Gestational Weight Gain in Women With Polycystic Ovary Syndrome: A Controlled Study

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Context: Women with polycystic ovary syndrome (PCOS) have increased risk for pregnancy complications, possibly related to pre-existing obesity and excessive gestational weight gain (GWG).

Objectives: To assess the contributions of diagnosis and preconception weight on GWG and perinatal outcomes.

Research Design and Methods: Prospective cohort study of singleton pregnancies in PCOS (n = 164) and ovulatory controls (n = 176) from infertility treatment.

Main Outcome Measures: GWG, birthweight, pregnancy complications.

Results: From preconception baseline, normal-weight women with PCOS gained 2.3 pounds more during the first trimester (95% CI, 0.3 to 4.3; $P = 0.02$), and by the end of the second trimester, 4.2 pounds more than controls (95% CI, 0.7 to 7.7; $P = 0.02$). Women who were overweight with PCOS gained significantly more weight than did controls by the end of the second trimester (5.2 pounds; 95% CI, 0.2 to 10.2; $P = 0.04$), whereas women with obesity and PCOS and control women had similar weight gain throughout pregnancy. Within normal-weight, overweight, and obese groups, prevalence of pre-eclampsia and gestational diabetes did not differ between the PCOS and control groups, nor was there a difference in birthweight. Preconception body mass index (BMI) was significantly associated with GWG; for every 1-kg/m^2 increase in preconception BMI, GWG decreased by 0.62 pounds (95% CI, −0.85 to −0.40; $P < 0.001$).

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Abbreviations: AGA, appropriate-for-gestational-age; AMIGOS, Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation; BMI, body mass index; GWG, gestational weight gain; IOM, Institute of Medicine; LGA, large-for-gestational-age; PCOS, polycystic ovary syndrome; PPCOS II, Pregnancy in Polycystic Ovary Syndrome II; SGA, small-for-gestational-age.

Conclusions: Women with PCOS who are of normal weight or are overweight before conception experience more GWG than do ovulatory controls. Within normal-weight, overweight, and obese groups, rates of perinatal complications do not significantly differ between women with PCOS and controls. Preconception BMI is the strongest predictor of GWG. (***J Clin Endocrinol Metab*** **103: 4315–4323, 2018)**

Polycystic ovary syndrome (PCOS) is a common endocrinopathy in women that consists of hyperandrogenism, chronic anovulation, and polycystic ovaries and is thought to affect 5% to 18% of reproductive age women (1, 2). Infertility is one of the most common presenting symptoms (3), and pregnancy outcomes in this group of women may be influenced by pre-existing metabolic and reproductive abnormalities (4). Obesity and metabolic abnormalities linked to insulin resistance are common among women with PCOS (5, 6) and may have additive adverse effects (7). Our own prospective randomized trials (8–10) and a recent meta-analysis of the epidemiologic literature have supported an increased incidence of perinatal complications in women with PCOS and their neonates (4).

Additionally, excessive weight gain during pregnancy has been associated with unfavorable maternal and fetal outcomes, including gestational hypertension and diabetes (4). Forty-eight percent of pregnant women continue to gain more than the recommended amount of weight set forth in the 2009 Institute of Medicine (IOM) guidelines (11). Numerous studies have elucidated preconception risk factors for increased weight gain during pregnancy, such as preconception body mass index (BMI), hypertension, primiparity, and age (12–14). PCOS is thought by some to predispose to excess gestational weight gain (GWG), although there are mixed data about whether women with PCOS are prone to excessive GWG compared with control women (15, 16).

However, it is often difficult to adequately control for the multiple confounders in such analyses of GWG and perinatal outcomes because pre-existing obesity, infertility diagnosis (*i.e.,* PCOS or ovulatory), subfertility *per se,* and infertility treatments may have independent effects. For example, subfertility and its treatment have been associated with increased rates of fetal anomalies (17), small-for-gestational-age (SGA) singleton pregnancies (18), and iatrogenic multiple pregnancies. Additionally, there have been few prospective studies to document different rates of GWG in women with PCOS compared with controls, and studies have failed to adequately match women who have PCOS with controls by preconception weight category (instead of diagnosis alone) (15, 16).

We performed a secondary analysis of two prospective randomized trials conducted concurrently by the Reproductive Medicine Network to more accurately investigate the effect of PCOS [the Pregnancy in Polycystic Ovary Syndrome II or PPCOS II study (9)] on the risk for both GWG and related perinatal complications compared with a population of ovulatory women with normal menses and unexplained infertility (*i.e.,* controls) [the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation or AMIGOS study (19)].

We hypothesized that (1) there is a clinically significant difference in GWG between pregestational weight-matched women diagnosed with PCOS and ovulatory controls; (2) birthweight adjusted for gestational age in children from singleton pregnancies as well as prevalence of pre-eclampsia and gestational diabetes will be similar between women diagnosed with PCOS and controls when matched for preconception BMI; and (3) baseline characteristics, including patient diagnosis (PCOS or control) and metabolic status (*i.e.,* centripetal obesity, insulin resistance, metabolic syndrome), can be used to predict GWG in singleton pregnancies for women with PCOS. We have not previously published any data specific to this cohort with a live birth (including baseline characteristics and GWG), other than reporting the pregnancy outcomes and complications in the primary papers published in the *New England Journal of Medicine* (9, 19).

Material and Methods

Participants and study synopsis

This secondary analysis was designed as a prospective cohort study examining all singleton live births (defined in both trials as a pregnancy delivering ≥20 weeks' gestation) that resulted from the prospective PPCOS II and AMIGOS randomized controlled studies. Women with PCOS (PPCOS II) and women with unexplained infertility and regular menses (AMIGOS) were recruited contemporaneously in the same geographic locations. All women were age 18 to 40 years, with no limitations on weight in either study and no other major infertility factors. The PPCOS II study randomly assigned 750 women with PCOS in a 1:1 ratio to clomiphene or letrozole for up to five cycles of ovulation induction combined with timed intercourse. PCOS was defined by modified Rotterdam criteria, and all women were required to have chronic anovulation as a criterion for ovulation induction. The AMIGOS study randomly assigned 900 women in a 1:1:1 ratio to clomiphene, letrozole, or gonadotropin therapy combined with intrauterine insemination for up to four cycles of treatment. In both studies clomiphene and letrozole were given in a double-blind manner, but gonadotropin in the AMIGOS study was given open-label. Participants in both studies were studied in a similar manner by history, exam, ultrasound, questionnaire, and serum assays that

were run in a central National Institute of Child Health and Human Development–supported core laboratory (Core Ligand Laboratory at the University of Virginia) (20, 21). We have previously published the quality control for these assays (20–22), but Supplemental Table 1 includes those measures for the assays reported in this paper. All participants gave written informed consent, and studies were institutional review board approved at each participating center and registered at ClinicalTrials.gov (PPCOS II: NCT00902382; AMIGOS: NCT00902382).

Baseline data in this study are reported from the last recorded study visit before pregnancy. All infertility treatment within the study ceased with a positive pregnancy test result. Pregnancies were followed from conception through documentation of fetal viability (visualization of fetal heart motion by transvaginal ultrasound) according to protocol and then patients were referred for prenatal care to their obstetricians. Prenatal care, delivery, and neonatal records were obtained systematically as part of the study. Additionally, all participants were contacted in the puerperium period to confirm the pregnancy outcome and were queried about their cumulative pregnancy weight gain because there was often a gap between the last weight on the prenatal record and weight at delivery (not routinely obtained on admission to labor and delivery).

Statistical plan

Participants were categorized according to preconception weight categories (normal BMI, 18.0 to 24.9 kg/m^2; overweight BMI, 25.0 to 29.9 kg/m^2; and obese BMI $\geq$30.0 kg/m^2) because the IOM-recommended GWG is based on these categories. For patients with normal BMI, the recommended GWG is 25 to 35 pounds; for patients with overweight BMI, the recommended weight gain is 15 to 25 pounds; and for patients with obesity, it is 11 to 20 pounds (23). Baseline preconception weight was taken from the last measured study weight before conception. Gestational weights were abstracted from prenatal records. Total GWG was obtained by patient self-report after delivery (*i.e.*, how much did they gain from preconception up until delivery?). Birth weights were collected from delivery records. The development of pre-eclampsia and gestational diabetes was determined by the obstetrician and verified by review of the prenatal and/or delivery records.

Baseline characteristics were compared between women with PCOS and controls (*i.e.,* women with unexplained infertility) within each preconception weight category using linear regression, adjusting for treatment (clomiphene, letrozole, or gonadotropin) and the number of treatment cycles. The natural logarithmic transformation was applied to insulin and anti-Müllerian hormone values to meet normality assumptions. The concordance correlation coefficient was used to assess the concordance between self-reported GWG and measured GWG abstracted from prenatal records in a subset of women whose last measured gestational weight was within $\pm$1 week of their gestational age. Analyses of GWG, pregnancy complications, and birthweight were performed separately by preconception weight category (*i.e.,* within normal-weight, overweight, and obese BMI categories). A quadratic random coefficients model (24) was used to generate gestational weight curves, adjusting for treatment and number of treatment cycles, for women with PCOS and for controls by preconception BMI categories over the whole pregnancy based on the weights abstracted from prenatal records. From these curve trajectories, estimates of cumulative GWG were constructed at 14 weeks, 28 weeks, and 40 weeks to represent the end of each trimester and were compared between the PCOS and control groups. The distributions of self-reported GWG based on IOM guidelines (achieved less than recommended weight gain, met recommended weight gain, or exceeded recommended weight gain) were compared between PCOS and control groups by using ordinal logistic regression, adjusting for gestational age, treatment, and number of treatment cycles. The presence of pre-eclampsia and gestational diabetes was compared between the PCOS and control groups within each preconception weight category by using logistic regression, adjusting for GWG, treatment, and number of treatment cycles. Birthweight was compared between PCOS and control groups within each preconception weight category using a general linear model, adjusting for gestational age, GWG, treatment, and number of treatment cycles. Birthweight was also classified as SGA, appropriate-for-gestational-age (AGA), or large-for-gestational-age (LGA), and rates were compared between PCOS and control groups via logistic regression. For this particular model, because of the relatively small sample sizes for some of the birthweight categories, the data were not analyzed separately by preconception weight category. One model including all participants (normal-weight, overweight, obese) was fit for the SGA/AGA/LGA outcome, adjusting for preconception BMI as well as GWG, treatment, and number of treatment cycles. SGA was defined as below the 10th percentile, AGA as 10th to 90th percentile, and LGA as above the 90th percentile based on the revised 2011 birth weight percentiles for neonates (25).

A multiple linear regression model using best subsets regression was fit to identify characteristics that could best predict self-reported GWG in women with PCOS and controls. Potential predictors for this model were first assessed for collinearity, and only variables where the variance inflation factor was $<$3 were kept as candidates. The regression model used the Mallow Cp-statistic as the selection criterion to determine the best set of baseline characteristics associated with the outcome of self-reported GWG to enhance the predictive accuracy. Additionally, a goal of the multivariable model was to determine whether PCOS status (*i.e.,* PCOS vs control) and preconception BMI, adjusting for treatment and number of treatment cycles, affected self-reported GWG, so these factors were forced into the final model. For the final model, two-way interactions among the final predictors were explored and subsequently removed if they were not significant. In a similar manner, a multivariable logistic regression model, using best subsets regression with the highest-score χ^2 statistic as the selection criteria, was fit to identify characteristics that could best predict meeting IOM GWG guidelines (met/not met) in women with PCOS and controls. All hypothesis tests were two-sided and all analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC) with graphics created using R software, version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics are shown in Table 1. The number of participants achieving singleton pregnancies was relatively similar across the two trials (n = 164 PCOS vs n = 176 controls). Women were categorized as normal,

Table 1. Baseline Characteristics of Women With PCOS and Controls

	All		Normal	
Baseline Characteristic	**PCOS (n = 164)**	**Control (n = 176)**	**PCOS (n = 37)**	**Control (n = 70)**
Age, y	28.3 (3.8) [164]	31.7 (4.3) [176]	27.9 (3.7)[a] [37]	31.9 (4.4) [70]
Preconception weight, lb[c]	193.8 (54.4) [164]	166.7 (41.8) [176]	127.8 (12.4) [37]	130.0 (16.2) [70]
Preconception BMI, kg/m^2	32.5 (8.8) [164]	27.7 (6.4) [176]	22.0 (1.8) [37]	21.8 (1.7) [70]
Waist circumference, cm	101.8 (19.9) [162]	90.5 (16.8) [175]	77.1 (8.3) [36]	78.1 (8.1) [69]
Systolic BP, mm Hg	118.7 (13.3) [152]	116.5 (12.7) [175]	111.2 (11.8) [32]	112.2 (13.8) [69]
Diastolic BP, mm Hg	75.4 (10.0) [152]	71.6 (8.8) [175]	70.0 (8.9) [32]	68.7 (8.6) [69]
Fasting insulin, mIU/L[d]	15.7 (9.3, 29.4) [151]	13.7 (8.0, 29.2) [171]	7.2 (5.0, 11.4)[e] [32]	10.4 (5.0, 23.6) [70]
Fasting glucose, mg/dL	88.3 (13.4) [152]	83.1 (17.6) [171]	81.4 (9.5) [32]	77.8 (17.9) [69]
AMH, ng/dL[d]	5.5 (3.2, 9.3) [152]	2.1 (1.3, 3.4) [171]	7.5 (4.9, 12.4)[b] [32]	2.1 (1.4, 3.6) [69]
Testosterone, ng/dL	54.4 (21.2) [152]	46.7 (20.0) [171]	53.7 (23.9) [32]	45.4 (21.5) [69]
Androstenedione, ng/dL	4.6 (1.6) [151]	4.4 (1.4) [170]	5.2 (1.8)[e] [32]	4.4 (1.5) [69]
SHBG, nmol/L	49.1 (37.0) [152]	70.8 (36.3) [170]	85.5 (54.5) [32]	91.5 (35.3) [69]
Sebum score	92.1 (51.3) [146]	86.5 (43.4) [169]	97.8 (56.1) [32]	76.6 (39.1) [66]
Ferriman-Gallwey score	14.9 (7.8) [156]	8.1 (6.2) [167]	11.5 (5.5)[b] [37]	7.5 (5.9) [67]

(*Continued*)

overweight, or obese based on their preconception BMI. Of the women diagnosed with PCOS, 23% were normal weight, 24% were overweight, and 53% were obese, compared with 40%, 26%, and 35%, respectively, of the ovulatory controls.

GWG

Self-reported GWG was available for 141 of 164 women with PCOS and 155 of 176 controls. A subset of these women (91 with PCOS and 99 controls) whose last measured gestational weight was within ±1 week of their gestational age was used to assess the concordance between self-reported GWG and measured GWG abstracted from prenatal records. In women with PCOS, the concordance correlation coefficient between self-reported GWG and measured GWG was 0.88 (95% CI, 0.83 to 0.92) and in controls the concordance correlation coefficient was 0.66 (95% CI, 0.54 to 0.76) (Supplemental Fig. S1). Based on patient self-report, only 34.5% of patients met the IOM-recommended GWG by their preconception BMI category (Fig. 1). Thirty-three percent of women with PCOS and 36% of controls met IOM GWG guidelines. Patients tended to exceed IOM GWG recommendations, specifically 54.6% of women with PCOS and 45.8% of controls. Within the overweight group, the distribution based on IOM GWG guideline categorizations (less than, met, exceeded recommendation) was significantly different between women with PCOS and controls (Supplemental Table S1). There was no evidence of a difference in the distribution of IOM GWG guideline categorizations between women with PCOS and controls for the normal-weight or obese groups. Furthermore, the average self-reported GWG (adjusting for gestational age, treatment, and number of treatment cycles) for women with PCOS and controls by preconception BMI categorization (Supplemental Fig. S2) provided results consistent with the findings from the IOM GWG guideline categorizations.

Based on measures of weight obtained before conception in each study and those obtained during prenatal visits in the obstetrician's office, we modeled weight gain trajectory curves for women with PCOS and controls by BMI group over the whole pregnancy (Fig. 2). Based on these curve trajectories, we examined the cumulative weight gain from preconception to the end of each trimester (Table 2). In the normal BMI group, weight gain was significantly higher in women with PCOS than in controls at each time point, and in the overweight group, weight gain was significantly higher in women with PCOS than in controls at the second and third trimester time points, with no difference in the first trimester. In the obese group, there were no differences in weight gain between women with PCOS and controls at any trimester time point. The average absolute weights at each trimester time point are found in Supplemental Table S2. Plots of individual weight per participant are found in the Supplemental Figures (Supplemental Fig. S3: normal BMI group; Supplemental Fig. S4: overweight BMI group; Supplemental Fig. S5: obese BMI group).

Infant Birth Weights

There were no significant differences in birth weight in any of the BMI groups between women with PCOS and controls (Supplemental Table S3). The mean birth weights for all groups exceeded 3000 g. The prevalence of SGA, AGA, and LGA infants were similar between women with PCOS and controls ($P = 0.31$). Specifically, women with PCOS had 12 (7.4%), 132 (81.5%), and 18 (11.1%) infants with SGA, AGA, and LGA, respectively, compared with the numbers in controls: 22 (12.7%) SGA, 132 (76.3%) AGA, and 19 (11.0%) LGA. When

Table 1. Baseline Characteristics of Women With PCOS and Controls (Continued)

Overweight		Obese	
PCOS (n = 40)	Control (n = 45)	PCOS (n = 87)	Control (n = 61)
27.8 (3.4)[b] [40]	31.4 (3.7) [45]	28.6 (3.9)[b] [87]	31.7 (4.5) [61]
164.1 (162.5) [40]	162.5 (17.5) [45]	235.6 (37.4)[b] [87]	211.9 (30.2) [61]
27.1 (1.5) [40]	27.1 (1.4) [45]	39.4 (6.0)[b] [87]	35.0 (4.6) [61]
91.6 (8.2) [39]	87.2 (11.1) [45]	116.5 (12.6)[b] [87]	107.1 (13.7) [61]
114.5 (10.2) [37]	116.4 (10.7) [45]	123.4 (13.2) [83]	121.5 (11.2) [61]
73.3 (9.3) [37]	72.2 (8.2) [45]	78.4 (9.7)[a] [83]	74.6 (8.6) [61]
12.3 (7.7, 18.0) [37]	11.7 (8.4, 19.3) [42]	23.2 (15.7, 36.3) [82]	22.8 (11.9, 35.1) [59]
86.7 (12.0) [38]	84.5 (19.7) [43]	91.7 (14.2) [82]	88.1 (13.8) [59]
7.7 (4.6, 13.9)[b] [38]	2.0 (1.3, 3.2) [43]	4.3 (2.6, 7.0)[b] [82]	2.1 (1.2, 3.4) [59]
52.8 (18.6) [38]	46.5 (21.8) [43]	55.4 (21.4) [82]	48.3 (16.6) [59]
4.7 (1.7) [38]	4.3 (1.4) [42]	4.4 (1.4) [81]	4.6 (1.4) [59]
44.7 (26.6)[e] [38]	69.4 (33.0) [42]	37.0 (20.4)[e] [82]	47.5 (23.3) [59]
102.8 (48.6) [36]	89.8 (34.8) [44]	84.8 (50.0) [78]	95.3 (51.5) [59]
14.9 (7.7)[a] [35]	9.3 (6.4) [43]	16.5 (8.3)[b] [84]	7.9 (6.3) [57]

Unless otherwise noted, values are expressed as mean (SD), with number of participants in square brackets. AMH, anti-Müllerian hormone; BP, blood pressure; SHBG, sex hormone binding globulin.

[a] $P < 0.01$ PCOS vs control (adjusted for treatment and number of treatment cycles).

[b] $P < 0.001$ PCOS vs control (adjusted for treatment and number of treatment cycles).

[c] To convert weight in pounds to kilograms, divide by 2.2.

[d] Median and (25th, 75th percentiles), with number of participants in square brackets.

[e] $P < 0.05$ PCOS vs control (adjusted for treatment and number of treatment cycles).

examining the prevalence of pre-eclampsia and gestational diabetes, we noted no differences between women with PCOS and controls with respect to any preconception BMI category (Table 3).

Multivariable modeling of GWG predictors

We constructed a multivariable model to identify a subset of preconception characteristics that could best predict self-reported GWG in women with PCOS and controls. The candidate pool of potential predictors for the multivariable model were PCOS status, treatment, number of treatment cycles, preconception BMI, systolic and diastolic blood pressure, insulin, glucose, anti-Müllerian hormone, testosterone, androstenedione, sex hormone binding globulin, sebum score, Ferriman-Gallwey score, and estimated gestational age. The final multivariable linear regression model consisted of five variables: PCOS status, treatment, number of treatment cycles, preconception BMI, and fasting insulin. Of these five, only two were significantly related to self-reported GWG: preconception BMI and number of treatment cycles. Preconception BMI was negatively associated with GWG (*i.e.*, higher preconception BMI is associated with a lower GWG, $\beta = -0.62$; 95% CI, -0.85 to -0.40; $P < 0.001$) and number of treatment cycles was negatively associated with GWG (*i.e.* higher number of treatment cycles is associated with lower GWG, $\beta = -1.46$; 95% CI, -2.77 to -0.15; $P = 0.03$) (Supplemental Table S4). With respect to the outcome of meeting IOM GWG guidelines (met/not met), the final multivariable logistic regression model consisted of five variables: PCOS status, treatment, number of treatment cycles, preconception BMI, and diastolic blood pressure. Of these five, only diastolic blood pressure was negatively associated with meeting IOM GWG guidelines (*i.e.*, increasing diastolic blood pressure is associated with a lower probability of meeting IOM guidelines; OR, 0.97; 95% CI, 0.94 to 0.99; $P = 0.02$) (Supplemental Table S5).

Discussion

We have examined GWG by preconception BMI category in women with PCOS who delivered singleton gestations and compared these findings to those in a group of ovulatory control women with normal menses. We found a significant difference in GWG between pregestational weight-matched women diagnosed with PCOS compared with our controls in preconception normal weight and overweight BMI groups when we modeled measured weight gain. We confirmed this in our categorical assessment of self-reported GWG by IOM guidelines only in women who were overweight with PCOS. We also confirmed our hypothesis that birth weight for gestational age was similar between women with PCOS and controls across all preconception weight groups. Finally, based on a multivariable model of both women with PCOS and controls that included the characteristics of PCOS status, treatment, number of

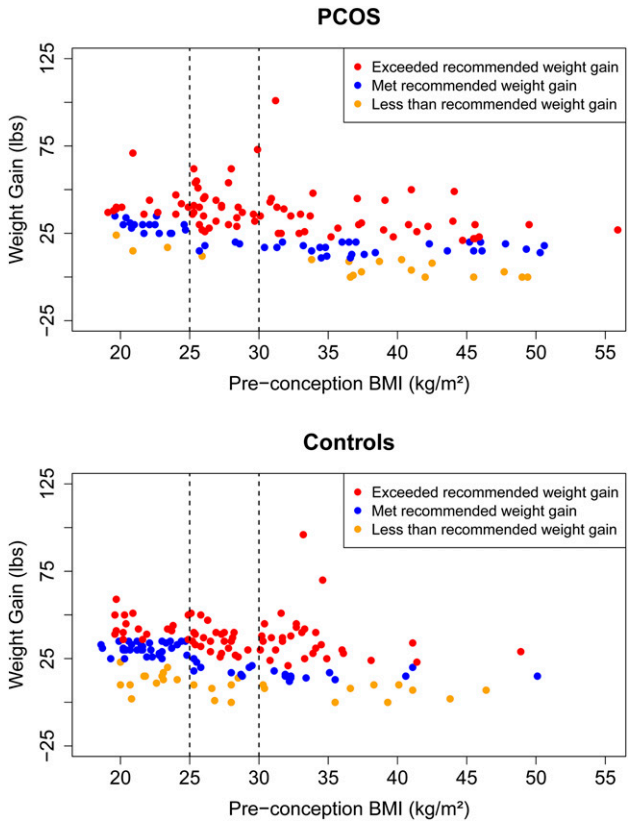

Figure 1. Scatterplot of self-reported GWG by preconception BMI (as measured in the studies) for women with PCOS and controls. Colored symbols indicate whether patients gained less than the IOM-recommended GWG, met that recommendation, or exceeded it.

treatment cycles, preconception BMI, and fasting insulin, we found that preconception BMI and number of treatment cycles were strongly associated with GWG.

Our findings suggest that both pre-existing obesity and excessive GWG are contributing factors that should be considered in addition to the diagnosis of PCOS as risk factors for perinatal complications in women with PCOS (4, 8, 26), although the contribution of GWG alone is likely modest. Our findings are consistent with the general experience of most women during pregnancy in which only 30% of women meet IOM guidelines for GWG (47% of women have excessive and 23% have inadequate weight gain) (27). Our findings on GWG in women with PCOS are also consistent with other observational studies that have supported increased GWG in women with PCOS compared with controls (3, 15, 16), especially in the third trimester (16). Our study, however, was able to track GWG from preconception throughout pregnancy and provided a comparable weight-matched reference group of ovulatory women with unexplained infertility. Other studies have documented that women with increased risk for obesity and diabetes [*i.e.* Hispanic women who are overweight preconception (as opposed to obese)] are more likely to experience excessive weight gain than the women with PCOS in our study (28).

Similarly, other studies have reported on the negative relationship between pregestational weight and GWG (29). Our study has also provided evidence that preconception circulating sex steroids (*i.e.*, testosterone) are negatively associated with GWG in women who do not have PCOS. Determining the mechanism of this finding (assuming this is not a type 1 error) is beyond the scope of this study, but one possible explanation is that simple obesity in ovulatory women is associated with higher testosterone levels (30), whereas in women with PCOS testosterone levels are related to ovarian and adrenal overactivity, independent of obesity (and therefore not associated with GWG) (31). Although the potential mechanisms for the finding of increased GWG in women who were normal or overweight with PCOS is beyond the scope of this paper, we note that there are multiple possible interacting mechanisms in women with PCOS, such as the underlying insulin resistance augmented by pregnancy, as well as an increased prevalence of eating disorders and mood disorders among women with PCOS that could predispose to excessive GWG. The greatest risk factor for weight gain may be increasing age, rather than

Table 2. Cumulative GWG (Based on Weights Measured in Clinic in Pounds) Estimated at the End of Each Trimester Compared Between Women With PCOS and Controls by Preconception BMI Category

	Normal			Overweight			Obese		
	PCOS	Control	PCOS vs Control	PCOS	Control	PCOS vs Control	PCOS	Control	PCOS vs Control
Trimester	Adjusted Mean (95% CI)	Adjusted Mean (95% CI)	Difference in Adjusted Means (95% CI) [*P* Value]	Adjusted Mean (95% CI)	Adjusted Mean (95% CI)	Difference in Adjusted Means (95% CI) [P Value]	Adjusted Mean (95% CI)	Adjusted Mean (95% CI)	Difference in Adjusted Means (95% CI) [*P* Value]
First trimester (14 wk)	9.4 (7.9–11.0)	7.1 (5.9–8.4)	2.3 (0.3–4.3) [0.02]	8.3 (6.3–10.3)	6.7 (4.8–8.6)	1.6 (−1.1 to 4.4) [0.24]	2.3 (0.6–3.9)	2.9 (1.1–4.7)	−0.6 (−3.0 to 1.8) [0.63]
Second trimester (28 wk)	24.4 (21.7–27.2)	20.2 (18.0–22.4)	4.2 (0.7–7.7) [0.02]	23.9 (20.3–27.5)	18.7 (15.3–22.1)	5.2 (0.2–10.2) [0.04]	11.2 (8.2–14.2)	12.9 (9.6– 16.2)	−1.7 (−6.1 to 2.8) [0.46]
Third trimester (40 wk)	41.7 (37.9–45.4)	36.1 (33.1–39.0)	5.6 (0.8–10.4) [0.02]	43.0 (38.0–48.0)	33.2 (28.4–37.9)	9.8 (2.9–16.7) [0.005]	24.3 (20.1–28.4)	27.2 (22.6– 31.8)	−3.0 (−9.2 to 3.3) [0.35]

GWG is expressed in pounds and was adjusted for treatment and number of treatment cycles. To convert pounds to kilograms, divide by 2.2.

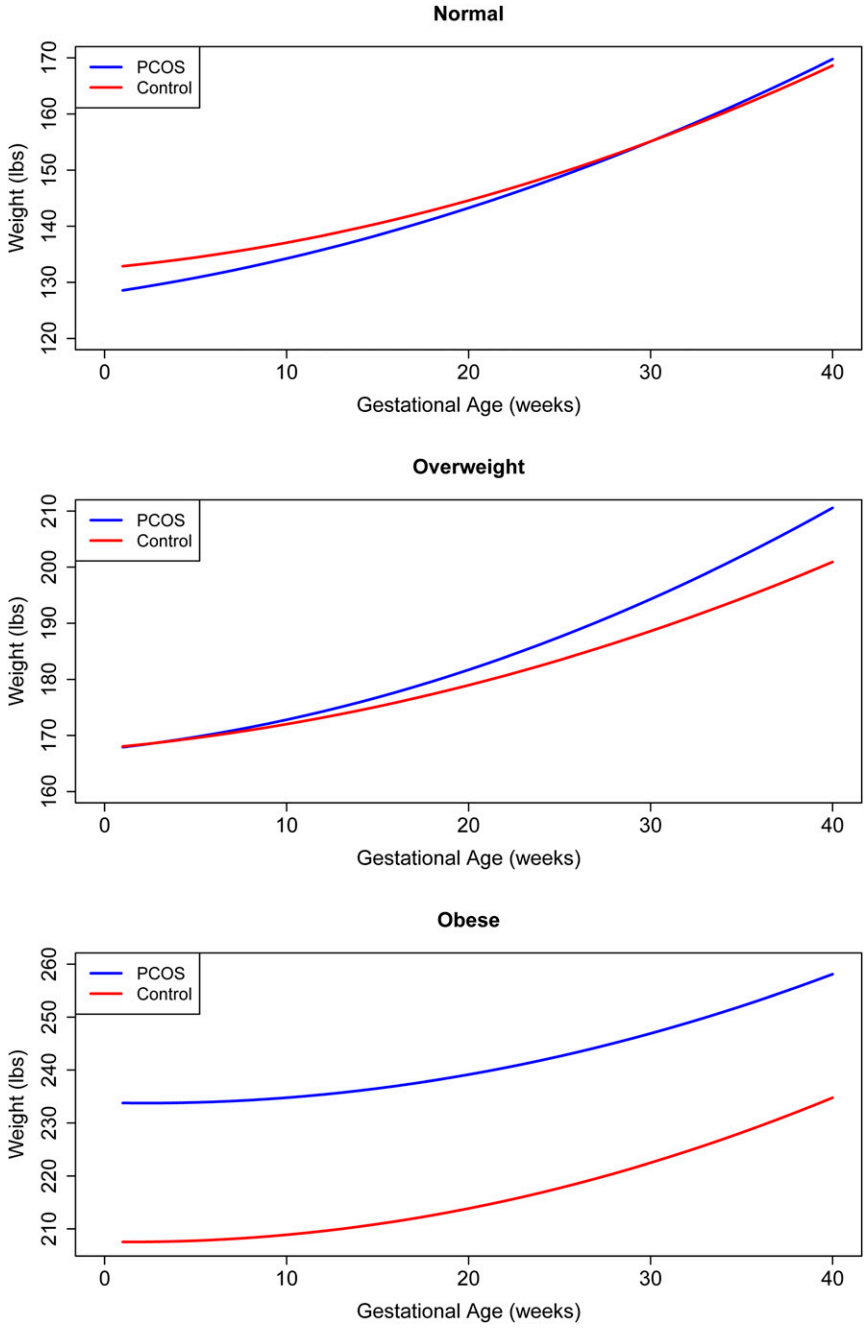

Figure 2. Modeled trajectory curves of GWG by preconception BMI category for women with PCOS and controls, adjusted for treatment and number of treatment cycles.

pregnancy—a longitudinal study of Australian women showed that during a 10-year period, women with PCOS consistently and steadily outgained the control women (32).

The strengths of our study are that women, both those with PCOS and controls, were systematically and in a standardized manner characterized before conception by using similar protocols and identical laboratory analysis methods in a central core laboratory. Prenatal records and maternal recall of weight gain after pregnancy information was collected by using identical protocols and case report forms.

Many studies must rely on preconception recall of weight or documentation of weight at some point distant to conception (33) or start the GWG measurement from a baseline of presentation for prenatal care at 8 to 12 weeks when, as our study documents, substantial differences in weight gain between groups have already occurred. We were able to model preconception predictors of GWG by using a broad palette of parameters that were obtained before conception. Our sample is diverse and multicenter and is representative of women across the United States. We were able to match for the confounder of infertility and infertility treatment by using both cases and controls with a history of infertility who received similar treatments.

The limitations include the lack of a consistent mode of collecting body weight because we switched from weights obtained in our sites (using identical equipment and protocols) to those obtained during pregnancy in the doctor's office or by patient recall. Unfortunately, women presenting in labor or for scheduled cesarean delivery are not weighed routinely in the United States, forcing us to model or to rely on recall to obtain complete GWG. Our sample size is also relatively small, and thus we were underpowered to detect possible associations of GWG and pregnancy complications. Finally, we were studying infertile women, who have varying perinatal risks and outcomes compared with women who conceive without assistance. For example, women who conceive singleton pregnancies by assisted reproductive technology are prone to shorter gestations and infants with lower birth weights (34). Therefore, our results may not be generalizable to women who conceive spontaneously. Treatments between the two groups also varied slightly and may have affected outcomes. Women with unexplained infertility had access to a gonadotropin arm, triggered ovulation with a human chorionic gonadotropin shot and an intrauterine insemination that were not part of the treatment protocol of women with PCOS. Prenatal care was not determined by the study protocol and was administered by many obstetric providers (and not the

Table 3. Rates of Pregnancy Complications by Preconception BMI Category

	Pre-eclampsia			Gestational Diabetes		
Preconception BMI	PCOS, n (%)	Control, n (%)	P Value for PCOS vs Control[a]	PCOS, n (%)	Control, n (%)	P Value for PCOS vs Control[a]
Normal	5 (15.6)	5 (7.9)	0.20	2 (6.3)	5 (7.9)	0.56
Overweight	3 (8.8)	2 (5.0)	0.38	7 (20.6)	4 (10.0)	0.26
Obese	16 (21.3)	8 (15.4)	0.25	19 (25.3)	6 (11.8)	0.23

[a]Adjusted for treatment, number of treatment cycles, and GWG.

investigators of the study). Varying definitions and practice patterns may have affected the perinatal outcomes of this study.

Interventions in women who were overweight or obese before conception to reduce weight have not shown perinatal benefit as projected (10, 35, 36), nor have the more extensive and larger trials to avoid excessive GWG demonstrated significant benefit beyond reduced cesarean delivery rates (37). The interaction of pregestational weight and GWG on perinatal complications suggests that a combined intervention in overweight or women with obesity beginning preconception and crossing into pregnancy would be a logical next step.

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References

1. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab*. 2004;**89**(6):2745–2749.
2. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod*. 2010;**25**(2):544–551.
3. Joham AE, Teede HJ, Ranasinha S, Zoungas S, Boyle J. Prevalence of infertility and use of fertility treatment in women with polycystic ovary syndrome: data from a large community-based cohort study. *J Womens Health (Larchmt)*. 2015;**24**(4):299–307.
4. Palomba S, de Wilde MA, Falbo A, Koster MP, La Sala GB, Fauser BC. Pregnancy complications in women with polycystic ovary syndrome. *Hum Reprod Update*. 2015;**21**(5):575–592.
5. Yildiz BO, Knochenhauer ES, Azziz R. Impact of obesity on the risk for polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2008;**93**(1):162–168.
6. Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN; PCOS/Troglitazone Study Group. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2006;**91**(1):48–53.
7. Dunaif A, Segal KR, Shelley DR, Green G, Dobrjansky A, Licholai T. Evidence for distinctive and intrinsic defects in insulin action in polycystic ovary syndrome. *Diabetes*. 1992;**41**(10):1257–1266.
8. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, Steinkampf MP, Coutifaris C, McGovern PG, Cataldo NA, Gosman GG, Nestler JE, Giudice LC, Leppert PC, Myers ER; Cooperative Multicenter Reproductive Medicine Network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med*. 2007;**356**(6):551–566.
9. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, Christman GM, Huang H, Yan Q, Alvero R, Haisenleder DJ, Barnhart KT, Bates GW, Usadi R, Lucidi S, Baker V, Trussell JC, Krawetz SA, Snyder P, Ohl D, Santoro N, Eisenberg E, Zhang H; NICHD Reproductive Medicine Network. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med*. 2014;**371**(2):119–129.
10. Legro RS, Dodson WC, Kris-Etherton PM, Kunselman AR, Stetter CM, Williams NI, Gnatuk CL, Estes SJ, Fleming J, Allison KC, Sarwer DB, Coutifaris C, Dokras A. Randomized controlled trial of preconception interventions in infertile women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2015;**100**(11):4048–4058.
11. American College of Obstetricians and Gynecologists. ACOG Committee opinion no. 548: weight gain during pregnancy. *Obstet Gynecol*. 2013;**121**(1):210–212.
12. Abrams B, Carmichael S, Selvin S. Factors associated with the pattern of maternal weight gain during pregnancy. *Obstet Gynecol*. 1995;**86**(2):170–176.
13. Weisman CS, Hillemeier MM, Downs DS, Feinberg ME, Chuang CH, Botti JJ, Dyer AM. Improving women's preconceptional

health: long-term effects of the Strong Healthy Women behavior change intervention in the central Pennsylvania Women's Health Study. *Womens Health Issues*. 2011;**21**(4):265–271.
14. Narayanan RP, Weeks AD, Quenby S, Rycroft D, Hart A, Longworth H, Charnley M, Abayomi J, Topping J, Turner MA, Wilding JP. Fit for Birth - the effect of weight changes in obese pregnant women on maternal and neonatal outcomes: a pilot prospective cohort study. *Clin Obes*. 2016;**6**(1):79–88.
15. Palomba S, Falbo A, Russo T, Tolino A, Orio F, Zullo F. Pregnancy in women with polycystic ovary syndrome: the effect of different phenotypes and features on obstetric and neonatal outcomes. *Fertil Steril*. 2010;**94**(5):1805–1811.
16. Sir-Petermann T, Hitchsfeld C, Maliqueo M, Codner E, Echiburú B, Gazitúa R, Recabarren S, Cassorla F. Birth weight in offspring of mothers with polycystic ovarian syndrome. *Hum Reprod*. 2005; **20**(8):2122–2126.
17. Davies MJ, Moore VM, Willson KJ, Van Essen P, Priest K, Scott H, Haan EA, Chan A. Reproductive technologies and the risk of birth defects. *N Engl J Med*. 2012;**366**(19):1803–1813.
18. Schieve LA, Meikle SF, Ferre C, Peterson HB, Jeng G, Wilcox LS. Low and very low birth weight in infants conceived with use of assisted reproductive technology. *N Engl J Med*. 2002;**346**(10): 731–737.
19. Diamond MP, Legro RS, Coutifaris C, Alvero R, Robinson RD, Casson P, Christman GM, Ager J, Huang H, Hansen KR, Baker V, Usadi R, Seungdamrong A, Bates GW, Rosen RM, Haisenleder D, Krawetz SA, Barnhart K, Trussell JC, Ohl D, Jin Y, Santoro N, Eisenberg E, Zhang H; NICHD Reproductive Medicine Network. Letrozole, gonadotropin, or clomiphene for unexplained infertility. *N Engl J Med*. 2015;**373**(13):1230–1240.
20. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Alvero R, Casson P, Christman GM, Huang H, Yan Q, Haisenleder DJ, Barnhart KT, Bates GW, Usadi R, Lucidi R, Baker V, Trussell JC, Krawetz SA, Snyder P, Ohl D, Santoro N, Eisenberg E, Zhang H; National Institute of Child Health and Human Development Reproductive Medicine Network. The Pregnancy in Polycystic Ovary Syndrome II study: baseline characteristics and effects of obesity from a multicenter randomized clinical trial. *Fertil Steril*. 2014;**101**(1):258–269 e8.
21. Diamond MP, Legro RS, Coutifaris C, Alvero R, Robinson RD, Casson P, Christman GM, Ager J, Huang H, Hansen KR, Baker V, Usadi R, Seungdamrong A, Bates GW, Rosen RM, Haisonleder D, Krawetz SA, Barnhart K, Trussell JC, Jin Y, Santoro N, Eisenberg E, Zhang H; National Institute of Child Health and Human Development Reproductive Medicine Network. Assessment of multiple intrauterine gestations from ovarian stimulation (AMIGOS) trial: baseline characteristics. *Fertil Steril*. 2015;**103**(4):962–973 e4.
22. Legro RS, Myers ER, Barnhart HX, Carson SA, Diamond MP, Carr BR, Schlaff WD, Coutifaris C, McGovern PG, Cataldo NA, Steinkampf MP, Nestler JE, Gosman G, Guidice LC, Leppert PC; Reproductive Medicine Network. The Pregnancy in Polycystic Ovary Syndrome study: baseline characteristics of the randomized cohort including racial effects. *Fertil Steril*. 2006;**86**(4):914–933.
23. Siega-Riz AM, Viswanathan M, Moos MK, Deierlein A, Mumford S, Knaack J, Thieda P, Lux LJ, Lohr KN. A systematic review of outcomes of maternal weight gain according to the Institute of Medicine recommendations: birthweight, fetal growth, and postpartum weight retention. *Am J Obstet Gynecol*. 2009;**201**(4):339 e1–14.
24. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;**38**(4):963–974.
25. Duryea EL, Hawkins JS, McIntire DD, Casey BM, Leveno KJ. A revised birth weight reference for the United States. *Obstet Gynecol*. 2014;**124**(1):16–22.
26. Aktun HL, Yorgunlar B, Acet M, Aygun BK, Karaca N. The effects of polycystic ovary syndrome on gestational diabetes mellitus. *Gynecol Endocrinol*. 2016; **32**(2):139–142.
27. Goldstein RF, Abell SK, Ranasinha S, Misso M, Boyle JA, Black MH, Li N, Hu G, Corrado F, Rode L, Kim YJ, Haugen M, Song WO, Kim MH, Bogaerts A, Devlieger R, Chung JH, Teede HJ. Association of gestational weight gain with maternal and infant outcomes: a systematic review and meta-analysis. *JAMA*. 2017; **317**(21):2207–2225.
28. Chasan-Taber L, Schmidt MD, Pekow P, Sternfeld B, Solomon CG, Markenson G. Predictors of excessive and inadequate gestational weight gain in Hispanic women. *Obesity (Silver Spring)*. 2008; **16**(7):1657–1666.
29. Nohr EA, Vaeth M, Baker JL, Sørensen TI, Olsen J, Rasmussen KM. Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy. *Am J Clin Nutr*. 2008;**87**(6):1750–1759.
30. Sowers MF, Beebe JL, McConnell D, Randolph J, Jannausch M. Testosterone concentrations in women aged 25-50 years: associations with lifestyle, body composition, and ovarian status. *Am J Epidemiol*. 2001;**153**(3):256–264.
31. Nelson VL, Legro RS, Strauss JF III, McAllister JM. Augmented androgen production is a stable steroidogenic phenotype of propagated theca cells from polycystic ovaries. *Mol Endocrinol*. 1999;**13**(6):946–957.
32. Teede HJ, Joham AE, Paul E, Moran LJ, Loxton D, Jolley D, Lombard C. Longitudinal weight gain in women identified with polycystic ovary syndrome: results of an observational study in young women. *Obesity (Silver Spring)*. 2013;**21**(8):1526–1532.
33. Frederick IO, Williams MA, Sales AE, Martin DP, Killien M. Prepregnancy body mass index, gestational weight gain, and other maternal characteristics in relation to infant birth weight. *Matern Child Health J*. 2008;**12**(5):557–567.
34. Pinborg A, Wennerholm UB, Romundstad LB, Loft A, Aittomaki K, Söderström-Anttila V, Nygren KG, Hazekamp J, Bergh C. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. *Hum Reprod Update*. 2013;**19**(2):87–104.
35. Mutsaerts MA, van Oers AM, Groen H, Burggraaff JM, Kuchenbecker WK, Perquin DA, Koks CA, van Golde R, Kaaijk EM, Schierbeek JM, Oosterhuis GJ, Broekmans FJ, Bemelmans WJ, Lambalk CB, Verberg MF, van der Veen F, Klijn NF, Mercelina PE, van Kasteren YM, Nap AW, Brinkhuis EA, Vogel NE, Mulder RJ, Gondrie ET, de Bruin JP, Sikkema JM, de Greef MH, ter Bogt NC, Land JA, Mol BW, Hoek A. Randomized trial of a lifestyle program in obese infertile women. *N Engl J Med*. 2016;**374**(20):1942–1953.
36. van Oers AM, Groen H, Mutsaerts MA, Burggraaff JM, Kuchenbecker WK, Perquin DA, Koks CA, van Golde R, Kaaijk EM, Schierbeek JM, Oosterhuis GJ, Broekmans FJ, Vogel NE, Land JA, Mol BW, Hoek A; LIFEstyle study group. Effectiveness of lifestyle intervention in subgroups of obese infertile women: a subgroup analysis of a RCT. *Hum Reprod*. 2017;**32**(2):482.
37. International Weight Management in Pregnancy Collaborative Group. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. *BMJ*. 2017;**358**:j3199.