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

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### ABSTRACT

#### BACKGROUND

The polycystic ovary syndrome is a common cause of infertility. Clomiphene and insulin sensitizers are used alone and in combination to induce ovulation, but it is unknown whether one approach is superior.

#### METHODS

We randomly assigned 626 infertile women with the polycystic ovary syndrome to receive clomiphene citrate plus placebo, extended-release metformin plus placebo, or a combination of metformin and clomiphene for up to 6 months. Medication was discontinued when pregnancy was confirmed, and subjects were followed until delivery.

#### RESULTS

The live-birth rate was 22.5% (47 of 209 subjects) in the clomiphene group, 7.2% (15 of 208) in the metformin group, and 26.8% (56 of 209) in the combination-therapy group ( $P < 0.001$  for metformin vs. both clomiphene and combination therapy;  $P = 0.31$  for clomiphene vs. combination therapy). Among pregnancies, the rate of multiple pregnancy was 6.0% in the clomiphene group, 0% in the metformin group, and 3.1% in the combination-therapy group. The rates of first-trimester pregnancy loss did not differ significantly among the groups. However, the conception rate among subjects who ovulated was significantly lower in the metformin group (21.7%) than in either the clomiphene group (39.5%,  $P = 0.002$ ) or the combination-therapy group (46.0%,  $P < 0.001$ ). With the exception of pregnancy complications, adverse-event rates were similar in all groups, though gastrointestinal side effects were more frequent, and vasomotor and ovulatory symptoms less frequent, in the metformin group than in the clomiphene group.

#### CONCLUSIONS

Clomiphene is superior to metformin in achieving live birth in infertile women with the polycystic ovary syndrome, although multiple birth is a complication. (ClinicalTrials.gov number, NCT00068861.)

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**T**HE POLYCYSTIC OVARY SYNDROME AFFECTS 7 to 8% of women<sup>1</sup> and may be the most common cause of female infertility.<sup>2</sup> Anovulation,<sup>2</sup> early pregnancy loss,<sup>3</sup> and later pregnancy complications<sup>4</sup> have all been implicated in the low fecundity of women with this disorder. Obesity is also common in such women,<sup>5</sup> and this condition alone appears to have an adverse effect on reproduction.<sup>6,7</sup> The cause of the polycystic ovary syndrome is poorly understood, and both the diagnosis and treatment of the disorder are controversial.<sup>5,8,9</sup>

Women with this syndrome have hyperandrogenism,<sup>10</sup> morphologic changes in the ovary (polycystic),<sup>10</sup> inappropriate gonadotropin secretion (elevated levels of circulating luteinizing hormone),<sup>11</sup> and insulin resistance with accompanying compensatory hyperinsulinemia.<sup>12</sup> Targeting these metabolic abnormalities has been noted to improve ovulation and fertility in women with this syndrome.<sup>13-17</sup> Results from small head-to-head trials have suggested that the efficacy of treatment with insulin sensitizers such as metformin (alone or in combination with clomiphene citrate) is equal or superior to that of clomiphene alone for infertility.<sup>13,16,17</sup>

We designed a trial to test the hypothesis that treatment of women with the polycystic ovary syndrome with extended-release metformin is more likely to result in a live birth than is treatment with clomiphene citrate and that the combination of the two therapies will result in the highest live-birth rate.

## METHODS

### STUDY DESIGN

We have previously described the rationale for choosing live birth as the primary outcome,<sup>18</sup> the power analysis and main statistical methods,<sup>19</sup> the use of infertility screening in the study,<sup>20</sup> and the study design and baseline characteristics of the subjects.<sup>21</sup>

The institutional review board at each center approved the protocol, and all subjects gave written informed consent. All subjects had received the diagnosis of the polycystic ovary syndrome, which was defined as oligomenorrhea (with a history of no more than eight spontaneous menses per year) and hyperandrogenemia (with an elevated testosterone level documented within the previous year in an outpatient setting on the basis

of local laboratory results, with a predetermined cutoff level set by the principal investigator at each study site). Subjects were excluded if they had hyperprolactinemia, congenital adrenal hyperplasia, thyroid disease, or other causes of amenorrhea, including premature ovarian failure. Clinically suspected Cushing's syndrome and androgen-secreting neoplasm were additional exclusion criteria.<sup>21</sup>

We randomly assigned 626 infertile women with the polycystic ovary syndrome to one of three study groups by means of an interactive voice system. The assignments were stratified according to the study site and the presence or absence of previous exposure to either of the study drugs.<sup>21</sup> Subjects with other causes of infertility were excluded on the basis of documentation of a normal uterine cavity and at least one patent fallopian tube; analysis of the semen of each woman's current partner was performed within 1 year before participation in the study, and a sperm concentration of at least 20 million per milliliter was required.<sup>21</sup> All subjects were in good health with no major medical disorders.<sup>21</sup>

### STUDY DRUGS

We used extended-release metformin because of its increased tolerability and proven efficacy in the treatment of type 2 diabetes.<sup>22,23</sup> Extended-release metformin (Glucophage XR) plus identical placebo were provided by Bristol-Myers Squibb. Overencapsulated clomiphene citrate tablets (purchased from Teva Pharmaceuticals) and matching placebo capsules were packaged and tested by a commercial pharmacy supply company (CTS) specifically for the study. Neither manufacturer had any other role in the study.

Baseline laboratory testing was performed after the subjects had fasted overnight. All specimens were analyzed in a core laboratory.<sup>21</sup> In subjects without recent menses, withdrawal bleeding was induced with a course of oral medroxyprogesterone acetate before the initiation of study medication. Each subject received a monthly medication package consisting of bottle M (metformin in 500-mg tablets or matching placebo) and blister pack C (clomiphene in 50-mg tablets or matching placebo). The two drugs were begun concurrently. Subjects gradually increased the dose of the study drug in bottle M until reaching the maximum dose of four tablets (two tablets twice a day). Subjects took one tablet a day from

blister pack C for 5 days, beginning on day 3 of menses; this dose was maintained if adequate ovulation was documented. However, in subjects who had no response or a poor response, the dose was increased by one tablet a day on a treatment-cycle basis (either after 5 weeks of anovulation or after a menses until the maximum dose of three tablets per day was reached).

After the baseline visit, subjects returned each month for a visit with a limited physical examination, urine pregnancy test, and repeated fasting blood tests.<sup>21</sup> Subjects were instructed to have regular intercourse every 2 to 3 days and to keep a diary recording intercourse, vaginal bleeding, and symptoms. The progesterone levels in all subjects were measured weekly or every other week in local laboratories in order to document ovulation.<sup>21</sup> If two consecutive measurements showed elevated levels of progesterone (above 5 ng per milliliter [16 nmol per liter]), a weekly pregnancy test was administered until a positive result or menses occurred. Induction of withdrawal bleeding with progestin was scheduled at the discretion of the principal investigator at each site. Ultrasonography for follicular and endometrial response was not included in the protocol, and ovulation triggering with human chorionic gonadotropin and intrauterine insemination were not permitted.

Subjects were treated for up to six cycles, or 30 weeks. All study medication was discontinued if a pregnancy test was positive. Pregnant subjects were followed until ultrasonography documented fetal viability and were then referred for prenatal care. Investigators reviewed all obstetrical records to obtain data on birth outcomes. We did not collect data on the use of other medications during pregnancy.

#### OUTCOMES

The primary outcome of the trial was the rate of live births. Secondary outcomes included the rate of pregnancy loss, singleton birth, and ovulation (a serum progesterone level above 5 ng per milliliter during a cycle). A serious adverse event was defined as any event that was fatal, immediately life-threatening, or severely or permanently disabling; an event that required or prolonged hospitalization; an overdose (intentional or accidental); a congenital anomaly; pregnancy loss after 12 weeks of gestation; or an event that was deemed to be serious by the principal investigator at each site.

#### DATA MANAGEMENT

All data entry, data management, and analyses were performed at the Data Coordinating Center at the Duke Clinical Research Institute. Subjects were enrolled in the study from November 2002 to December 2004. The last conception was in June 2005, the last subject finished medication in August 2005, and the last birth was reported in February 2006. Data were analyzed according to the intention-to-treat principle.

#### STATISTICAL ANALYSIS

We assumed a dropout rate of 15% and the following rates of live birth: 45% in the combination-therapy group, 30% in the metformin group, and 25% in the clomiphene group. On the basis of these assumptions, we needed to enroll 678 subjects<sup>19</sup> for the study to have a power of 80% with a type I error rate of 0.05 to detect a 15% absolute difference in live-birth rates for the following two primary comparisons: the combination-therapy group versus the next best group and the metformin group versus the clomiphene group.

Because of limitations in the supply of metformin and matching placebo, the number of subjects was reduced to 626 after the data safety and monitoring board reviewed blinded data in November 2004. Because the live-birth rate was lower than projected, the final number of subjects provided adequate power ( $\geq 80\%$ ) to detect the same 15% absolute difference in live-birth rates for the original two primary comparisons because of the increased power for detecting the same difference in proportions when the magnitude of the proportion was decreased.

Either a chi-square test or Fisher's exact test was used for testing differences among the three study groups for categorical variables. A Wilcoxon rank-sum test was used for testing differences between two groups, and a Kruskal-Wallis test was used for testing differences among groups of three or more. Kaplan-Meier curves were used for time-to-event analyses. Generalized estimating equations were used for analysis of the ovulation rate to account for correlation of multiple ovulation cycles for each subject. Post hoc stratification of outcomes was performed on the basis of the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) and presence or absence of previous exposure to medication. All analyses were performed with SAS software, version 8.2 (SAS Institute).

## RESULTS

## STUDY POPULATION

There were no significant differences in baseline variables among the study groups (Table 1).<sup>21</sup> The numbers of subjects who dropped out of the study were 55 of 209 (26.3%) in the clomiphene group, 72 of 208 (34.6%) in the metformin group, and 49 of 209 (23.4%) in the combination-therapy group (P=0.07 for the metformin group vs. the clomiphene group, and P=0.01 for the metformin group vs. the combination-therapy group) (Fig. 1). The reasons for dropout were similar among the three groups, except that the metformin group had a higher rate of loss to follow-up than did the other two groups (P=0.03 for the comparison with the clomiphene group, and P=0.01 for the comparison with the combination-therapy group).

## PRIMARY OUTCOME

The rate of live birth was significantly lower in the metformin group than in the clomiphene group and the combination-therapy group (P<0.001 for both comparisons), and there was no significant advantage of the combination therapy over clomiphene (Table 2 and Fig. 2A). However, independently of treatment, subjects with a BMI below 30 had a significantly higher rate of live births than did women whose BMI was 30 or more (P<0.001 by univariate analysis) (Fig. 2B). The relationship between treatment and live birth was similar in post hoc analyses of subgroups stratified according to BMI (<30, 30 to 34, and ≥35) (see Table 1 of the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)) and according to previous treatment (Table 2 of the Supplementary Appendix).

Table 1. Baseline Characteristics of the Subjects.\*

Variable	Clomiphene Group (N=209)	Metformin Group (N=208)	Combination- Therapy Group (N=209)
<b>Biometric features</b>			
Age — yr	27.9±4.0	28.1±4.0	28.3±4.0
BMI	36.0±8.9	35.6±8.5	34.2±8.4
Clinically significant hirsutism (FG >16) — no. (%)	81 (38.8)	76 (36.5)	86 (41.1)
Waist circumference — cm	105.0±22.3	102.4±17.6	100.2±18.2
Race or ethnic group — no. (%) <sup>†</sup>			
White	147/208 (70.7)	140/207 (67.6)	148/208 (71.2)
Hispanic or Latino	53/209 (25.4)	61/208 (29.3)	50/209 (23.9)
Black	37/208 (17.8)	40/207 (19.3)	32/208 (15.4)
Asian	5/208 (2.4)	5/207 (2.4)	7/208 (3.4)
American Indian or Alaska Native	21/208 (10.1)	27/207 (13.0)	24/208 (11.5)
Native Hawaiian or Pacific Islander	1/208 (0.5)	0	0
<b>Fertility history</b>			
Length of time subject had been attempting conception — mo	41.4±39.4	39.0±31.9	40.7±36.0
Previous therapy for infertility — no. (%)	116 (55.5)	111 (53.4)	116 (55.5)
Previous pregnancy — no. (%)			
Conception	77 (36.8)	66 (31.7)	67 (32.1)
Live birth	33 (15.8)	33 (15.9)	28 (13.4)
Pregnancy loss	53 (25.4)	40 (19.2)	45 (21.5)
Previous exposure to study drug — no. (%)			
None	89 (42.6)	87 (41.8)	86 (41.1)
Metformin only	14 (6.7)	16 (7.7)	24 (11.5)
Clomiphene only	67 (32.1)	68 (32.7)	53 (25.4)
Combination therapy	39 (18.7)	37 (17.8)	46 (22.0)

**SECONDARY OUTCOMES**

The rate of ovulation was significantly higher in the combination group than in either of the single-agent groups (Table 2). Over the course of the study, the mean ( $\pm$ SD) number of ovulations per subject was  $2.22\pm 1.87$  in the clomiphene group,  $1.43\pm 1.72$  in the metformin group, and  $2.80\pm 2.04$  in the combination-therapy group ( $P<0.001$  for the comparisons of the clomiphene and combination-therapy groups with the metformin group). However, as previously noted, the differences in ovulation rates did not translate into an increase in the live-birth rate among subjects receiving combination therapy. Rates of conception and live birth per cycle in which ovulation occurred and per subject who ovulated were significantly higher in the clomiphene group and the combination-therapy group than in the metformin group. All multiple pregnancies occurred in either the clomiphene group or the combination-therapy group, although rates were low, and the differences among

the three groups were not significant ( $P=0.56$  for the metformin group vs. the clomiphene group, and  $P=1.0$  for the metformin group vs. the combination-therapy group).

Over the course of the study, there were no documented ovulations in 52 of 209 women (24.9%) in the clomiphene group, 93 of 208 (44.7%) in the metformin group, and 35 of 209 (16.7%) in the combination-therapy group ( $P<0.001$  for both comparisons with the metformin group). There was no significant linear effect of time on the rate of ovulation in the metformin group and the clomiphene group, but there was such an effect on ovulation and live birth in the combination-therapy group ( $P=0.002$  and  $P=0.05$ , respectively).

**OTHER TREATMENT EFFECTS**

We analyzed metabolic and hormonal effects associated with the medications by comparing baseline data with data recorded at the last study visit

**Table 1. (Continued.)**

Variable	Clomiphene Group (N=209)	Metformin Group (N=208)	Combination- Therapy Group (N=209)
<b>Ultrasonographic findings</b>			
Morphologic features of polycystic ovary — no. (%)‡	192 (91.9)	189 (90.9)	192 (91.9)
Ovarian volume — cm <sup>3</sup>			
Left ovary	10.9±6.9	11.2±6.1	11.2±6.2
Right ovary	11.8±6.9	11.8±5.9	12.5±8.1
<b>Fasting serum levels</b>			
Proinsulin — pmol/liter	25.4±24.3	25.5±27.5	23.9±25.7
Insulin — $\mu$ U/ml	22.6±20.7	24.0±28.4	22.4±30.0
Glucose — mg/dl	89.2±16.5	88.8±17.1	88.9±18.6
SHBG — nmol/liter	29.8±18.7	27.5±14.4	31.8±20.3
Testosterone — ng/dl	61.3±32.0	61.6±25.0	63.1±28.4
Free androgen index§	9.4±7.1	9.9±6.2	9.4±6.8
HOMA-IR¶	5.2±5.3	5.6±8.9	5.6±10.2

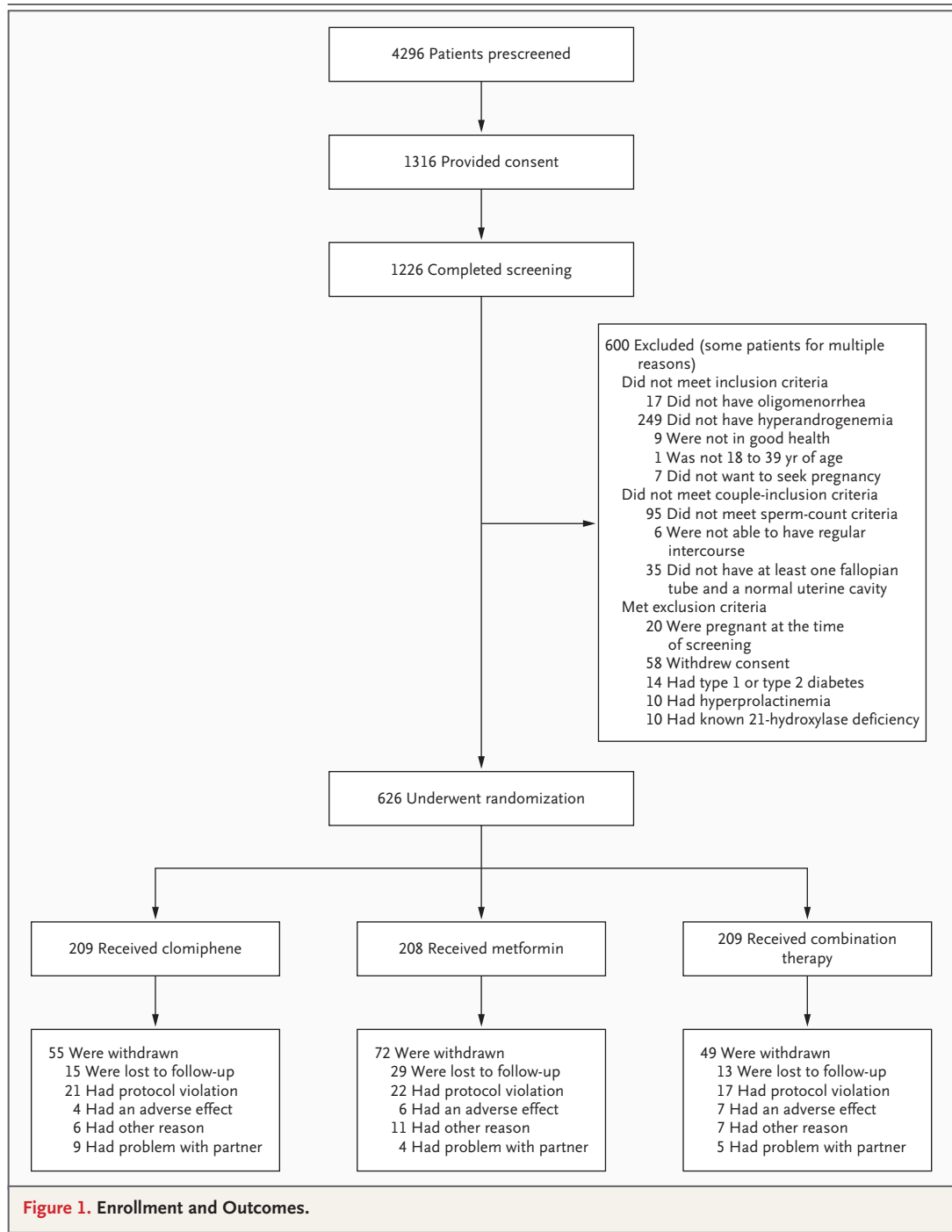
\* Plus–minus values are means  $\pm$ SD. Percentages may not total 100 because of rounding. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for insulin to picomoles per liter, multiply by 6. To convert the values for testosterone to nanomoles per liter, multiply by 0.03467. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters), FG Ferriman–Gallwey score, and SHBG sex hormone–binding globulin.

† Race or ethnic group was designated by the subjects. Some subjects chose more than one category, including Hispanic or Latino.

‡ One or both ovaries were affected.

§ The free androgen index was calculated according to the following formula: (total testosterone [nanomoles per liter]  $\div$  SHBG [nanomoles per liter])  $\times$  100.

¶ A homeostasis model assessment of insulin resistance (HOMA-IR) was calculated according to the following formula: (insulin  $\times$  glucose)  $\div$  405.



before pregnancy was documented or at the final study visit, whichever came first (Table 3). As compared with the baseline values, the clomiphene group had a significant increase in BMI ( $P=0.05$ ), levels of insulin ( $P=0.01$ ), insulin resistance as determined by homeostasis model assessment (HOMA) ( $P=0.01$ ), and levels of sex hormone–

binding globulin ( $P<0.001$ ) and a corresponding decrease in the free androgen index ( $P<0.001$ ). Conversely, the metformin group had a significant decrease in BMI and total testosterone and a significant increase in sex hormone–binding globulin levels, with a corresponding decrease in the free androgen index ( $P<0.001$  for all comparisons).

The combination-therapy group had changes similar to those in the metformin group, including a significant decrease in BMI, levels of testosterone, and the free androgen index and a significant increase in sex hormone-binding globulin levels ( $P < 0.001$  for all comparisons), and a significant decrease in waist circumference ( $P = 0.004$ ).

Over the course of the study, as compared with the metformin group, both the clomiphene group and the combination-therapy group had significant increases in sex hormone-binding globulin levels ( $P < 0.001$  for both comparisons) and decreases in the free androgen index ( $P < 0.001$  for the combination-therapy group vs. the metformin group, and  $P = 0.01$  for the clomiphene group vs. the metformin group). As compared with the clomiphene group, the combination-therapy group had a significant decrease in BMI ( $P < 0.001$ ) and in levels of testosterone ( $P < 0.001$ ), proinsulin ( $P = 0.04$ ), insulin ( $P = 0.01$ ), and insulin resistance as determined by HOMA ( $P = 0.006$ ).

#### ADVERSE EVENTS AND PREGNANCY COMPLICATIONS

Serious adverse events, most of which were complications of pregnancy, were more common among subjects in the clomiphene group and the combination-therapy group than among those in the metformin group: 7 of 209 (3.3%), 11 of 209 (5.3%; 1 subject had two events), and 2 of 208 (1.0%), respectively ( $P = 0.12$  for metformin vs. clomiphene, and  $P = 0.02$  for metformin vs. combination therapy) (Table 4). Gastrointestinal symptoms were more frequent in the groups receiving metformin, whereas hot flashes and symptoms associated with ovarian enlargement and ovulation were more common in the groups receiving clomiphene.

The rates of compliance with the recommended frequency of sexual intercourse ranged from 74 to 76% at the first visit and declined to 54 to 56% at the visit at 6 months. The compliance rates were similar across groups at all cycles except cycle 4, during which the rates were 71% in the clomiphene group, 66% in the metformin group, and 76% in the combination-therapy group ( $P = 0.04$  for the combination-therapy group vs. the metformin group).

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#### DISCUSSION

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Our findings do not support the hypothesis that extended-release metformin, either alone or in

combination with clomiphene citrate, improves the rate of live birth in women with the polycystic ovary syndrome. Conception, pregnancy, and live birth were significantly more likely to occur after treatment with clomiphene alone than after metformin alone. Adverse-event rates were similar among the study groups, although serious adverse events, primarily related to pregnancy, tended to occur in the groups receiving clomiphene (either alone or in combination therapy); these groups had correspondingly higher rates of pregnancy than did the metformin group.

These results are inconsistent with data from several other studies reporting benefits of metformin, especially in combination with clomiphene, in stimulating ovulation in women with the polycystic ovary syndrome.<sup>16,17,24-26</sup> Previous data have generally come from small, primarily single-center trials<sup>18,26,27</sup> that did not assess pregnancy rates but rather focused on metabolic and hormonal measures, rates of ovulation, or both.<sup>26</sup> As in the earlier studies, we found that the groups receiving metformin (both the metformin group and the combination-therapy group) had improved insulin sensitivity (including effects on BMI, proinsulin and insulin levels, and insulin resistance as determined by HOMA), as compared with the clomiphene group. However, these effects did not translate into increased live-birth rates. Instead, increases in sex hormone-binding globulin levels were associated with improved live-birth rates.

Our results also differed from those of a previous randomized trial by Palomba et al.,<sup>17</sup> which included 100 subjects and used a design similar to ours. In that study, the live-birth rate was 52% after 6 months of metformin, as compared with 18% after clomiphene. In contrast to our results, levels of fecundity improved over time among subjects receiving metformin, as compared with clomiphene. Unlike our trial, the study by Palomba et al. excluded subjects whose BMI was greater than 30. However, our post hoc analysis of women with a BMI of less than 30 also showed an increased live-birth rate with clomiphene, as compared with metformin.

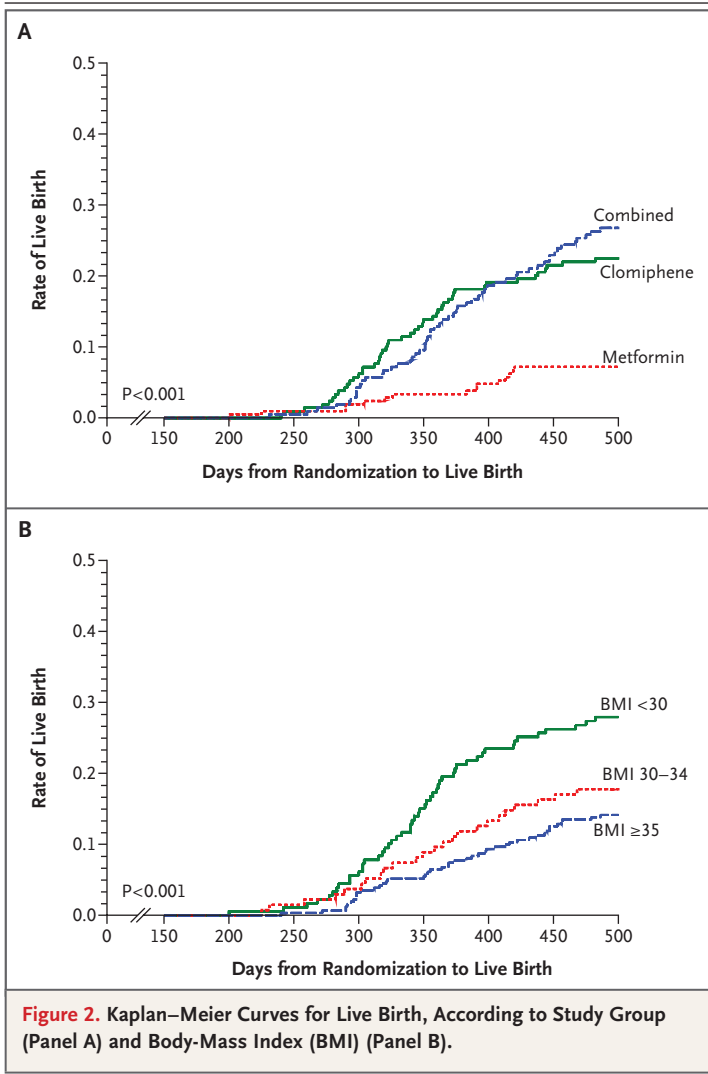
Our findings regarding the effects of the combination of metformin and clomiphene are consistent with those of another large, multicenter, randomized trial, reported by Moll et al.,<sup>28</sup> in which the rate of ovulation was the primary outcome. Among 228 subjects with the polycystic ovary syndrome who were randomly assigned to

**Table 2. Rates of Ovulation, Pregnancy, and Pregnancy Loss.\***

Variable	Clomiphene Group (N=209)	Metformin Group (N=208) <i>no./total no. (%)</i>	Combination- Therapy Group (N=209)	Absolute Difference between Combination Therapy and Metformin % (95% CI)
Ovulation	462/942 (49.0)	296/1019 (29.0)	582/964 (60.4)	31.4 (24.7 to 38.0)
Conception	62/209 (29.7)	25/208 (12.0)	80/209 (38.3)	26.3 (18.4 to 34.2)
Pregnancy	50/209 (23.9)	18/208 (8.7)	65/209 (31.1)	22.4 (15.0 to 29.8)
Singleton	47/50 (94.0)	18/18 (100.0)	63/65 (96.9)	-3.1 (-7.3 to 1.1)
Twins	2/50 (4.0)	0	2/65 (3.1)	-3.1 (-10.1 to 16.3)
Triplets	1/50 (2.0)	0	0	0 (-12.7 to 12.7)
Other	0	0	0	0 (-12.7 to 12.7)
Live birth	47/209 (22.5)	15/208 (7.2)	56/209 (26.8)	19.6 (12.6 to 26.6)
Pregnancy loss				
Total losses among subjects who conceived	16/62 (25.8)	10/25 (40.0)	24/80 (30.0)	-10.0 (-31.7 to 11.7)
Loss in first trimester	14/62 (22.6)	10/25 (40.0)	20/80 (25.0)	-14.5 (-35.9 to 6.9)
Biochemical factor or no fetal heart motion	10/62 (16.1)	7/25 (28.0)	13/80 (16.2)	-11.7 (-31.1 to 7.7)
Ectopic pregnancy	2/62 (3.2)	0	2/80 (2.5)	2.5 (-7.8 to 12.8)
Loss after observed heart motion	2/62 (3.2)	3/25 (12.0)	5/80 (6.2)	-5.7 (-19.5 to 8.1)
Loss in second or third trimester	2/62 (3.2)	0	4/80 (5.0)	5.0 (-5.7 to 15.7)
Events among ovulated cycles				
Conception	62/462 (13.4)	25/296 (8.4)	80/582 (13.7)	5.4 (1.2 to 9.6)
Singleton pregnancy	47/462 (10.2)	18/296 (6.1)	63/582 (10.8)	4.7 (1.0 to 8.4)
Singleton live birth	47/462 (10.2)	15/296 (5.1)	56/582 (9.6)	4.5 (1.0 to 8.0)
Events among subjects who ovulated				
Conception	62/157 (39.5)	25/115 (21.7)	80/174 (46.0)	24.3 (13.7 to 34.9)
Singleton pregnancy	47/157 (29.9)	18/115 (15.7)	63/174 (36.2)	20.5 (10.7 to 30.3)
Singleton live birth	47/157 (29.9)	15/115 (13.0)	56/174 (32.2)	19.2 (9.9 to 28.5)
Ovulation per monthly visit				
Visit 1	90/209 (43.1)	45/208 (21.6)	109/209 (52.2)	30.6 (21.8 to 39.4)
Visit 2	90/181 (49.7)	72/189 (38.1)	114/185 (61.6)	23.5 (13.6 to 33.4)
Visit 3	86/159 (54.1)	44/169 (26.0)	97/163 (59.5)	33.5 (23.5 to 43.5)
Visit 4	70/141 (49.6)	49/153 (32.0)	92/144 (63.9)	31.9 (21.1 to 42.7)
Visit 5	58/119 (48.7)	38/138 (27.5)	81/125 (64.8)	37.3 (26.1 to 48.5)
Visit 6	55/99 (55.6)	38/120 (31.7)	74/106 (69.8)	38.1 (26.0 to 50.2)
After Visit 6	13/34 (38.2)	10/42 (23.8)	15/32 (46.9)	23.1 (1.5 to 44.7)
Live birth per monthly visit				
Visit 1	10/209 (4.8)	3/208 (1.4)	9/209 (4.3)	2.9 (-0.3 to 6.1)
Visit 2	10/199 (5.0)	3/205 (1.5)	5/200 (2.5)	1.0 (-1.7 to 3.7)
Visit 3	9/189 (4.8)	1/202 (0.5)	11/195 (5.6)	5.1 (1.7 to 8.5)
Visit 4	10/180 (5.6)	2/201 (1.0)	8/184 (4.3)	3.3 (0.1 to 6.5)
Visit 5	2/170 (1.2)	4/199 (2.0)	6/176 (3.4)	1.4 (-1.9 to 4.7)
Visit 6	6/168 (3.6)	2/195 (1.0)	15/170 (8.8)	7.8 (3.3 to 12.3)
After Visit 6	0	0	2/155 (1.3)	1.3 (-1.5 to 4.1)

\* Ovulation was defined as a serum progesterone level of more than 5 ng per milliliter. Conception was defined as any positive serum level of human chorionic gonadotropin. Pregnancy was defined as an intrauterine pregnancy with fetal heart motion, as determined by transvaginal ultrasonography. Live birth was defined as the delivery of a viable infant.

P Value	Absolute Difference between Combination Therapy and Clomiphene % (95% CI)	P Value	Absolute Difference between Clomiphene and Metformin % (95% CI)	P Value
<0.001	11.4 (4.2 to 18.4)	0.003	20.0 (9.1 to 30.9)	<0.001
<0.001	8.6 (-0.4 to 17.6)	0.06	17.7 (10.1 to 25.3)	<0.001
<0.001	7.2 (-1.3 to 15.7)	0.10	15.2 (8.3 to 22.1)	<0.001
0.96	2.9 (-4.9 to 10.7)	0.45	-6.0 (-12.6 to 0.6)	0.95
1.0	-0.9 (-9.8 to 8.0)	1.0	4.0 (-9.9 to 17.9)	1.0
1.0	-2.0 (-12.7 to 12.7)	1.0	2.0 (-11.5 to 15.5)	1.0
1.0	0 (-6.4 to 6.4)	1.0	0 (-13.0 to 13.0)	1.0
<0.001	4.3 (-4.0 to 12.6)	0.31	15.3 (8.6 to 22.0)	<0.001
0.35	4.2 (-10.6 to 19.0)	0.58	-14.2 (-36.3 to 7.9)	0.19
0.15	2.9 (-11.2 to 17.0)	0.74	-17.4 (-39.2 to 4.4)	0.10
0.18	0.2 (-12.0 to 12.4)	0.98	-11.9 (-31.7 to 7.9)	0.21
0.57	-0.7 (-8.0 to 6.6)	0.80	3.2 (-7.7 to 14.1)	0.97
0.35	3.1 (-3.8 to 10.0)	0.42	-8.8 (-22.3 to 4.7)	0.14
0.57	1.8 (-6.2 to 9.8)	0.61	3.2 (-7.7 to 14.1)	0.97
0.02	0.4 (-3.8 to 4.6)	0.88	5.0 (0.6 to 9.4)	0.03
0.02	0.6 (-3.1 to 4.3)	0.73	4.1 (0.2 to 8.0)	0.05
0.02	-0.6 (-4.3 to 3.1)	0.77	5.1 (1.4 to 8.8)	0.01
<0.001	6.5 (-4.1 to 17.1)	0.23	17.8 (7.1 to 28.5)	0.002
<0.001	6.3 (-3.8 to 16.4)	0.23	14.2 (4.4 to 24.0)	0.006
<0.001	2.3 (-7.7 to 12.3)	0.66	16.9 (7.5 to 26.3)	<0.001
<0.001	9.1 (-0.4 to 18.6)	0.06	21.5 (12.8 to 30.2)	<0.001
<0.001	11.9 (1.8 to 22.0)	0.02	11.6 (1.6 to 21.6)	0.02
<0.001	5.4 (-5.4 to 16.2)	0.33	28.1 (17.9 to 38.3)	<0.001
<0.001	14.3 (2.9 to 25.7)	0.02	17.6 (6.5 to 28.7)	0.002
<0.001	16.1 (3.8 to 28.4)	0.01	21.2 (9.5 to 32.9)	<0.001
<0.001	14.2 (1.1 to 27.3)	0.03	23.9 (11.1 to 36.7)	<0.001
0.04	8.7 (-15.1 to 32.5)	0.48	14.4 (-6.4 to 35.2)	0.17
0.07	-0.5 (-4.5 to 3.5)	0.81	3.4 (0.1 to 6.7)	0.04
0.50	-2.5 (-6.2 to 1.2)	0.18	3.5 (0 to 7.0)	0.04
0.001	0.8 (-3.6 to 5.2)	0.70	4.3 (1.1 to 7.5)	0.009
0.05	-1.3 (-5.8 to 3.2)	0.60	4.6 (1.0 to 8.2)	0.008
0.53	2.2 (-0.9 to 5.3)	0.28	-0.8 (-3.3 to 1.7)	0.69
<0.001	5.2 (0.1 to 10.3)	0.04	2.6 (-0.5 to 5.7)	0.15
1.0	1.3 (-1.6 to 4.2)	1.0	0 (-2.1 to 2.1)	1.0



receive either clomiphene alone or a combination of metformin and clomiphene for up to six ovulatory cycles, there were no significant differences in ovulation rates or pregnancy rates between the combination-therapy group and the group that received clomiphene alone, with a cumulative pregnancy rate of 40% in the combination-therapy group and 46% in the clomiphene group (absolute change in the combination-therapy group, -6%; 95% confidence interval [CI], -20 to 7).<sup>28</sup>

Although we found no significant benefit of the combination of metformin and clomiphene, as compared with clomiphene alone, the possibility of some benefit cannot be excluded. On the basis of the 95% CIs, plausible differences in the live-birth rate between groups range from a 12.6% absolute increase to a 4.2% absolute decrease in

**Table 3.** Absolute Changes in Key Measures between Baseline and Last Visit.\*

Measure	Clomiphene Group	Metformin Group	Combination-Therapy Group	P Value for Combination Therapy vs. Metformin	P Value for Combination Therapy vs. Clomiphene	P Value for Clomiphene vs. Metformin
BMI				0.72	<0.001	<0.001
No. of subjects	209	207	209			
Mean change (95% CI)	0.2±1.6 (0 to 0.4)	-0.6±2.2 (-0.9 to -0.2)	-0.5±1.4 (-0.7 to -0.3)			
P value	0.05	<0.001	<0.001			
Waist circumference — cm				0.24	0.18	0.96
No. of subjects	209	207	207			
Mean change (95% CI)	-0.1±12.4 (-1.7 to 1.6)	-0.9±7.6 (-1.9 to 0.2)	-1.5±6.9 (-2.4 to -0.5)			
P value	0.83	0.12	0.004			



<b>Table 4. Adverse Events.*</b>			
<b>Event</b>	<b>Clomiphene Group</b>	<b>Metformin Group</b>	<b>Combination-Therapy Group</b>
		<i>number (percent)</i>	
<b>Before conception in subjects who received a study drug</b>			
Total no. of subjects	209	208	209
Serious adverse event			
Hemorrhagic corpus luteum cyst†	1 (0.5)	0	0
Hypersensitivity reaction‡	0	1 (0.5)	0
Bronchitis or back pain§	1 (0.5)	0	1 (0.5)
Death¶	0	1 (0.5)	0
Other adverse event			
Abdominal distention	45 (21.5)	56 (26.9)	39 (18.7)
Abdominal pain or discomfort**	110 (52.6)	123 (59.1)	137 (65.6)
Constipation	32 (15.3)	21 (10.1)	22 (10.5)
Diarrhea***††	48 (23.0)	135 (64.9)	126 (60.3)
Dyspepsia††	9 (4.3)	24 (11.5)	14 (6.7)
Flatulence	38 (18.2)	37 (17.8)	39 (18.7)
Nausea***††	82 (39.2)	128 (61.5)	138 (66.0)
Stomach discomfort	8 (3.8)	15 (7.2)	16 (7.7)
Vomiting***††	28 (13.4)	62 (29.8)	72 (34.4)
Decreased appetite**	17 (8.1)	27 (13.0)	33 (15.8)
Back pain	25 (12.0)	22 (10.6)	22 (10.5)
Dizziness	26 (12.4)	35 (16.8)	34 (16.3)
Impaired sense of taste	10 (4.8)	11 (5.3)	10 (4.8)
Headache	92 (44.0)	88 (42.3)	87 (41.6)
Altered mood or mood swings	32 (15.3)	36 (17.3)	27 (12.9)
Hot flashes  ††	58 (27.8)	32 (15.4)	59 (28.2)
Adnexal pain	10 (4.8)	4 (1.9)	12 (5.7)
Anovulatory bleeding  ††	6 (2.9)	18 (8.7)	7 (3.3)
Breast tenderness or pain	41 (19.6)	36 (17.3)	47 (22.5)
Dysmenorrhea or cramps  ††	42 (20.1)	26 (12.5)	43 (20.6)
Sore throat	13 (6.2)	14 (6.7)	8 (3.8)
Respiratory tract infection	27 (12.9)	24 (11.5)	16 (7.7)
Fatigue	38 (18.2)	42 (20.2)	45 (21.5)
<b>After conception (with observed fetal heart motion) in subjects who discontinued study drug</b>			
Total no. of subjects	50	18	65
Serious adverse event before birth			
Pregnancy loss after 12 weeks	2 (4.0)	0	4 (6.2)
Ectopic pregnancy	2 (4.0)	0	2 (3.1)
Cervical incompetence or preterm labor‡‡	1 (2.0)	0	1 (1.5)
Severe preeclampsia	0	0	2 (3.1)
Congenital anomaly§§	0	0	2 (3.1)

**Table 4. (Continued.)**

Event	Clomiphene Group	Metformin Group	Combination-Therapy Group
	<i>number (percent)</i>		
Other adverse event before birth			
Preterm labor	4 (8.0)	1 (5.6)	5 (7.7)
Mild preeclampsia	6 (12.0)	1 (5.6)	7 (10.8)
HELLP syndrome	1 (2.0)	0	1 (1.5)
Gestational diabetes			
Diet controlled (class A1)	6 (12.0)	1 (5.6)	4 (6.2)
Insulin required (class A2)	3 (6.0)	1 (5.6)	1 (1.5)
Intrauterine growth restriction	0	0	0
Preterm premature rupture of membranes ¶¶	1 (2.0)	1 (5.6)	3 (4.6)
Placental abruption	2 (4.0)	0	2 (3.1)
Placenta accreta	0	0	0
Placenta previa	1 (2.0)	0	1 (1.5)
Other placental abnormality	1 (2.0)	1 (5.6)	1 (1.5)
Other pregnancy complication	6 (12.0)	2 (11.1)	4 (6.2)
Serious adverse event after birth	0	0	0
Other adverse event after birth			
Postpartum depression requiring intervention	1 (2.0)	0	2 (3.1)
Endometritis	0	0	3 (4.6)
Postpartum hemorrhage	2 (4.0)	0	0
Other disorder	3 (6.0)	1 (5.6)	3 (4.6)

\* Diagnoses after pregnancy were made by the treating physician. HELLP syndrome denotes hemolysis, elevated liver-enzyme levels, and a low platelet count.

† This event resulted in hospitalization and surgery.

‡ One subject in the metformin group had an anaphylactic reaction during a dinner of shellfish and tuna, resulting in a visit to the emergency department, during which patient was treated with Benadryl and a corticosteroid and discharged home. She took a dose of metformin that evening and continued in the study.

§ The subjects with bronchitis (in the clomiphene group) and back pain (in the combination-therapy group) were hospitalized.

¶ One patient in the metformin group had a fatal subarachnoid hemorrhage. She had received the drug for one cycle and was not pregnant, according to the autopsy report.

|| P<0.05 for the comparison between combination therapy and metformin.

\*\* P<0.05 for the comparison between combination therapy and clomiphene.

†† P<0.05 for the comparison between clomiphene and metformin.

‡‡ One subject in the clomiphene group had cervical incompetence and delivered at 37 weeks, and one subject in the combination-therapy group had preterm labor.

§§ One subject, who had severe preeclampsia and nephrolithiasis during her pregnancy, delivered an infant with the Prader-Willi syndrome, and one patient delivered an infant with a congenital diaphragmatic hernia.

¶¶ Preterm premature rupture of membranes is membrane rupture before contractions begin and at less than 37 weeks' gestation.

the combination-therapy group. Furthermore, when ovulation is used as the outcome, the combination of metformin and clomiphene was superior to either clomiphene alone or metformin alone.<sup>13</sup> The pregnancy rates in our trial were lower than those reported by others,<sup>16,17,28,29</sup> perhaps reflecting the inclusion of obese women and the fact that many of the subjects had a long-

standing history of infertility. These factors may also have contributed to a high rate of pregnancy complications.<sup>6,7,30</sup> Our selection criteria were consistent with both National Institutes of Health criteria and the revised Rotterdam diagnostic criteria<sup>8,9</sup> for the polycystic ovary syndrome, and more than 90% of our subjects had polycystic ovaries on baseline ultrasonography.<sup>21</sup> Our cohort

was similar in age and BMI to the cohort in a large, multicenter trial that showed a benefit of the insulin sensitizer troglitazone on ovulatory frequency in the polycystic ovary syndrome.<sup>15</sup>

Our study demonstrates the limitations of relying on ovulation rates as a surrogate for live-birth rates.<sup>18,27</sup> We found that pregnancy was approximately twice as likely when ovulation was induced by clomiphene as when it was induced by metformin. Our study did not address mechanisms for improved fecundity per ovulation with clomiphene, as compared with metformin. Multiple follicular recruitment, which is characteristic of the induction of ovulation with clomiphene,<sup>31</sup> may have resulted in an increased opportunity for fertilization and successful implantation (as evidenced by multiple pregnancies only in the groups receiving clomiphene), as compared with the presumed monofollicular ovulation rate with metformin. We did not perform routine ultrasonography to monitor follicular development because the addition of such a procedure exceeds the normal standard of care in this setting and because it might have led to unblinding in the presence of multiple follicles.<sup>31</sup>

Early pregnancy loss may be another mechanism for subfecundity in women with the polycystic ovary syndrome. The observed rate of loss of intrauterine pregnancies in our study was similar to or lower than that observed after *in vitro* fertilization among women of a similar age range using their own eggs (approximately 13%) on the basis of 2003 data from the Society for Assisted Reproductive Technology.<sup>32</sup> Our study was not adequately powered to detect a difference in the first-trimester loss rate between the clomiphene group (22.6%) and the metformin group (40.0%), but our results appear to be inconsistent with those of Palomba et al.,<sup>17,29</sup> in which study medication was likewise discontinued after a positive pregnancy test. These investigators reported significantly lower first-trimester loss rates with metformin than with clomiphene (9.7% vs. 37.5%)<sup>17</sup> or fertility treatment with laparoscopic ovarian diathermy (9.3% vs. 29%),<sup>29</sup> although these results were based on small numbers (six events<sup>17</sup> and four events,<sup>29</sup> respectively). Another group reported no significant difference in rates of spontaneous abortion between groups treated with clomiphene (11%) and combination therapy (12%).<sup>27</sup>

Our study cannot address the effects of continu-

ing metformin throughout pregnancy,<sup>33</sup> though our findings raise concern and highlight the need for randomized trials for this indication.<sup>34</sup> Our results, however, support other studies suggesting an increased rate of pregnancy complications in women with the polycystic ovary syndrome,<sup>4</sup> such as gestational diabetes (12% among subjects in our study, as compared with 2 to 5% in the U.S. population<sup>35</sup>) and preeclampsia (12% in our study, as compared with 3 to 8% in the U.S. population<sup>36</sup>), although obesity clearly contributes to these risks.<sup>7,30</sup>

Subjects in our study received extended-release metformin, and this form of the drug may be less efficacious in women with the polycystic ovary syndrome than is immediate-release metformin.<sup>37</sup> Our study demonstrates that the tolerability of extended-release metformin is similar to that of clomiphene, although metformin had more gastrointestinal side effects and fewer vascular side effects and ovulation-related symptoms.

In summary, our study supports the use of clomiphene citrate alone as first-line therapy for infertility in women with the polycystic ovary syndrome. We did not find a significant benefit of combination therapy with clomiphene and metformin over clomiphene alone with respect to the live-birth rate. In addition, the results of our study underscore the limitations of the use of ovulation as a surrogate marker for live birth in infertility trials.

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## APPENDIX

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## REFERENCES

- 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;89:2745-9.
- Hull MG. Epidemiology of infertility and polycystic ovarian disease: endocrinological and demographic studies. *Gynecol Endocrinol* 1987;1:235-45.
- Homburg R, Armar NA, Eshel A, Adams J, Jacobs HS. Influence of serum luteinising hormone concentrations on ovulation, conception, and early pregnancy loss in polycystic ovary syndrome. *BMJ* 1988;297:1024-6.
- 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;12:673-83.
- Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med* 2005;352:1223-36.
- Bolumar F, Olsen J, Rebagliato M, Saez-Lloret I, Bisanti L. Body mass index and delayed conception: a European multicenter study on infertility and subfertility. *Am J Epidemiol* 2000;151:1072-9.
- Weiss JL, Malone FD, Emig D, et al. Obesity, obstetric complications and cesarean delivery rate — a population-based screening study. *Am J Obstet Gynecol* 2004;190:1091-7.
- Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine FP, Merriam GR, eds. *Polycystic ovary syndrome*. Boston: Blackwell Scientific; 1992:377-84.
- 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.
- Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol* 1935;29:181-91.
- Rebar R, Judd HL, Yen SS, Rakoff J, Vandenberg G, Naftolin F. Characterization of the inappropriate gonadotropin secretion in polycystic ovary syndrome. *J Clin Invest* 1976;57:1320-9.
- Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* 1989;38:1165-74.
- Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med* 1998;338:1876-80.
- Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. *N Engl J Med* 1999;340:1314-20.
- Azziz R, Ehrmann D, Legro RS, et al. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 2001;86:1626-32.
- Vandermolen DT, Ratts VS, Evans WS, Stovall DW, Kauma SW, Nestler JE. Metformin increases the ovulatory rate and pregnancy rate from clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone. *Fertil Steril* 2001;75:310-5.
- Palomba S, Orio F Jr, Falbo A, et al. Prospective parallel randomized, double-blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2005;90:4068-74.
- Legro RS, Myers E. Surrogate endpoints or primary outcomes in clinical trials in women with polycystic ovary syndrome? *Hum Reprod* 2004;19:1697-704.
- Myers ER, Silva SG, Hafley G, Kunselman AR, Nestler JE, Legro RS. Estimating live birth rates after ovulation induction in polycystic ovary syndrome: sample size calculations for the Pregnancy in Polycystic Ovary Syndrome trial. *Contemp Clin Trials* 2005;26:271-80.
- McGovern PG, Legro RS, Myers ER, et al. Utility of screening for other causes of infertility in women with "known" polycystic ovary syndrome. *Fertil Steril* (in press).
- Legro RS, Myers ER, Barnhart HX, et al. The Pregnancy in Polycystic Ovary Syndrome study: baseline characteristics of the randomized cohort including racial effects. *Fertil Steril* 2006;86:914-33.
- Fujioka K, Brazg RL, Raz I, et al. Efficacy, dose-response relationship and safety of once-daily extended-release metformin (Glucophage XR) in type 2 diabetic patients with inadequate glycaemic control despite prior treatment with diet and exercise: results from two double-blind, placebo-controlled studies. *Diabetes Obes Metab* 2005;7:28-39.
- Schwartz S, Fonseca V, Berner B, Cramer M, Chiang YK, Lewin A. Efficacy, tolerability, and safety of a novel once-daily extended-release metformin in patients with type 2 diabetes. *Diabetes Care* 2006;29:759-64.
- Kocak M, Caliskan E, Simsir C, Haberal A. Metformin therapy improves ovulatory rates, cervical scores, and pregnancy rates in clomiphene citrate-resistant women with polycystic ovary syndrome. *Fertil Steril* 2002;77:101-6.
- Sahin Y, Yirmibes U, Kelestimur F, Aygen E. The effects of metformin on insulin resistance, clomiphene-induced ovulation and pregnancy rates in women with polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol* 2004;113:214-20.
- Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ* 2003;327:951-3.
- Johnson NP. No more surrogate endpoints in randomised trials: the PCOSMIC trial protocol for women with polycystic ovary syndrome using metformin for infertility with clomiphene. *Aust N Z J Obstet Gynaecol* 2006;46:141-5.
- Moll E, Bossuyt PM, Korevaar JC, Lambalk CB, van der Veen F. Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. *BMJ* 2006;332:1485.
- Palomba S, Orio F Jr, Nardo LG, et al. Metformin administration versus laparoscopic ovarian diathermy in clomiphene citrate-resistant women with polycystic

- ovary syndrome: a prospective parallel randomized double-blind placebo-controlled trial. *J Clin Endocrinol Metab* 2004;89:4801-9. [Erratum, *J Clin Endocrinol Metab* 2005;90:3945.]
30. Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. *Obstet Gynecol* 2004;103:219-24.
31. Takahashi K, Uchida A, Yamasaki H, Ozaki T, Kitao M. Transvaginal ultrasonic assessment of the response to clomiphene citrate in polycystic ovarian syndrome. *Fertil Steril* 1994;62:48-53.
32. 2003 Assisted reproductive technology (ART) report: section 2 — ART cycles using fresh, nondonor eggs or embryos. Atlanta: Centers for Disease Control and Prevention, 2003. (Accessed January 18, 2007, at <http://www.cdc.gov/ART/ART2003/section2a.htm#f12>.)
33. Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA, Nestler JE. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2002;87:524-9.
34. Norman RJ, Wang JX, Hague W. Should we continue or stop insulin sensitizing drugs during pregnancy? *Curr Opin Obstet Gynecol* 2004;16:245-50.
35. American College of Obstetricians and Gynecologists Committee on Practice Bul-
- letins — Obstetrics. ACOG Practice Bulletin: clinical management guidelines for obstetricians-gynecologists. Number 30, September 2001 (replaces Technical Bulletin Number 20, December 1994): gestational diabetes. *Obstet Gynecol* 2001;98:525-38.
36. *Idem*. ACOG Practice Bulletin: diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol* 2002;99:159-67.
37. Gusler G, Gorsline J, Levy G, et al. Pharmacokinetics of metformin gastric-retentive tablets in healthy volunteers. *J Clin Pharmacol* 2001;41:655-61.

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