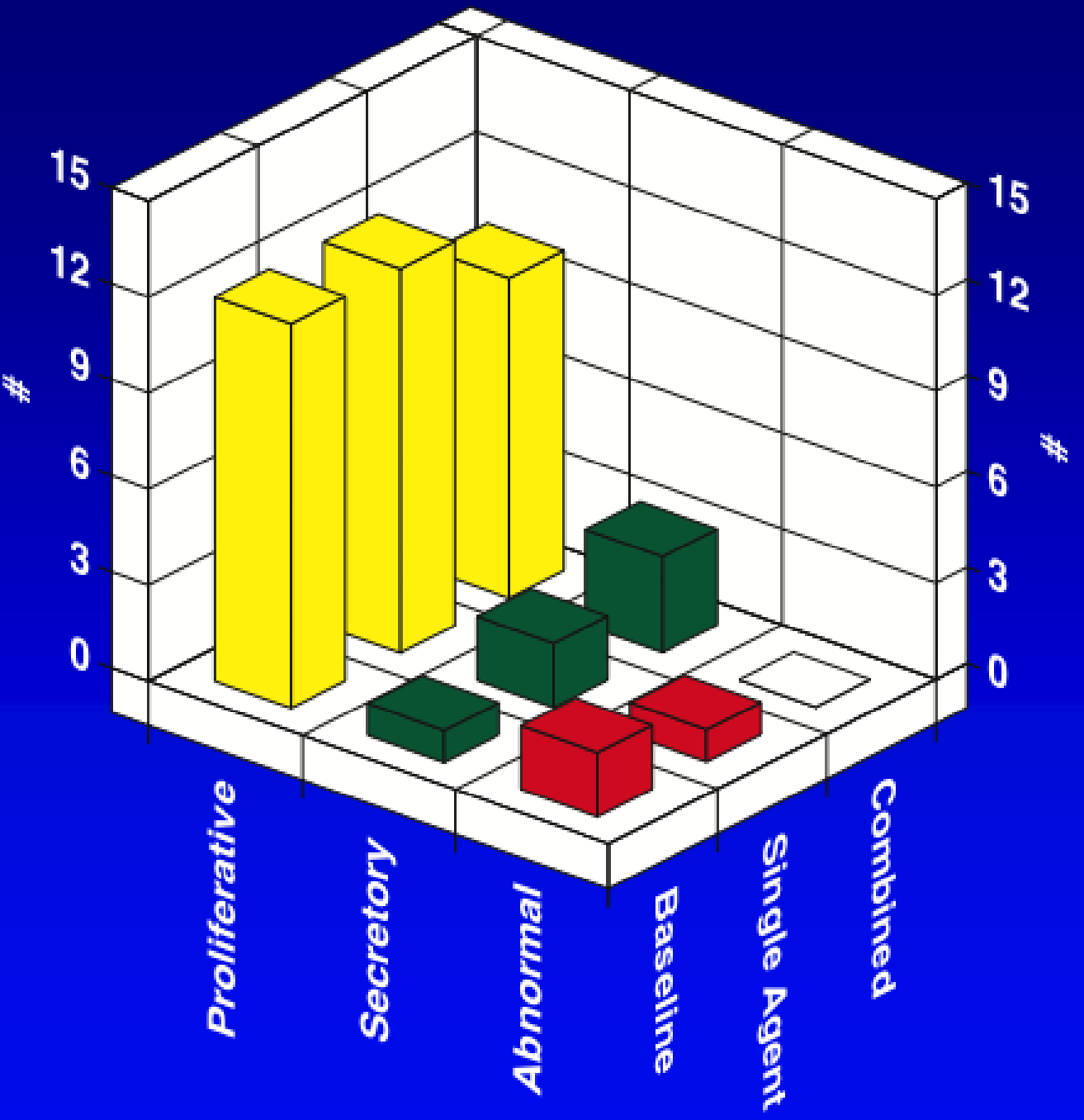


Moghetti et al, JCEM, 2000

Ovulation Rate(%) Per Treatment Cycle



Legro et al, 2007, NEJM



Endometrium Normalizes on Insulin Sensitizers in PCOS

Legro et al, AJOG, 2008

Meta-Analysis: OCP vs Metformin in the Treatment of PCOS

- Metformin was less effective than the OCP
  - in improving menstrual pattern
  - resulted in a higher incidence of gastrointestinal side effects
  - but a lower incidence of non-gastrointestinal severe adverse effects requiring stopping of medication.

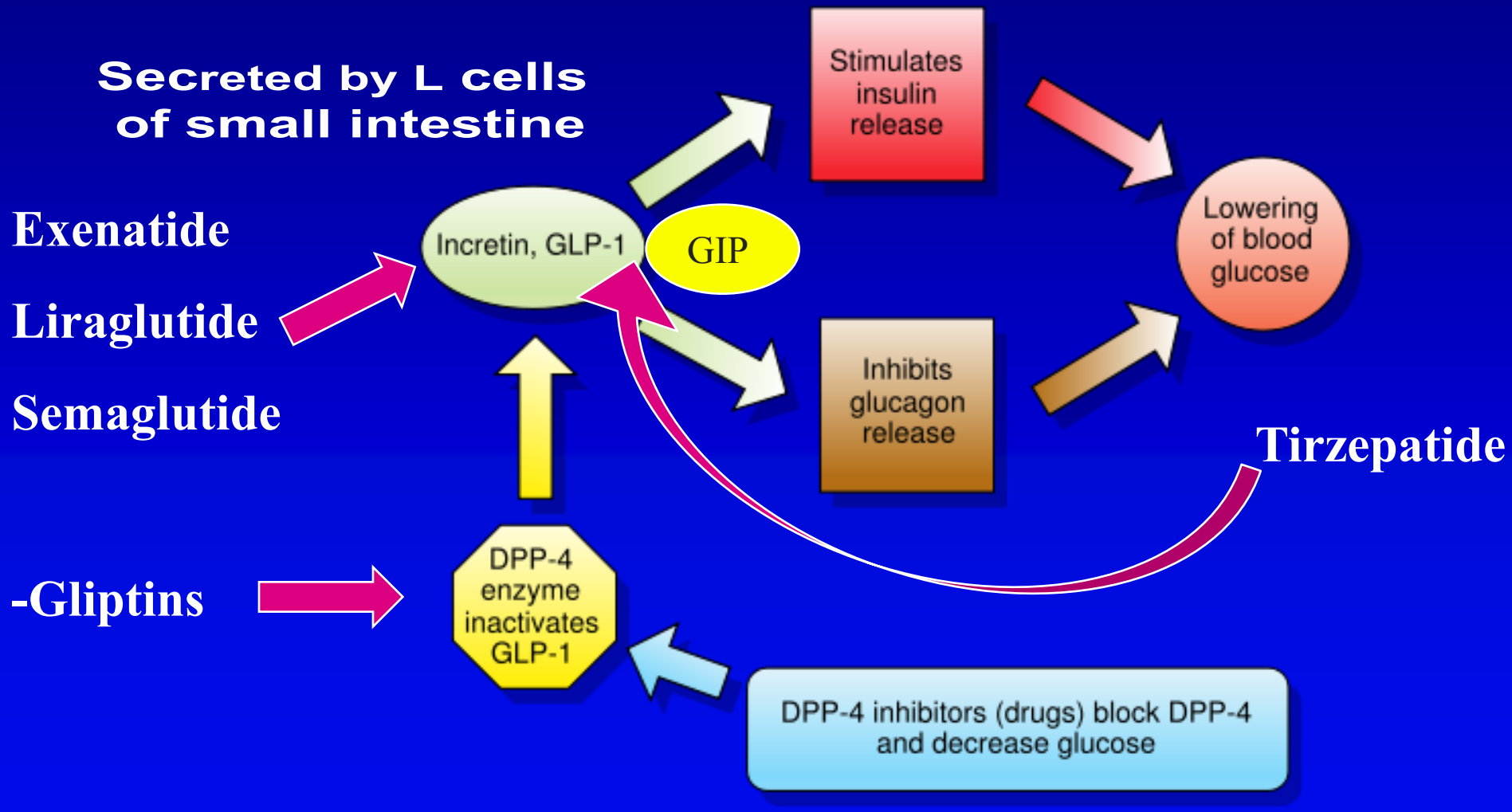
Costello et al, Cochrane Database Syst Rev. 2007 Jan 24;(1):CD005552.

Meta-Analysis: OCP vs Metformin in the Treatment of PCOS (2)

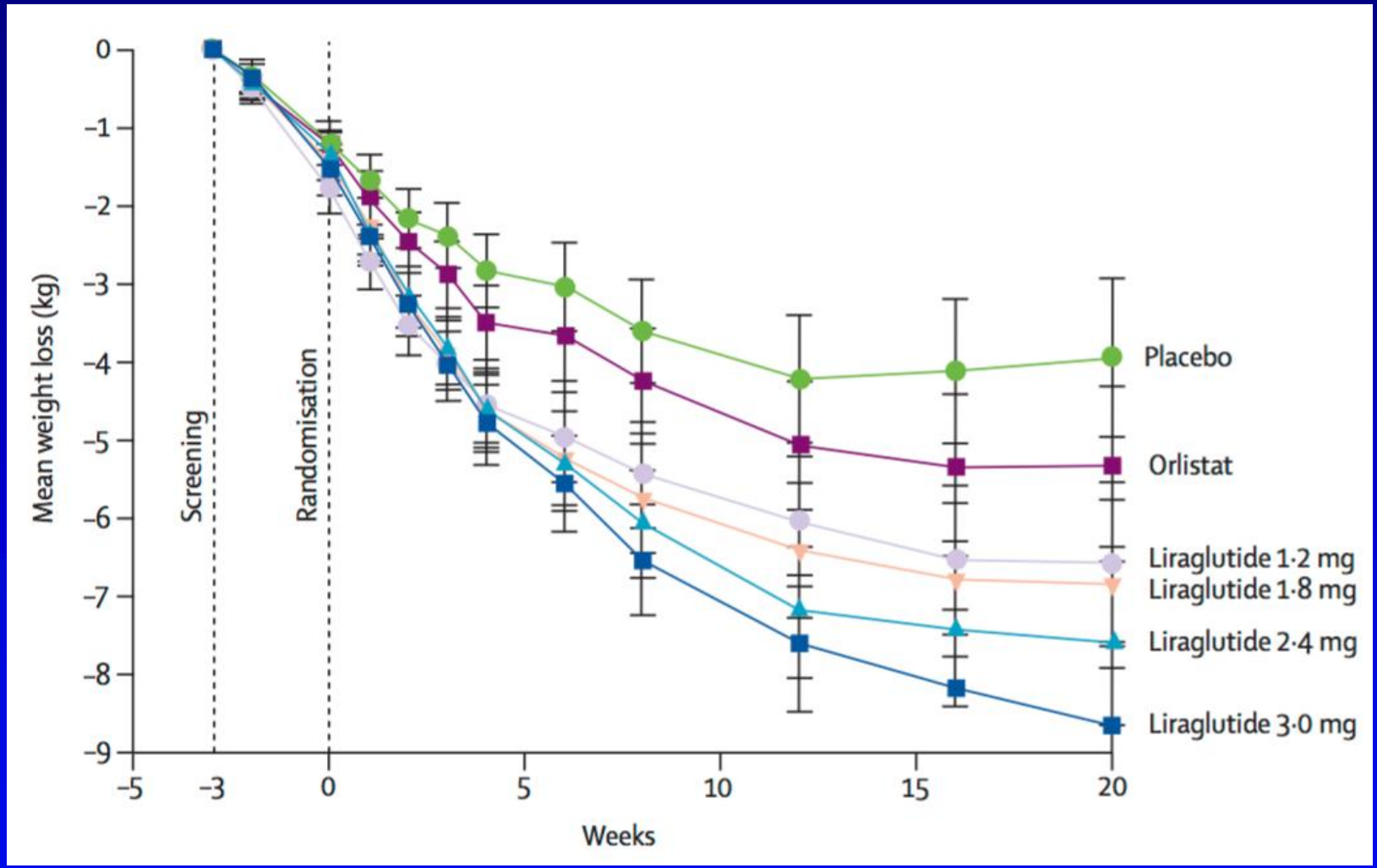
- Metformin was less effective than OCP
  - in reducing serum androgen levels;
- Metformin was more effective the OCP
  - reducing fasting insulin and not increasing triglyceride
  - but there was insufficient evidence regarding comparative effects on reducing fasting glucose levels.

Costello et al, Cochrane Database Syst Rev. 2007 Jan 24;(1):CD005552.

Incretins: The Next Frontier of Treatment of PCOS??

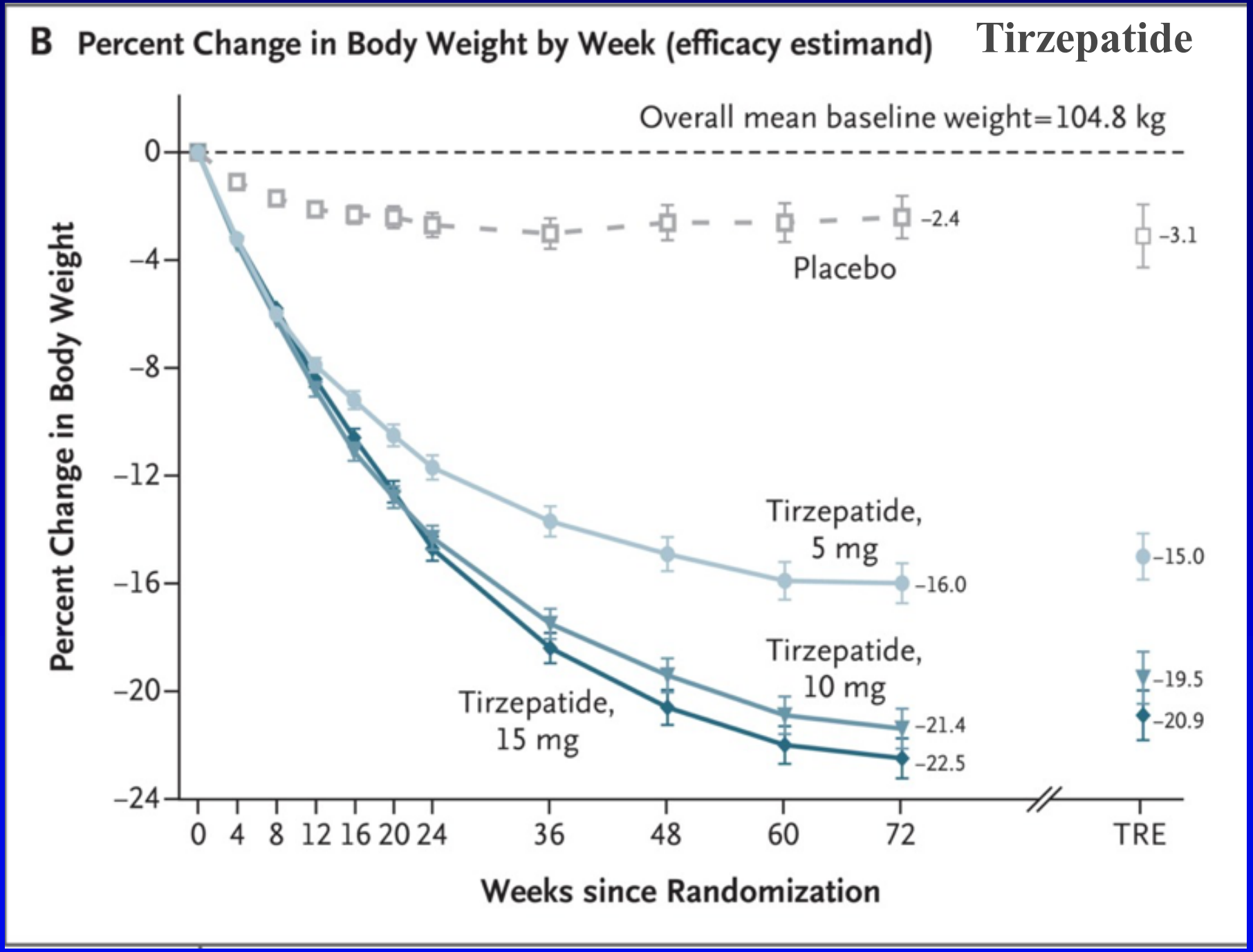


Liraglutide: Also Approved as a weight loss drug in the U.S.



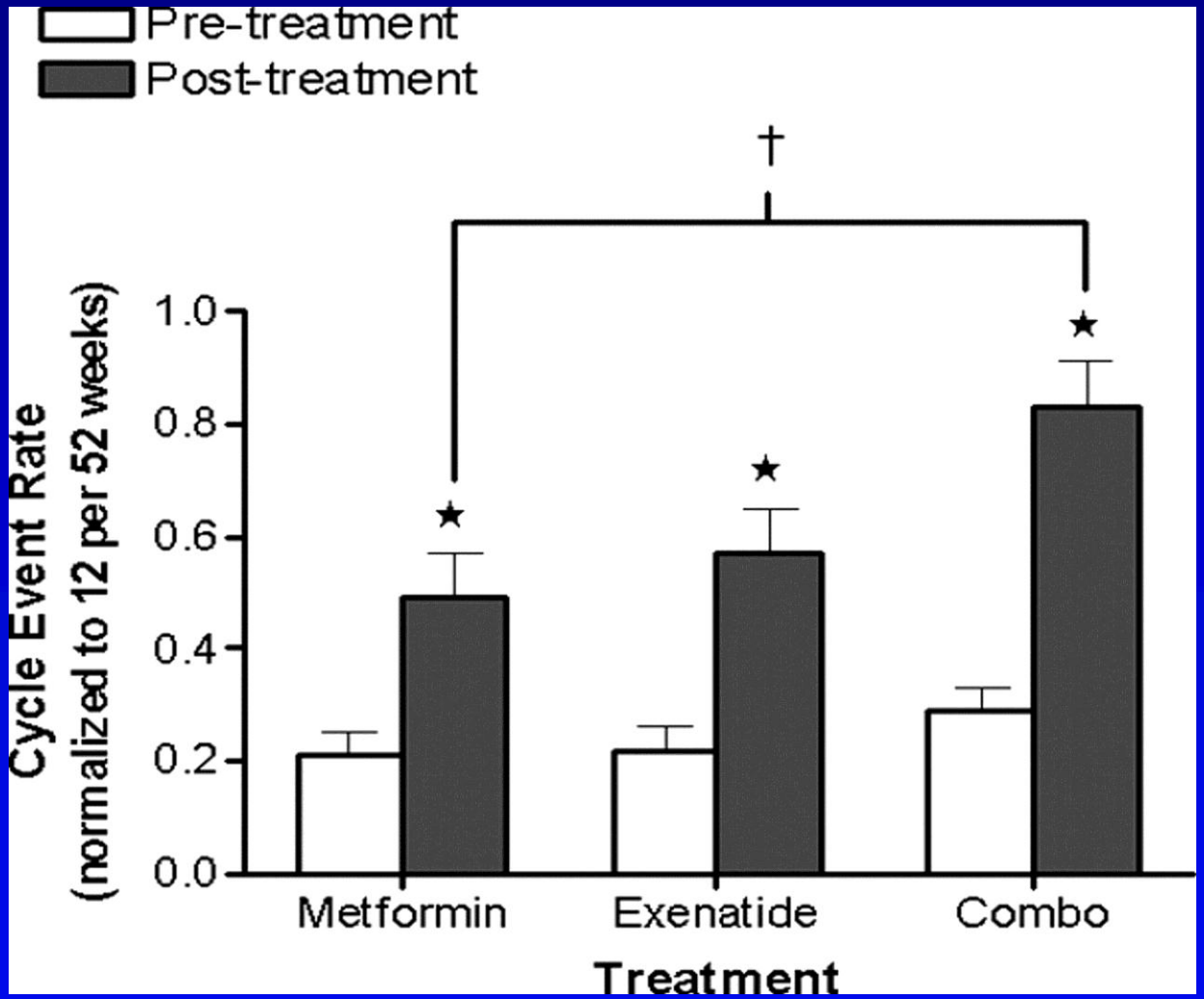
Astrup et al, Lancet, 2009

Tirzepatide



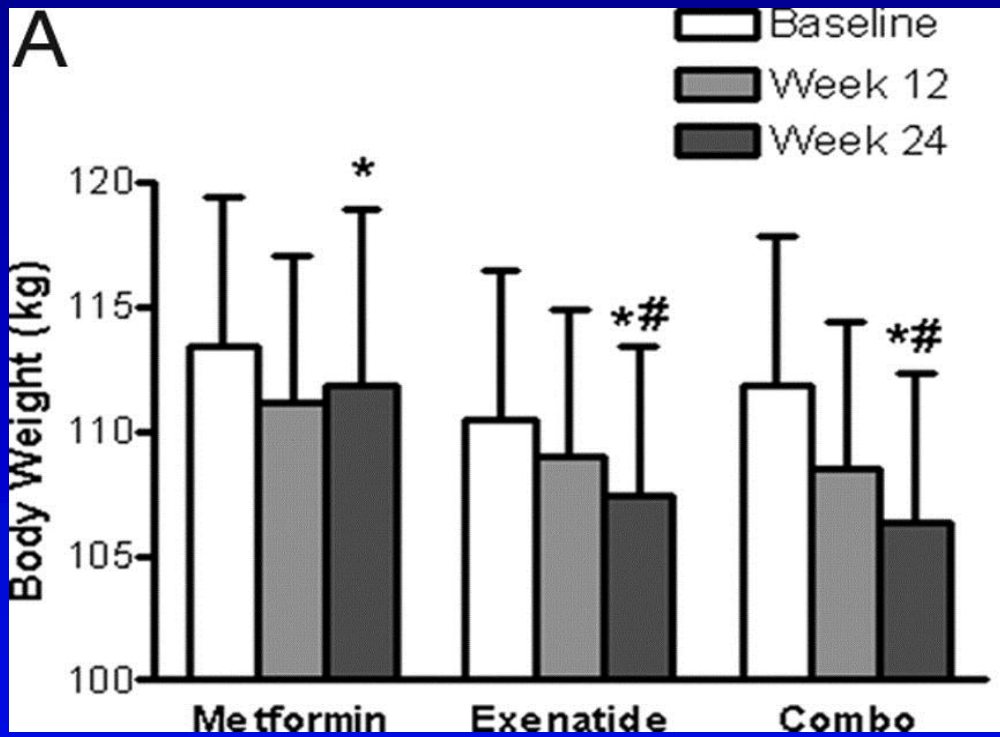
Jastreboff AM et al. N Engl J Med2022;387:205-216

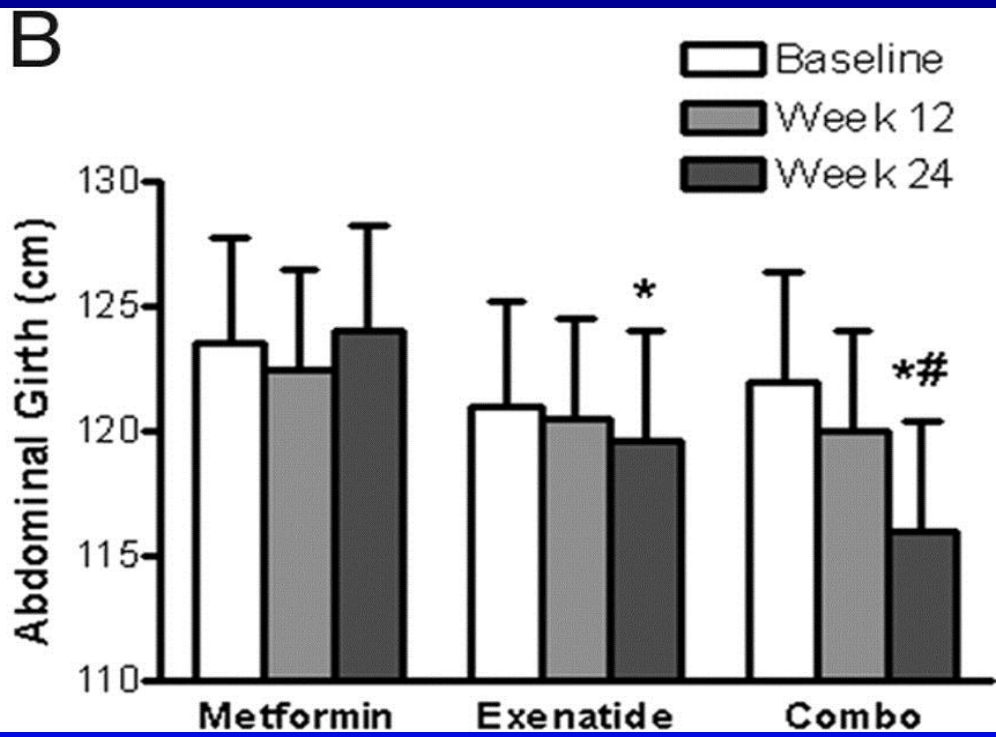
Menstrual Frequency at Baseline and after 24 Weeks



Elkind-Hirsch, K. et al. J Clin Endocrinol Metab 2008;93:2670-2678

Change in Body Weight and Waist During Treatment



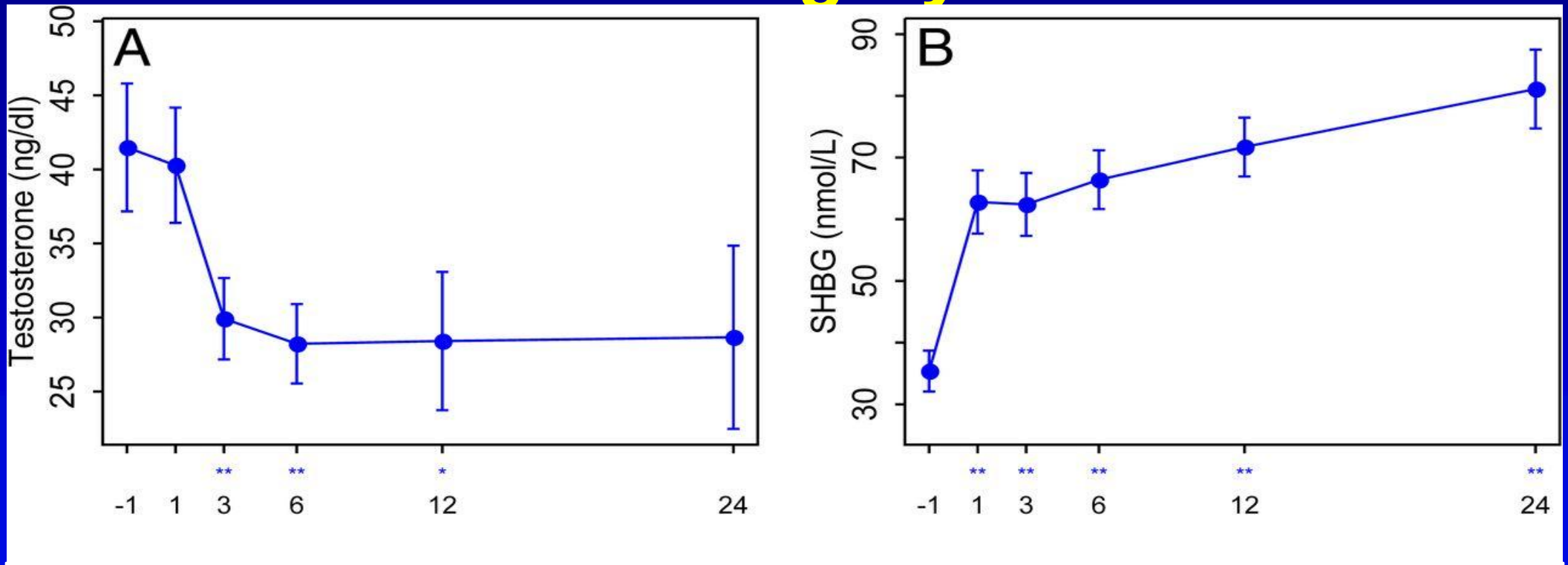


Elkind-Hirsch, K. et al. J Clin Endocrinol Metab 2008;93:2670-2678

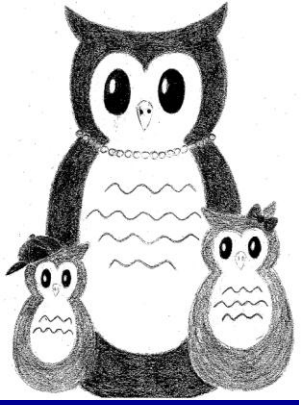
Best Estimates of Weight Loss at 12 mos of Treatment among Compliant Patients

BMI Category	Type of Weight loss	Specific Intervention	Amount of weight loss
30-34.9	Lifestyle	Diabetes Prevention Program	7%
35-35.9	Medication	Phentermine/ Topiramate (Qysmia in U.S.)	15%
≥ 40	Bariatric Surgery	Swedish Obesity Study (Roux-en-Y Gastric Bypass)	45%

Marked Peri-operative Decline in Hyperandrogenism after Bariatric Surgery



Legro R S et al. JCEM 2012;97:4540-4548



OWL
PCOS

Clinicaltrials.gov: NCT00704912

Infertile
Overweight/Obese
Women (BMI 27-42) with
PCOS N = 149

Lifestyle Modification

Continuous OCP

Combined

16 Weeks

Ovulation Induction with Clomiphene: 4 cycles

Conception: Follow q trimester

PRIMARY OUTCOME: Live Birth

Legro et al, JCEM, 2015

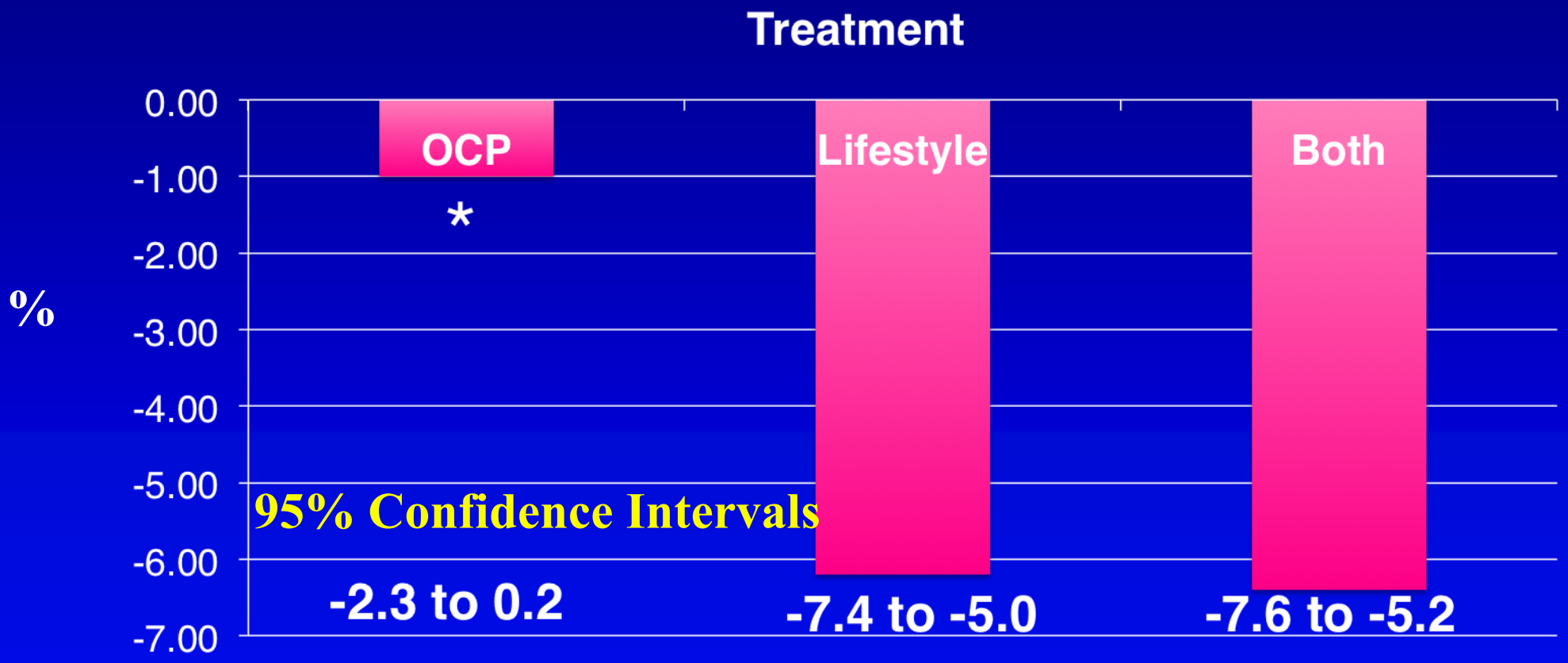
Continuous OCP

- Ethinyl Estradiol 20 mcg/ Norethindrone Acetate 1 mg taken daily for 14 weeks
- Washout
  - 2 Weeks prior to baseline ovulation induction visit
  - Allow rebound ovulation

Lifestyle Modification with Weight Loss (7% Target)

- Meal Replacements for all 3 meals with fresh vegetables/fruit
  - 500kcal/day Deficit
- Weight loss medication
  - Sibutramine 5-15 mg/d,
  - After the FDA Sibutramine Advisoryin 2010 we used over the counter orlistat (60 mg) TID with meals
- Increased Physical Activity (Walking)
- Brief Behavioral Modification Lessons
  - Adapted from the Diabetes Prevention Program

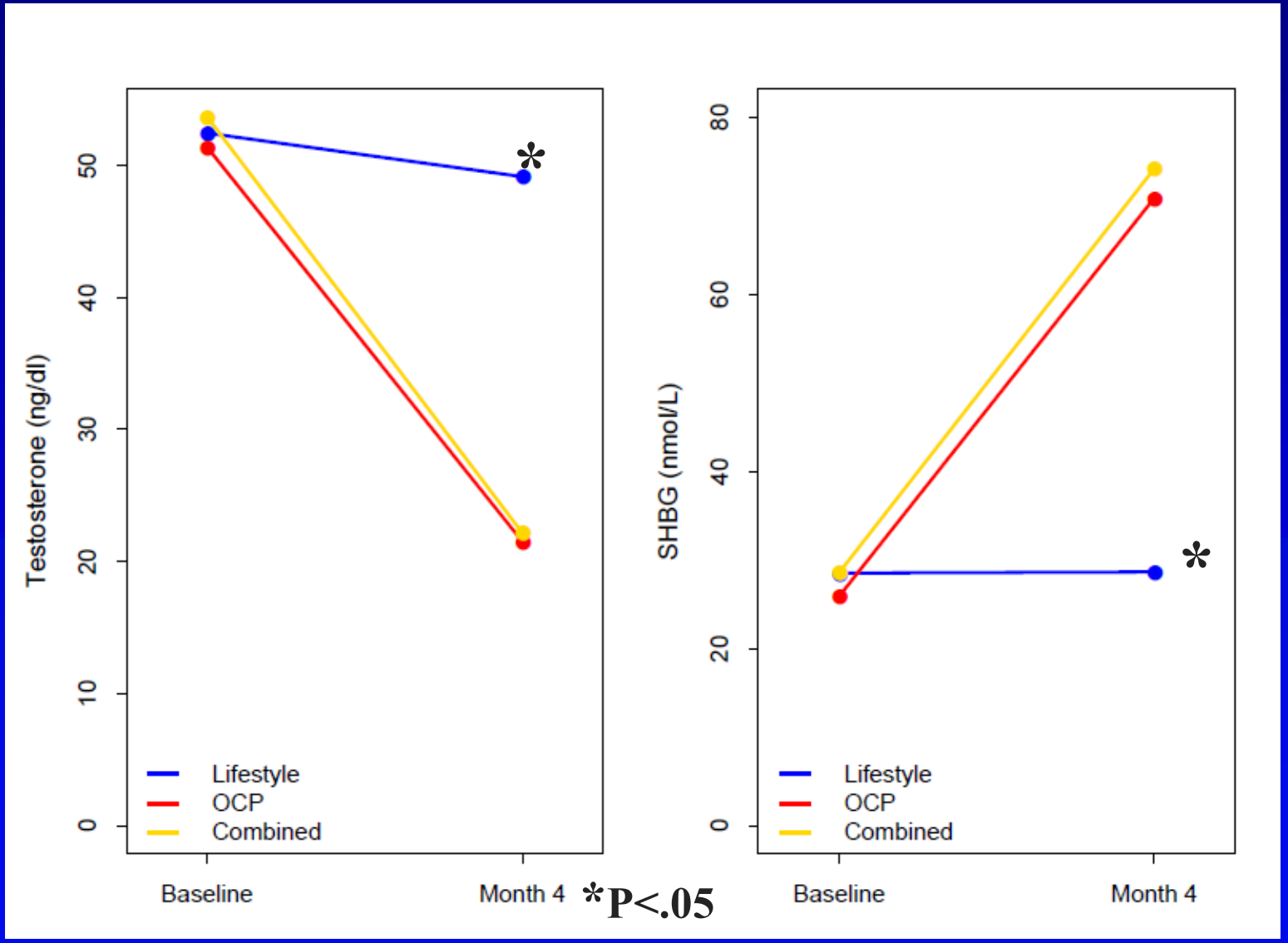
Percent Weight Loss After Preconception Intervention of 16 Weeks



No difference between weight loss with sibutramine or orlistat

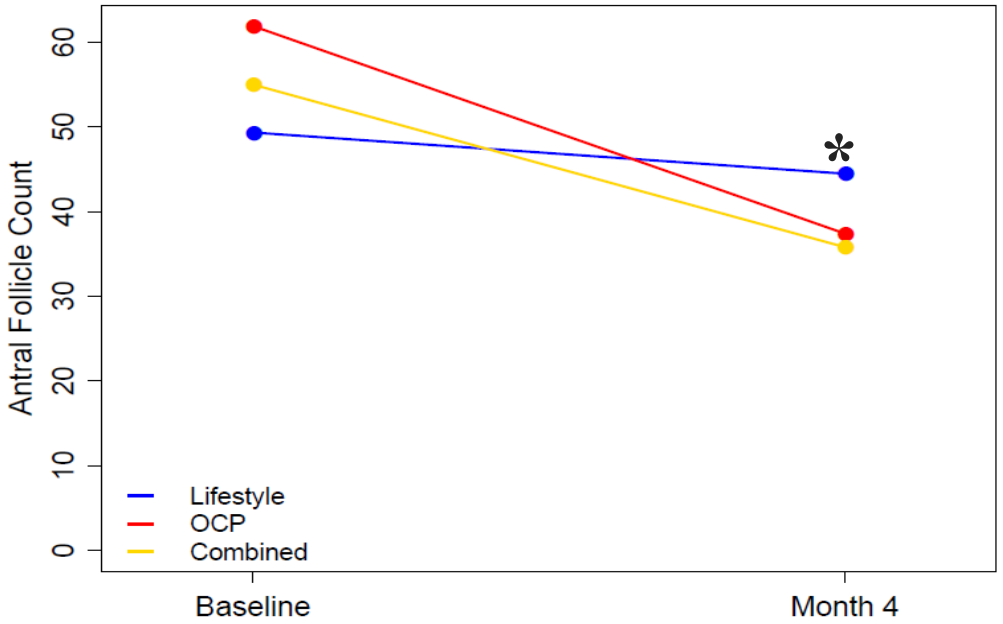
*** P < .0001**

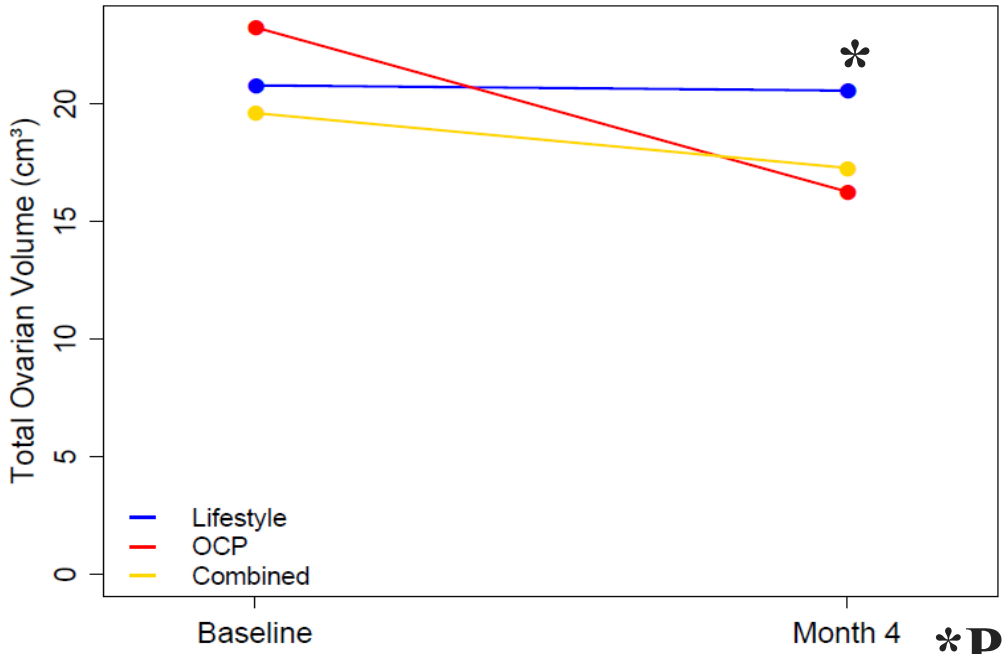
Beneficial Reproductive Effects of OCP Treatment

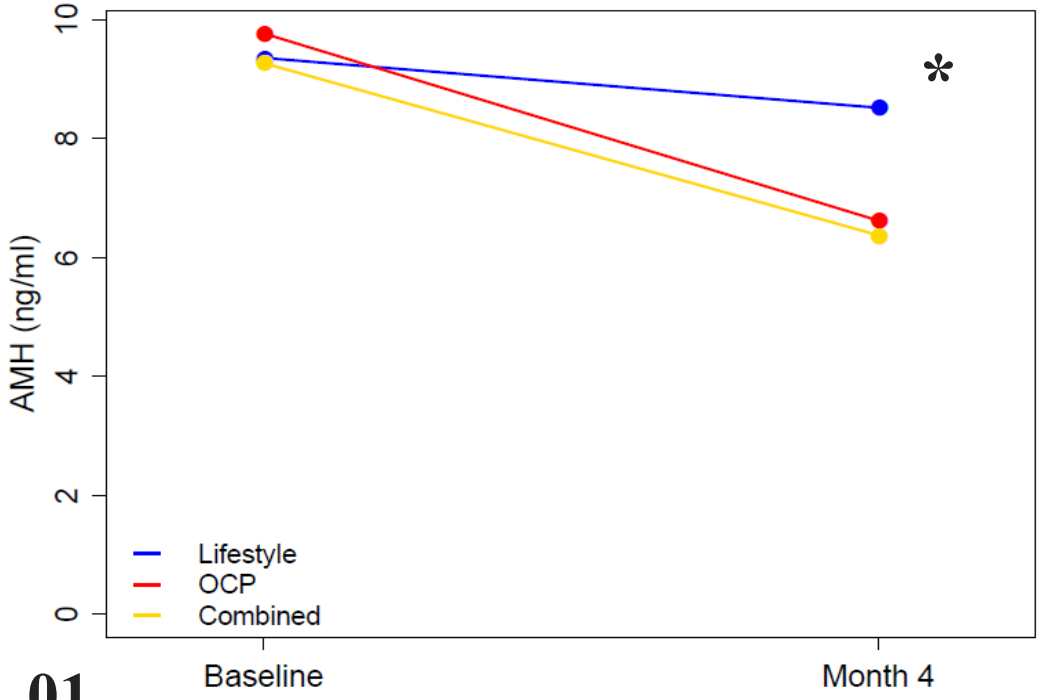


*P<.05

Significant Ovarian Suppression with OCP Treatment

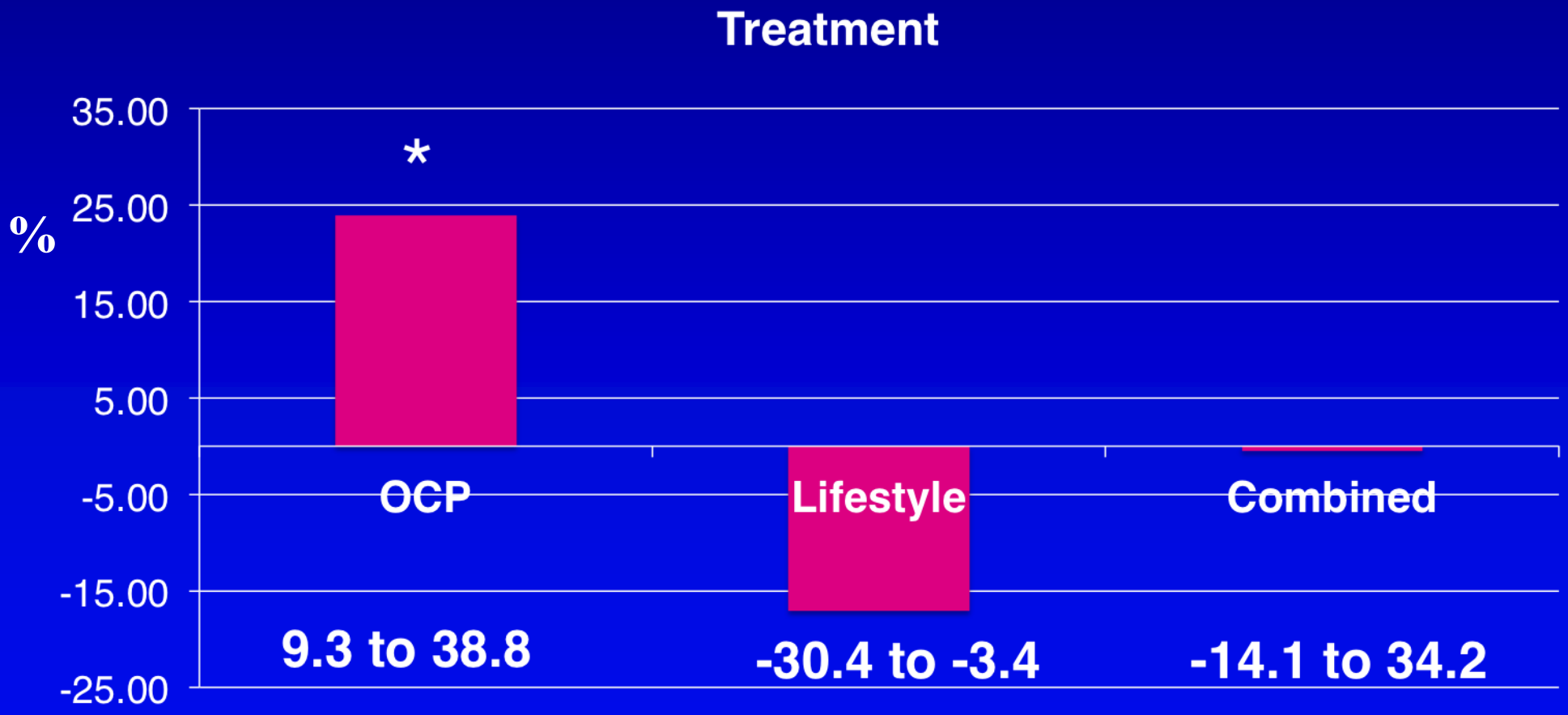






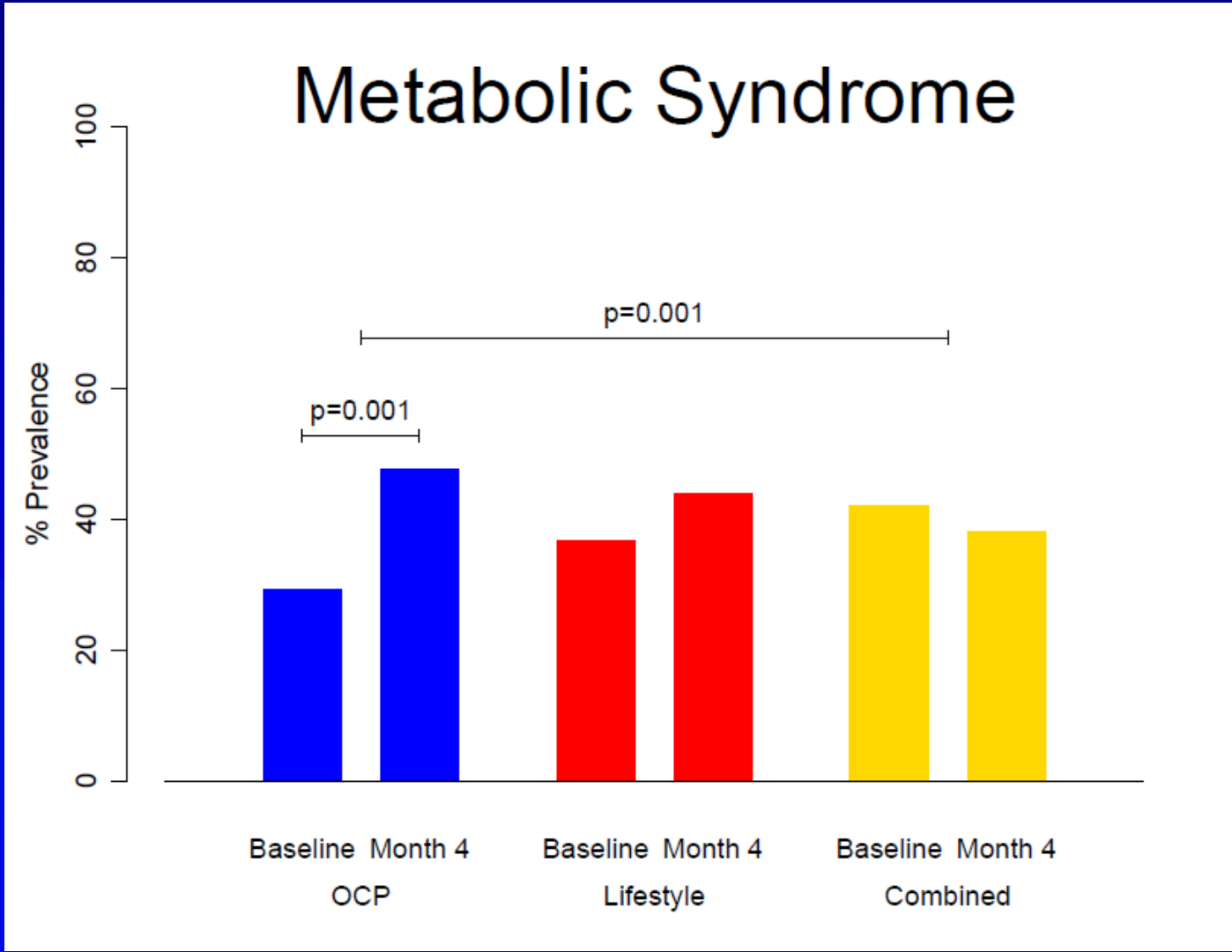
*P < .01

Percent Change in AUC Glucose (mg/dL*hr) During OGTT After Preconception Intervention of 16 Weeks



* P < .0001 vs Lifestyle and P < .02 vs Both

Prevalence of Metabolic Syndrome (MBS) Before and After Preconception Treatment



Odds ratio of developing MBS on OCP =2.5; 95% CI = (1.4 to 4.3)

No change in MBS was detected in Lifestyle or Combined

Quality of Life by PCOSQ* Improved in all Groups

	OCP	Lifestyle	Combined
General Physical Well-Being	Improved	Improved	Improved**
General Emotional Well-Being	No Change	Improved	Improved
Overall General Well-Being	Improved	Improved	Improved

*** *Only between group difference was improvement vs OCP**

***Cronin et al, JCEM, 1998**

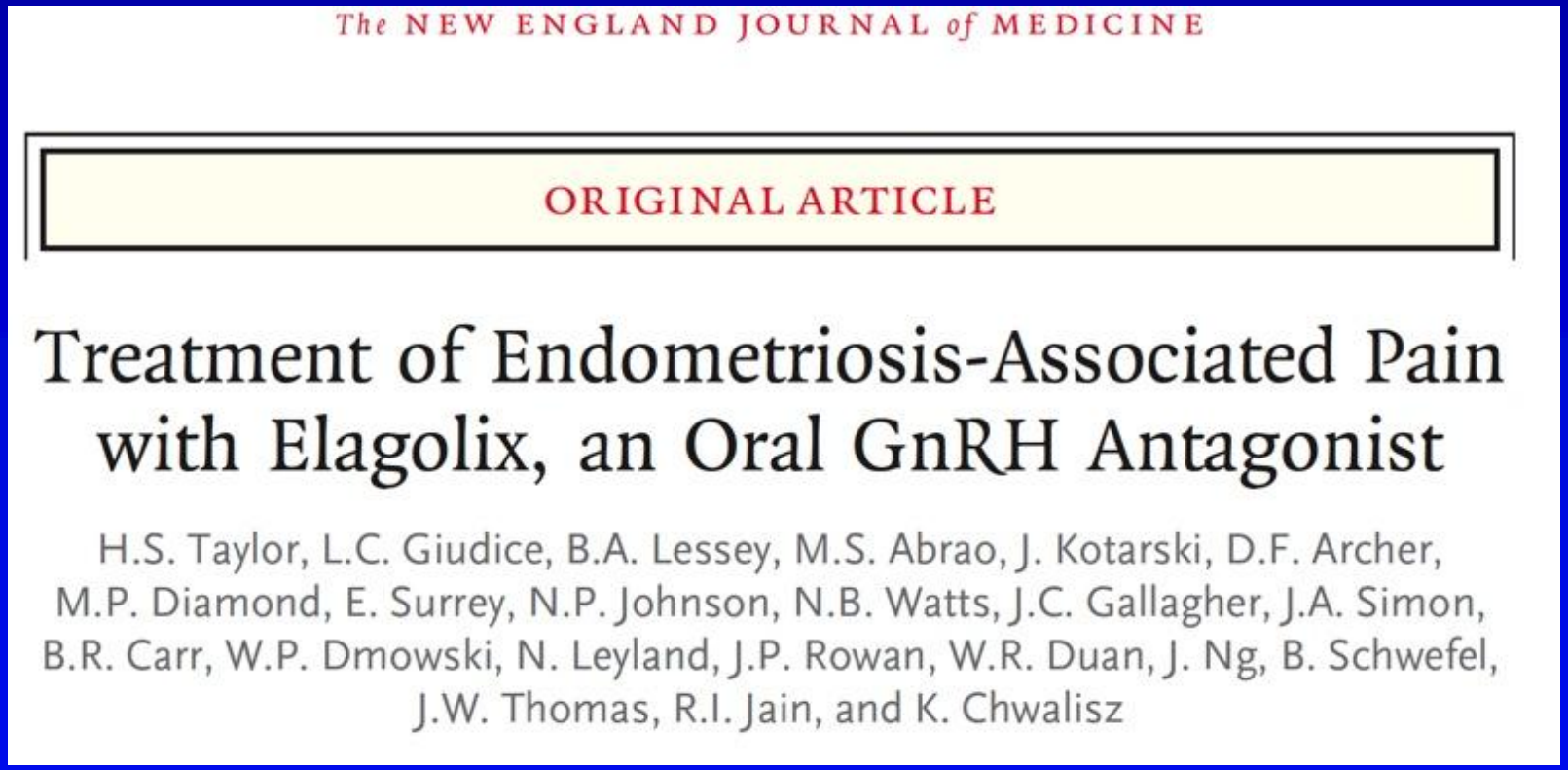
Summary of Effects of Preconception Intervention on PCOS Phenotype

	OCP	Lifestyle	Combined
Weight	Neutral	Improved	Improved
Reproductive	Improved	Neutral	Improved
Metabolic	Worsened	Improved	Neutral

***Bone Mineral Density by DXA increased significantly in all groups from baseline.**

The Future

- Repurposing of existing drugs



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist

H.S. Taylor, L.C. Giudice, B.A. Lessey, M.S. Abrao, J. Kotarski, D.F. Archer, M.P. Diamond, E. Surrey, N.P. Johnson, N.B. Watts, J.C. Gallagher, J.A. Simon, B.R. Carr, W.P. Dmowski, N. Leyland, J.P. Rowan, W.R. Duan, J. Ng, B. Schwefel, J.W. Thomas, R.I. Jain, and K. Chwalisz

SUMMARY 1

Weight Loss must be a component of the long term management of women with both PCOS and obesity

SUMMARY 2

There is no one ***pharmaceutical*** that will address all the reproductive and metabolic abnormalities (or obesity) in PCOS.

Polypharmacy is needed to treat patient complaints and prevent long-term complications.

The Unbundled Pharmacologic Treatment of PCOS

Abnormality	Treatment
Obesity (Centripetal	Lifestyle, liraglutide?, bariatric surgery,
Dyslipidemia (assuming increased LDL-C)	Statin therapy (usually above age 40)
Hypertension	Spironolactone ??
Hyperglycemia (impaired fasting or glucose tolerance)	Metformin
Anovulation	Progestin therapy (micronized progesterone), IUD/progestin eluting

Ongoing Trials at Penn State

RO1: Inositol Supplementation to Treat PCOS (INSUPP-PCOS)

PI: Dr. Richard Legro

Clinicaltrials.gov: NCT03864068

RO1: Comparing the Effects of Oral Contraceptive Pills Versus Metformin versus Both (COMET-PCOS)

PI: Dr Anuja Dokras

Clinicaltrials.gov: NCT03229057

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