Challenges in Diagnosis and Treatment of Polycystic Ovary Syndrome

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PCOS Challenge
Lake Lanier, Georgia
September 21, 2014

Proposed Diagnostic Criteria for PCOS

	NIH	Rotterdam (2 of 3 Met)	Androgen Excess PCOS Society (Hyper-Androgenism With 1 of 2 Remaining Criteria)
Androgen statues			
• Clinical Hyperandrogenom	XX or	X or	XX or
• Biochemical Hyperadrogenism	XX	X	XX
Menstrual history			
• Oblig- or anovulation	XX	X	XX
Ovarian apperance			
• Ovarian size/morphology		X	X

Legro et al JCEM 98:4565, 2013

Diagnostic Strengths and Weaknesses - Hyperandrogenism -

	Strength	Limitation
Hyperandrogenism	• Included as a component in all major classifications • A major clinical concern for patients • Animal models employing androgen excess resembling but not fully mimicking human disease	• Measurement is only performed in blood • Concentrations differ during time of day • Concentrations differ with age • Normative date are not clearly defined • Assays are not standardized across laboratories • Clinical hyperandrogenism is difficult to quantify and may vary by ethnic group, eg, low rates of hirsutism in women with PCOS from east Asia • Tissue sensitivity is not assessed

Legro et al JCEM 98:4565, 2013

Diagnostic Strengths and Weaknesses
- Ovulatory Dysfunction -

	Strength	Limitation
Ovulatory Dysfunction	• Included as a component in all major classifications • A major clinical concern for patients • Infertility a common clinical complaint	• Normal ovulation is poorly defined • Normal ovulation varies over a woman's lifetime • Ovulatory dysfunction is difficult to measure objectively • Anovulatory cycles may have bleeding patterns that are interpreted as normal

Legro et al JCEM 98:4565, 2013

Diagnostic Strengths and Weaknesses
- PCO Morphology -

	Strength	Limitation
PCO Morphology	• Historically associated with syndrome • May be associated with hypersensitivity to ovarian stimulation	• **Technique dependent** • **Difficult to obtain standardized measurement** • **Lack of normative standards across the menstrual cycle and lifespan (notably in adolescence)** • **May be present in other disorders that mimic PCOS** • **Technology required to accurately image not universally available** • **Transvaginal imaging possibly inappropriate in certain circumstances (eg, adolescence) or certain cultures**

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Diagnosis to Exclude

Disorder	Test	Abnormal Values
Thyroid Disease	Serum TSH	TSH > the upper limit of normal suggests hypothyroidism; TSH < the lower limit, usually < 0.1 mIU/L, suggests hyperthyroidism
Prolactin excess	Serum prolactin	>Upper limit of normal for the assay
Nonclassical congenital adrenal hyperplasia	Early morning (before 8 AM) serum 17-OHP	200-400 ng/dL depending on the assay (applicable to the early follicular phase of a normal menstrual cycle as levels rise with ovulation), but a cosyntropin stimulation test (250 µg) is needed if levels fall near the lower limit and should stimulate 17 –OHP > 1000 ng/dL

Legro et al JCEM 98:4565, 2013

Cardiovascular Risk Stratification in Women with PCOS

At risk – PCOS women with any of the following risk factors:

- Obesity (especially increased abdominal adiposity)
- Cigarette smoking
- Hypertension
- Dyslipidemia (increased LDL-cholesterol and/or non-HDL-cholesterol
- Subclinical vascular disease
- Impaired glucose tolerance
- Family history of premature cardiovascular disease (< 55 y of age in male relative; < 65 y of age in female relative)

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Cardiovascular Risk Stratification in Women with PCOS

- **At high risk – PCOS women with:**
  - Metabolic syndrome
  - Type 2 Diabetes Mellitus
  - Overt vascular or renal disease, cardiovascular diseases
  - Obstructive Sleep Apnea

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Considerations for Use of Contraception

Criteria	Further Classification	Condition 1	Condition 2	Condition 3	Condition 4
		A condition for which there is no restriction	A condition for which the advantages outweigh risks	A condition for which the risks outweigh advantages	A condition that represent unacceptable health risk
Age	Menarche to < 40 y	X			
	> 40 y		X		
Smoking	Age < 35 y		X		
	Age ≥ 35 y and smokes < 15 cigarettes/d			X	
	Age ≥ 35 y and smokes ≥ 15 cigarettes/d				X
Obesity	BMI < 30 kg/m^2		X		
	BMI ≥ 30 kg/m^2		X		

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		A condition for which there is no restriction	A condition for which the advantages outweigh risks	A condition for which the risks outweigh advantages	A condition that represent unacceptable health risk
Hypertension	**History of gestational** hypertension	X			
	Adequately controlled hypertension			X	
	Elevated blood pressure levels systolic, 140-159 mm Hg; or diastolic, 90-99 mm Hg			X	
	Elevated blood pressure levels systolic, ≥ 160 mm Hg; or diastolic, ≥ 100 mm Hg				X

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Criteria	Further Classification	Condition 1	Condition 2	Condition 3	Condition 4
		A condition for which there is no restriction	A condition for which the advantages outweigh risks	A condition for which the risks outweigh advantages	A condition that represent unacceptable health risk
Dyslipidemia	Known hyperlipidemias		X	X	
Depression	Depressive disorders	X			

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Considerations for Use of Contraception

Criteria	Further Classification	Condition 1	Condition 2	Condition 3	Condition 4
		A condition for which there is no restriction	A condition for which the advantages outweigh risks	A condition for which the risks outweigh advantages	A condition that represent unacceptable health risk
Diabetes	**History of** gestational diabetes		X		
	Nonvascular diabetes		X		
	Vascular disease including neuropathy, retinopathy, nephropathy			X	X
	Diabetes duration > 20 y			X	X

Legro et al JCEM 98:4565, 2013

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 8, 2007 VOL. 356 NO. 6

Clomiphene, Metformin, or Both for Infertility in the Polycystic Ovary Syndrome

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February 8, 2007

Enrollment and Outcomes

The NEW ENGLAND JOURNAL of MEDICINE

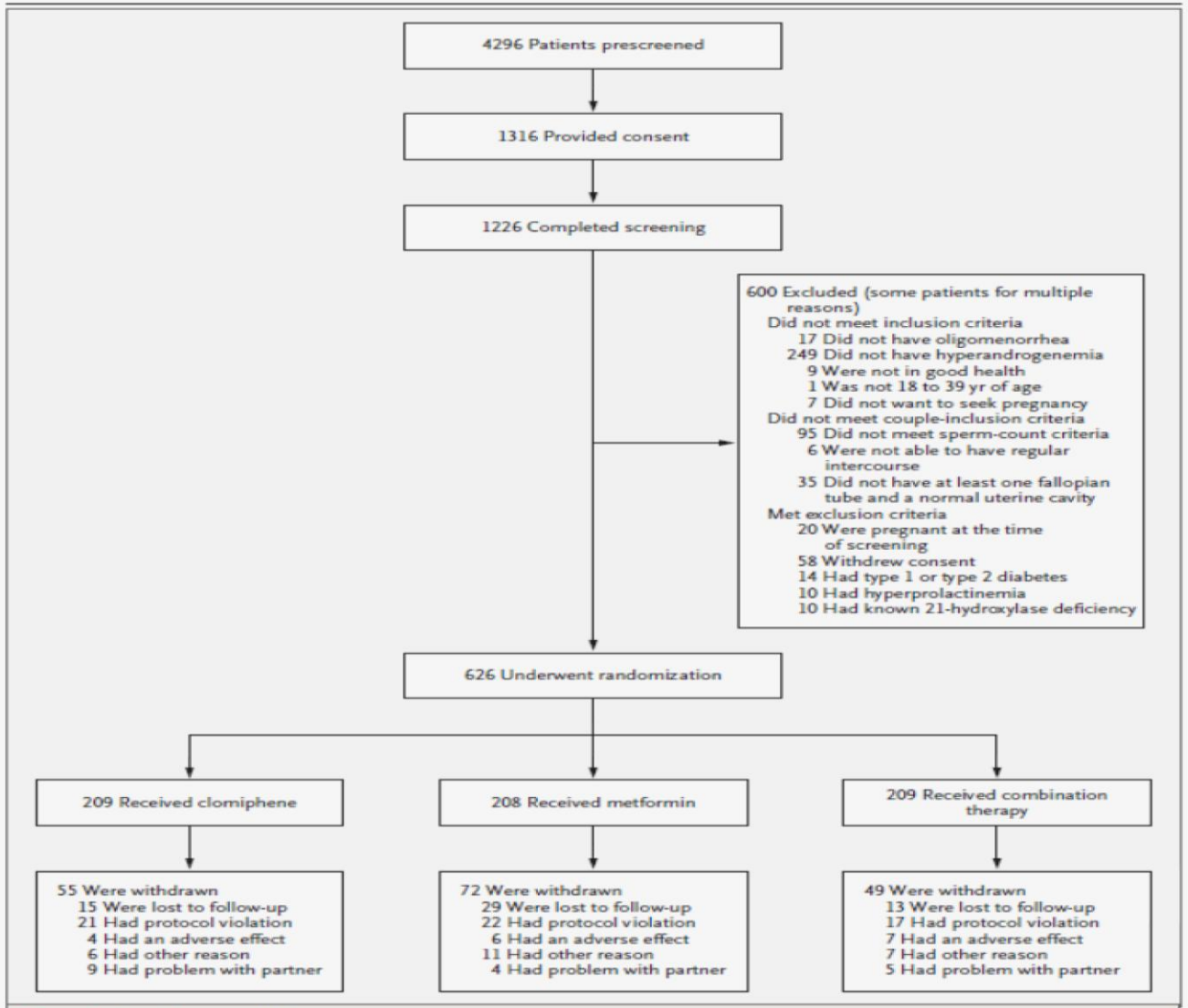
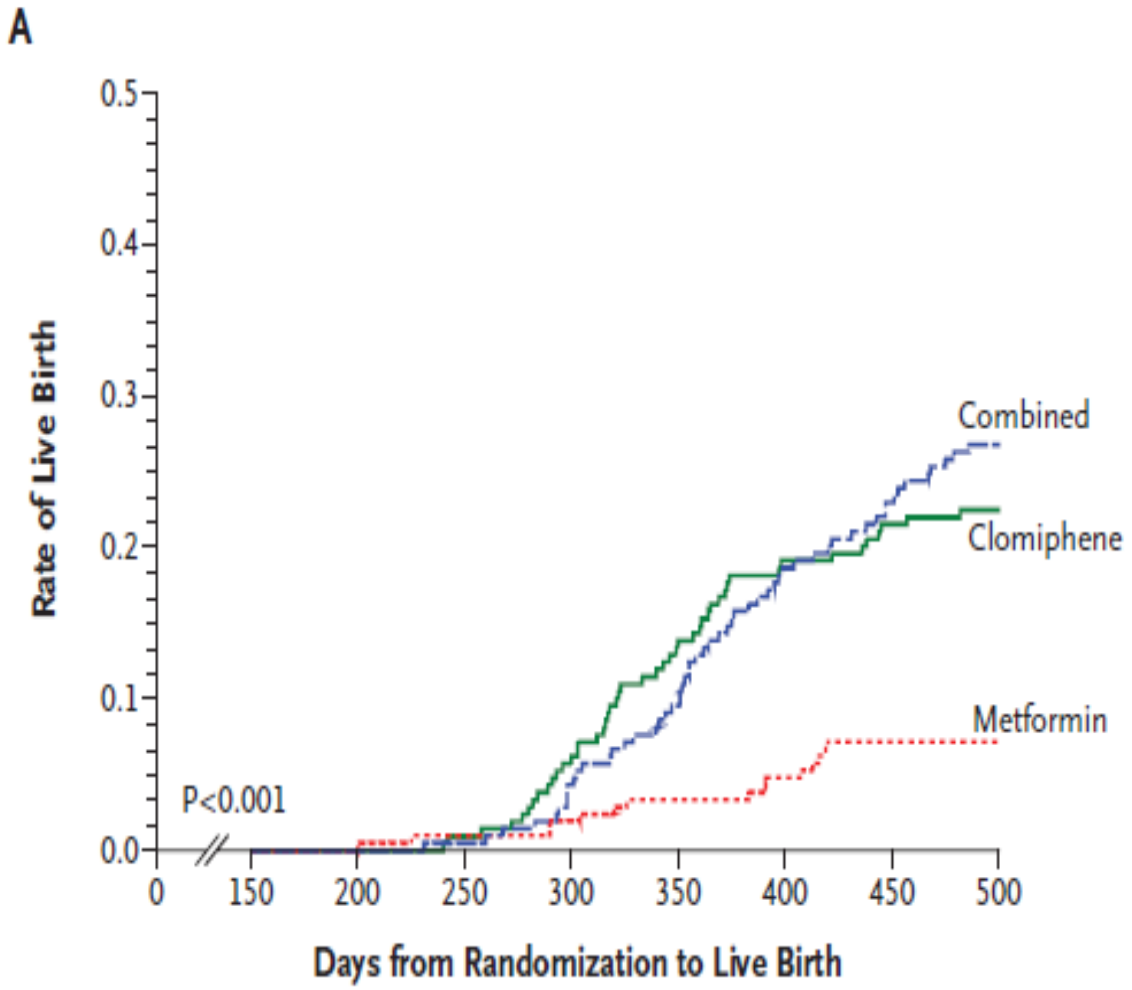


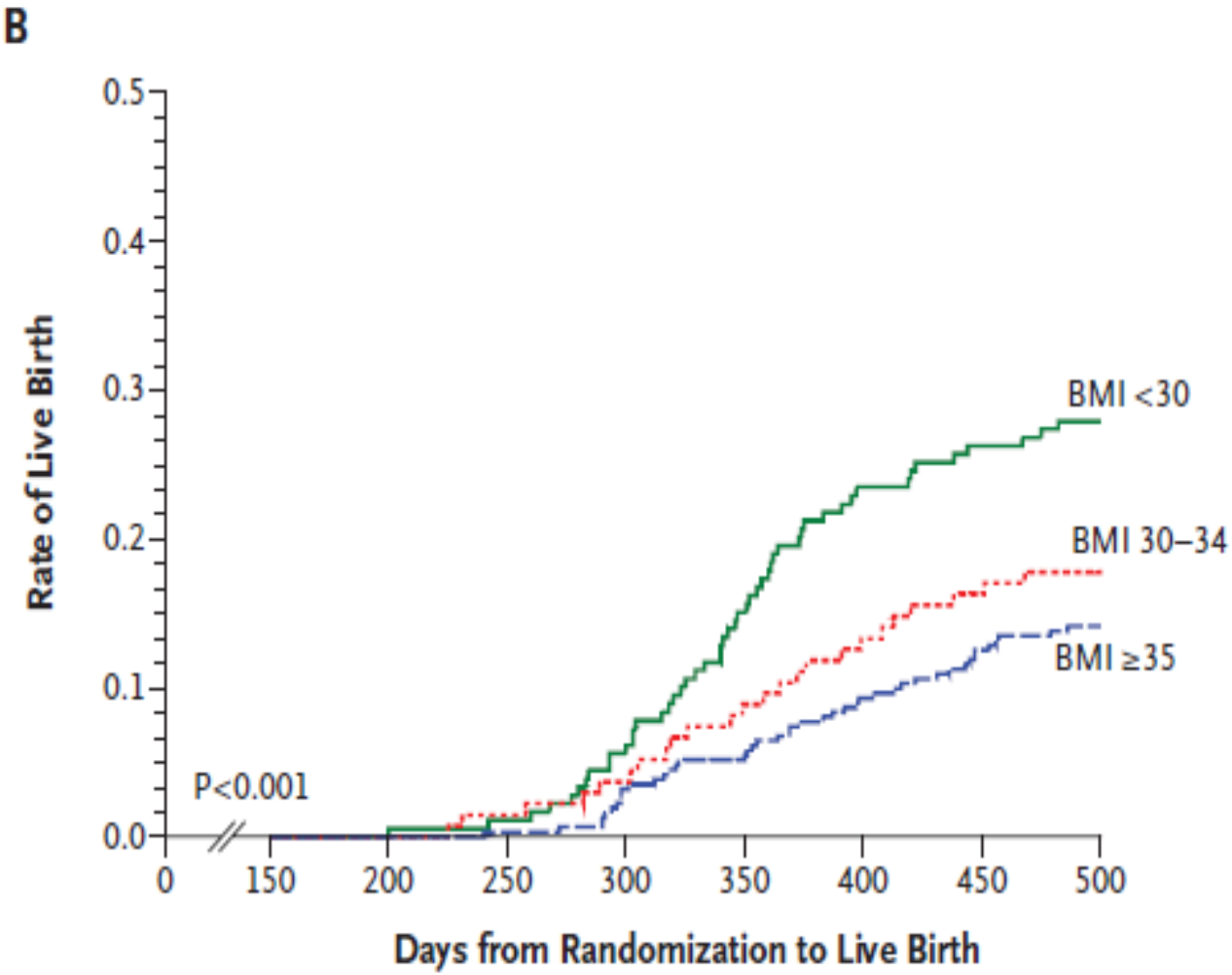
Figure 1. Enrollment and Outcomes.

Rates of Ovulation, Pregnancy, and Pregnancy Loss

Variable	Clominphene Group (N=209)	Metformin Group (N=208) *no./total no. (%)*	Combination-Therapy Group (N=209)	Absolute Difference between Combination Therapy and Metformin % (95% CI)
Ovulation	462/942 (49.0)	296/1019 (29.0)	582/964 (60.4)	31.4 (24.7 to 38.0)
Conception	62/209 (29.7)	25/208 (12.0)	809/209 (38.3)	26.3 (18.4 to 34.2)
Pregnancy	50/209 (23.9)	18/208 (8.7)	65/209 (31.1)	22.4 (15.0 to 29.8)
Singleton	47/50 (94.0)	18/18 (100.0)	63/65 (96.9)	-3.1 (-7.3 to 1.1)
Twins	2/50 (4.0)	0	2/65 (3.1)	-3.1 (-10.1 to 16.3)
Triplets	1/50 (2.0)	0	0	0 (-12.7 to 12.7)
Live Birth	47/209 (22.5)	15/208 (7.2)	56/209 (26.8)	19.6 (12.6 to 26.6)

Kaplan-Meier Curves for Live Birth





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome

Richard S. Legro, M.D., Robert G. Brzyski, M.D., Ph.D., Michael P. Diamond, M.D., Christos Coutifaris, M.D., Ph.D., William D. Schlaff, M.D., Peter Casson, M.D., Gregory M. Christman, M.D., Hao Huang, M.D., M.P.H., Qingshang Yan, Ph.D., Ruben Alvero, M.D., Daniel J. Haisenleder, Ph.D., Kurt T. Barnhart, M.D., G. Wright Bates, M.D., Rebecca Usadi, M.D., Scott Lucidi, M.D., Valerie Baker, M.D., J.C. Trussell, M.D., Stephen A. Krawetz, Ph.D., Peter Snyder, M.D., Dana Ohl, M.D., Nanette Santoro, M.D., Esther Eisenberg, M.D., M.P.H., and Heping Zhang, Ph.D., for the NICHD Reproductive Medicine Network*

July 10, 2014

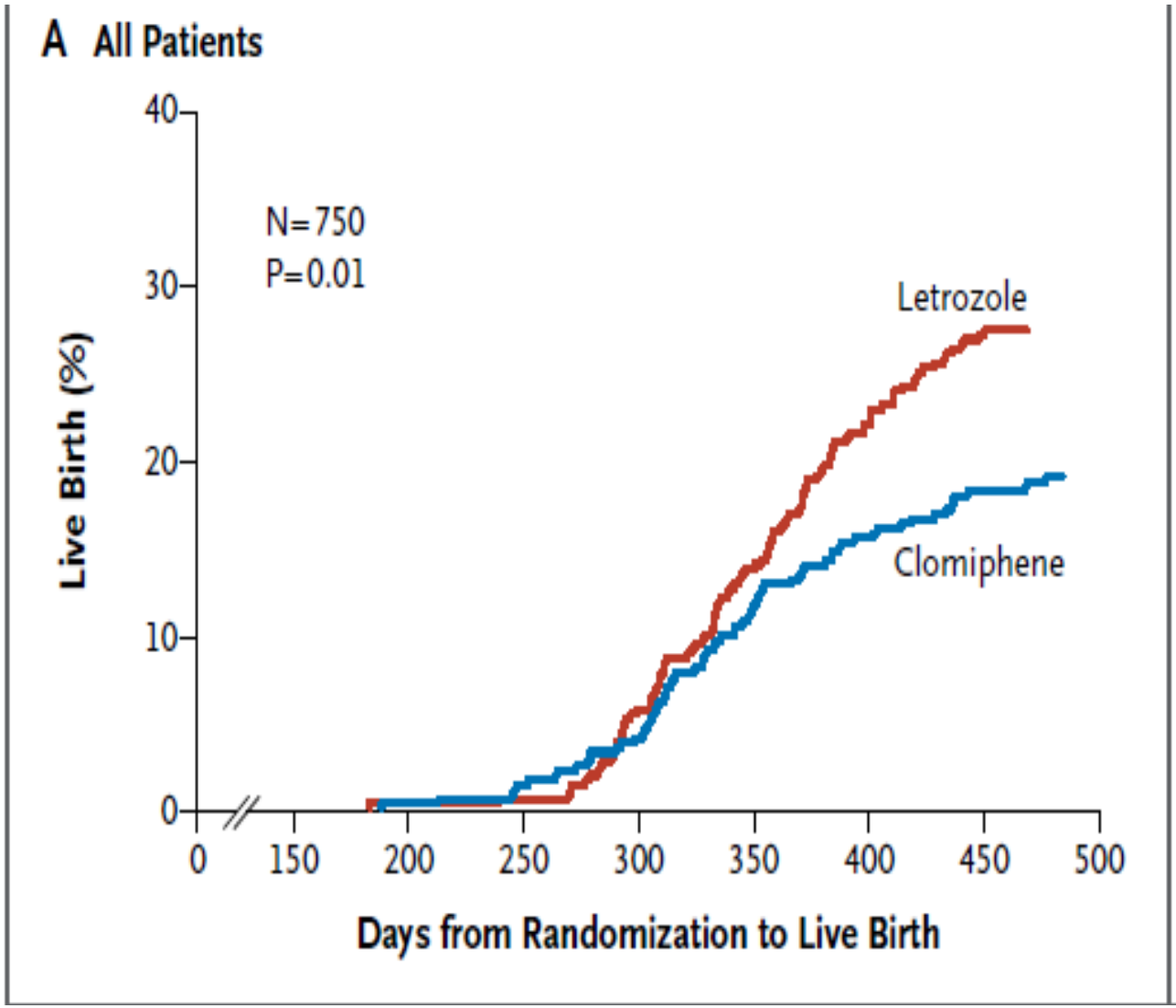
Primary Outcomes

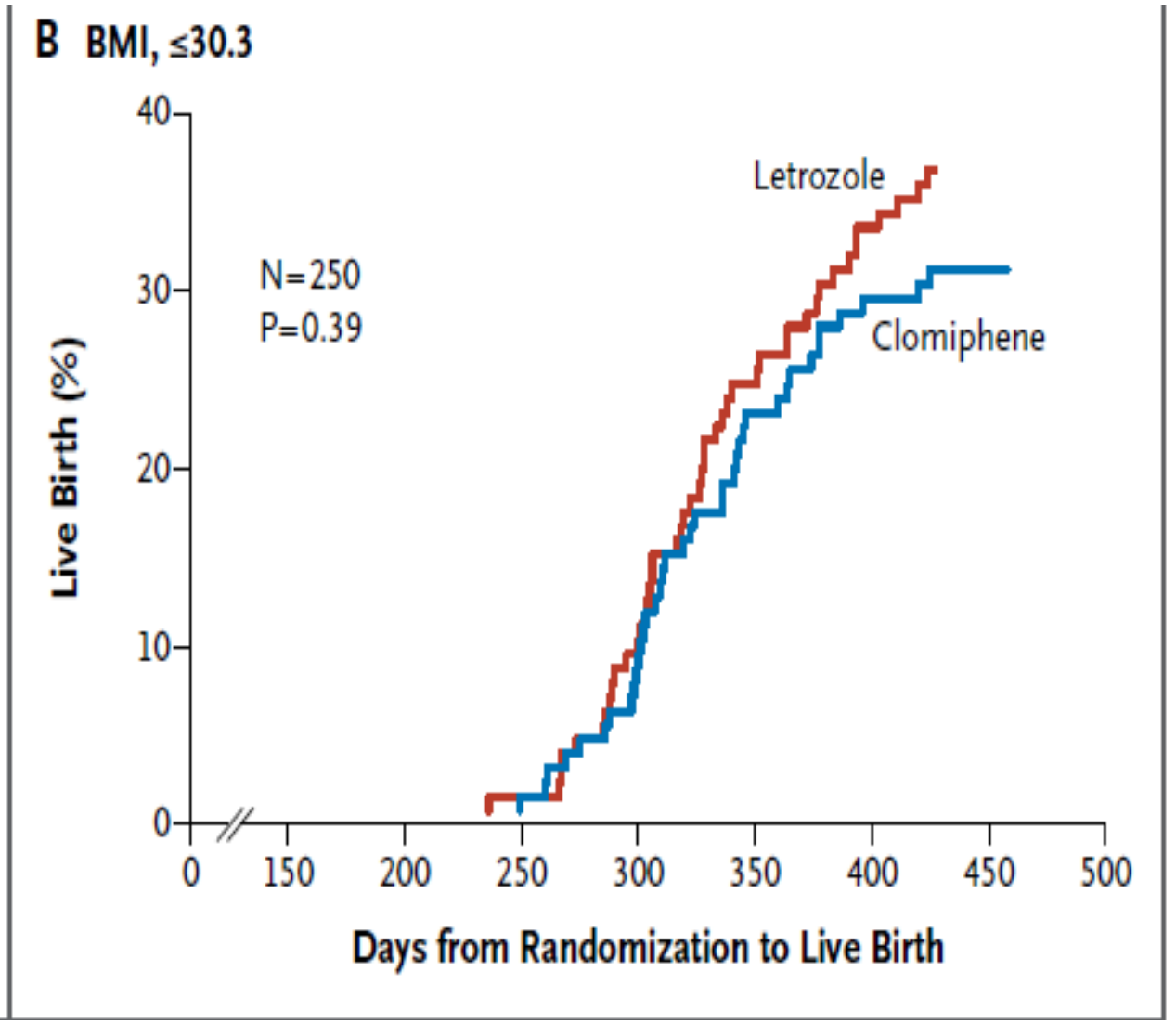
Outcome	Clomiphene Group (N=376)	Letrozole Group (N=374)	Absolute Difference between Groups (95% CI)†	Rate Ratio in Letrozole Group (95% CI)	P Value‡
Primary outcome					
Live birth — no. (%)	72 (19.1)	103 (27.5)	8.4 (2.4 to 14.4)	1.44 (1.10 to 1.87)	0.007
Singleton live birth — no./total no. (%)	67/72 (93.1)	99/103 (96.1)	3.1 (–3.9 to 10.0)	1.03 (0.96 to 1.11)	0.49
Twin live birth — no./total no. (%)§	5/72 (6.9)	4/103 (3.9)	–3.0 (–10.0 to 3.9)	0.56 (0.16 to 2.01)	0.49
Birth weight					
No. of infants	71	102			
Mean weight — g	3229.9±715.3	3232.3±657.4	2.4 (–205.6 to 210.4)		0.83
Sex ratio at birth (boys:girls)	0.88 (36:41)	0.65 (42:65)		0.74 (0.41 to 1.33)¶	
Duration of pregnancy					
No. of women	72	101			
Mean duration — wk	38.0±3.6	38.4±2.7	0.4 (–0.6 to 1.4)		0.59

Secondary Outcomes

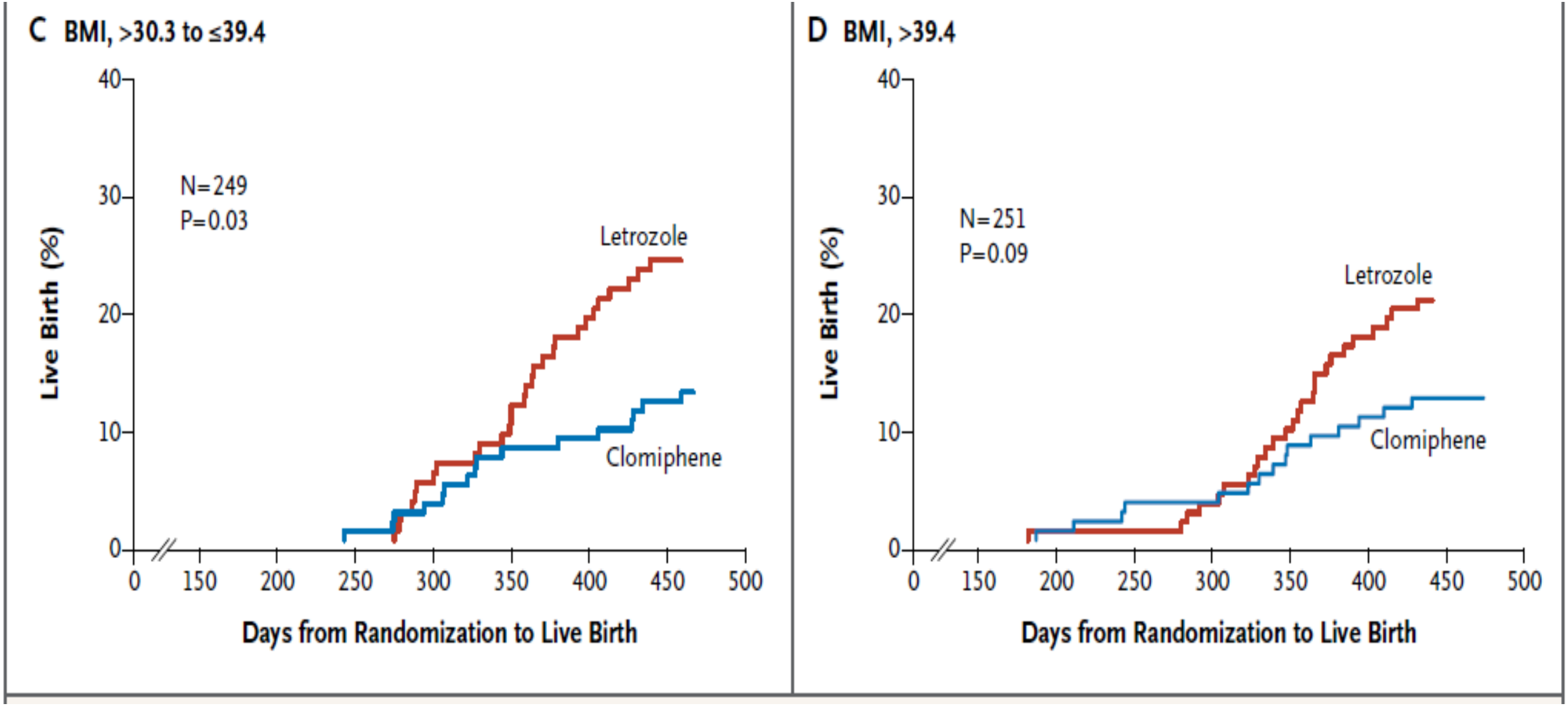
Secondary outcomes	Clomiphene Group	Letrozole Group	Absolute Difference between Groups	Rate Ratio in Letrozole Group	P Value
Pregnancy					
Conception — no. of women (%)	103 (27.4)	154 (41.2)	13.8 (7.1 to 20.5)	1.50 (1.23 to 1.84)	<0.001
Pregnancy — no. of women (%)	81 (21.5)	117 (31.3)	9.7 (3.5 to 16.0)	1.45 (1.14 to 1.85)	0.003
Twin pregnancy — no. of women/ total no. of pregnancies (%)	6/81 (7.4)	4/117 (3.4)	−4.0 (−10.6 to 2.6)	0.46 (0.13 to 1.58)	0.32
Time to pregnancy					
No. of women	90	145			
Mean time — days	85.9±48.8	90.4±44.4	4.5 (−8.0 to 17.0)		0.27
Pregnancy loss					
Pregnancy loss among women who conceived — no./total no. (%)	30/103 (29.1)	49/154 (31.8)	2.7 (−8.7 to 14.1)	1.09 (0.75 to 1.60)	0.65
Loss in first trimester — no./ total no. (%)	29/103 (28.2)	45/154 (29.2)	1.1 (−10.2 to 12.3)	1.04 (0.70 to 1.54)	0.85
Ovulation					
Women who ovulated — no. (%)	288 (76.6)	331 (88.5)	11.9 (6.5 to 17.3)	1.16 (1.08 to 1.24)	<0.001
No. of ovulations/total treatment cycles (%)	688/1425 (48.3)	834/1352 (61.7)	13.4 (9.7 to 17.1)	1.28 (1.19 to 1.37)	<0.001
Fecundity among women who ovulated — no./total no. (%)					
Conception	103/288 (35.8)	154/331 (46.5)	10.8 (3.1 to 18.5)	1.31 (1.07 to 1.58)	0.007
Singleton pregnancy	75/288 (26.0)	113/331 (34.1)	8.1 (0.9 to 15.3)	1.31 (1.03 to 1.58)	0.03
Singleton live birth	67/288 (23.3)	99/331 (29.9)	6.6 (−0.3 to 13.6)	1.29 (0.98 to 1.68)	0.06

Kaplan-Meier Curves for Live Birth





Kaplan-Meier Curves for Live Birth



All Serious Adverse Events

Event	Clomiphene Group	Letrozole Group
	no. of women/total no. (%)	
Event before conception in women who received a study drug		
Serious adverse event		
Ovarian torsion	1/355 (0.3)	0/359
Ruptured corpus luteum cyst	0/355	1/359 (0.3)
Hospitalization†	3/355 (0.8)	2/359 (0.6)
Other adverse event		
Hot flushes‡	117/355 (33.0)	73/359 (20.3)
Fatigue§	53/355 (14.9)	78/359 (21.7)
Dizziness§	27/355 (7.6)	44/359 (12.3)

All Serious Adverse Events

Serious adverse event after conception in women who discontinued the study drug		
First trimester		
Ectopic pregnancy	3/94 (3.2)	4/149 (2.7)
Heterotopic pregnancy	1/94 (1.1)	0/149
Pregnancy of unknown location	1/94 (1.1)	1/149 (0.7)
Hospitalization	2/94 (2.1)	4/149 (2.7)
Second and third trimester		
Hospitalization for premature labor	0/94	2/149 (1.3)
Hospitalization for other reasons	2/94 (2.1)	7/149 (4.7)
Postpartum anemia requiring transfusion after delivery	0/94	1/149 (0.7)
Serious adverse event after 20 wk of pregnancy in fetus through neonatal period in infant		
Congenital anomaly	1/66 (1.5)	4/102 (3.9)
Fetal death	1/66 (1.5)	1/102 (1.0)
Neonatal death	2/66 (3.0)	1/102 (1.0)