Randomized Controlled Trial of Preconception Interventions in Infertile Women With Polycystic Ovary Syndrome

Richard S. Legro, William C. Dodson, Penny M. Kris-Etherton, Allen R. Kunselman, Christy M. Stetter, Nancy I. Williams, Carol L. Gnatuk, Stephanie J. Estes, Jennifer Fleming, Kelly C. Allison, David B. Sarwer, Christos Coutifaris, and Anuja Dokras

Departments of Obstetrics and Gynecology (R.S.L., W.C.D., C.L.G., S.J.E.) and Public Health Sciences (R.S.L., A.R.K., C.M.S.), Penn State College of Medicine, Hershey, PA, Departments of Nutritional Sciences (P.M.K., J.F.) and Kinesiology (N.I.W.), Penn State College of Health and Human Development, University Park, Pennsylvania 16802; and Departments of Psychiatry (D.B.S., K.C.A.), Surgery (D.B.S.), and Obstetrics and Gynecology (A.D., C.C.), Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania 19104

Context: Lifestyle modification is recommended in women with polycystic ovary syndrome (PCOS) prior to conception but there are few randomized trials to support its implementation or benefit.

Objective: This study aimed to determine the relative efficacy of preconception intervention on reproductive and metabolic abnormalities in overweight/obese women with PCOS.

Design, Setting, and Participants: This was a randomized controlled trial of preconception and infertility treatment at Academic Health Centers in women with infertility due to PCOS, age 18–40 y and body mass index 27–42 kg/m^2.

Intervention: Women were randomly assigned to receive either 16 weeks of 1) continuous oral contraceptive pills (OCPs) (ethinyl estradiol 20 mcg/1 mg norethindrone acetate) ("OCP"); 2) lifestyle modification consisting of caloric restriction with meal replacements, weight loss medication (either sibutramine, or orlistat), and increased physical activity to promote a 7% weight loss ("Lifestyle"); or 3) combined treatment with both OCP and lifestyle modification ("Combined"). After preconception intervention, women underwent standardized ovulation induction with clomiphene citrate and timed intercourse for four cycles. Pregnancies were followed with trimester visits until delivery.

Main Outcome Measures: Weight, ovulation, and live birth were measured.

Results: We consented 216 and randomly assigned 149 women (Lifestyle: n = 50; OCP: n = 49; Combined: n = 50). We achieved significant weight loss with both Lifestyle (mean weight loss, −6.2%; 95% confidence interval (CI), −7.4–−5.0; and Combined (mean weight loss, −6.4%; 95% CI, −7.6–−5.2) compared with baseline and OCP (both $P < .001$). There was a significant increase in the prevalence of metabolic syndrome at the end of preconception treatment compared with baseline within OCP (odds ratio [OR, 2.47; 95% CI, 1.42–4.27) whereas no change in metabolic syndrome was detected in the Lifestyle (OR, 1.18; 95% CI, 0.63–2.19) or Combined (OR, 0.72; 95% CI, 0.44–1.17) groups. Cumulative ovulation rates were superior after weight loss: OCP, 46%; Lifestyle, 60%; and Combined, 67% ($P < .05$). Live birth rates were OCP, 12%; Lifestyle, 26%; and Combined, 24% ($P = .13$).

Conclusions: A preconception weight loss intervention eliminates the adverse metabolic oral contraceptive effects and, compared with oral contraceptive pretreatment, leads to higher ovulation rates. (***J Clin Endocrinol Metab*** **100: 4048–4058, 2015)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received July 3, 2015. Accepted August 17, 2015.
First Published Online September 24, 2015

Abbreviations: AUC, area under the curve; BMI, body mass index; BP, blood pressure; CI, confidence interval; DPP, Diabetes Prevention Program; DSMB, data safety monitoring board; DXA, dual energy x-ray absorptiometry; HgbA1c, glycosylated hemoglobin; HRQOL, Health-Related Quality of Life questionnaire; OCP, oral contraceptive pill; OR, odds ratio; PCOS, polycystic ovary syndrome.

Polycystic ovary syndrome (PCOS), characterized by hyperandrogenism and chronic anovulation, is the most common female endocrinopathy as well as a major cause of female infertility. How best to achieve pregnancy and improved health concurrently is uncertain. Treatment with oral ovulation induction agents is the first line of therapy, but most women fail to conceive and many never ovulate, and this treatment does not address underlying metabolic abnormalities (1, 2). Women with PCOS are frequently obese and insulin resistant (3), which is associated with resistance to ovulation, lower pregnancy rates, and higher risk of pregnancy complications (1, 2, 4). Expert panels have recommended that women with obesity and PCOS lose weight prior to infertility treatment (5, 6), primarily on the basis of observational trials supporting a fertility benefit with weight loss (7, 8).

Meta-analysis of lifeststyle intervention in women with PCOS has shown modest evidence of improvement in the PCOS phenotype (primarily metabolic) (9). There also have been few randomized controlled trials to support the

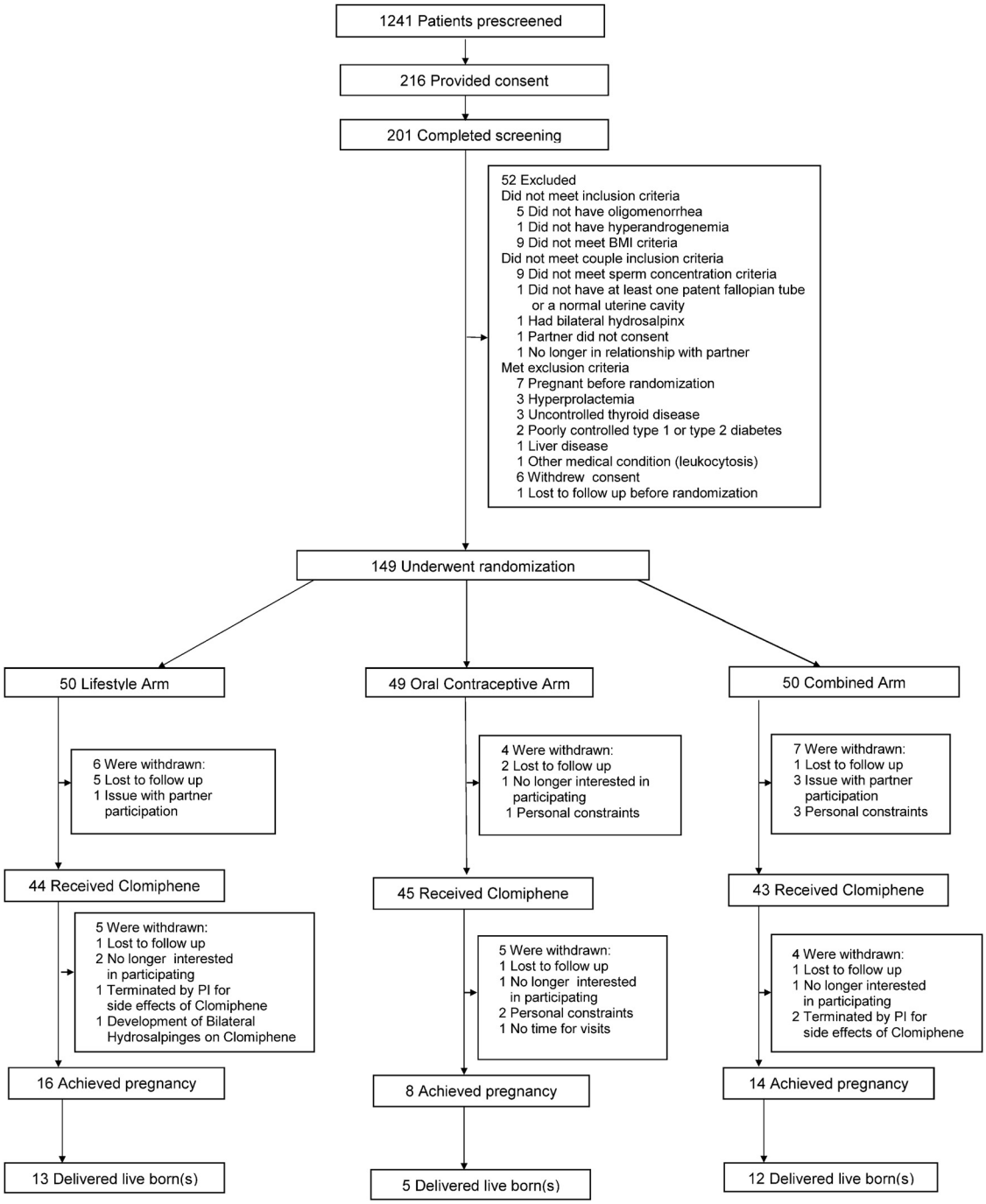

Figure 1. CONSORT flow diagram.

benefit of weight loss as a preconception infertility treatment (10, 11). In fact, there is some evidence that excessive caloric restriction (12) and physical activity (13) in such women impairs fertility. In addition to obesity, hyperandrogenism also has been associated with resistance to ovulation induction and lower pregnancy and live birth rates in women with PCOS (14, 15). At least one clinical trial has shown higher pregnancy rates following pretreatment with hormonal contraceptives (16).

We designed this trial to compare varying preconception interventions that we hypothesized would improve health as well as live birth rates in women with obesity and PCOS.

Table 1. Baseline Characteristics of Patients by Treatment Group

Characteristics	OCP (n = 49), Mean (SD)	Lifestyle (n = 50), Mean (SD)	Combined (n = 50), Mean (SD)
Demographics			
Age, y	29.8 (3.7)	28.6 (3.4)	28.7 (4.2)
Hispanic, N (%)	6 (12.2%)	6 (12.0%)	5 (10.0%)
Race, N (%)			
Caucasian	40 (81.6%)	35 (70.0%)	31 (62.0%)
Black/African-American	7 (14.3%)	7 (14.0%)	14 (28.0%)
Other/multi-racial	2 (4.1%)	8 (16.0%)	5 (10.0%)
Nulliparous, N (%)	38 (77.6%)	41 (82.0%)	45 (90.0%)
Biometric			
Weight, kg	94.6 (14.4)	96.0 (15.8)	95.2 (14.5)
BMI, kg/m^2	35.1 (4.2)	35.1 (4.6)	35.5 (4.4)
Waist circumference, cm	106.2 (11.0)	107.2 (14.0)	106.5 (11.8)
Systolic BP, mm Hg	116.7 (10.6)	114.8 (14.0)	118.3 (12.2)
Diastolic BP, mm Hg	74.2 (8.2)	71.5 (8.3)	74.1 (9.6)
Ferriman-Gallwey Hirsutism Score	16.6 (7.8)	19.3 (8.7)	17.7 (9.1)
Sebum, mcg/cm^2	101.1 (59.1)	98.0 (50.1)	107.1 (52.9)
Ultrasound parameters			
Antral follicle count (both ovaries)	66.0 (39.4)	53.8 (33.9)	58.4 (34.0)
Total ovarian volume, cm^3[a]	22.3 (17.5, 29.7)	21.2 (13.5, 26.9)	19.3 (13.7, 25.1)
Serum results			
Anti-Müllerian hormone, ng/mL	9.1 (5.1)	8.7 (5.9)	8.7 (5.4)
T, ng/dL[a]	53.0 (38.0, 72.9)	52.7 (34.8, 70.4)	51.9 (38.3, 78.7)
SHBG, nmol/L[a]	27.1 (20.2, 34.3)	27.8 (21.6, 38.1)	26.9 (20.0, 41.9)
Cholesterol, mg/dL	187.6 (31.0)	185.2 (34.1)	184.6 (32.2)
HDL, mg/dL[a]	44.0 (40.0, 52.0)	42.0 (36.0, 48.0)	42.5 (39.0, 48.0)
LDL, mg/dL	115.6 (26.3)	114.7 (30.8)	112.8 (30.2)
Triglycerides, mg/dL[a]	117.0 (94.0, 155.0)	121.5 (99.0, 171.0)	120.0 (87.0, 165.0)
Fasting glucose, mg/dL	87.0 (9.4)	86.8 (8.7)	89.7 (14.7)
Fasting insulin, uU/mL[a]	24.0 (17.0, 31.5)	24.5 (18.0, 32.0)	24.0 (15.0, 33.0)
2-hour glucose, mg/dL	111.7 (25.5)	119.4 (36.5)	124.2 (41.0)
2-hour insulin, uU/mL[a]	119.0 (81.0, 175.0)	144.0 (72.0, 228.0)	146.0 (76.0, 253.0)
AUC glucose, mg/dL · h	242.1 (42.5)	257.9 (50.2)	265.7 (69.8)
AUC insulin, uU/dL · h[a]	219.1 (180.3, 305.3)	262.5 (151.8, 424.0)	223.3 (153.0, 400.3)
Insulin sensitivity index[a]	2.0 (1.4, 2.6)	1.7 (1.0, 2.7)	1.9 (1.2, 3.2)
DXA parameters			
Total bone mineral density, g/cm^2	1.19 (0.09)	1.17 (0.09)	1.16 (0.08)
Fat, kg	41.6 (8.8)	42.0 (8.9)	42.5 (9.2)
Lean, kg	51.0 (6.8)	52.1 (8.2)	50.8 (6.4)
Percent fat	44.6 (4.4)	44.4 (4.2)	45.2 (4.3)
PCOS HRQOL[b]			
Emotion mean score	4.8 (1.3)	4.6 (1.1)	4.4 (1.2)
Body hair mean score	4.4 (1.8)	4.0 (1.8)	4.0 (1.6)
Weight mean score	3.0 (1.5)	2.9 (1.5)	2.6 (1.6)
Infertility mean score	3.2 (1.4)	3.0 (1.4)	2.5 (1.4)
Menstrual problems mean score	4.1 (1.2)	3.9 (1.1)	4.2 (1.0)
Overall physical wellbeing	4.0 (1.3)	4.1 (1.2)	3.8 (1.5)
Overall emotional wellbeing	4.4 (1.2)	4.3 (1.1)	4.3 (1.5)
Overall general wellbeing	4.6 (1.0)	4.5 (1.2)	4.5 (1.2)

Abbreviation: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a] Median (25th percentile, 75th percentile) are reported.

[b] Total scores on the PCOS HRQOL, a questionnaire for measuring health-related quality of life in women with the PCOS, range from 1 to 7, with higher scores indicating better function. Scores on the body-hair component of the PCOS HRQOL range from 1 to 7, with higher scores indicating more satisfaction with body hair.

Materials and Methods

Trial design

The trial was a randomized, open-label, two-site study with equal allocation to three treatment groups: 1) oral contraceptives pills ("OCP"); 2) lifestyle modification ("Lifestyle"); and 3) combined OCP and lifestyle modification ("Combined"). The study protocol was approved by the institutional review boards of the Penn State College of Medicine, Hershey, PA and the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA. A data safety monitoring board (DSMB) oversaw the study. Female participants and their male partners gave written informed consent and the trial was registered at Clinicaltrials.gov (NCT00704912). The full protocol and case report forms are publically available at: http://ctsi.psu.edu/owl-pcos/.

Enrollment began in October 2008 but was closed from January through March 2010 after the US Food and Drug Administration advisory about safety concerns with sibutramine. Orlistat was subsequently substituted for sibutramine in March 2010. Enrollment ceased in December of 2012 based on the DSMB recommendation. We followed subjects through completion of treatment and collected all pregnancy outcomes into March of 2014. All data entry, data management, and analyses were coordinated or performed through investigators (A.R.K., C.M.S.) in the Department of Public Health Sciences at Penn State.

Participants

We randomly assigned 149 women with a body mass index (BMI) of 27–42 kg/m^2, 18–40 years of age with PCOS who had no major medical conditions (including diabetes with a glycosylated hemoglobin [HgbA1c $>$ 7.0%] or contraindications to sibutramine or oral contraception use (such as uncontrolled hypertension $\geq$ 150/100 mm Hg or an abnormal electrocardiograph) and who were off confounding medications (1 mo for cyclic progestins such as Provera or 2 mo for all others including hormonal contraceptives, insulin sensitizers, and other infertility drugs). We used modified Rotterdam criteria (2, 17) to diagnose PCOS: all women had ovulatory dysfunction with either hyperandrogenism [by hirsutism (18) or an elevated T level (19)] or a polycystic ovary on transvaginal ultrasound. This was defined by an excess of small antral follicles ($\geq$ 12 follicles $<$ 10 mm in diameter) or an individual ovarian volume greater than 10 cm^3 or both (18). Other common disorders leading to ovulatory dysfunction including thyroid disease and prolactin excess were excluded (1, 2).

Additional eligibility criteria were the documentation of at least one patent fallopian tube and a normal uterine cavity by either hysterosalpingogram or sonohysterogram. Male partners were required to have a sperm concentration of at least 14 million per milliliter (20) with documented motility in at least one ejaculate within the last year and the commitment to have vaginal intercourse during the study with the intent of pregnancy.

Table 2. Change in Key Metabolic and Reproductive Parameters After the 16 Week Pre Conception Intervention

	OCP		Lifestyle		Combined	
Parameter	Mean Change From Baseline (95% CI)	*P* Value	Mean Change From Baseline (95% CI)	*P* Value	Mean Change From Baseline (95% CI)	*P* Value
Biometric						
Weight, kg	−1.1 (−2.0–−0.3)	.01	−6.2 (−7.1–−5.3)	<.0001	−6.1 (−7.0–−5.2)	<. 0001
Percent change in weight	−1.0 (−2.3–0.2)	.10	−6.2 (−7.4–−5.0)	<.0001	−6.4 (−7.6–−5.2)	<. 0001
Waist circumference, cm	−1.9 (−4.7–1.0)	.20	−6.3 (−9.2–−3.4)	<. 0001	−6.2 (−9.1–−3.3)	<. 0001
Sebum, mcg/cm^2	−20.8 (−42.4–0.8)	.06	6.9 (−14.9–28.7)	.54	−28.1 (−49.7–−6.5)	.01
Ultrasound parameters						
Antral follicle count, both ovaries	−24.5 (−33.9–−15.1)	<. 0001	−4.9 (−14.2–4.5)	.31	−19.2 (−29.2–−9.2)	.0002
Total ovarian volume[a]	0.70 (0.62–0.79)	<. 0001	0.99 (0.89–1.11)	.85	0.88 (0.78–1.00)	.05
Serum results						
Anti-Müllerian hormone, ng/mL	−3.2 (−4.4–−1.9)	<. 0001	−0.8 (−2.1–0.5)	.20	−2.9 (−4.2–−1.6)	<. 0001
T[a]	0.42 (0.36–0.48)	<. 0001	0.94 (0.81–1.09)	.39	0.41 (0.36–0.48)	<. 0001
SHBG[a]	2.74 (2.28–3.29)	<. 0001	1.00 (0.83–1.21)	.96	2.60 (2.15–3.13)	<. 0001
Triglycerides[a]	1.19 (1.08–1.32)	.001	0.97 (0.87–1.08)	.54	1.04 (0.94–1.16)	.43
2-hour glucose, mg/dL	18.4 (9.2–27.7)	.0001	−9.4 (−18.7–−0.2)	.05	1.0 (−8.3–10.4)	.83
2-hour insulin,[a] uU/mL	1.21 (1.00–1.46)	.05	0.78 (0.64–0.94)	.010	0.80 (0.66–0.98)	.03
AUC glucose, mg/mL · h	23.9 (9.1–38.8)	.002	−17.1 (−30.4–−3.8)	.01	−0.5 (−14.0–13.1)	.95
AUC insulin,[a] uU/mL · h	1.05 (0.90–1.23)	.54	0.87 (0.75–0.99)	.04	0.84 (0.73–0.97)	.02
Insulin sensitivity index[a]	0.89 (0.77–1.03)	.13	1.25 (1.09–1.43)	.001	1.21 (1.06–1.39)	.006
DXA parameters						
Total bone mineral density, g/cm^2	0.010 (0.001–0.018)	.02	0.012 (0.004–0.020)	.004	0.009 (0.000–0.017)	.04
Fat, kg	−0.6 (−1.5–0.3)	.18	−4.4 (−5.3–−3.6)	<. 0001	−4.5 (−5.4–−3.6)	<. 0001
Percent fat	−0.2 (−0.8–0.3)	.44	−2.0 (−2.5–−1.4)	<. 0001	−2.0 (−2.5–−1.4)	<. 0001
Android fat/gynoid fat ratio	−0.01 (−0.04–0.01)	.41	−0.03 (−0.06–0.00)	.07	−0.04 (−0.06–−0.01)	.01
PCOS HRQOL[b]						
Emotion mean score	0.3 (0.1–0.6)	.01	0.2 (−0.0–0.5)	.08	0.6 (0.3–0.8)	<. 0001
Body hair mean score	0.7 (0.4–0.9)	<.0001	0.0 (−0.2–0.3)	.76	0.8 (0.5–1.1)	<. 0001
Weight mean score	0.7 (0.3–1.0)	.0001	0.8 (0.4–1.1)	<. 0001	1.4 (1.1–1.7)	<. 0001
Infertility mean score	0.6 (0.3–0.9)	.0001	0.7 (0.3–1.0)	<. 0001	1.1 (0.8–1.4)	<. 0001
Menstrual problems mean score	0.4 (0.2–0.7)	.002	0.4 (0.1–0.7)	.004	0.7 (0.4–1.0)	<. 0001
Overall physical wellbeing	0.4 (0.0–0.8)	.03	0.8 (0.4–1.2)	<. 0001	1.2 (0.8–1.6)	<. 0001
Overall emotional wellbeing	0.3 (−0.1–0.7)	.21	0.1 (−0.3–0.5)	.48	0.5 (0.1–0.9)	.02
Overall general wellbeing	0.3 (−0.0–0.6)	.07	0.5 (0.2–0.8)	.001	0.6 (0.3–0.9)	.0003

Analyses are adjusted for site, protocol version, and baseline BMI status.

[a] Data were log transformed and represent a ratio of geometric means.

[b] Total scores on the PCOS HRQOL, a questionnaire for measuring health-related quality of life in women with the polycystic ovary syndrome, range from 1 to 7, with higher scores indicating better function. A change of 0.5 U is thought to be meaningful.

Randomization

After qualifying for the study, 149 women were randomly assigned in a 1:1:1 ratio to the three treatments in permuted blocks of size two, four, or six. The randomization was stratified by clinical site and baseline BMI (< 35 or ≥ 35 kg/m^2) and administered using a password-protected, secure Microsoft Excel application. The random allocation sequence generated by the biostatistician was unknown to the investigators.

Baseline visit

At this visit, women completed a physical examination, fasting blood work for hormones and metabolic parameters, and a transvaginal ultrasound examination (21). The PCOS Health-Related Quality of Life (HRQOL) questionnaire was administered. The measure is validated for women with PCOS and includes five domains: emotional, body hair, infertility, weight, and menstrual problems (22). Each domain score is graded on a scale of 1 (poorest function) to 7 (optimal) with a change of 0.5 approximating the minimal important difference, the smallest change in score that women feel is important in their daily lives. They also completed a 3-day diet log to assess food intake. Sebum was measured in the middle forehead using a Sebumeter (SM 815, CK Electronic GmbH) (23).

They then underwent a 2-hour 75-g oral glucose tolerance test, a standardized submaximal aerobic exercise test on a treadmill, and bone mineral density and body composition were determined by dual energy x-ray absorptiometry (DXA) using a Hologic Discover (Hologic Inc) (21, 24). Participants underwent whole-body, lumbar spine, and dual hip scans using fan-beam mode at baseline, completion of phase 1 and, if not pregnant, again at the completion of phase 2 of the study. We modeled subregion analysis of visceral and central abdominal fat using Hologic automatic software (Patent No 7725153 [Hologic, Inc, 2011]) (24). Metabolic syndrome was determined by conventional criteria (25) and insulin sensitivity from the measures of Matsuda et al (26). This visit was replicated at the end of the preconception intervention.

Assays

Glucose and insulin levels were measured at the Penn State College of Medicine according to standard methods (21). All other reported laboratory values were determined in a central laboratory (Ligand Core Laboratory, University of Virginia, Charlottesville, VA) (18), using the same assays as in our previous Pregnancy in Polycystic Ovary Syndrome II study (2). All assays had coefficients of variation <10% as previously reported (2).

Treatments

Phase 1: Preconception intervention lasting 16 weeks

The three treatments were continuous OCP (20 mcg ethinyl estradiol/1 mg norethindrone acetate every day), Lifestyle with a

Table 2. Continued

Lifestyle Versus OCP		Combined Versus OCP		Lifestyle Versus Combined	
Difference in Mean Change (95% CI)	*P* Value	Difference in Mean Change (95% CI)	*P* Value	Difference in Mean Change (95% CI)	*P* Value
−5.0 (−6.3–−3.8)	<. 0001	−5.0 (−6.2–−3.7)	<. 0001	−0.1 (−1.3–1.2)	.92
−5.2 (−6.7–−3.6)	<. 0001	−5.4 (−7.0–−3.9)	<. 0001	0.2 (−1.4–1.8)	.79
−4.4 (−8.5–−0.4)	.03	−4.3 (−8.4–−0.3)	.03	−0.1 (−4.1–4.0)	.97
27.7 (−3.0–58.3)	.08	−7.3 (−37.8–23.2)	.64	34.9 (4.3–65.6)	.03
19.6 (6.4–32.9)	.004	5.3 (−8.4–19.0)	.45	14.3 (0.7–28.0)	.04
1.41 (1.20–1.66)	<. 0001	1.26 (1.06–1.49)	.008	1.12 (0.95–1.33)	.17
2.3 (0.5–4.1)	.01	0.3 (−1.6–2.1)	.79	2.1 (0.2–3.9)	.03
2.24 (1.82–2.76)	<. 0001	0.99 (0.80–1.22)	.90	2.27 (1.83–2.81)	<. 0001
0.37 (0.28–0.48)	<. 0001	0.95 (0.73–1.23)	.69	0.39 (0.30–0.50)	<. 0001
0.81 (0.70–0.94)	.006	0.87 (0.75–1.01)	.07	0.93 (0.80–1.08)	.32
−27.8 (−40.9–−14.8)	<. 0001	−17.4 (−30.5–−4.2)	.010	−10.5 (−23.6–2.7)	.12
0.64 (0.49–0.84)	.001	0.67 (0.51–0.87)	.004	0.97 (0.74–1.27)	.81
−41.1 (−61.0–−21.1)	<. 0001	−24.4 (−44.5–−4.3)	.02	−16.7 (−35.7–2.4)	.09
0.83 (0.67–1.02)	.07	0.80 (0.65–0.99)	.04	1.03 (0.85–1.26)	.76
1.40 (1.15–1.70)	.001	1.35 (1.11–1.65)	.003	1.03 (0.85–1.25)	.74
0.002 (−0.009–0.014)	.68	−0.001 (−0.013–0.011)	.87	0.003 (−0.008–0.015)	.57
−3.8 (−5.1–−2.6)	<. 0001	−3.9 (−5.2–−2.6)	<. 0001	0.1 (−1.2–1.4)	.88
−1.8 (−2.5–−1.0)	<. 0001	−1.7 (−2.5–−1.0)	<. 0001	−0.0 (−0.8–0.8)	.99
−0.02 (−0.06–0.02)	.37	−0.03 (−0.06–0.01)	.19	0.01 (−0.03–0.05)	.72
−0.1 (−0.5–0.3)	.58	0.2 (−0.1–0.6)	.19	−0.3 (−0.7–0.0)	.06
−0.6 (−1.0–−0.3)	.001	0.1 (−0.2–0.5)	.48	−0.8 (−1.1–−0.4)	<. 0001
0.1 (−0.4–0.6)	.73	0.7 (0.2–1.2)	.003	−0.6 (−1.1–−0.2)	.010
0.0 (−0.4–0.5)	.83	0.5 (0.0–0.9)	.03	−0.4 (−0.9–0.0)	.05
−0.0 (−0.4–0.4)	.92	0.2 (−0.1–0.6)	.21	−0.3 (−0.7–0.1)	.18
0.4 (−0.2–0.9)	.16	0.7 (0.2–1.3)	.008	−0.4 (−0.9–0.2)	.20
−0.1 (−0.7–0.5)	.70	0.2 (−0.4–0.8)	.44	−0.3 (−0.9–0.2)	.25
0.2 (−0.2–0.6)	.31	0.3 (−0.1–0.7)	.17	−0.1 (−0.5–0.3)	.73

goal of 7% weight loss, or Combined (both treatments). We chose OCPs as our control for the lifestyle arms because multiple predictive models of success (ie, ovulation and/or livebirth) have identified hyperandrogenism as a significant negative predictor (15, 27, 28). OCPs were given continuously to avoid the pill free interval rebound in ovarian function of cyclic regimens and provide more complete suppression of ovarian hyperandrogenism (29).

The lifestyle program was multifocal, based on studies showing additive weight-loss effects of such designs (30, 31), consisting of caloric restriction, behavioral modification, increased physical activity, and if BMI was at least 30 kg/m^2, use of a weight loss medication. We chose 16 weeks as the duration of preconception intervention given that studies have demonstrated that weight loss with these interventions typically plateaus at this time point (30, 31). The study began with sibutramine (Meridia) at a dose of 5 mg per day and was titrated up to a maximum dose of 15 mg per day if tolerated. As noted above, sibutramine was substituted with over-the-counter orlistat, 60 mg (Alli) with breakfast, lunch, and dinner during the study.

Caloric restriction consisted of prescribed diets centered on meal replacement items that included prepared entrees for breakfast, lunch, and dinner. In addition, patients consumed two servings of fruit, three servings of vegetables, and two servings of skim milk per day. This diet was designed to create a calorie deficit based on initial weight with a macronutrient profile as follows: at least 15% calories from protein, less than 30% calories from fat, and the remaining calories from carbohydrate. Participants were assigned to an energy level that provided one of the following: 1200 calories per day (for persons who weighed 120–170 lb), 1500 calories per day (175–215 lb), 1800 calories per day (220–245 lb), or 2000 calories per day for those who weighed between 250 and 300 pounds. The approach was consistent with the lifestyle-modification protocol of the Look AHEAD and Diabetes Prevention Program (DPP) trials (32, 33). Patients were provided with breakfast and snacks during phase 1, but purchased the other meal replacement and food items following instruction from study coordinators.

We followed established recommendations for increased physical activity (principally brisk walking or similar aerobic activity) 5 days per week. Activity goals began at 10 minutes on each of those 5 days and gradually increased over 4 months to 30–35 minutes, for a total activity goal of 150 minutes per week (33). Behavioral modification lessons were selected from the DPP (33) and delivered by trained study coordinators. We collected monthly menstrual diaries. Women in the Lifestyle group were required to use barrier contraception during preconception treatment. All treatment groups had identical treatment visit schedules and study contacts. Compliance with interventions was tracked in all groups with diet and activity logs.

Phase 2: Four cycles of ovulation induction

After completing preconception treatment, women went directly into the ovulation induction phase consisting of four consecutive cycles of clomiphene citrate and timed intercourse. Subjects were advised to maintain their weight and level of activity from the end of the preconception phase; meal replacements were discontinued. Ultrasound and serum progesterone at the end of phase 1 was used to determine the start of clomiphene. Anovulatory patients were started immediately, ovulatory patients waited for day 5 of the subsequent menses to begin clomiphene 50 mg for 5 days. A visit 3 weeks later confirmed ovulation based on ultrasound monitoring and serum progesterone level. Patients with documented ovulation (Progesterone level $\geq$ 3 ng/mL) had a serum pregnancy test 2 weeks later without menses; with menses they began clomiphene at the same dose. No other ultrasound monitoring was performed. Women without evidence of ovulation were elevated to the next higher dose of clomiphene (100 mg for 5 d or if anovulatory at the next visit, up to a maximum of 150 mg for 5 d) and underwent ultrasound and serum progesterone monitoring 3 weeks later for ovulation. Investigators had the option to induce menstrual bleeding with progestin.

Phase 3: Pregnancy

Women who conceived were followed with serial serum human chorionic gonadotropin levels until an ultrasound could document fetal viability; subsequently, they were referred to local providers for prenatal care. Pregnancies were followed with trimester study visits

Table 3. Ovulation After Clomiphene Citrate and Pregnancy Outcomes

Outcome	OCP, No./Total No. (%)	Lifestyle, No./Total No. (%)	Combined, No./Total No. (%)	Lifestyle Versus OCP[c]	
				Absolute Difference, % (95% CI)	Risk Ratio (95% CI)
Ovulation					
Ovulation (total No. of ovulations/total treatment cycles)	71/154 (46.1)	82/136 (60.3)	94/140 (67.1)	14.1 (2.8–25.3)	1.3 (1.0–1.7)
Pregnancy					
Conception (serum hCG level >10 mIU/mL)	8/49 (16.3)	16/50 (32.0)	14/50 (28.0)	15.7 (−0.9–32.2)	1.9 (0.9–4.1)
Clinical pregnancy (fetal heart motion visualized on ultrasound)	7/49 (14.3)	13/50 (26.0)	13/50 (26.0)	11.7 (−3.9–27.3)	1.8 (0.8–4.2)
Pregnancy loss					
Pregnancy loss among patients who conceived	3/8 (37.5)	3/16 (18.8)	2/14 (14.3)	−18.8 (−57.4–19.9)	0.6 (0.1–2.5)
Birth outcomes					
Live birth	5/49 (10.2)	13/50 (26.0)	12/50 (24.0)	15.9 (1.2–30.6)	2.5 (1.0–6.6)
Infant birth weight, g[a,b]	3555 (290) [5]	3116 (603) [11]	3409 (505) [12]	−468 (−1144–208)	
Duration of pregnancy, wk[a,b]	39.0 (0.7) [5]	38.4 (2.7) [11]	39.3 (1.3) [12]	−0.1 (−2.4–2.3)	
Fecundity per ovulated patient					
Live birth	5/36 (13.9)	13/36 (36.1)	12/39 (30.8)	22.6 (3.6–41.7)	2.6 (1.0–6.6)

Abbreviation: hCG, human chorionic gonadotropin.

[a] Data are presented as Mean (SD) [n].

[b] Two twin deliveries were omitted; one set of twins delivered at 35 weeks (birthweights of 1928 and 1871 g), one set of twins delivered at 20 weeks with the result of one intrauterine fetal demise and one live birth (255 g).

[c] Analyses are adjusted for site, protocol time period, and BMI status.

until delivery. Medical records from pregnancy (mother and infant) were reviewed to ascertain birth outcomes.

Outcomes

The primary outcome was live birth. Secondary outcomes included the effects of the preconception intervention on PCOS phenotype, ovulation rates, and change in maternal weight, blood pressure (BP), and glucose tolerance during pregnancy. Adverse events were queried at each visit. A serious adverse event was defined as fatal or immediately life threatening, severely or permanently disabling, requiring or prolonging inpatient hospitalization, overdose, congenital anomaly, intrauterine fetal demise after 20 weeks of gestation, or any event so deemed as serious by the site principal investigator.

Statistical analysis

We hypothesized the smallest cumulative live birth proportion would be 0.20 with Lifestyle and that the other treatments would be useful if the log odds of live birth increase by 0.55 (adjacent categories model slope) per treatment arm. Thus, the study was designed to have 81% power to detect a trend in the live birth proportions of 0.20 with Lifestyle, 0.30 with OCP, and 0.43 with Combined using a two-sided Cochran-Armitage trend test with a significance level of 0.05. We calculated the sample size as 65 patients per treatment group; and estimated a dropout rate of 20% for the trial so the total target sample size was 246 patients. No interim analyses were planned, but the DSMB examined all pregnancy and live birth outcomes every 6 months. Because of a low likelihood of showing a clinically meaningful difference between the Lifestyle and Combined groups as determined by a value of information analysis, the DSMB recommended closing the study to enrollment in December of 2012.

Data were analyzed according to the intention-to-treat principle. All analyses included covariates to adjust for clinical site, BMI status at baseline, and protocol time period for when either sibutramine or orlistat was provided. Categorical variables are reported as frequencies and percentages. Continuous variables are reported as the mean and SD if the data were normally distributed or as the median (25th percentile, 75th percentile) if the data were not normally distributed. For binary outcomes (eg, pregnancy, live birth, ovulation per cycle), a log-binomial regression model was used to assess differences between the treatment groups. Because this was a prospective study, the log-binomial model allows us to estimate the risk ratio rather than the odds ratio (OR), which is provided when using ordinary logistic regression. In addition to the risk ratio, the effect size also is reported in terms of the absolute difference. Generalized estimating equations with a logit link to account for the correlation of multiple visits for each patient were used to assess the change from baseline to the end of the preconception phase with respect to the metabolic syndrome and its individual components.

Contrasts were constructed from linear mixed-effects models, which account for the correlation of multiple visits for each patient, to assess differences in continuous outcomes (eg, weight, T levels) between the treatment groups over time. Effect sizes are reported as the difference in means and 95% confidence intervals (CIs). If the data were not normally distributed, a logarithmic transformation was applied prior to analysis and then back transformed after analysis to their original scale for ease of interpretation resulting in the comparisons between groups being reported as the ratio of geometric means. Linear regression was used to assess differences between treatment groups for continuous pregnancy and birth outcomes (eg, infant birth weight) as well as for the percent change in weight from baseline.

Kaplan-Meier curves were constructed to visually display the time from randomization to live birth according to treatment group. Cox proportional hazards regression was used to compare the treatment groups with respect to the time from randomization to live birth because this model allows for the adjustment of covariates, with the effect size reported as a hazard ratio and 95% CI. All hypothesis tests were two sided and all analyses and graphics were performed using SAS software, version 9.3 (SAS Institute, Inc.) or R software (R Foundation for Statistical Computing).

Role of the funding source

This study was funded by the National Institutes of Health. The funding source had no role in the design, conduct, analysis, or reporting of the study.

Table 3. Continued

Combined Versus OCP[c]		Lifestyle Versus Combined[c]				
P Value[d]	Absolute Difference, % (95% CI)	Risk Ratio (95% CI)	*P* Value[d]	Absolute Difference, % (95% CI)	Risk Ratio (95% CI)	*P* Value[d]
0.06	20.7 (9.9–31.6)	1.5 (1.1–1.9)	0.002	−7.1 (−18.2–4.1)	0.9 (0.7–1.1)	0.28
0.09	11.7 (−4.2–27.5)	1.7 (0.8–3.7)	0.16	4.3 (−13.5–22.2)	1.1 (0.6–2.0)	0.72
0.16	11.6 (−3.7–27.0)	1.8 (0.8–4.2)	0.15	0.3 (−16.8–17.3)	1.0 (0.5–1.9)	0.99
0.47	−23.2 (−61.4–15.0)	0.3 (0.1–1.6)	0.18	4.5 (−22.0–31.0)	1.7 (0.3–9.5)	0.56
0.06	13.8 (−0.5–28.0)	2.3 (0.9–6.1)	0.08	2.2 (−14.7–19.0)	1.1 (0.5–2.1)	0.82
0.17	−149 (−771–473)		0.62	−319 (−846–208)		0.22
0.96	0.5 (−1.7–2.7)		0.64	−0.6 (−2.4–1.3)		0.54
0.04	17.7 (−0.2–35.5)	2.2 (0.9–5.6)	0.10	5.5 (−15.7–26.8)	1.2 (0.6–2.3)	0.59

Results

Patient characteristics

A total of 149 patients were randomly assigned (Figure 1) and the groups were well matched at baseline with no significant differences between groups (Table 1). We found no difference in prior exposure to clomiphene by treatment arm (48% for Lifestyle, 53% for OCP, and 48% for Combined). Our dropout rates after preconception intervention met our projections (12% for Lifestyle, 8% for OCP, and 14% for Combined).

Phase 1 Results

Patients in the Lifestyle and Combined groups achieved a significant weight loss and loss of body fat by DXA scan (Table 2) compared with the OCP group ($P < .0001$) as well as a significant decrease in waist circumference ($P = .03$). There was no difference in the weight lost with either sibutramine or orlistat (Supplemental Figure 1). Facial sebum declined in the Combined vs Lifestyle ($P = .03$), and both OCP and Combined had improved subjective hirsutism scores compared with Lifestyle ($P < .01$). OCP and Combined, compared with Lifestyle, showed significant decreases in serum T ($P < .0001$), increases in serum SHBG ($P < .0001$), and decreases in serum Anti-Müllerian hormone ($P < .05$) and antral follicle count ($P < .05$). OCP showed a significant decrease in total ovarian volume compared with both Lifestyle ($P < .0001$) and Combined ($P = .008$). Bone mineral density increased in all three groups from baseline ($P < .05$) with no differences between groups.

Serum triglycerides increased significantly in the OCP vs Lifestyle groups ($P = .006$). Glucose area under the curve (AUC) during the 2-hour oral glucose tolerance test increased significantly ($P < .05$) and the derived insulin sensitivity index worsened ($P < .01$) in the OCP compared with Lifestyle and Combined groups. Physical wellbeing as assessed by the PCOS HRQOL measure improved significantly in both Lifestyle ($P = .0001$) and Combined ($P = .008$) vs OCP group. In the Lifestyle group, percent bleeding days was constructed based on however many diary records were returned per subject. The median bleeding days was 3%; 25th and 75th percentiles 0 and 9%.

At baseline, 29% of the OCP, 37% of Lifestyle, and 42% of Combined groups had metabolic syndrome. There was a significant increase in the prevalence of metabolic syndrome at the end of preconception treatment compared with baseline within the OCP group (OR, 2.47; 95% CI, 1.42–4.27) whereas no change in metabolic syndrome was detected in the Lifestyle (OR, 1.18; 95% CI, 0.63–2.19) or Combined (OR, 0.72; 95% CI, 0.44–1.17) groups. The conversion rate for the OCP group was significant compared with the Combined ($P = .001$), but not the Lifestyle group ($P = .08$). Of the individual components, only the prevalence of elevated triglycerides increased significantly for the OCP group (Supplemental Figure 2).

Phase 2 and 3 outcomes

Ovulation was significantly more common in the Combined compared with the OCP group ($P < .05$; Table 3). There was no significant difference in pregnancy or pregnancy loss between groups, nor in the primary outcome of live birth (Figure 2A). When patients from both Lifestyle and Combined groups were combined in a post-hoc analysis and compared with the OCP group, the rate of live birth bordered statistical significance ($P = .05$; Figure 2B). The fecundity per patient who ovulated was significantly higher with lifestyle vs OCP ($P = .04$). There was no sig-

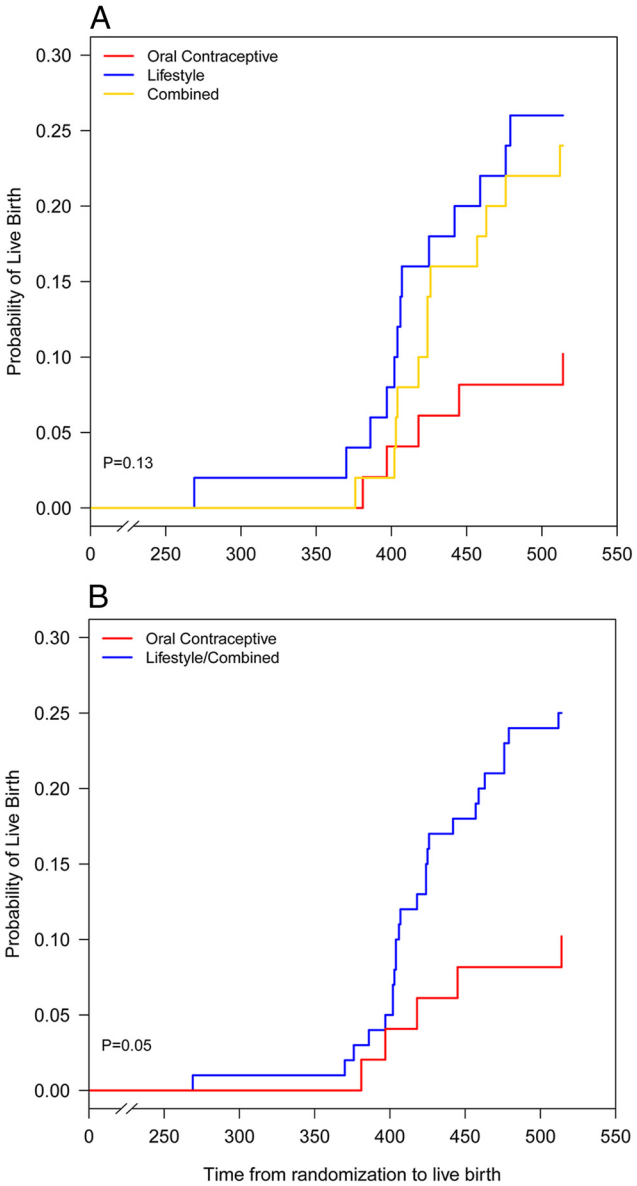

Figure 2. Kaplan-Meier curves of live birth by treatment groups (A) and after combining Lifestyle and Combined groups in a post-hoc analysis (B).

nificant difference in ovulation or live birth rates depending on whether a patient received sibutramine or orlistat (Supplemental Table 1).

Adverse events

There were no pregnancies during the pretreatment intervention. The multiple pregnancy rate (all twins) was: OCP, 0/8 (0%); Lifestyle, 2/16 (13%); and Combined, 0/14 (0%). There were five serious adverse events and most were associated with pregnancy (Table 4). There were no congenital anomalies. During the preconception intervention, diarrhea/steatorrhea was more common in the Lifestyle and Combined groups than in the OCP group ($P < .05$), and abnormal uterine bleeding was more common in the OCP and Combined compared with the Lifestyle group ($P < .05$). During ovulation induction, headaches were more common with Combined vs Lifestyle ($P < .05$). There were no differences between groups in major pregnancy complications (Supplemental Table 4). The prevalence of gestational diabetes and pre-eclampsia by all live births was 20 and 24%, respectively.

Discussion

Our study provides proof of concept that preconception lifestyle modification is possible and effective with beneficial metabolic and reproductive effects and minimal risk to participants. In contrast, use of preconception oral contraception alone may worsen the metabolic profile with no benefit to ovulation, and possibly detriment to fertility. Preconception lifestyle modification interventions resulted in significant weight loss, improvement in reproductive and metabolic health, and ovulation with clomiphene citrate. The study was stopped by the DSMB because of the similarity in live birth rates in the two groups, Lifestyle and Combined, which achieved weight loss, as a value of information analysis supported that additional study would not lead to the ability to detect the difference we hypothesized. However, the study can be viewed as an important and innovative investigation that follows a group of infertile women to delivery and provides a model for future studies on this critical life transition.

Strengths of the study include the randomized multicenter design conducted according to CONSORT and Harbin Consensus guidelines for infertility trials (34). We used treatments for the preconception intervention that are readily available, require relatively little clinical oversight, and largely achieved their stated goals. Our lifestyle modification intervention for weight loss was developed from "gold standard" efficacy studies in the obesity literature, and we were able to observe comparable results in a sample of women with PCOS. The results of our preconception intervention are relevant for women with PCOS not seeking pregnancy given that these same treat-

Table 4. Adverse Events With Significant Differences Between Groups by Phase of Study and All Serious Adverse Events

Adverse event	OCP, No. Patients[e] (%)	Lifestyle, No. Patients[e] (%)	Combined, No. Patients[e] (%)
Phase 1: Lifestyle intervention			
Steatorrhea/diarrhea[a,b]	0/49 (0.0)	6/50 (12.0)	12/50 (24.0)
Breast pain[a]	10/49 (20.4)	1/50 (2.0)	6/50 (12.0)
Abdominal pain[a,b]	1/49 (2.0)	5/50 (10.0)	10/50 (20.0)
Dysmenorrhea[a]	8/49 (16.3)	1/50 (2.0)	3/50 (6.0)
Abnormal uterine bleeding[c]	4/49 (8.2)	0/50 (0.0)	6/50 (12.0)
Phase 2: Ovulation induction			
Headache[c]	6/44 (13.6)	4/44 (9.1)	12/43 (27.9)
Serious adverse events: All phases[d]			
Phase 2: Episode of abnormal uterine bleeding leading to ER visit	0/44 (0.0)	1/44 (2.3)	0/43 (0.0)
Phase 3: Ectopic pregnancy requiring surgery	0/8 (0.0)	1/16 (6.3)	0/14 (0.0)
Phase 3: Preterm delivery of twins at 20 wk: one live birth and one IUFD secondary to infection	0/8 (0.0)	1/16 (6.3)	0/14 (0.0)
Phase 3: Postpartum hospitalization for perforated appendix	0/8 (0.0)	0/16 (0.0)	1/14 (7.1)

Abbreviation: ER, emergency room; IUFD, intrauterine fetal demise.

[a] $P < .05$ for the comparison between Lifestyle and OCP.

[b] $P < .05$ for the comparison between Combined and OCP.

[c] $P < .05$ for the comparison between Lifestyle and Combined.

[d] In addition to the four serious adverse events reported above, there was one additional serious adverse event in a nonrandomized subject. The patient developed a pelvic infection following the screening hysterosalpingogram and was diagnosed with pelvic inflammatory disease that required hospitalization.

[e] Number of patients experiencing the event/total number of patients active during the respective phase of the trial.

ments are commonly used for hirsutism, obesity, and menstrual disorders (6). The primary weakness is that our study was underpowered to detect a difference in live birth between the two lifestyle modification groups. Nevertheless, the trend toward benefit supports the epidemiologic association of lower maternal weight with better birth outcome (35) and cardiovascular risk (36) and thus, the health changes are relevant to all women with PCOS.

Our lifestyle modification program achieved significant weight loss approaching our target of 7%, with much less dropout (<20%) compared with other similar studies in this population (~50% in a 16-wk period) (21, 37). We attribute this to a greater emphasis on caloric restriction, promoted with the use of meal replacement products rather than on increased physical activity, which may be difficult for women with Class II or III obesity. Women on OCPs experienced worsening lipid and glycemic parameters during preconception treatment, replicating other studies (38, 39), and a meta-analysis, which noted increased triglycerides (40). However, we showed that a concomitant lifestyle intervention promoting weight loss can significantly abrogate adverse metabolic effects of oral contraception, whereas at the same time providing the full reproductive benefits of ovarian suppression, suggesting additive health benefits to combined treatment. Our adverse events were consistent with those reported previously with these treatments. Few serious adverse events could be linked to a specific treatment. In a properly selected and monitored group of participants, these preconception interventions are safe and well tolerated and result in increased bone mineral density.

This study provides level 1 evidence of the benefits of a lifestyle intervention on improving the reproductive and metabolic abnormalities, as well as patient-reported physical wellbeing associated with PCOS prior to infertility treatment. In addition, the combined treatment showed an improvement in the ovulation rate with clomiphene treatment. It provides strong clinical trial evidence to encourage lifestyle modification and weight loss prior to infertility treatment in obese women with PCOS. These observations provide critical evidence to expert opinion recommending weight loss to improve reproductive and metabolic abnormalities (5, 6).

At this juncture, additional, adequately powered studies around the primary outcome of a healthy live born are necessary to confirm our trends in risk/benefit ratio. Such results combined with patient and physician education will likely lead to an increased proportion of women deferring immediate infertility treatment for preconception lifestyle modification to promote weight loss and metabolic improvement. Finally, extending lifestyle modification throughout infertility treatment and pregnancy may be necessary to prevent excessive gestational weight gain and associated adverse outcomes.

Acknowledgments

In addition to the authors, we acknowledge the outstanding leadership of the study coordinators Patsy Rawa (Penn State) and Karen Lecks (University of Pennsylvania). Amy Ciccarella (Penn State University) at the Clinical Research Center at Penn State University Park for analyzing the 3-day dietary records; Urs Leuenberger, MD, (Penn State College of Medicine) for interpreting electrocardiographs and providing cardiology guidance; Mardi Sawyer (Penn State College of Medicine) for help with DXA scans and analysis; and the nursing staff at the Clinical Research Center at Penn State Hershey for assistance with oral glucose tolerance and exercise testing. We also wish to acknowledge the collaboration with the Core Ligand Laboratory at the University of Virginia under the leadership of Dan Haisenleider, PhD (University of Virginia) for their expertise in running our assays. Other members of the research team were as follows: Penn State College of Medicine, Hershey: Christy Bartlebaugh; Sandy Eyer; Jamie Ober, RN; Barb Scheetz; Janis Moessner;, University of Pennsylvania: Kurt Barnhart, MD; Karen Lecks; Linda Martino, RN; R. Marunich; and Jacqueline Spitzer, MS. We also acknowledge and thank the Chair of the DSMB, Evan Myers (Duke University).

Address all correspondence and requests for reprints to: Richard S. Legro, MD, Department of Obstetrics and Gynecology, Penn State College of Medicine, M.S. Hershey Medical Center, 500 University Drive, H103, Hershey PA, 17033. E-mail: rsl1@psu.edu.

This study was registered in ClinicalTrials.gov as trial number NCT00704912.

This work was supported by the Eunice Kennedy Shriver National Institutes of Child Health and Human Development (NICHD), National Center for Research Resources, and the National Center for Advancing Translational Sciences at the National Institutes of Health through Grants R01 HD056510 (to R.S.L.), UL1 TR000127 (Penn State Clinical and Translational Institute), and U54 HD29834 (UVA Core Ligand Assay Core of the Specialized Cooperative Centers Program in Reproduction of the NICHD). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosure Summary: R.S.L. reports consulting fees from Euroscreen, Astra Zeneca, Clarus Therapeutics, Takeda, Kindex, and research funding from Ferring and Astra Zeneca; A.R.L. reports ownership of Merck stock; S.J.E. reports research funding from AbbVie; D.B.S. reports consulting fees from BARONova, EnteroMedics, and Ethicon; C.C. is on the Medical Advisory Board of NORA Therapeutics; W.C.D., P.M.K.-E., C.M.S., N.I.W., C.L.G., J.F., K.C.A., and A.D. have nothing to disclose.

References

1. **Legro RS, Barnhart HX, Schlaff WD, et al.** Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med*. 2007;356:551–566.
2. **Legro RS, Brzyski RG, Diamond MP, et al.** Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med*. 2014;371:119–129.
3. **Diamanti-Kandarakis E, Dunaif A.** Insulin resistance and the polycystic ovary syndrome revisited: An update on mechanisms and implications. *Endocr Rev*. 2012;33:981–1030.
4. **Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS.** A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Hum Reprod Update*. 2006;12:673–683.
5. **Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group.** Consensus on infertility treatment related to polycystic ovary syndrome. *Fertil Steril*. 2008;89:505–522.
6. **Legro RS, Arslanian SA, Ehrmann DA, et al.** Diagnosis and treatment of polycystic ovary syndrome: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2013;98:4565–4592.
7. **Kiddy DS, Hamilton-Fairley D, Bush A, et al.** Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clin Endocrinol*. 1992;36:105–111.
8. **Clark AM, Ledger W, Galletly C, et al.** Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum Reprod*. 1995;10:2705–2712.
9. **Domecq JP, Prutsky G, Mullan RJ, et al.** Lifestyle modification programs in polycystic ovary syndrome: Systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2013;98:4655–4663.
10. **Anderson K, Norman RJ, Middleton P.** Preconception lifestyle advice for people with subfertility. *Cochrane Database Syst Rev*. 2010; CD008189.
11. **Sim KA, Partridge SR, Sainsbury A.** Does weight loss in overweight or obese women improve fertility treatment outcomes? A systematic review. *Obes Rev*. 2014;15:839–850.
12. **Tsagareli V, Noakes M, Norman RJ.** Effect of a very-low-calorie diet on in vitro fertilization outcomes. *Fertil Steril*. 2006;86:227–229.
13. **Morris SN, Missmer SA, Cramer DW, Powers RD, McShane PM, Hornstein MD.** Effects of lifetime exercise on the outcome of in vitro fertilization. *Obstet Gynecol*. 2006;108:938–945.
14. **Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC.** A nomogram to predict the probability of live birth after clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. *Fertil Steril*. 2002;77:91–97.
15. **Rausch ME, Legro RS, Barnhart HX, et al.** Predictors of pregnancy in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2009;94:3458–3466.
16. **Branigan EF, Estes MA.** Treatment of chronic anovulation resistant to clomiphene citrate (CC) by using oral contraceptive ovarian suppression followed by repeat CC treatment. *Fertil Steril*. 1999;71:544–546.
17. **Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group.** Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril*. 2004; 81:19–25.
18. **Legro RS, Brzyski RG, Diamond MP, et al.** The Pregnancy in Polycystic Ovary Syndrome II study: Baseline characteristics and effects of obesity from a multicenter randomized clinical trial. *Fertil Steril*. 2014;101:258–269 e258.
19. **Legro RS, Schlaff WD, Diamond MP, et al.** Total testosterone assays in women with polycystic ovary syndrome: Precision and correlation with hirsutism. *J Clin Endocrinol Metab*. 2010;95:5305–5313.
20. **Cooper TG, Noonan E, von Eckardstein S, et al.** World Health Organization reference values for human semen characteristics. *Hum Reprod Update*. 2010;16:231–245.
21. **Ladson G, Dodson WC, Sweet SD, et al.** The effects of metformin with lifestyle therapy in polycystic ovary syndrome: A randomized double-blind study. *Fertil Steril*. 2011;95:1059–1066 e1051–1057.
22. **Cronin L, Guyatt G, Griffith L, et al.** Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS). *J Clin Endocrinol Metab*. 1998;83: 1976–1987.
23. **Kim MK, Choi SY, Byun HJ, et al.** Comparison of sebum secretion, skin type, pH in humans with and without acne. *Arch Dermatol Res*. 2006;298:113–119.
24. **Micklesfield LK, Goedecke JH, Punyanitya M, Wilson KE, Kelly TL.** Dual-energy X-ray performs as well as clinical computed tomography for the measurement of visceral fat. *Obesity*. 2012;20:1109–1114.
25. **Ford ES, Giles WH, Dietz WH.** Prevalence of the metabolic syndrome among US adults: Findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287:356–359.
26. **Matsuda M, DeFronzo RA.** Insulin sensitivity indices obtained from oral glucose tolerance testing: Comparison with the euglycemic insulin clamp. *Diabetes Care*. 1999;22:1462–1470.
27. **Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC.** Predictors of patients remaining anovulatory during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. *J Clin Endocrinol Metab*. 1998;83:2361–2365.
28. **Imani B, Eijkemans MJ, de Jong FH, et al.** Free androgen index and leptin are the most prominent endocrine predictors of ovarian response during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. *J Clin Endocrinol Metab*. 2000;85:676–682.
29. **Legro RS, Pauli JG, Kunselman AR, et al.** Effects of continuous versus cyclical oral contraception: a randomized controlled trial. *J Clin Endocrinol Metab*. 2008;93:420–429.
30. **Wadden TA, Berkowitz RI, Womble LG, et al.** Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med*. 2005;353:2111–2120.
31. **Wadden TA, Volger S, Sarwer DB, et al.** A two-year randomized trial of obesity treatment in primary care practice. *N Engl J Med*. 2011;365:1969–1979.
32. **Wadden TA, West DS, Delahanty L, et al.** The Look AHEAD study: A description of the lifestyle intervention and the evidence supporting it. *Obesity*. 2006;14:737–752.
33. **Knowler WC, Barrett-Connor E, Fowler SE, et al.** Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.
34. **Harbin Consensus Conference Workshop Group.** Improving the Reporting of Clinical Trials of Infertility Treatments (IMPRINT): Modifying the CONSORT statement. *Fertil Steril*. 2014;102:952–959 e915.
35. **Sebire NJ, Jolly M, Harris JP, et al.** Maternal obesity and pregnancy outcome: A study of 287,213 pregnancies in London. *Int J Obes Relat Metab Disord*. 2001;25:1175–1182.
36. **Manson JE, Colditz GA, Stampfer MJ, et al.** A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med*. 1990;322:882–889.
37. **Thomson RL, Buckley JD, Noakes M, Clifton PM, Norman RJ, Brinkworth GD.** The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2008;93:3373–3380.
38. **Korytkowski MT, Mokan M, Horwitz MJ, Berga SL.** Metabolic effects of oral contraceptives in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 1995;80:3327–3334.
39. **Nader S, Riad-Gabriel MG, Saad MF.** The effect of a desogestrel-containing oral contraceptive on glucose tolerance and leptin concentrations in hyperandrogenic women. *J Clin Endocrinol Metab*. 1997;82:3074–3077.
40. **Halperin IJ, Kumar SS, Stroup DF, Laredo SE.** The association between the combined oral contraceptive pill and insulin resistance, dysglycemia and dyslipidemia in women with polycystic ovary syndrome: A systematic review and meta-analysis of observational studies. *Hum Reprod*. 2011;26:191–201.