Benefit of Delayed Fertility Therapy With Preconception Weight Loss Over Immediate Therapy in Obese Women With PCOS

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Context: In overweight/obese women with polycystic ovary syndrome (PCOS), the relative benefit of delaying infertility treatment to lose weight vs seeking immediate treatment is unknown.

Objective: We compared the results of two, multicenter, concurrent clinical trials treating infertility in women with PCOS.

Design, Setting, and Participants: This was a secondary analysis of two randomized trials conducted at academic health centers studying women 18–40 years of age who were overweight/obese and infertile with PCOS.

Intervention: We compared immediate treatment with clomiphene from the Pregnancy in Polycystic Ovary Syndrome II (PPCOS II) trial (N = 187) to delayed treatment with clomiphene after preconception treatment with continuous oral contraceptives, lifestyle modification (Lifestyle: including caloric restriction, antiobesity medication, behavioral modification, and exercise) or the combination of both (combined) from the Treatment of Hyperandrogenism Versus Insulin Resistance in Infertile Polycystic Ovary Syndrome (OWL PCOS) trial (N = 142).

Main Outcome Measures: Live birth, pregnancy loss, and ovulation were measured.

Results: In PPCOS II, after four cycles of clomiphene, the cumulative per-cycle ovulation rate was 44.7% (277/619) and the cumulative live birth rate was 10.2% (19/187), nearly identical to that after oral contraceptive pretreatment in the OWL PCOS trial (ovulation 45% [67/149] and live birth: 8.5% [4/47]). In comparison, deferred clomiphene treatment preceded by lifestyle and combined treatment in OWL PCOS offered a significantly better cumulative ovulation rate compared to immediate treatment with clomiphene. (Lifestyle: 62.0% [80/129]; risk ratio compared to PPCOS II = 1.4; 95% confidence interval [CI], 1.1–1.7; $P = .003$; combined: 64.3% [83/129]; risk ratio compared to PPCOS II = 1.4; 95% CI, 1.2–1.8; $P < .001$ and a significantly better live birth rate lifestyle: 25.0% [12/48]; risk ratio compared to PPCOS II = 2.5; 95% CI, 1.3–4.7; $P = .01$ and combined: 25.5% [12/47]; risk ratio compared to PPCOS II = 2.5; 95% CI, 1.3–4.8; $P = .01$).

Conclusions: These data show the benefit of improved ovulation and live birth with delayed infertility treatment with clomiphene citrate when preceded by lifestyle modification with weight loss compared with immediate treatment. Pretreatment with oral contraceptives likely has little effect on the ovulation and live birth rate compared with immediate treatment. **(*J Clin Endocrinol Metab* 101: 2658–2666, 2016)**

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Abbreviations: OWL PCOS, Treatment of Hyperandrogenism Versus Insulin Resistance in Infertile Polycystic Ovary Syndrome; PPCOS, Pregnancy in Polycystic Ovary Syndrome.

Couples face a dilemma when confronted with both infertility and a modifiable morbidity (such as obesity) that may limit their chance for conception and/or a healthy pregnancy: Should they start infertility therapy and ignore the morbidity or delay treatment to improve that morbidity? In general, there may be inadequate treatments to correct the morbidity or, as often may be the case, limited information exists supporting that modification improves outcomes. Finally, although there may be accepted treatments for the morbidity, the time required to achieve a benefit may significantly shrink the remaining fertility window of the woman, exhausting both patience and precious fecundability because advancing female age remains the single most important factor predicting infertility treatment failure (1). Delay in treatment as perceived by patients is like time's (and fertility's) winged chariot (2) speeding away without them.

Obesity contributes to significant periconceptional and perinatal morbidity in females and is associated with prolonged time to conception (3), increased pregnancy loss (4), and higher rates of adverse pregnancy outcomes such as preeclampsia and preterm labor, in turn, leading to fetal morbidity and mortality (5, 6). When combined with other medical conditions such as diabetes or polycystic ovary syndrome (PCOS), there are synergistic deteriorations in these outcomes (7–9). Expert opinion has uniformly recommended that obese women with PCOS delay infertility therapy and pursue lifestyle modification (10–12), though there is a paucity of high-quality evidence to document the efficacy (13, 14), let alone the optimum weight loss or duration of preconception intervention. Further, there are difficulties in designing such a trial of immediate fertility treatment vs delayed treatment after morbidity modification, especially if life table analyses are used for the primary outcome (ie, the delayed fertility treatment group by definition will start later than the immediate treatment group) (15, 16). The delayed treatment group will have a longer period of observation for pregnancy (eg, both preconception and infertility treatment vs immediate infertility treatment), which may serve to blunt the adverse effects of preconception intervention or augment it if successful. Further, the Kaplan-Meier curve would likely initially be skewed in favor of immediate treatment with its higher per-cycle pregnancy rate (compared to the low, if absent, pregnancy rate during preconception intervention). Thus an overall proportion comparing the cumulative live birth rates may be the preferred summary statistic for trials comparing varying interventions of different lengths.

Recently, we demonstrated a significant benefit of lifestyle modification on ovulation in overweight and obese women. We showed a trend towards improved live birth (The Treatment of Hyperandrogenism vs. Insulin Resistance in Infertile PCOS Women [OWL PCOS] study), an outcome the study was underpowered to address (17). Concurrently, we led a multicenter trial of immediate ovulation induction in infertile women with PCOS with clomiphene or letrozole without a preconception intervention (The Pregnancy in Polycystic Ovary Syndrome II [PPCOS II] study) (18). The intentional similar design in inclusion and exclusion criteria for PCOS, the administration of the same ovulatory agent, clomiphene citrate, and the tracking of pregnancy outcomes allows for a post hoc analysis to examine the effects of immediate treatment with clomiphene citrate in overweight/obese women with PCOS vs preconception treatment with either lifestyle modification, oral contraceptives, or the combination of the two.

Materials and Methods

Design of the trials

Both the OWL PCOS and the PPCOS II studies were multicenter trials supported by the National Institutes of Health with the same lead investigator (R.S.L.) and significant overlap in the investigative teams (R.S.L., W.C.D., C.L.G., S.J.E., A.R.K., C.C., K.T.B., A.D.) and trial design (Table 1). We have previously published the baseline (19) and main outcome data for PPCOS II (18) and the protocol is online at: http://www.nejm.org/doi/full/10.1056/NEJMoa1313517. We have also published the main outcomes for the OWL PCOS Study (17) and the protocol and case report forms can be accessed at http://ctsi.psu.edu/owl-pcos/. Both trials were approved by the investigational review boards at all sites and female participants and their male partners gave written informed consent. The trials were registered at Clinicaltrials.gov (OWL PCOS: NCT00704912 and PPCOS II: NCT00719186).

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Table 1. Comparison Between the OWL PCOS and the PPCOS II Trials

	OWL PCOS	PPCOS II
Enrollment period	October 2008–December 2012	February 2009–January 2012
Primary outcome	Live birth	Same
Number of subjects	149 (142 met criteria for this study)	750 (376 in clomiphene arm and 187 met criteria for this study)
Inclusion criteria		
PCOS	Modified Rotterdam criteria (2, 18): all women had ovulatory dysfunction with either hyperandrogenism (by hirsutism (19) or an elevated testosterone level (20)) or a polycystic ovary on transvaginal ultrasound (19)	Same
Age	18–40 y	Same
BMI	27–42 kg/m^2	No BMI restrictions
Exclusion criteria		
Other comorbidities	Type 2 diabetes and major medical comorbidities	Same
Confounding medications	Sex steroids, insulin sensitizers, and other infertility drugs	Same
Other infertility factors	Tubal/uterine: at least one patent Fallopian tube and a normal uterine cavity Male: a sperm concentration of >14 million per milliliter with documented motility in at least one ejaculate within the past year and the commitment to have vaginal intercourse during the study with the intent of pregnancy	Same
Treatment groups		
Preconception intervention	16-week preconception treatment with either continuous oral contraception, lifestyle modification, or a combination of both followed by four cycles of ovulation induction with clomiphene citrate	None
Infertility treatment	Four cycles of treatment with clomiphene citrate and timed intercourse	Five cycles of ovulation induction with letrozole or clomiphene citrate and timed intercourse
Blinding	Open-label preconception treatments and clomiphene	Double blinding of study drugs
Central laboratory	University of Virginia Core Ligand Laboratory	Same
Pregnancy outcomes	Maternal and infant pregnancy and hospital records reviewed	Same

Abbreviations: BMI, body mass index; OWL PCOS, Treatment of Hyperandrogenism Versus Insulin Resistance in Infertile Polycystic Ovary Syndrome; PPCOS, Pregnancy in Polycystic Ovary Syndrome.

In brief, OWL PCOS was a randomized open-label two-site study of overweight/obese infertile women with PCOS with equal allocation to three treatment groups: 1) oral contraceptives (OCP) given continuously; 2) lifestyle modification (lifestyle), consisting of caloric restriction with meal replacements, antiobesity medication (sibutramine or orlistat) brief behavioral modification and increased physical activity; and 3) combined OCP and lifestyle modification (combined). Orlistat was substituted for sibutramine after the Food and Drug Administration issued an advisory about excess cardiovascular events associated with the drug and the drug was eventually removed from the market. In OWL PCOS, up to four cycles of induction of ovulation study medication were used (14). In brief, PPCOS II was a randomized, double-blind, multisite study of two ovulation induction agents: letrozole or clomiphene citrate in infertile women with PCOS. In PPCOS II, up to five cycles of induction of ovulation study medication were used (18), though we only examined the first four cycles in this study.

In both OWL PCOS and PPCOS II, oral ovulation induction agents were given in a standardized regimen. Baseline monitoring determined if patients were anovulatory or ovulatory. If anovulatory in PPCOS II, menses was induced with progestin and study drug started with subsequent menses. In OWL PCOS, investigators had the option to begin clomiphene immediately or induce menses with progestin. If ovulatory, women in both studies waited for a subsequent menses and began ovulation induction medication in the early follicular phase of their next menstrual cycle. Subjects in OWL PCOS were advised to maintain their weight and level of activity from the end of the preconception phase (ie, the end of the lifestyle modification and/or oral contraceptive phase), whereas meal replacements were discontinued. In PPCOS II, there were no instructions given regarding weight and activity during treatment. In both studies, a visit 3 weeks following clomiphene treatment ovulation was confirmed based on ultrasound monitoring and serum progesterone level. Patients with documented ovulation (progesterone level ≥3 ng/dl) had a serum pregnancy test 2 weeks later if no menses had occurred; with menses, they began clomiphene at the same dose at which they had ovulated. No other ultrasound monitoring was performed in either study.

In women without evidence of ovulation, the dose of clomiphene was increased to the next higher dose (100 mg for 5 days, up to a maximum of 150 mg for 5 days). In both studies, 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. Medical records from pregnancy (mother and infant) were obtained and reviewed to ascertain birth outcomes.

Assays

All reported laboratory values from both studies (except glucose and lipid levels) were determined in a central laboratory (Ligand Core Laboratory, University of Virginia) (19), using the same assays as previously reported in our PPCOS II study (18, 20). All assays had intra- and interassay coefficients of variation of less than 10% (18, 20). Glucose levels were measured by the glucose oxidase method at both the Penn State College of Medicine (OWL PCOS) and the Core Ligand Lab (PPCOS II). Lipid levels (total cholesterol, high-density lipoprotein cholesterol and triglyceride levels) were measured through commercial laboratories at both the Penn State College of Medicine (OWL PCOS) and the Core Ligand Lab (PPCOS II). The low-density lipoprotein cholesterol level was calculated using the Friedewald equation (21).

Statistical analysis

The primary outcome in both trials was live birth. We extracted from the PPCOS II database all patients from the clomiphene treatment group who met the same body mass index in-

clusion criteria of the OWL PCOS study and only used the first four ovulation induction cycles of the PPCOS II study to match the OWL-PCOS treatment protocol. Of the initial 200 women selected from the clomiphene arm of the PPCOS II database that met the OWL PCOS inclusion criteria, 20 had participated sequentially in both studies. For those 20 patients, our analysis used only the first study in which they participated. This yielded a final sample of 187 women from the PPCOS II study and 142 women from the OWL PCOS study. Predetermined secondary outcomes included ovulation rates, conception, and pregnancy loss rates. For binary outcomes (eg, live birth, pregnancy, ovulation), a log-binomial regression model was used to assess differences between the OWL PCOS treatment groups and the PPCOS II group. Because this was a prospective study, the log-binomial model allows us to estimate the risk ratio rather than the odds ratio, which is provided when using ordinary logistic regression. Linear regression was used to assess differences between the OWL PCOS treatment groups and the PPCOS II group for continuous birth outcomes (eg, infant birth weight). All hypothesis tests were two-sided and all analyses were performed using SAS software, version 9.4 (SAS Institute Inc.).

Results

Baseline characteristics of key demographic, reproductive, and metabolic parameters were evenly matched between treatment groups from the two studies (Table 2). Compared to immediate treatment with clomiphene in the PPCOS II trial, patients in the lifestyle group of the OWL PCOS study as well as patients in the combined group of the OWL PCOS study had a 2.5-fold ($P = .01$) increase in live births (Table 3). Patients in the Lifestyle and combined groups also had a 1.4-fold increase in cumulative ovulation rate ($P = .003$ and $P < .001$, respectively) compared to treatment with clomiphene in PPCOS II. In contrast, women in the OWL PCOS group who received OCP preconception treatment had no significant difference in live birth or ovulation rates compared to immediate treatment with clomiphene in PPCOS II. There were no differences in risk for pregnancy loss in any of the OWL PCOS treatment groups compared to treatment with clomiphene in PPCOS II.

Table 2. Baseline Characteristics From the PPCOS II Clomiphene and OWL PCOS Selected Cohorts

	PPCOS II (n = 187) Mean (SD)	OWL PCOS: OCP (n = 47) Mean (SD)	OWL PCOS: Lifestyle (n = 48) Mean (SD)	OWL PCOS: Combined (n = 47) Mean (SD)
Demographics				
Age (y)	28.9 (4.1)	29.8 (3.8)	28.6 (3.4)	28.5 (4.0)
Hispanic: N (%)	41 (21.9)	6 (12.8)	5 (10.4)	4 (8.5)
Caucasian: N (%)	147 (78.6)	38 (80.9)	35 (72.9)	29 (61.7)
Black/African-American: N (%)	29 (15.5)	7 (14.9)	7 (14.6)	13 (27.7)
Other/multiracial: N (%)	11 (5.9)	2 (4.3)	6 (12.5)	5 (10.6)
Duration of time attempting to conceive (mo)	44.4 (38.3)	43.3 (33.1)	32.5 (27.5)	34.5 (28.7)
Nulliparous: N (%)	147 (78.6)	37 (78.7)	39 (81.3)	42 (89.4)
Biometric				
Weight (kg), preweight reduction intervention	NA	94.2 (14.3)	96.0 (15.6)	95.5 (14.8)
Weight (kg), at start of ovulation induction	93.2 (14.2)	93.5 (14.8)	90.6 (13.9)	88.4 (14.4)
% Weight Loss after weight reduction intervention	NA	1.3 (3.1)	6.4 (3.9)	6.7 (4.2)
BMI (kg/m^2), preweight reduction intervention	NA	35.0 (4.2)	35.0 (4.6)	35.4 (4.5)
BMI (kg/m^2), at start of ovulation induction	34.8 (4.3)	34.8 (4.4)	33.0 (4.3)	32.8 (4.2)
Waist (cm)	107.1 (12.2)	105.7 (11.0)	107.2 (13.5)	106.6 (12.1)
Systolic BP (mm Hg)	121.0 (12.1)	116.0 (10.2)	114.7 (13.8)	118.9 (11.8)
Diastolic BP (mm Hg)	77.5 (9.1)	73.6 (7.8)	71.7 (8.2)	74.6 (9.6)
Ferriman-Gallwey hirsutism score	17.4 (8.2)	16.6 (7.8)	19.2 (8.8)	18.0 (9.0)
Ultrasound parameters				
Antral follicle count (both ovaries)	46.2 (27.6)	63.6 (36.0)	54.5 (34.4)	60.1 (34.5)
Total ovarian volume (cm^3)[a]	22.1 (16.7–28.8)	22.0 (17.3–29.1)	21.3 (14.0–26.9)	19.0 (13.7–27.2)
Endometrial thickness (mm)	6.6 (3.0)	6.5 (2.2)	7.2 (2.5)	7.0 (2.6)
Polycystic ovaries according to modified Rotterdam criteria: N (%)	179 (95.7)	43 (97.7)	46 (97.9)	43 (95.6)
Serum results				
AMH (ng/ml)	8.1 (6.4)	9.1 (5.2)	8.8 (6.0)	8.9 (5.5)
Testosterone (ng/dl)[a]	51.4 (35.4–72.0)	48.3 (36.8–72.9)	52.7 (35.3–70.8)	53.5 (38.4–79.0)
SHBG (nmol/liter)[a]	22.3 (17.6–31.5)	26.1 (20.2–34.4)	28.9 (21.5–38.1)	25.7 (18.6–40.4)
Free androgen index[a]	7.7 (5.0–12.0)	6.0 (3.8–12.2)	6.4 (4.0–8.9)	6.7 (4.9–10.3)
Estradiol (pg/ml)	52.6 (39.7)	55.1 (41.4)	54.2 (39.6)	59.0 (47.7)
Progesterone (ng/ml)	1.3 (2.4)	1.5 (2.5)	1.4 (2.4)	1.5 (3.3)
Cholesterol (mg/dl)	181.4 (39.5)	187.9 (31.4)	184.9 (34.8)	184.9 (33.2)
HDL (mg/dl)[a]	37.0 (30.0–44.0)	44.0 (39.0–52.0)	42.0 (36.0–48.0)	43.0 (39.0–49.0)
LDL (mg/dl)	123.1 (33.2)	116.2 (26.7)	114.1 (31.3)	113.1 (31.1)
Triglycerides (mg/dl)[a]	116.0 (83.0–167.0)	117.0 (90.0–161.0)	131.5 (99.5–174.5)	120.0 (86.0–165.0)
Fasting glucose (mg/dl)	87.0 (15.1)	87.1 (9.6)	86.8 (8.9)	90.1 (15.0)

Abbreviations: BP, blood pressure; NA, not applicable to the PPCOS II trial as there was no preconception intervention before ovulation induction; OWL PCOS, Treatment of Hyperandrogenism Versus Insulin Resistance in Infertile Polycystic Ovary Syndrome; PPCOS, Pregnancy in Polycystic Ovary Syndrome.

[a] Median (25th–75th percentile) is reported.

Table 3. Primary Outcome of Live Birth and Secondary Outcomes From the PPCOS II Clomiphene and OWL PCOS Selected Cohorts

		OWL PCOS: OCP		
Outcome	**PPCOS II No./Total No. (%)**	**No./Total No. (%)**	**RR (95% CI) Compared to PPCOSII**	***P* Value[e]**
Ovulation				
Ovulation (total number of ovulations/total treatment cycles)[a]	277/619 (44.7)	67/149 (45.0)	1.0 (0.8–1.3)	.96
Pregnancy				
Conception (serum hCG level >10 mIU/ml)	38/187 (20.3)	7/47 (14.9)	0.7 (0.3–1.5)	.41
Clinical pregnancy (fetal heart motion visualized on ultrasound)	25/187 (13.4)	6/47 (12.8)	1.0 (0.4–2.2)	.91
Pregnancy loss				
Pregnancy loss among subjects who conceived[b]	18/38 (47.4)	3/7 (42.9)	0.9 (0.4–2.3)	.83
Birth outcomes				
Live birth	19/187 (10.2)	4/47 (8.5)	0.8 (0.3–2.3)	.74
Infant birth weight (grams)[c,d]	3198 (916) [19]	3487 (284) [4]	290 (−519 to 1098)	.47
Duration of pregnancy (weeks)[c,d]	37.4 (4.5) [19]	38.8 (0.5) [4]	1.3 (−2.3 to 5.0)	.47
Fecundity per ovulated patient				
Live birth	19/135 (14.1)	4/34 (11.8)	0.8 (0.3–2.3)	.73

Abbreviations: CI, confidence interval; hCG, human chorionic gonadotropin; OCP, oral contraceptives; OWL PCOS, Treatment of Hyperandrogenism Versus Insulin Resistance in Infertile Polycystic Ovary Syndrome; RR, risk ratio.

[a] Cycles for which ovulation status could not be determined (no progesterone value/no pregnancy) are excluded.

[b] Pregnancy loss does not include twin pregnancies that resulted in a singleton live birth.

[c] Data are presented as mean (SD) [n] and difference in means (95% CI).

[d] Calculations based on singleton deliveries that resulted in live birth, ranging in gestational age of 22–41 weeks; two twin deliveries from OWL PCOS are omitted.

[e] Log-binomial model for categorical data and linear regression model for continuous data.

In regards to per-cycle results, only the lifestyle group in OWL PCOS had a significantly improved chance of pregnancy and live birth in the first ovulation induction cycle compared to the first ovulation induction cycle in PPCOS II (Table 4). The ovulation rate was significantly improved in the first, second, and fourth cycles of ovulation induction in the combined group from OWL PCOS compared to treatment with clomiphene in PPCOS II. Further, there was a significantly improved chance of ovulation in the first and fourth ovulation induction cycles with lifestyle alone in the OWL PCOS study compared to treatment with clomiphene in PPCOS II. No per-cycle differences were noted between the OCP group in OWL PCOS and treatment with clomiphene in PPCOS II.

Discussion

In this post hoc comparison of two randomized, concurrently performed clinical trials to treat infertility in women with PCOS, we found that pretreatment lifestyle modification for weight loss, with or without concurrent oral contraceptive therapy, was associated with a significant improvement in the rate of ovulation and an even greater increase in live birth rate than immediate fertility treatment with clomiphene. Further, ovulation and live birth rates were nearly identical between pretreatment with oral contraceptives vs immediate treatment with clomiphene, suggesting that there is little fertility benefit to pretreatment with hormonal suppression, alone or in combination with lifestyle modification. The weight maintenance in the oral contraceptive group further supports the conclusion that it was some aspect(s) of the weight loss intervention that led to the improved outcomes.

These data are relevant because we are unaware of any published randomized trials of lifestyle intervention promoting weight loss vs immediate treatment in women with PCOS (14). Patients and practitioners require a justification to delay immediate fertility treat-

Table 3. Continued

Outcome	OWL PCOS: Lifestyle			OWL PCOS: Combined		
	No./Total No. (%)	RR (95% CI) Compared to PPCOSII	*P* Value[e]	No./Total No. (%)	RR (95% CI) Compared to PPCOSII	*P* Value[e]
Ovulation						
Ovulation (total number of ovulations/total treatment cycles)[a]	80/129 (62.0)	1.4 (1.1–1.7)	0.003	83/129 (64.3)	1.4 (1.2–1.8)	<.001
Pregnancy						
Conception (serum hCG level >10 mIU/ml)	15/48 (31.3)	1.5 (0.9–2.6)	0.10	14/47 (29.8)	1.5 (0.9–2.5)	.15
Clinical pregnancy (fetal heart motion visualized on ultrasound)	12/48 (25.0)	1.9 (1.0–3.4)	0.04	13/47 (27.7)	2.1 (1.1–3.7)	.02
Pregnancy loss						
Pregnancy loss among subjects who conceived[b]	3/15 (20.0)	0.4 (0.1–1.2)	0.11	2/14 (14.3)	0.3 (0.1–1.1)	.08
Birth outcomes						
Live birth	12/48 (25.0)	2.5 (1.3–4.7)	.01	12/47 (25.5)	2.5 (1.3–4.8)	.01
Infant birth weight (grams)[c,d]	3090 (629) [10]	−107 (−682 to 467)	.71	3409 (505) [12]	212 (−330 to 753)	.44
Duration of pregnancy (weeks)[c,d]	38.2 (2.7) [10]	0.8 (−1.8 to 3.4)	.55	39.3 (1.3) [12]	1.8 (−0.6 to 4.3)	.14
Fecundity per ovulated patient						
Live birth	12/34 (35.3)	2.5 (1.4–4.6)	.004	12/36 (33.3)	2.4 (1.3–4.4)	.01

ment in the current practice environment with a greater tendency to immediate treatment and acceleration to expensive and invasive infertility therapies such as in vitro fertilization. Although there are data from at least one prospective randomized trial documenting a benefit to OCP pretreatment before clomiphene, (22), this was a single-center study done in women who were initially clomiphene resistant. This was not replicated in our study, which did not require clomiphene resistance as an entry criterion.

The strengths of the present study include the similarity of protocols, with a near uniform definition of PCOS and exclusion of other infertility disorders, the common means of administering and monitoring clomiphene, and the tracking of all pregnancy outcomes. Other strengths included the multicenter design, the concurrent and overlapping study sites, and that the similarity of metabolic and reproductive phenotypes of the population in both trials. There were, however, slight differences between the protocols, most prominently the focus on overweight/body mass index women with PCOS in the OWL PCOS, which we compensated for in the analysis by excluding women from PPCOS II who fell outside of these weight brackets. We allowed five cycles of ovulation induction in PPCOS II and only four in OWL PCOS, which we again compensated for by only including the first four cycles of both studies. Another difference was the option not to induce menses at the start of infertility treatment in OWL PCOS, which may have contributed to the markedly elevated chance of live birth in the first cycle of ovulation induction with clomiphene in the Lifestyle group (and trend in the combined group) vs immediate treatment with clomiphene in PPCOS II. We have previously shown that progestin exposure before ovulation is associated with lower pregnancy rates (23). Clomiphene was given open label in OWL PCOS and blinded in PPCOS II. Finally, the greatest discrepancy is the difference in sample size between the two study cohorts in this post hoc analysis where type I and type II errors are more likely. This may have contributed to the variable per-cycle ovulatory benefits of preconception weight loss compared to immediate treatment where some cycles lacked a statistically improved benefit. We note that with the larger sample sizes of our PPCOS I and II trials, we showed no time-related increase

Table 4. Per-Cycle Results of Ovulation Induction in PPCOS II Clomiphene and OWL PCOS Selected Cohorts

Outcome	PPCOS II No./Total No. (%)	OWL PCOS: OCP			OWL PCOS: Lifestyle			OWL PCOS: Combined		
		No./Total No. (%)	RR (95% CI)	*P* Value[a]	No./Total No. (%)	RR (95% CI)	*P* Value[a]	No./Total No. (%)	RR (95% CI)	*P* Value[a]
Primary outcome: live birth per treatment cycle										
Cycle 1	3/187 (1.6)	1/47 (2.1)	1.3 (0.1–12.5)	.80	5/48 (10.4)	6.5 (1.6–26.2)	.01	3/47 (6.4)	4.0 (0.8–19.1)	.08
Cycle 2	8/184 (4.3)	1/46 (2.2)	0.5 (0.1–3.9)	.51	4/43 (9.3)	2.1 (0.7–6.8)	.20	5/44 (11.4)	2.6 (0.9–7.6)	.08
Cycle 3	3/176 (1.7)	1/45 (2.2)	1.3 (0.1–12.2)	.82	2/39 (5.1)	3.0 (0.5–17.4)	.22	1/39 (2.6)	1.5 (0.2–14.1)	.72
Cycle 4	5/173 (2.9)	1/44 (2.3)	0.8 (0.1–6.6)	.82	1/37 (2.7)	0.9 (0.1–7.8)	.95	3/38 (7.9)	2.7 (0.7–10.9)	.16
Secondary outcome: clinical pregnancy (fetal heart motion on ultrasound) per treatment cycle										
Cycle 1	5/187 (2.7)	2/47 (4.3)	1.6 (0.3–7.9)	.57	5/48 (10.4)	3.9 (1.2–12.9)	.03	3/47 (6.4)	2.4 (0.6–9.6)	.22
Cycle 2	9/182 (4.9)	2/45 (4.4)	0.9 (0.2–4.0)	.89	4/43 (9.3)	1.9 (0.6–5.8)	.27	6/44 (13.6)	2.8 (1.0–7.3)	.04
Cycle 3	5/173 (2.9)	1/43 (2.3)	0.8 (0.1–6.7)	.84	2/39 (5.1)	1.8 (0.4–8.8)	.48	1/38 (2.6)	0.9 (0.1–7.6)	.93
Cycle 4	6/168 (3.6)	1/42 (2.4)	0.7 (0.1–5.4)	.70	1/37 (2.7)	0.8 (0.1–6.1)	.79	3/37 (8.1)	2.3 (0.6–8.7)	.23
Secondary outcome: conception (serum hCG level >10 mIU/ml) per treatment cycle										
Cycle 1	10/187 (5.3)	3/47 (6.4)	1.2 (0.3–4.2)	.78	5/48 (10.4)	1.9 (0.7–5.4)	.20	4/47 (8.5)	1.6 (0.5–4.9)	.41
Cycle 2	11/177 (6.2)	2/44 (4.5)	0.7 (0.2–3.2)	.68	6/43 (14.0)	2.2 (0.9–5.7)	.09	6/43 (14.0)	2.2 (0.9–5.7)	.09
Cycle 3	8/166 (4.8)	1/42 (2.4)	0.5 (0.1–3.8)	.50	3/37 (8.1)	1.7 (0.5–6.0)	.43	1/37 (2.7)	0.6 (0.1–4.3)	.58
Cycle 4	9/158 (5.7)	1/41 (2.4)	0.4 (0.1–3.3)	.41	1/34 (2.9)	0.5 (0.1–3.9)	.52	3/36 (8.3)	1.5 (0.4–5.1)	.55
Secondary outcome: ovulation per treatment cycle										
Cycle 1	68/181 (37.6)	15/41 (36.6)	1.0 (0.6–1.5)	.91	27/42 (64.3)	1.7 (1.3–2.3)	<.001	23/40 (57.5)	1.5 (1.1–2.1)	.01
Cycle 2	78/164 (47.6)	21/39 (53.8)	1.1 (0.8–1.6)	.46	19/35 (54.3)	1.1 (0.8–1.6)	.45	25/35 (71.4)	1.5 (1.2–2.0)	.003
Cycle 3	74/146 (50.7)	14/36 (38.9)	0.8 (0.5–1.2)	.24	17/29 (58.6)	1.2 (0.8–1.6)	.41	19/29 (65.5)	1.3 (0.9–1.8)	.10
Cycle 4	57/128 (44.5)	17/33 (51.5)	1.2 (0.8–1.7)	.46	17/23 (73.9)	1.7 (1.2–2.3)	.001	16/25 (64.0)	1.4 (1.0–2.0)	.04

Abbreviations: CI, confidence interval; hCG, human chorionic gonadotropin; OCP, oral contraceptives; OWL PCOS, Treatment of Hyperandrogenism Versus Insulin Resistance in Infertile Polycystic Ovary Syndrome; RR, risk ratio.

[a] Log-binomial model.

or decrease in the ovulation rate in response to clomiphene up to six cycles (17, 24).

One of the striking findings of this study is the marked improvement in live birth rates, out of proportion to the more modest, but still significant improvement, in ovulation rates, suggesting yet again that improving quality of ovulation is as important as improving the frequency of ovulation (24). Pregnancy loss rates were similar between the treatment groups in this study, so the differences in live birth rates were not completely explained by the trends favoring reduced pregnancy loss in the lifestyle modification groups. Weight loss is the simplest explanation for the improved ovulation and live birth rates, though there are concurrent improvements in a variety of metabolic parameters and to a lesser extent reproductive parameters with weight loss (17, 25, 26) that have also been implicated in poor reproductive outcomes. Thus, the mechanism(s) for improved fecundity per ovulation remain speculative, but the findings from the OCP arm in the OWL PCOS study support weight loss as a target goal of preconception treatment. To modify our opening analogy (with apologies to Andrew Marvell) (2), lightening time's winged chariot's load may allow a longer flight and greater chance of reaching a final destination of a healthy baby.

Our research holds significant implications for current practice and supports the concept of delaying fertility treatment to pursue lifestyle modification in overweight/obese women with PCOS. It provides momentum to test this concept more completely and prospectively in properly designed and adequately powered multicenter studies to generate level I evidence for the practice. Future studies may also want to use other ovulation induction agents in the infertility treatment phase such as low-dose gonadotropin (27) or letrozole, (28) which tend to have greater success rates combined with comparable rates of multiple pregnancy and congenital anomalies as clomiphene.

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