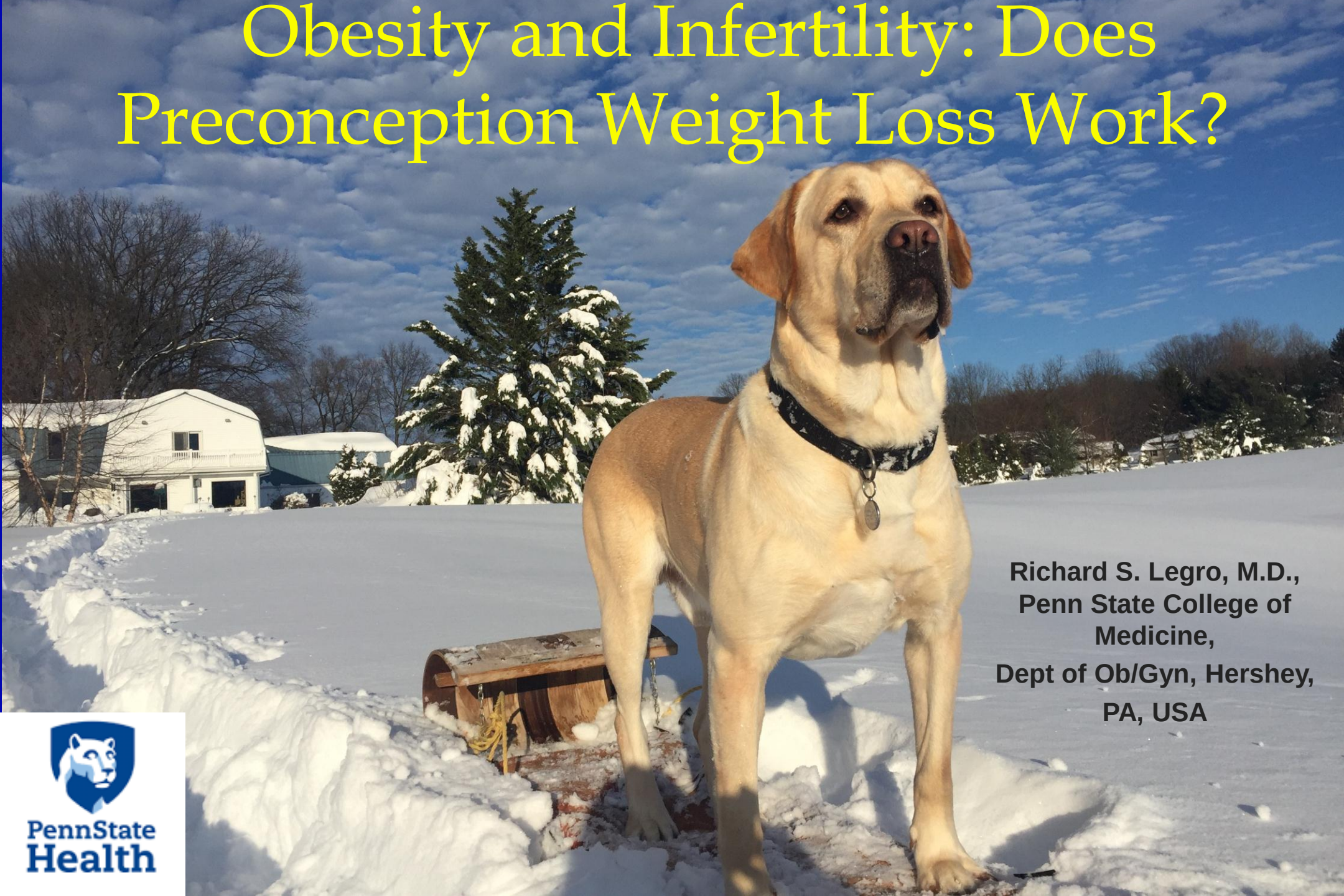
Obesity and Infertility: Does Preconception Weight Loss Work?



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

PennState Health

Disclosures

- Consultant: Novo Nordisk, NIH
- Research Funding: NIH, Pennsylvania DOH, Guerbet

Off Label Medications

Metformin, Sibutramine, Orlistat, Phentermine/Topiramate: Not indicated for infertility

Obesity and Fertility

- There is exhaustive epidemiologic and observational data that female obesity is associated with:
- 1) Menstrual disorders/anovulation
- 2) Infertility
- 3) Delayed time to pregnancy
- 4) Increased pregnancy loss
- 5) Increased risk of pregnancy complications:
  - Preterm Delivery, Pre-eclampsia, Gestational Diabetes

Preconception weight loss in women with infertility improves pregnancy rates

A) Agree

B) Disagree

C) Undecided

Systematic Review: Preconception Weight Loss in Obese Infertile Women

- The current evidence suggests: more weight loss and an increase in clinical pregnancy rates (CPR) and live birth rates (LBR) RR = 2.20 (95% CI 1.23,3.94) following lifestyle intervention compared to no intervention
- but no effect of lifestyle intervention preceding assisted reproductive technique (ART).

Hoek A et al, Fertil Steril, In Press

Unknown Risk Benefit Ratio: Incomplete Trial Reporting

Table 1: Overview of randomized controlled studies lifestyle intervention in infertile women and reported main outcomes

Study	Sample size	Main fertility outcome	Fertility complications	Pregnancy complications	Fetal/neonatal complications	SC/MC RCT	Drop out
Studies included in SR (11)							
Guzick 1994	12	Ovulation	-	-	-	SC	-
Hoeger 2004	38	Ovulation	-	-	-	SC	+
Palomba 2010	26	CPR	-	-	-	SC	+
Moran 2011	46	LBR	-	-	-	SC	+
Sim 2014	49	CPR	-	-	-	SC	+
Legro 2015	379	LBR	+	+	+	MC	+
Becker 2015	26	LBR	-	-	-	SC	+
Duval 2015 abstract	105	LBR	-	-	-	SC	+
Nasrekani 2016	20	Weight loss	-	-	-	SC	-
Nagelberg 2016	21	CPR	-	-	-	SC	-
Rothberg 2016	14	LBR	-	-	-	SC	+
Mutsaerts 2016	577	LBR	+	+	+	MC	+
Espinos 2017	41	LBR	-	-	-	SC	+
Einnarson 2017, 2019	317	LBR	+	+	+	MC	+
Kiel 2018	18	CPR	-	-	-	MC	+
Study published after SR							
Legro 2022	379	LBR	+	+	+	MC	+

Legend: CPR: clinical pregnancy rate; LBR: live birth rate; SC: single center; MC: multicenter; RCT: randomized controlled trial

Hoek et al, Fertil Steril, In Press

Women who undergo bariatric surgery and go on to conceive are at risk for which perinatal complications compared to obese controls?

A) spontaneous preterm delivery

B) increased rate of small for gestational age infants

C) a trend towards increased stillbirths

D) all of the above

E) none of the above

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

2015

Outcomes of Pregnancy after Bariatric Surgery

Kari Johansson, Ph.D., Sven Cnattingius, M.D., Ph.D., Ingmar Näslund, M.D., Ph.D., Nathalie Roos, M.D., Ph.D., Ylva Trolle Lagerros, M.D., Ph.D., Fredrik Granath, Ph.D., Olof Stephansson, M.D., Ph.D., and Martin Neovius, Ph.D.

They identified 627,693 singleton pregnancies in the Swedish Medical Birth Registery, 670 after bariatric surgery: Used a 5 obese control to 1 case analysis

CONCLUSIONS

Bariatric surgery was associated with reduced risks of gestational diabetes and excessive fetal growth, shorter gestation, an increased risk of small-for-gestational-age infants, and possibly increased mortality. (Funded by the Swedish Research Council and others.)

? Increased Risk of Fetal/Neonatal Mortality after Bariatric Surgery

- The risk of stillbirth or neonatal death was 1.7% versus 0.7% (odds ratio, 2.39; 95% CI, 0.98 to 5.85; P=0.06).
- There was no significant between-group difference in the frequency of congenital malformations.

Johansson K et al. N Engl J Med 2015;372:814-824.

A 30 y/o female with a BMI of 42 presents with a history of one year of unexplained infertility and is in good health. What preconception endocrinologic evaluation should be performed?

A) Screen thyroid function

B) Screen for diabetes and pre-diabetes

C) Screen for hypertension

D) all of the above

E) none of the above

Thyroid Disease and Fertility

- Both hypo- and hyperthyroidism associated with infertility
- Anti-thyroid antibodies are associated with unexplained first trimester pregnancy loss
  - Treatment with thyroxine ineffective
- Recognition and treatment of subclinical hypothyroidism during pregnacy has not reduced any perinatal complications or improved infant development up to 5 years after birth

Dysglycemia and Adverse Maternal and Fetal Outcomes

- Elevated glucose levels preconception in women with diabetes is associated with increased rate of fetal anomalies
- Poorly controlled diabetes during pregnancy accelerates vascular disease
- Prediabetes and impaired glucose tolerance are strong risk factors for gestational diabetes and related complications

The NEW ENGLAND JOURNAL of MEDICINE

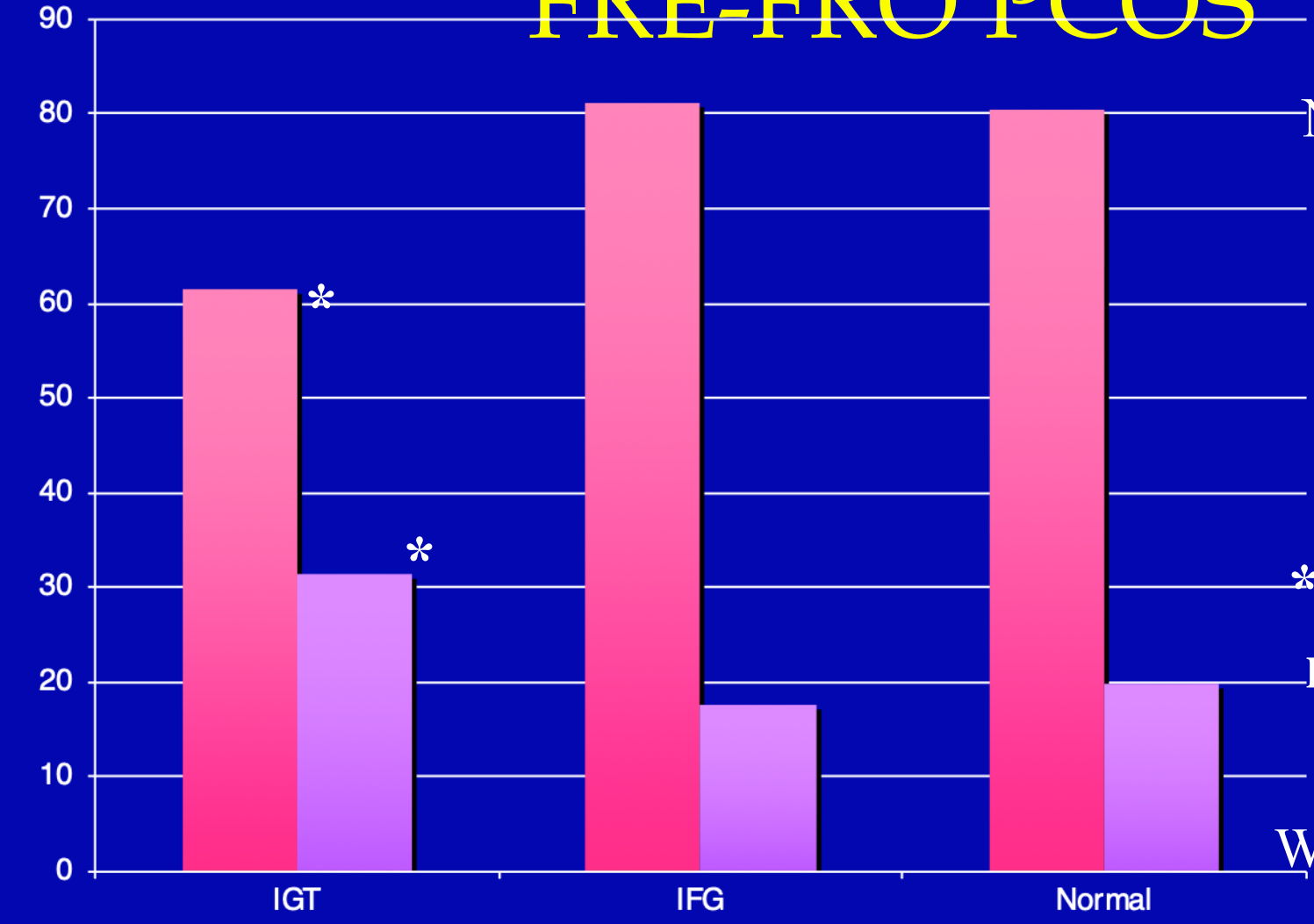
ORIGINAL ARTICLE

Fresh versus Frozen Embryos for Infertility in the Polycystic Ovary Syndrome

Z.-J. Chen, Y. Shi, Y. Sun, B. Zhang, X. Liang, Y. Cao, J. Yang, J. Liu, D. Wei, N. Weng, L. Tian, C. Hao, D. Yang, F. Zhou, J. Shi, Y. Xu, J. Li, J. Yan, Y. Qin, H. Zhao, H. Zhang, and R.S. Legro

2016

Singleton Pregnancy Outcomes by Preconception Glucose Category in FRE-FRO PCOS



N = 1492 Subjects

Live Birth

Pregnancy Loss

***P < .05 vs IFG and normoglycemia**

Wei et al, JCEM, 2017

Research

JAMA | Original Investigation

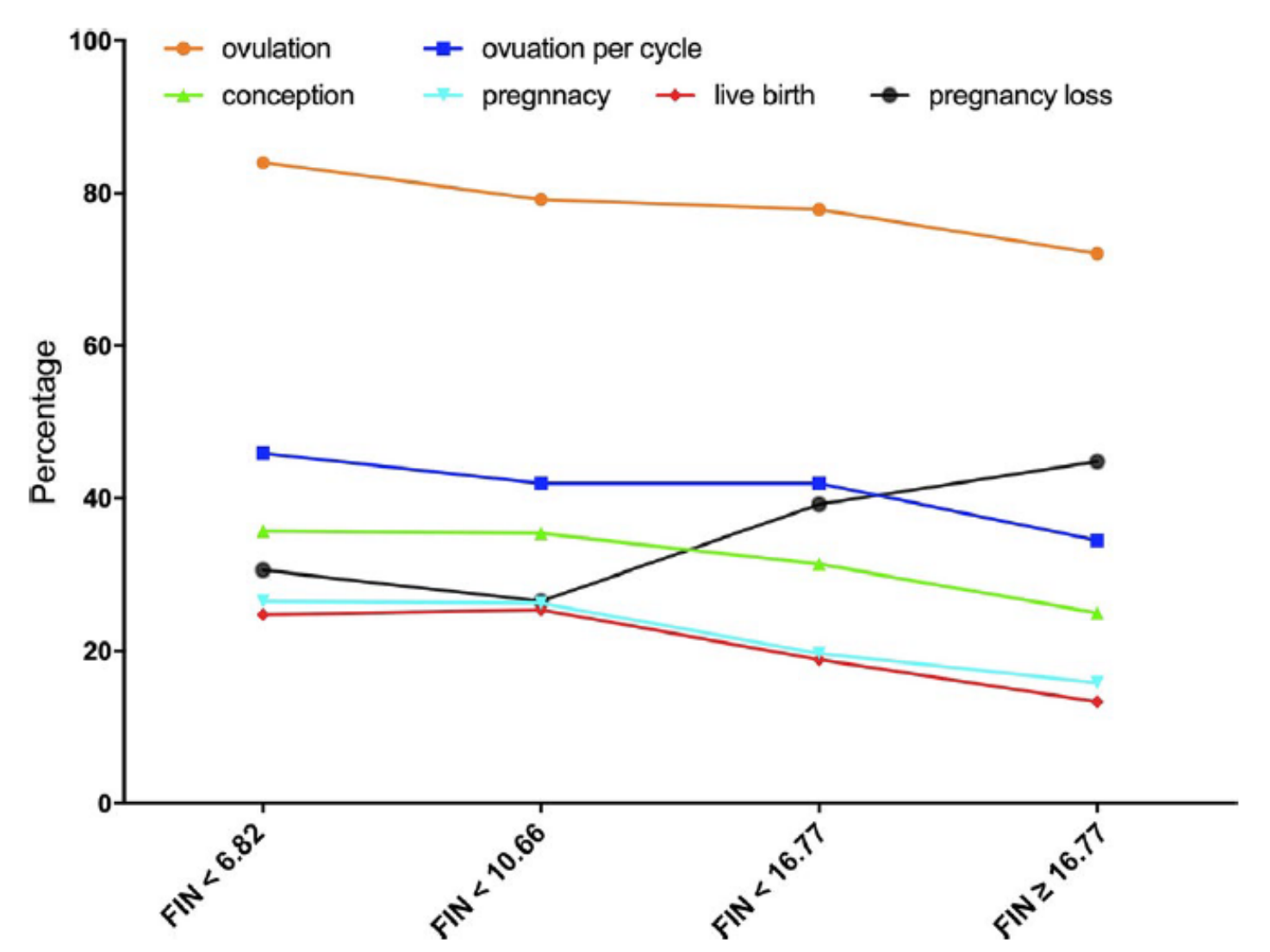
Effect of Acupuncture and Clomiphene in Chinese Women With Polycystic Ovary Syndrome
A Randomized Clinical Trial

Xiao-Ke Wu, MD, PhD; Elisabet Stener-Victorin, PhD; Hong-Ying Kuang, MD; Hong-Li Ma, MD; Jing-Shu Gao, MSc; Liang-Zhen Xie, MSc; Li-Hui Hou, MD; Zhen-Xing Hu, MD; Xiao-Guang Shao, MD; Jun Ge, MD; Jin-Feng Zhang, MD; Hui-Ying Xue, MD; Xiao-Feng Xu, MD; Rui-Ning Liang, MD; Hong-Xia Ma, MD; Hong-Wei Yang, MD; Wei-Li Li, MD; Dong-Mei Huang, MD; Yun Sun, MD; Cui-Fang Hao, MD; Shao-Min Du, MD; Zheng-Wang Yang, MD; Xin Wang, MD; Ying Yan, MD; Xiu-Hua Chen, MD; Ping Fu, MD; Cai-Fei Ding, MD; Ya-Qin Gao, MD; Zhong-Ming Zhou, MD; Chi Chiu Wang, PhD; Tai-Xiang Wu, PhD; Jian-Ping Liu, MD; Ernest H. Y. Ng, MD; Richard S. Legro, MD; Heping Zhang, PhD; for the PCOSAct Study Group

Editorial page 2489

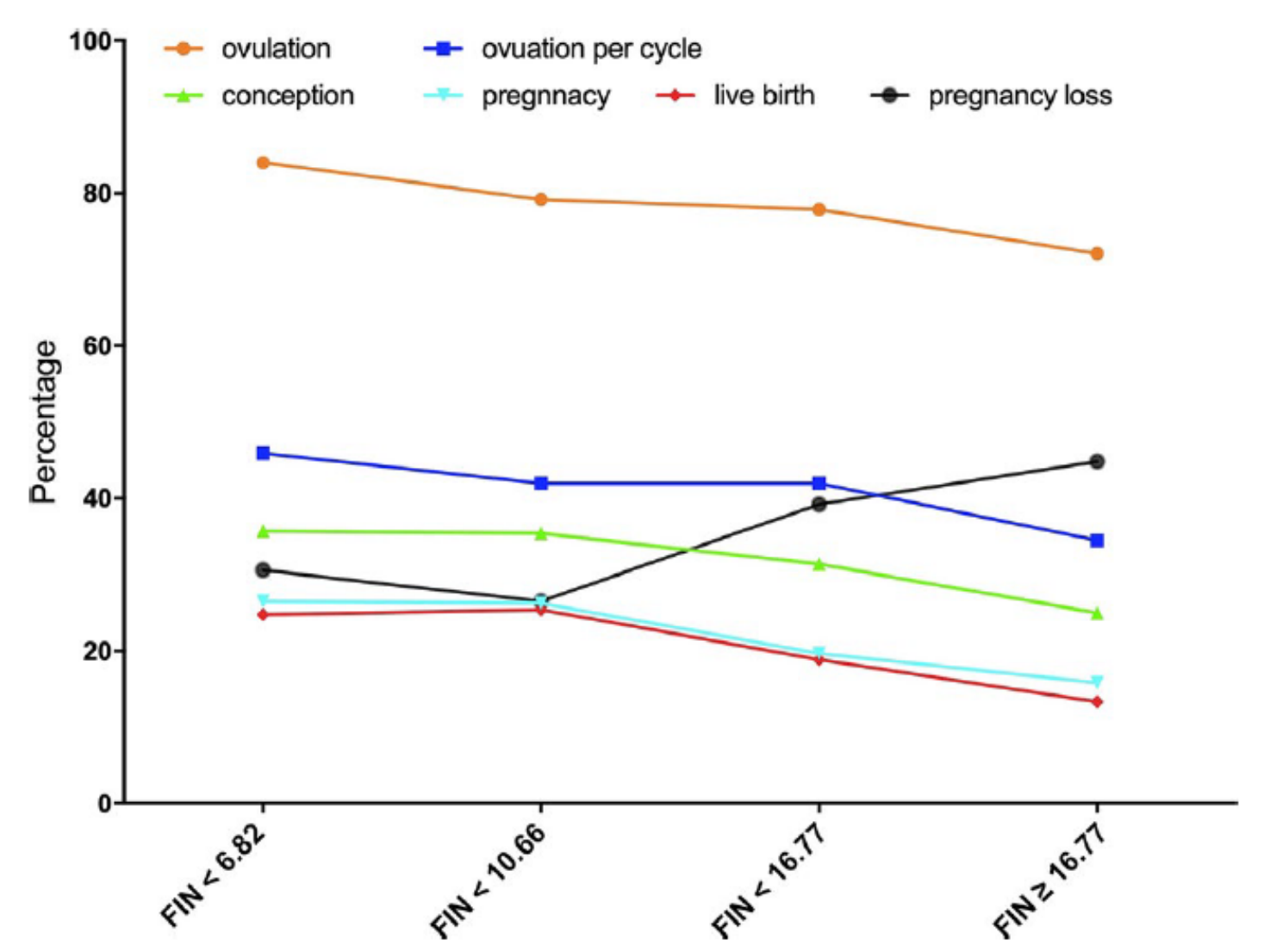
2017

Pregnancy Loss in PCOSAct Associated with Hyperinsulinemia



Zhang et al, Clin Endocrinol, 2019

Pregnancy Loss in PCOSAct Associated with Hyperinsulinemia

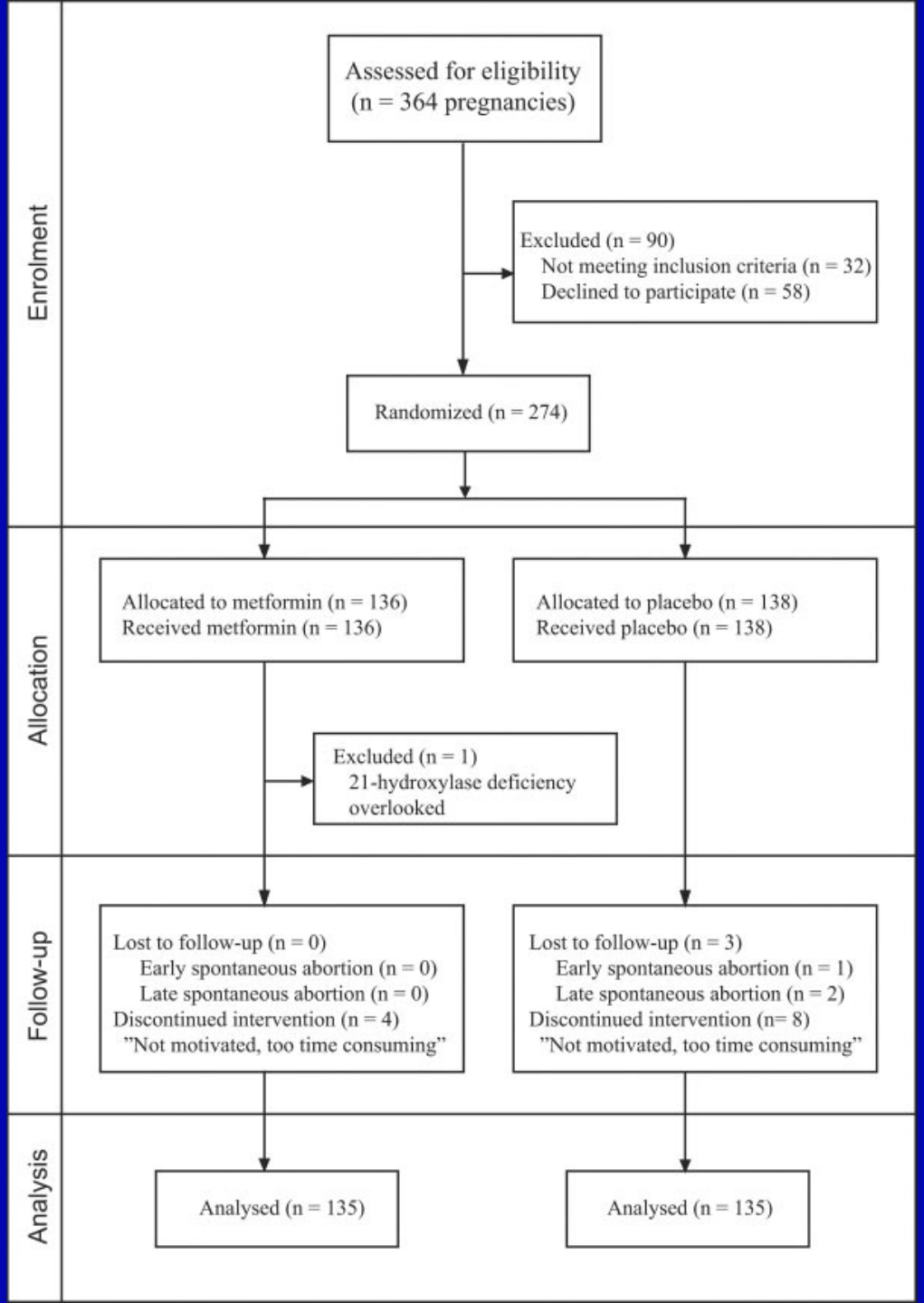


Zhang et al, Clin Endocrinol, 2019

Should we treat IGT or Prediabetes by HgbA1c Preconception?

A) Yes

B) No



ORIGINAL ARTICLE
Endocrine Research

Metformin *Versus* Placebo from First Trimester to Delivery in Polycystic Ovary Syndrome: A Randomized, Controlled Multicenter Study

Eszter Vanky, Solhild Stridsklev, Runa Heimstad, Pål Romundstad, Kristin Skogøy, Odrun Kleggetveit, Sissel Hjelle, Philip von Brandis, Torunn Eikeland, Karin Flo, Kristin Flaten Berg, Gabor Bunford, Agnethe Lund, Cecilie Bjerke, Ingunn Almås, Ann Hilde Berg, Anna Danielson, Gulim Lahmami, and Sven Magnus Carlsen*

PREGMET 1: Study 2

Metformin initiated after documentation of Intrauterine Pregnancy on U/S at ~10 wks

30% conceived on and continued metformin

JCEM, 2010

No Benefit of Metformin on Composite or Individual Enpoints

	Metformin (N=135)	Placebo (N =135)	P Value
Preeclampsia	7.4%	3.7%	0.18
Preterm Delivery	3.7%	8.7%	0.12
New Gestational Diabetes	17.6%	16.9%	0.87
Primary Composite Outcome	**25.9%**	**24.4%**	**0.78**

Vanky et al, JCEM, 2010

PREGMET 2 Study: Study 3

- 487 women randomized to metformin(n=244) or placebo (n=243).
- In the intention-to-treat analysis, the composite primary outcome of late miscarriage and preterm birth occurred in 12 (5%) of 238 women in the metformin group and 23 (10%) of 240 women in the placebo group (odds ratio [OR] 0·50, 95% CI 0·22–1·08; p=0·08).
- When all 3 studies combined: **(OR 0·43, 95% CI 0·23–0·79; p=0·004).**

» **Lovik et al, Lancet Diab Endocrinol, 2019**

A 39 y/o with BMI of 38.0 presents with unexplained infertility. She has been referred to you for treatment

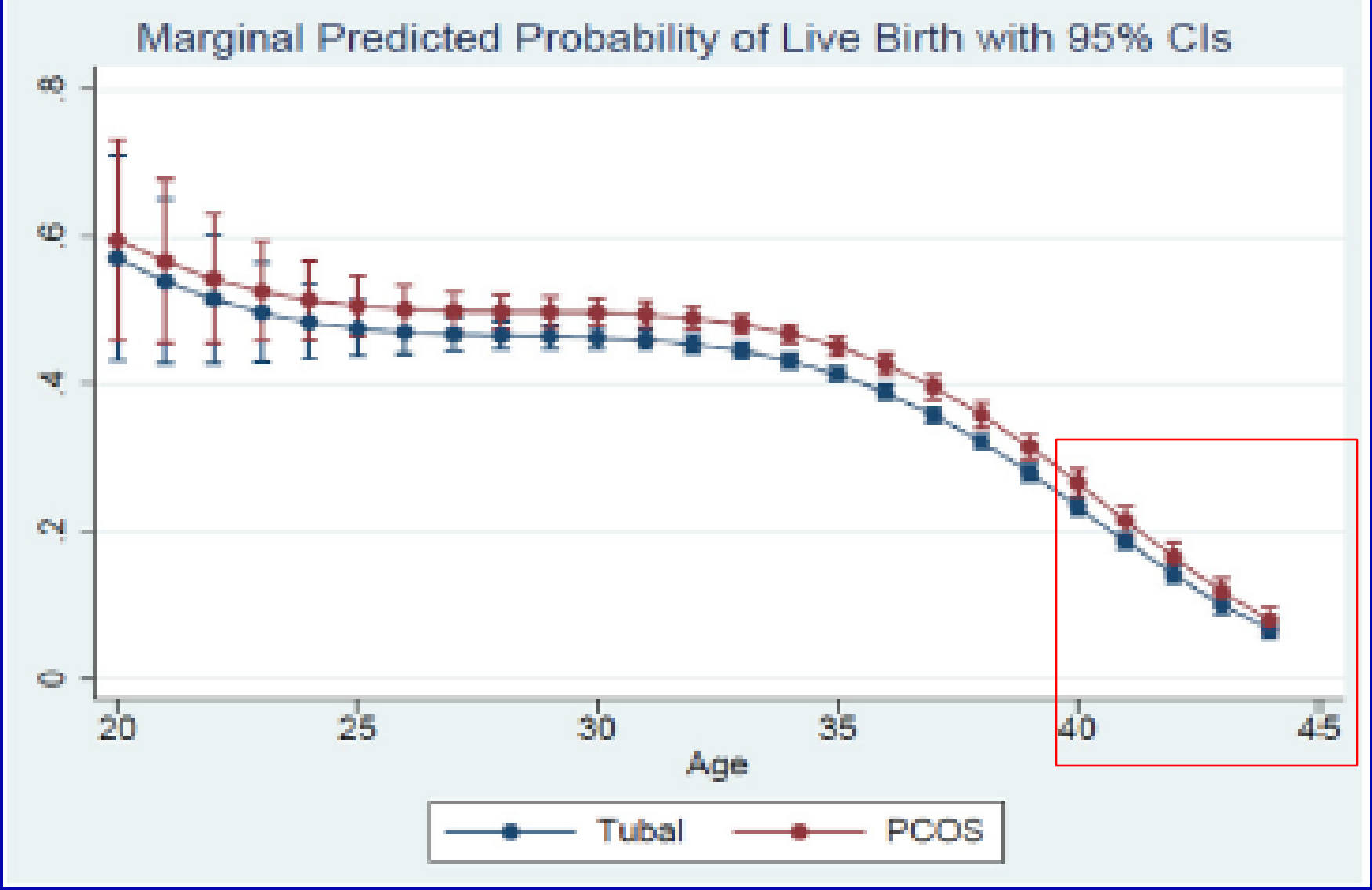
Your initial recommendation is to:

A) Lose 5% body weight before seeking fertility therapy

B) Screen for ovarian reserve

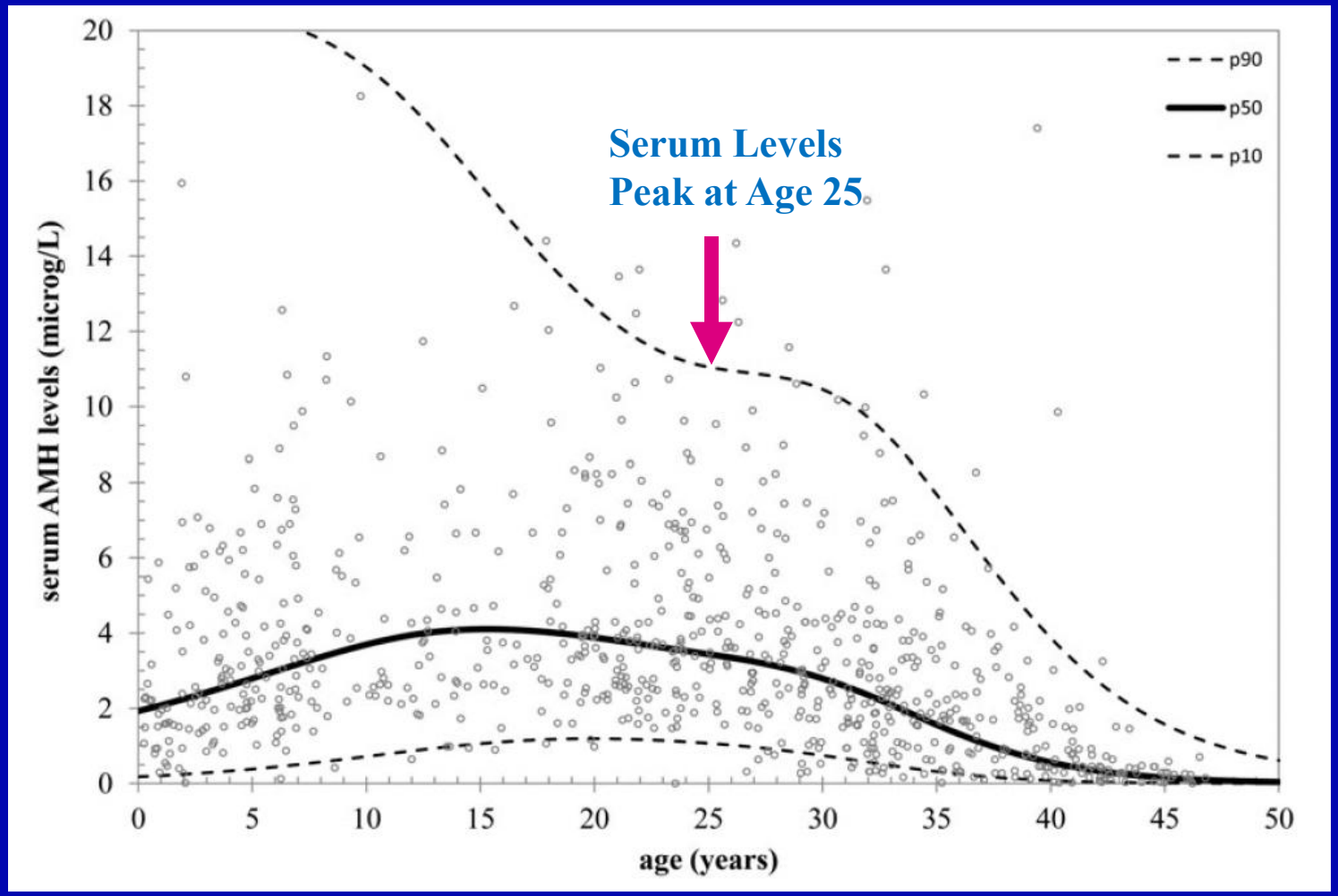
C) Recommend immediate fertility treatment

Age is the single most important predictor of Live Birth



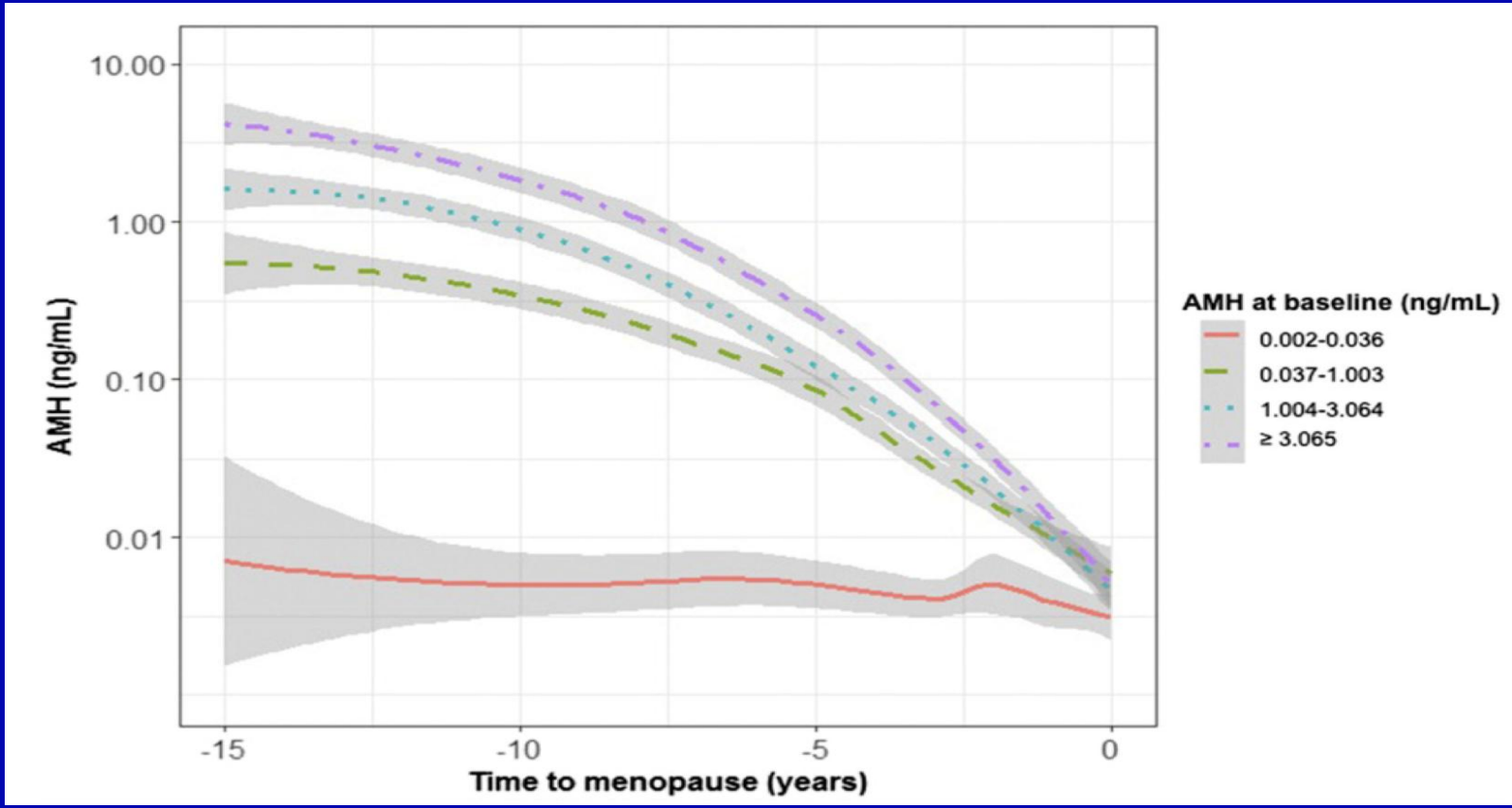
Kalra et al, Fertil Steril 2013

Anti-Mullerian Hormone (AMH) nomogram from birth to menopause in 804 healthy females



Lie Fong
JCEM,
2012

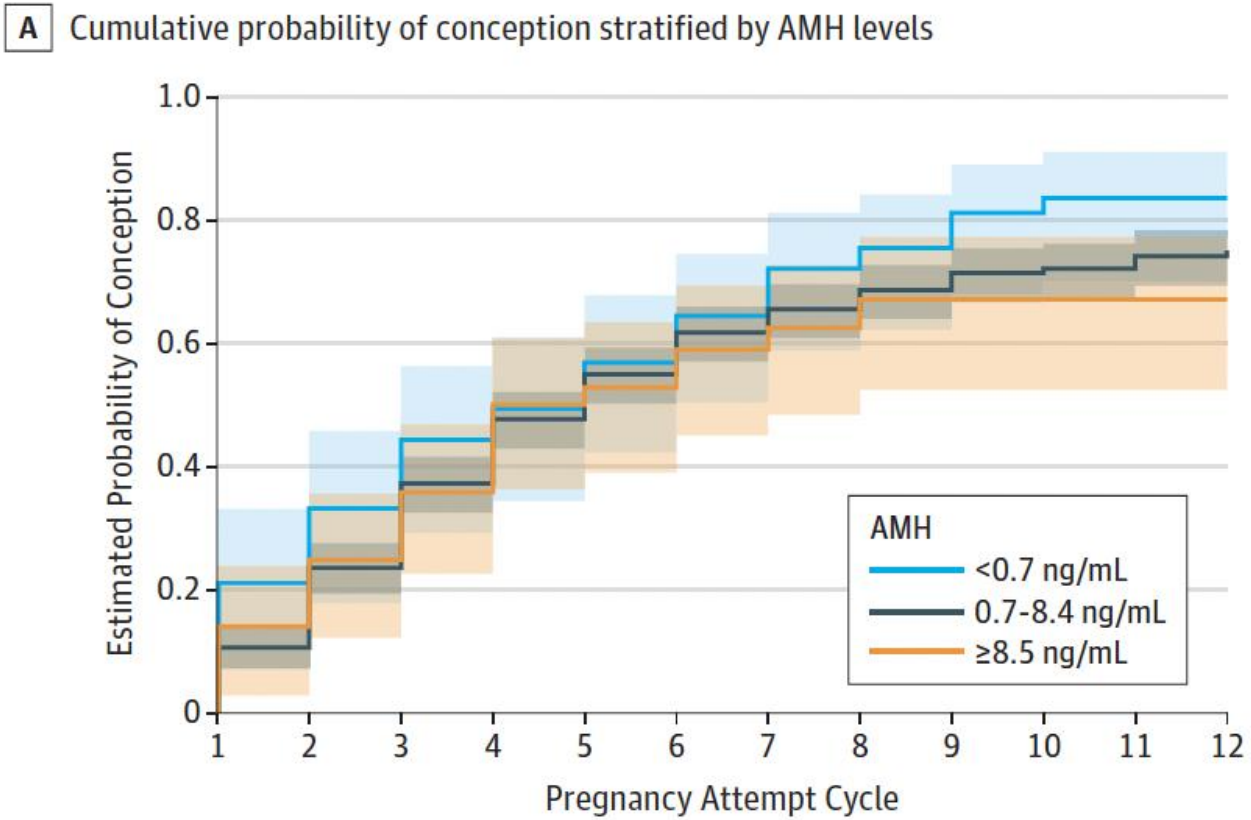
Analyzing Individual Patterns of AMH Change over time does not increase the predictive value of menopause



de Kat et al. J Clin Endocrinol Metab. 2019.

2434 premenopausal women from the Dutch population-based Doetinchem Cohort Study. Participants were followed up every 5 years for a total of 20 years, and AMH was measured in 6699 plasma samples with the picoAMH assay

Poor Predictive Value of AMH on Fecundity



No. at risk by serum AMH level, ng/mL

<0.7	39	49	59	51	45	37	30	19	14	8	6	5
0.7-8.4	309	405	404	340	277	221	170	133	104	83	70	58
≥8.5	33	52	52	43	32	27	20	14	10	8	6	6

Among women aged 30 to 44 years without a history of infertility who had been trying to conceive for 3 months or less, biomarkers indicating diminished ovarian reserve compared with normal ovarian reserve were not associated with reduced fertility.

Steiner et al, JAMA, 2017

What amount of weight loss can be expected preconception through a monitored 6 month Lifestyle (diet and exercise alone) Program in women with obesity and infertility?

A) None
B) less than 5%
C) 5-10%
D) greater than 10%

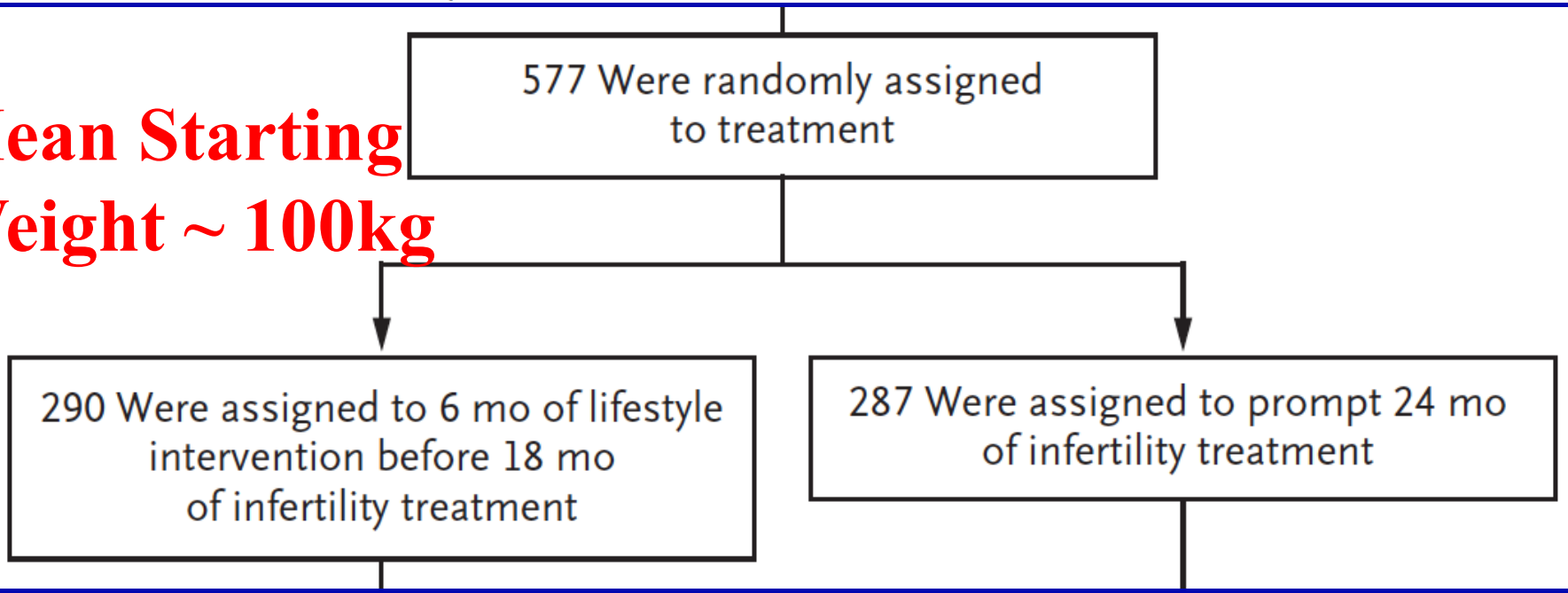
The NEW ENGLAND JOURNAL of MEDICINE 2016

ORIGINAL ARTICLE

Randomized Trial of a Lifestyle Program in Obese Infertile Women

Meike A.Q. Mutsaerts, M.D., Ph.D., Anne M. van Oers, M.D.,

Mean Starting Weight ~ 100kg



Lifestyle intervention: 6-month structured program

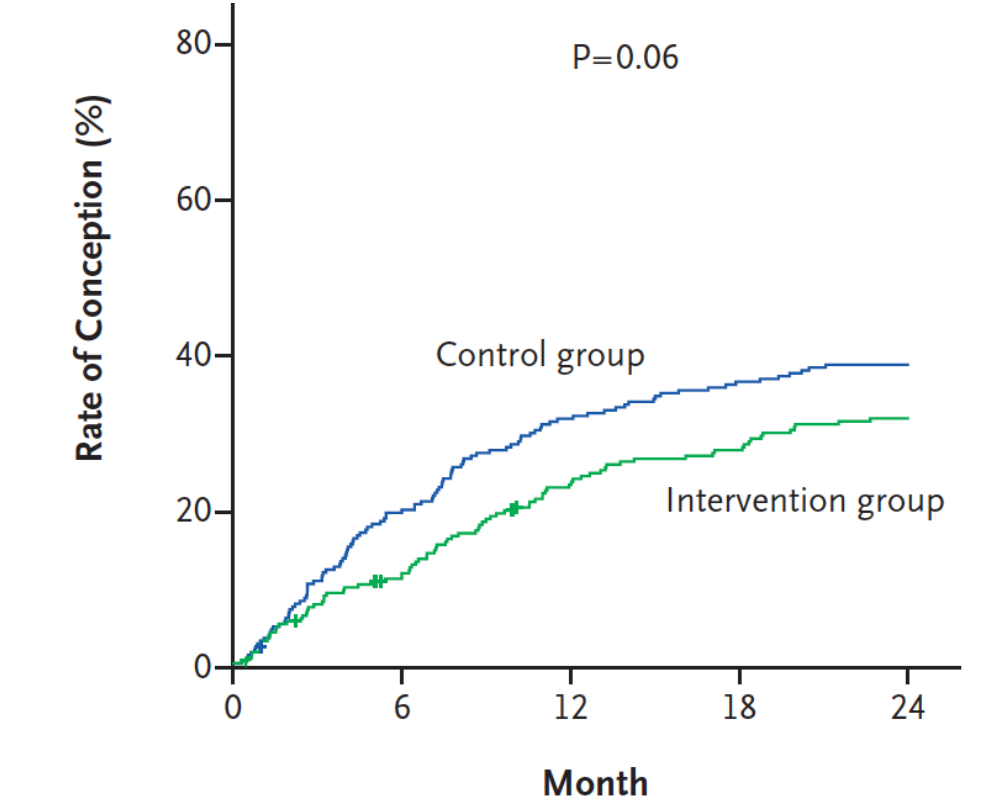
- goal of loss of 5 to 10% body weight
- Based on NIH guidelines
- 6 outpatient visits/ 4 telephone conultations
- Participants were guided by trained intervention coaches (nurses) or by dietitians who were trained before the trial.

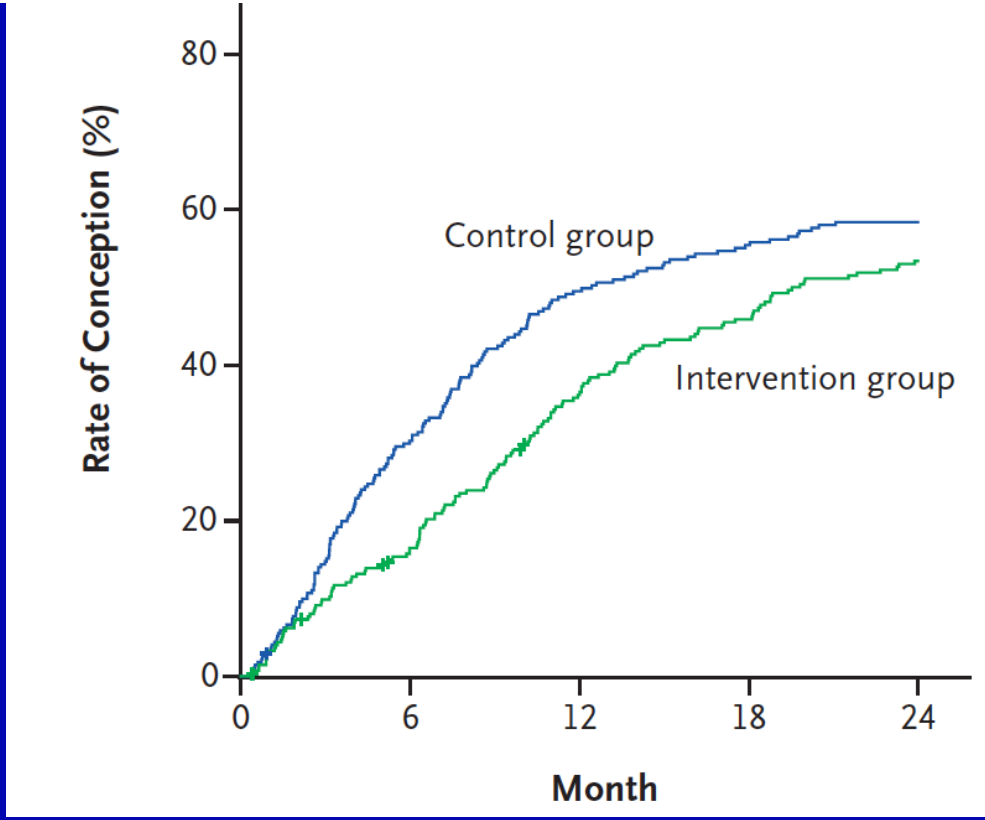
Weight Change in LifeStyle Study

	Lifestyle Intervention	Immediate Fertility Treatment	P Value
Baseline BMI (median)	36.0	36.0	NS
Absolute Change in BMI (IQR)	-1.3 (-2.5 to -0.07)	-0.30 (-1.0 to 0.60)	<.001
PercentChange in BMI	3.6% **-4.4 kg**	NS	<.001
Lost 5% of Body Weight	38%	0%	<.001

CONCLUSIONS

In obese infertile women, a lifestyle intervention preceding infertility treatment, as compared with prompt infertility treatment, did not result in higher rates of a vaginal birth of a healthy singleton at term within 24 months after randomization. (Funded by the Netherlands Organization for Health Research and Development; Netherlands Trial





Mutsaerts et al, NEJM, 2016

Mode of Conception Leading to Ongoing Pregnancy

	Lifestyle intervention (N = 280)	Immediate Treatment (N = 284)	RR 95% CIs
Natural	26%	16%	1.6 (1.2-2.3)
Ovulation Induction	13%	23%	0.6 (0.4-0.8)
IUI	8%	9%	0.9 (0.5-1.5)
IVF/ICSI	8%	11%	0.7 (0.4-1.2)

What amount of weight loss can be expected preconception through a an Enhanced 16 week Lifestyle, Counseling and Anti-Obesity Medication Program in women with obesity and infertility?

A) None

B) less than 5%

C) 5-10%

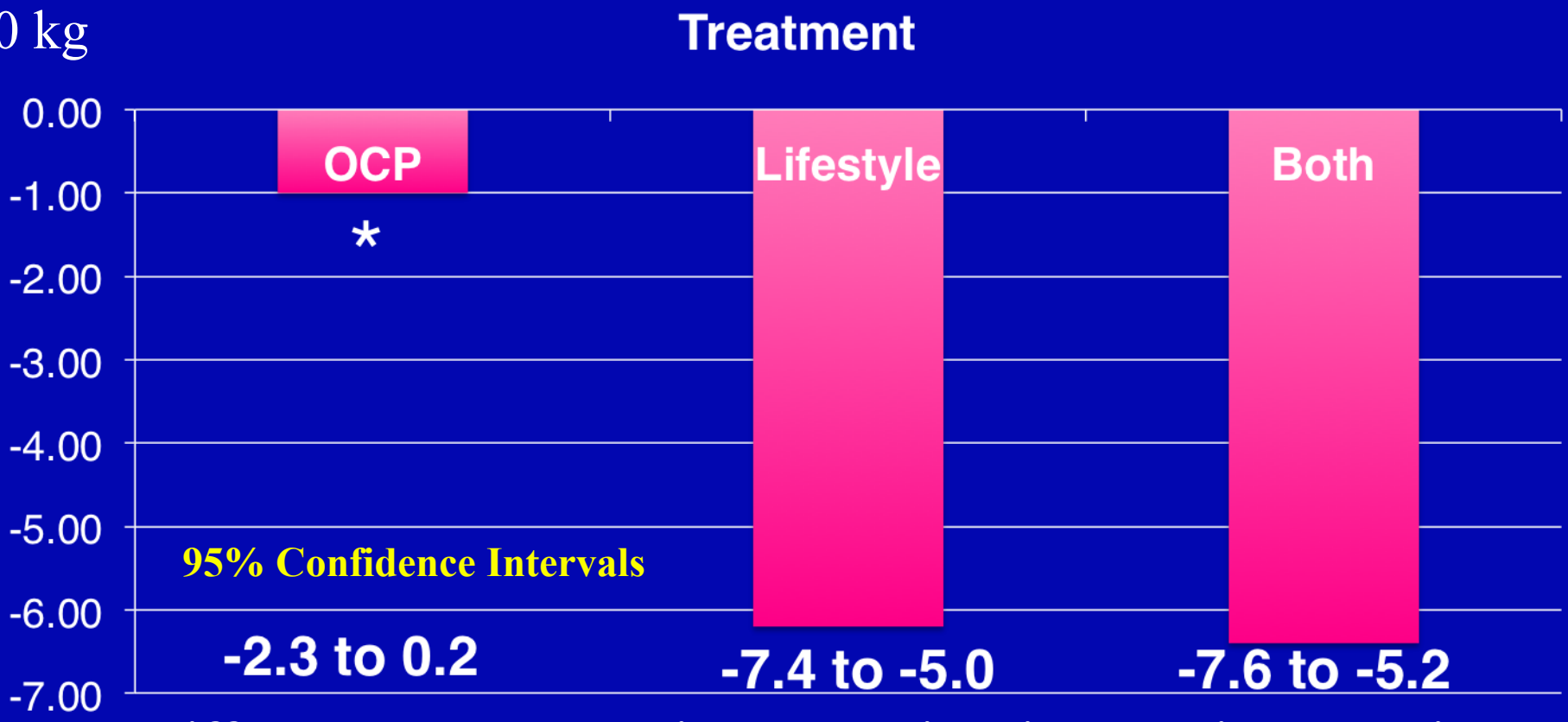
D) greater than 10%

Lifestyle Modification with Weight Loss (7% Target)

- Increased Physical Activity (Target:150 mins/wk)
- Brief Behavioral Modification Lessons (Monthly)
  - Adapted from the Diabetes Prevention Program
- Meal Replacements for all 3 meals with fresh vegetables/fruit supplement (Caloric Restriction)
  - 500kcal/day Deficit
- Weight loss medication (BMI ≥ 30 only)
  - Sibutramine 5-15 mg/d
  - After the FDA Sibutramine Advisory in 2010 we used over the counter orlistat (60 mg) TID with meals

Weight Loss in Kg After Preconception Intervention of 16 Weeks in women with PCOS

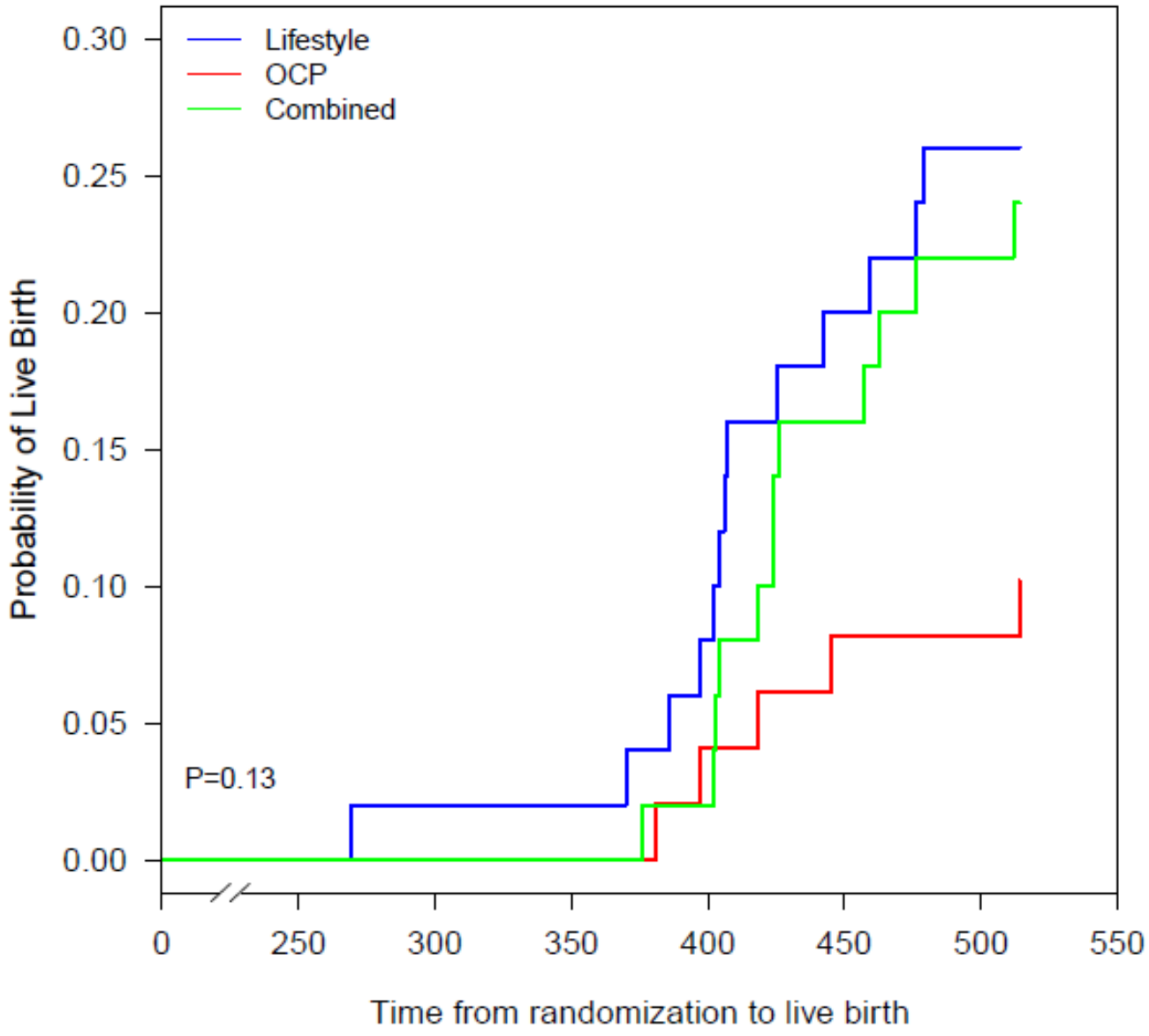
Starting BMI
~100 kg



No difference between weight loss with sibutramine or orlistat

*** P < .0001**

Legro et al, JCEM, 2015



Kaplan Meier Curve: Live Birth

Primary Outcome

Legro et al, JCEM, 2015

PLOS MEDICINE

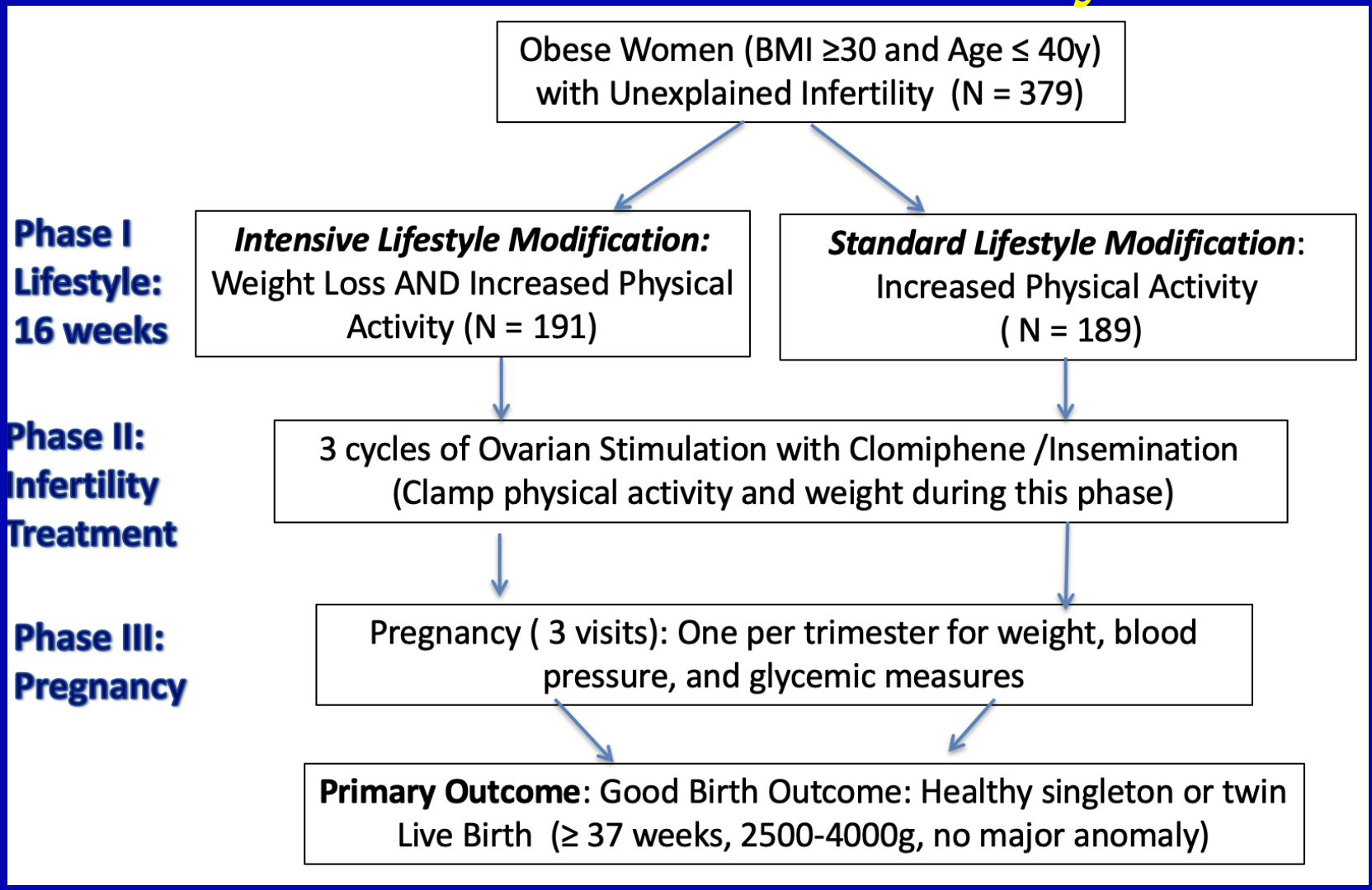
RESEARCH ARTICLE

Effects of preconception lifestyle intervention in infertile women with obesity: The FIT-PLESE randomized controlled trial

Richard S. Legro[1]*, Karl R. Hansen[2], Michael P. Diamond[3], Anne Z. Steiner[4], Christos Coutifaris[5], Marcelle I. Cedars[6], Kathleen M. Hoeger[7], Rebecca Usadi[8], Erica B. Johnstone[9], Daniel J. Haisenleder[10], Robert A. Wild[2], Kurt T. Barnhart[5], Jennifer Mersereau[4], J. C. Trussell[11], Stephen A. Krawetz[12], Penny M. Kris-Etherton[13], David B. Sarwer[14], Nanette Santoro[15], Esther Eisenberg[16], Hao Huang[17], Heping Zhang[17], for the Reproductive Medicine Network[¶]

2022

FIT-PLESE Study



Legro et al, 2022

16 Week Lifestyle Intervention: Phase 1

- Physical Activity (Aim for 10,000 steps a day)
  - increasing by baseline 500 steps a day per week.
- Weight loss (Aim for 7% weight loss)
  - Meal replacements (nutritionally replete for pregnancy-Nutrisystems)
    - Vegetable/fruit supplements, snacks 100 kcal/day
  - Drug
    - Over the counter use of Orlistat 60 mg with meals (ALLI).
    - Vitamin supplement
- Digital: Wireless Weight (ARIA scale) activity tracking devices (FIT BITs) were incorporated into the intervention to increase compliance

Legro et al, 2022

Significant Improvement in Metabolic Parameters with Weight Loss

	Standard Lifestyle	Intensive Lifestyle	P value
Sex Hormone Binding Globulin (SHBG) (nmol/L)	1.5 ± 14.1	4.6 ± 14.2	0.018
Fasting insulin (uIU/mL)	-1.2± 22.1	-4.1 ± 15.0	<0.001
HgbA1c (%)	0.09 ± 0.33	-0.03 ± 0.25	0.005
Adiponectin (ng/mL)	-3245±7402	1900 ± 6334	0.001
Highly sensitive C-Reactive Protein (hsCRP) (mg/L)	0.4 ± 5.2	-2.3 ± 14.1	<0.001

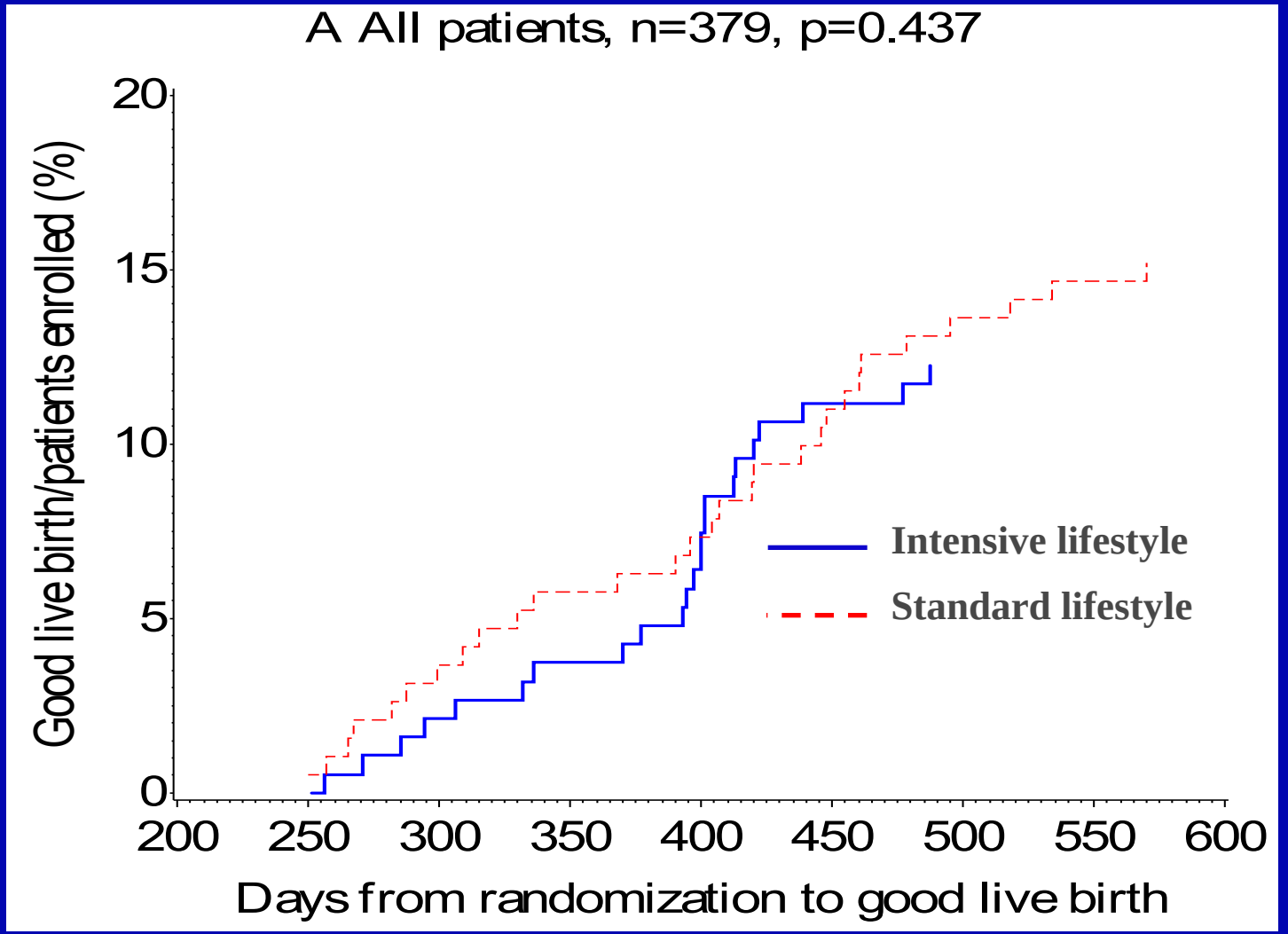
Legro et al, 2022

No difference in Primary Outcome- Good Live Birth

Birthweight: 2,500-4,000g.

Term,

No major anomaly



Legro et al, 2022

A 25 y/o presents with a BMI of 41 and desires pregnancy after she "becomes more healthy". Her w/u is negative: MHO. You recommend:

A) Weight loss with bariatric surgery

B) Weight loss with medication

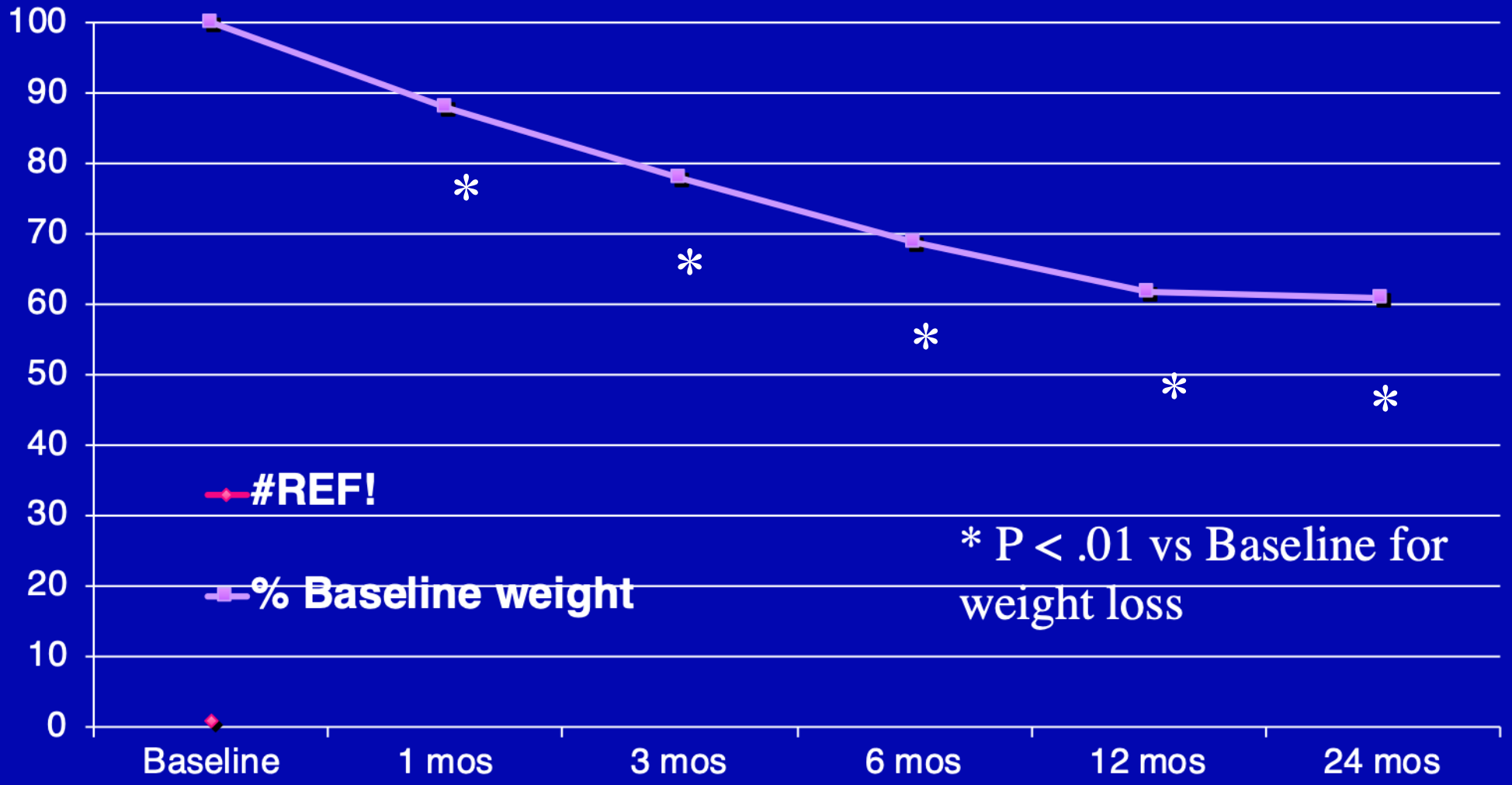
C) Weight loss with enhanced multifocal lifestyle intervention

D) Weight loss with lifestyle alone

E) Immediate infertility treatment

Weight Loss in Reproductive Age Women after Roux-en-Y Gastric Bypass Surgery

Legro et al, JCEM, 2012



GLP-1 Agonist: Preferred Anti-Obesity Drug

- Strengths
  - Well tolerated
  - Weekly administration
  - Few adverse side effects
  - Few mental status effects
  - Very Efficacious
- Weaknesses
  - Parenteral
  - Expensive
  - Usually no insurance coverage for obesity
  - No studies of subsequent fertility

Tirzepatide: ? Future Drug of Choice

- Dual GIP and GLP-1 agonist

The NEW ENGLAND JOURNAL of MEDICINE

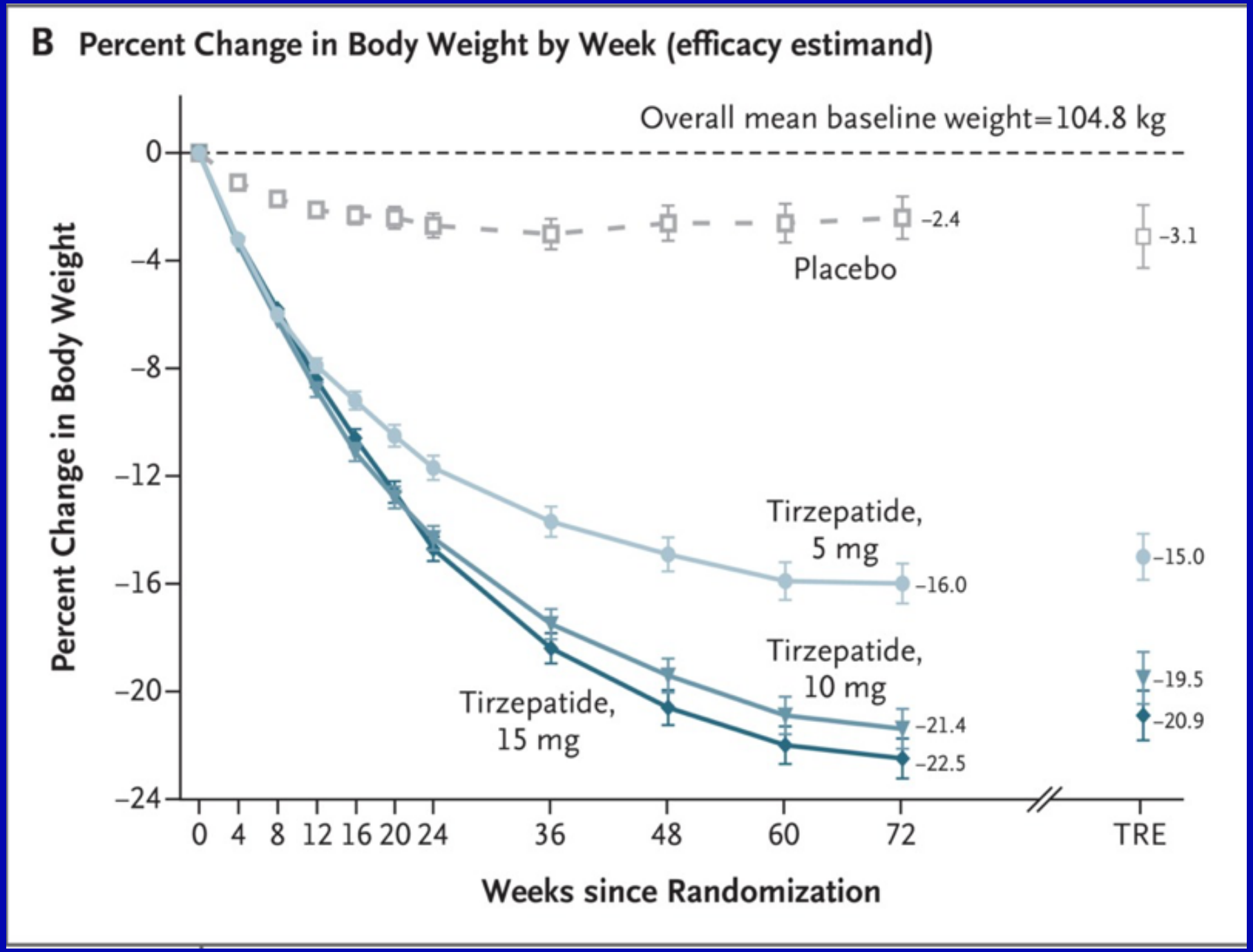
RESEARCH SUMMARY

Tirzepatide Once Weekly for the Treatment of Obesity

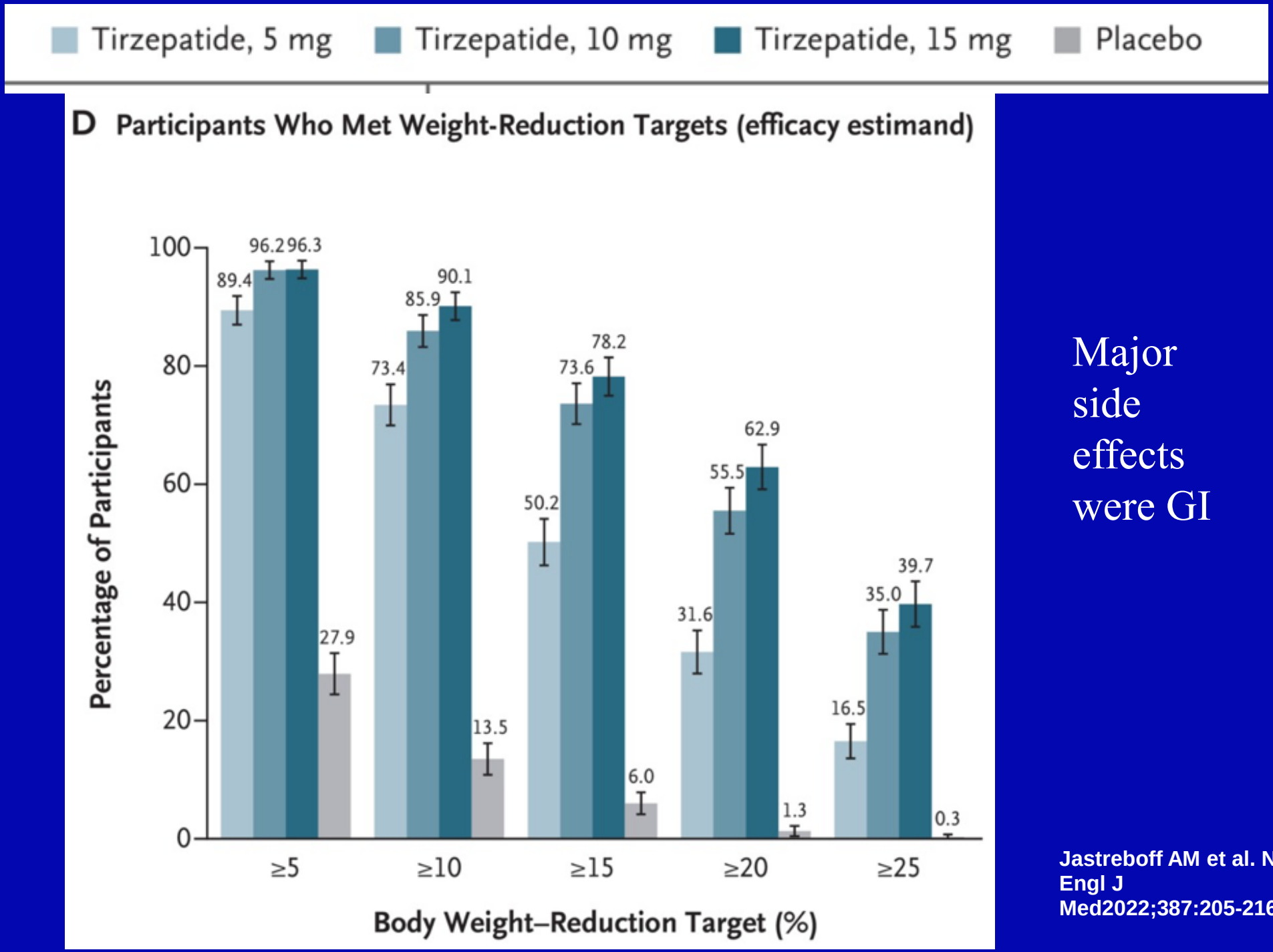
Jastreboff AM et al. DOI: 10.1056/NEJMoa2206038

CLINICAL PROBLEM

2022



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



Major side effects were GI

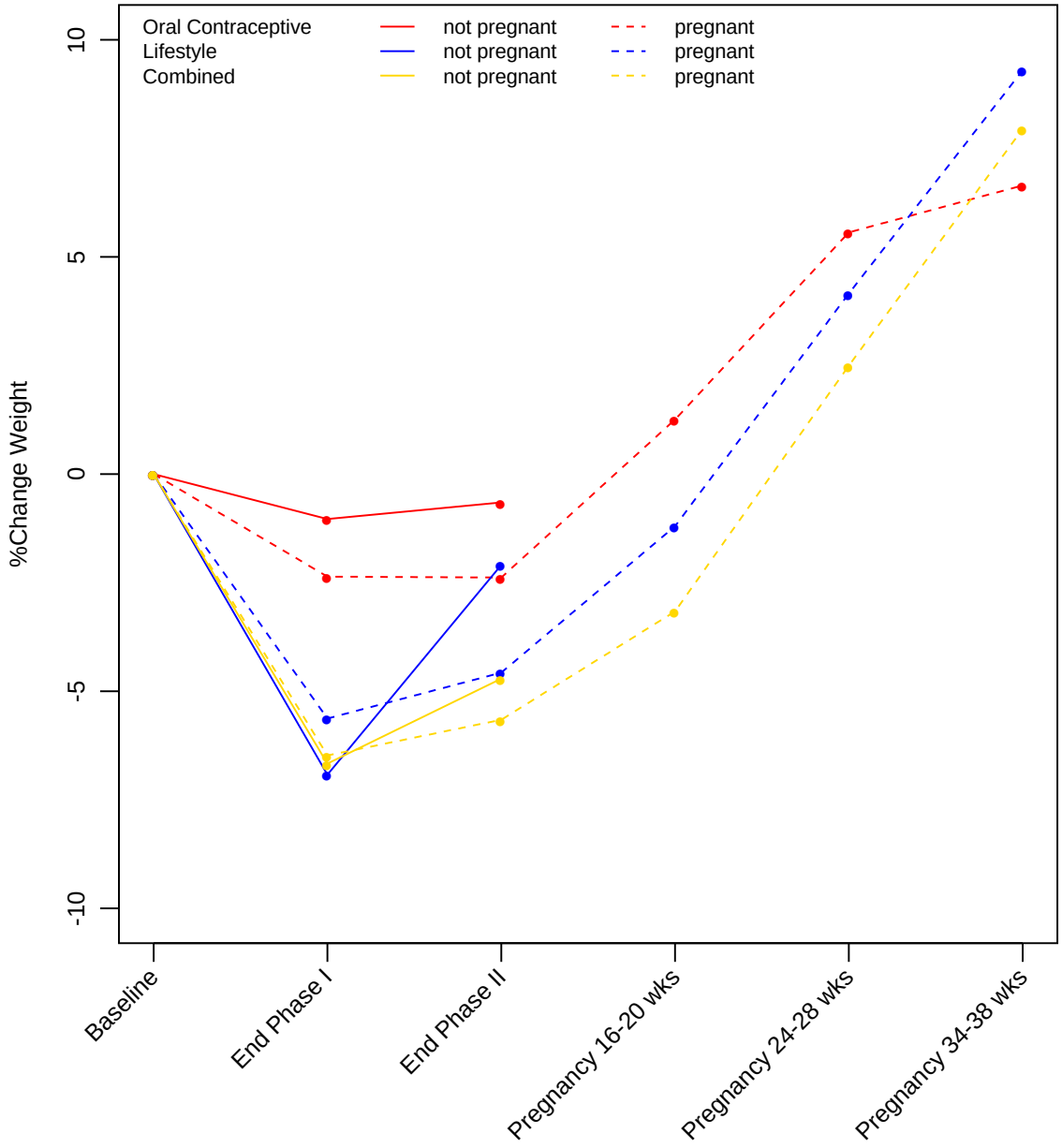
Jastreboff AM et al. N Engl J Med2022;387:205-216

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%

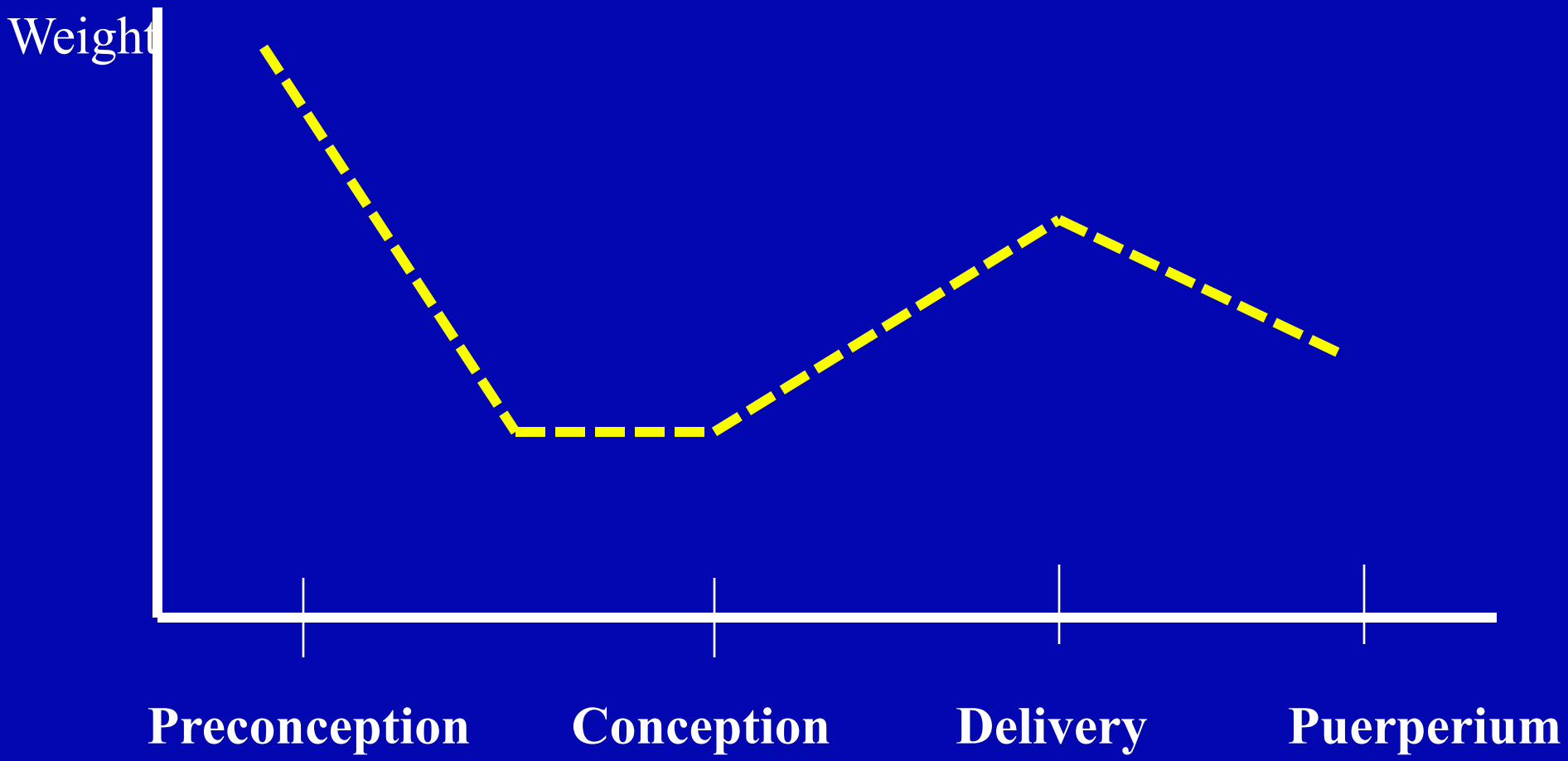
Knowledge Gaps of Weight Loss in Obese Women with Infertility

- Dose?
  - Is there an ideal rate of weight loss or activity increase
- Duration?
  - How long should the intervention be instituted
- Timing?
  - Is the intervention before or during infertility treatment or both?
- Weight stabilization?
  - Should there be a period of weight stabilization before treatment?
- Varying Response Ovulatory vs Anovulatory (PCOS)?

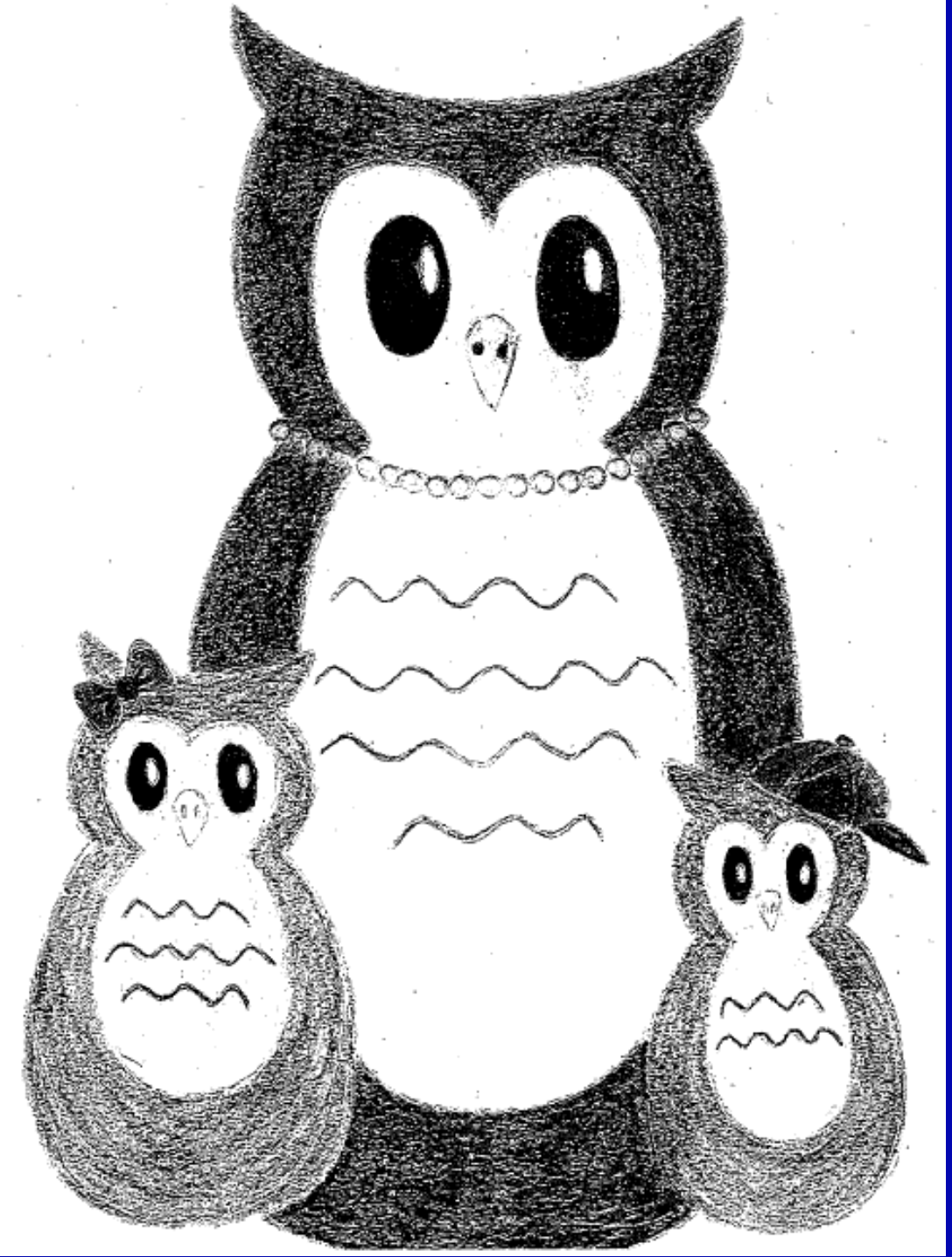


Weight Rebound During Pregnancy After Preconception intervention

The Expert Based Yo-Yo-ing of Weight in Obese Women Seeking Pregnancy




Thanks to all! And to the NIH who has funded most of it: K08, K24, U54, U10,RO1 grants
多囊卵巢综合征治疗RCT培训



Thank you Patient Participants!