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Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome

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Abstract

BACKGROUND—Clomiphene is the current first-line infertility treatment in women with the polycystic ovary syndrome, but aromatase inhibitors, including letrozole, might result in better pregnancy outcomes.

METHODS—In this double-blind, multicenter trial, we randomly assigned 750 women, in a 1:1 ratio, to receive letrozole or clomiphene for up to five treatment cycles, with visits to determine ovulation and pregnancy, followed by tracking of pregnancies. The polycystic ovary syndrome was defined according to modified Rotterdam criteria (anovulation with either hyperandrogenism or polycystic ovaries). Participants were 18 to 40 years of age, had at least one patent fallopian tube and a normal uterine cavity, and had a male partner with a sperm concentration of at least 14 million per milliliter; the women and their partners agreed to have regular intercourse with the intent of conception during the study. The primary outcome was live birth during the treatment period.

RESULTS—Women who received letrozole had more cumulative live births than those who received clomiphene (103 of 374 [27.5%] vs. 72 of 376 [19.1%], P = 0.007; rate ratio for live birth, 1.44; 95% confidence interval, 1.10 to 1.87) without significant differences in overall congenital anomalies, though there were four major congenital anomalies in the letrozole group versus one in the clomiphene group (P = 0.65). The cumulative ovulation rate was higher with letrozole than with clomiphene (834 of 1352 treatment cycles [61.7%] vs. 688 of 1425 treatment cycles [48.3%], P<0.001). There were no significant between-group differences in pregnancy loss (49 of 154 pregnancies in the letrozole group [31.8%] and 30 of 103 pregnancies in the clomiphene group [29.1%]) or twin pregnancy (3.4% and 7.4%, respectively). Clomiphene was

*Additional members of the National Institute of Child Health and Human Development (NICHD) Reproductive Medicine Network are listed in the Supplementary Appendix, available at NEJM.org.

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associated with a higher incidence of hot flushes, and letrozole was associated with higher incidences of fatigue and dizziness. Rates of other adverse events were similar in the two treatment groups.

CONCLUSIONS—As compared with clomiphene, letrozole was associated with higher live-birth and ovulation rates among infertile women with the polycystic ovary syndrome. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and others; ClinicalTrials.gov number, NCT00719186.)

The polycystic ovary syndrome, which is diagnosed on the basis of hyperandrogenism, oligo-ovulation with associated oligomenorrhea, and polycystic ovaries on ultrasonography, affects 5 to 10% of reproductive-age women and is the most common cause of anovulatory infertility.[1] Although the syndrome is a complex reproductive–metabolic disorder, the hypothalamic–pituitary axis has been the target of first-line ovulation-induction therapy. Clomiphene citrate, a selective estrogen-receptor modulator that antagonizes the negative feedback of estrogen at the hypothalamus with a consequent increase in ovarian stimulation by endogenous gonadotropin, has been used for this indication for decades.

Clomiphene has drawbacks, including its overall poor efficacy (only a 22% rate of live birth with up to six cycles of clomiphene in our previous study[2]), a relatively high multiple-pregnancy rate (3 to 8%) as compared with the rate associated with unassisted conception (<1%), and an undesirable side-effect profile, including mood changes and hot flushes. Failure either to ovulate (clomiphene resistance), which occurred in 25% of the patients in the clomiphene group in our prior study,[2] or to conceive with ovulation (clomiphene failure) often results in the use of more expensive treatment options for infertility that may be associated with higher multiple-pregnancy rates and an increased risk of the ovarian hyperstimulation syndrome.[3]

The development of effective, simple, and safe treatments for infertility is an important public health goal.[4] Metformin improves insulin action and anovulation. In our previous trial, however, treatment with metformin alone or in combination with clomiphene was not superior to clomiphene alone.[2] Other trials have confirmed that finding.[5] Aromatase inhibitors, which block estrogen synthesis, directly affect hypothalamic–pituitary–ovarian function and theoretically might increase pregnancy rates.[6] Potential advantages of aromatase inhibitors over selective estrogen-receptor modulators include a more physiologic hormonal stimulation of the endometrium, a lower multiple-pregnancy rate through single-follicle recruitment, a better side-effect profile with fewer vasomotor and mood symptoms, and more rapid clearance, thus reducing the chances of periconceptional exposure.[6] However, potential fetal teratogenicity remains a concern with letrozole (see the Supplementary Appendix, available with the full text of this article at NEJM.org).[7] We designed a double-blind, multicenter, randomized trial to test the hypothesis that letrozole would be superior to clomiphene as an infertility treatment and would have a similar safety profile.

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METHODS

STUDY OVERSIGHT

We previously reported the trial rationale and a detailed protocol summary,[8] as well as study methods and the full baseline characteristics of the study participants.[9] The protocol (available at NEJM.org) was designed by the steering committee of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Reproductive Medicine Network and was approved before study initiation by both a National Institutes of Health–appointed advisory board and a data and safety monitoring board; the latter board subsequently oversaw the study. We obtained a certificate of confidentiality and established a data and specimen repository.[9] Letrozole was used under an Investigational New Drug application (number 101,671) to the Food and Drug Administration (FDA). The institutional review board at each center approved the protocol, and all participants (women and their male partners) gave written informed consent. Enrollment began in February 2009 and was completed in January 2012. All data entry, data management, and analyses were coordinated or performed at the Collaborative Center for Statistics in Science at Yale University, the data coordinating center for this study. All drafts of the manuscript were written by the first and last authors with input from all the authors. The steering committee of the Reproductive Medicine Network vouches for the accuracy and completeness of the data. All the authors vouch for the fidelity of the study to the protocol.

PATIENTS

A total of 750 infertile women 18 to 40 years of age with the polycystic ovary syndrome who had no major medical disorders and who were not taking confounding medications (primarily sex steroids, other infertility drugs, and insulin sensitizers, as described in the study protocol), their male partners, and their neonates participated in the study.[9] We used modified Rotterdam criteria[1] to diagnose the polycystic ovary syndrome. Accordingly, all participating women had ovulatory dysfunction combined with hyperandrogenism (on the basis of hirsutism[9] or an elevated testosterone level[10]), polycystic ovaries (defined by an increased number of small antral follicles [≥12 follicles that were <10 mm in diameter] or an increased individual ovarian volume [>10 cm^3] in ≥1 ovary), or both.[9] Other disorders that mimic the polycystic ovary syndrome, including thyroid disease and prolactin excess, were ruled out.

Additional eligibility criteria were at least one patent fallopian tube and a normal uterine cavity, as determined by sonohysterography (on the basis of the presence of free fluid in the pelvis), hysterosalpingography, a combined hysteroscopy and laparoscopy, or evidence of an intrauterine pregnancy within the previous 3 years; a male partner with a sperm concentration of at least 14 million per milliliter, with documented motility according to World Health Organization cutoff points,[11] in at least one ejaculate during the previous year; and a commitment on the part of the women and their partners to have regular intercourse during the study with the intent of pregnancy.

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STUDY OVERVIEW

After spontaneous menses or withdrawal bleeding induced by progestin administration (medroxy-progesterone acetate [Provera], 5 mg per day for 10 days), 750 women were randomly assigned to either clomiphene citrate (50 mg daily) or letrozole (2.5 mg daily) in a 1:1 ratio in permuted blocks of two, four, or six, beginning on cycle day 3 for 5 days and for up to five menstrual cycles. The dose was increased in subsequent cycles in both treatment groups in cases of nonresponse (progesterone level during the midluteal phase, <3 ng per milliliter) or a poor ovulatory response (progesterone levels indicative of ovulation but with values clustering just above the cutoff point [see the Supplementary Appendix]), noted in 2% of 2777 treatment cycles. The maximum daily dose of clomiphene was 150 mg (three pills), and the maximum daily dose of letrozole was 7.5 mg (three pills), both given for 5 days. Investigators had the option to induce menstrual bleeding with medroxyprogesterone acetate after an anovulatory cycle; this option was exercised in 309 of 1255 anovulatory cycles (24.6%). Couples were instructed to have regular intercourse two to three times a week, and the women kept an intercourse diary. Ovulation predictor kits were not used.

The purchased study drugs — clomiphene citrate (ClomiPHENE, Teva Pharmaceuticals USA) and letrozole (Femara, Novartis Pharmaceuticals) — were overencapsulated to look the same, tested, and packaged by a commercial supply company (Almac Clinical Services). No placebo was used, because the two drugs were given for the same duration and with the same stepwise increase in dose. Neither manufacturer had a role in the study. All reported laboratory values were determined by a central laboratory (Ligand Core Laboratory, University of Virginia).

Participants who conceived were followed until a viable intrauterine pregnancy was observed (fetal heart motion visualized on ultrasonography) and were then referred for prenatal care. Outcomes were tracked through review of maternal and infant medical records. Participants who delivered had the option to participate in a separate, FDA-mandated pregnancy registry (after giving written informed consent for registry participation) that required examination of the infant by a qualified developmental pediatrician or geneticist within 6 weeks after birth; 73.1% of couples (128 of 175 couples) with a live birth participated in this registry, and we have incorporated the results of testing for anomalies into our reporting of adverse events. This ongoing registry follows infants to 3 years of age for developmental delays (ClinicalTrials.gov number, NCT00902382).

OUTCOMES

The primary outcome was live birth during the treatment period. Secondary outcomes included ovulation, pregnancy loss, singleton birth, and congenital anomalies. Serious adverse events were defined as events that were fatal or immediately life-threatening, that were severely or permanently disabling, or that required or prolonged inpatient hospitalization; overdoses (intentional or accidental); congenital anomalies; pregnancy loss after 12 weeks of gestation; and any event deemed to be serious by the site principal investigator.

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STATISTICAL ANALYSIS

The study was designed to have 81% power to detect an absolute difference of 10 percentage points in cumulative live-birth proportions between treatment groups (20% in the clomiphene group on the basis of the results for the clomiphene-only group after five cycles in our prior study[2] vs. 30% in the letrozole group), with the use of Pearson's chi-square test at a two-sided significance level of 0.05. We calculated that the analysis would require a sample of 300 patients per treatment group, which we increased to 375 to allow for a dropout rate of 20%. A chi-square test (or Fisher's exact test if any frequency count was <5) was used for testing differences between the two treatment groups. For all continuous variables, the mean and standard deviation in each group are reported.

We used Kaplan–Meier curves to report the time from randomization to live birth according to treatment group and according to treatment group and tertile of maternal body-mass index (BMI). A log-rank test was used to test the interaction between BMI tertile and study treatment with regard to the time from randomization to live birth. Although these BMI groups were not pre-specified in the study protocol, our previous studies have suggested that BMI affects infertility treatment in women with the polycystic ovary syndrome.[2] To avoid type I errors from multiple comparisons, we did not explore various BMI stratifications but instead used simple tertiles. All analyses were performed with the use of SAS software, version 9.2 (SAS Institute). Data were analyzed according to the intention-to-treat principle.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 750 patients with the polycystic ovary syndrome were randomly assigned to a treatment group (Fig. S1 in the Supplementary Appendix), and the two groups were well matched at baseline (Table 1). The last enrolled patient finished taking the study medication in July 2012, and the last birth was reported in February 2013. A total of 158 women (85 of 376 in the clomiphene group [22.6%] and 73 of 374 in the letrozole group [19.5%], P = 0.30) dropped out or were excluded from further analyses, with no significant differences between treatment groups in the reason for withdrawal (Table S1 in the Supplementary Appendix).

LIVE BIRTHS AND SECONDARY OUTCOMES

The group of women who received letrozole had more cumulative live births than the group of women who received clomiphene (103 of 374 women [27.5%] vs. 72 of 376 [19.1%], P = 0.007; rate ratio for live birth with letrozole, 1.44; 95% confidence interval, 1.10 to 1.87) (Table 2 and Fig. 1A). There were no significant between-group differences in live-birth rates according to treatment cycle (Table S2 in the Supplementary Appendix). We performed an analysis according to tertile of maternal BMI (Fig. 1B, 1C, and 1D). Both the study treatment and BMI tertile were significant factors in the primary outcome of live birth (P = 0.009 and P<0.001, respectively), but no significant interaction was detected (P = 0.42). The live-birth rates after an anovulatory cycle were similar with and without progestin-induced withdrawal bleeding in both treatment groups (see the Supplementary Appendix).

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The rates of pregnancy loss after conception were similar in the two treatment groups (Table 2, and Table S3 in the Supplementary Appendix). The ovulation rate was significantly higher with letrozole than with clomiphene at each monthly visit ($P<0.01$ for all comparisons) beginning with the second visit (Table S2 in the Supplementary Appendix). Among patients who ovulated, there was a significantly greater chance of singleton pregnancy with letrozole than with clomiphene ($P = 0.03$). The sex ratio at birth favored girls (Table 2).

ADVERSE EVENTS AND PREGNANCY AND NEONATAL COMPLICATIONS

Three serious adverse events related to ovarian-cyst formation occurred during infertility treatment: two with letrozole (a ruptured corpus luteum cyst in one patient and hospitalization for the drainage and removal of an ovarian cyst in another patient) and one with clomiphene (ovarian torsion) (Table 3). Clomiphene was associated with a significantly higher incidence of hot flushes; letrozole was associated with significantly higher incidences of fatigue and dizziness. During pregnancy, the most common complication was gestational diabetes, followed by preeclampsia or eclampsia, preterm labor, and premature rupture of membranes, with no significant differences between treatment groups (Table S4 in the Supplementary Appendix). There were five major congenital anomalies (four with letrozole and one with clomiphene); the between-group difference was not significant ($P = 0.65$) (Table 3, and Table S5 in the Supplementary Appendix). The most common neonatal complications were jaundice, the respiratory distress syndrome, a condition requiring hospitalization for more than 3 days, and intrauterine growth restriction, without significant differences between treatment groups.

OTHER TREATMENT EFFECTS

We noted no significant difference in maternal BMI or any metabolic variable between or within groups from baseline to the last midluteal-phase visit in the study (Table S6 in the Supplementary Appendix). As compared with letrozole, clomiphene was associated with an improvement in biochemical hyperandrogenemia and a subjective improvement in hirsutism (Table 4). However, letrozole was associated with a greater decrease in the antral follicle count (and a decrease in levels of antimüllerian hormone), a lesser increase in endometrial thickness, and a significantly lower estradiol level in the midluteal phase.

DISCUSSION

We found that letrozole was more effective as a fertility treatment than clomiphene in women with the polycystic ovary syndrome. Ovulation, conception, pregnancy, and live birth were significantly more likely after treatment with letrozole. The rate of pregnancy loss, the mean pregnancy duration and birth weight, and rates of neonatal complications (including anomalies) did not differ significantly between treatment groups. Although the twin pregnancy rate was lower with letrozole than with clomiphene, our study was underpowered to detect a significant between-group difference (23% power with an alpha level of 0.05). The overall birth-defect rate was similar in the two treatment groups, but there were four major congenital anomalies in the letrozole group and one in the clomiphene

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group; this difference was not significant but given the group size, we cannot rule out a potential difference.

Both drugs used in our study have been designated by the FDA as pregnancy category X (although clomiphene is approved for ovulation induction). The anomaly types seen with letrozole in our study are diverse, a finding that argues against a common mechanism. Furthermore, the anomaly rates are lower than those reported in a large population-based study in Australia that examined birth-defect rates after any means of assisted reproduction (8.4%) or ovulation induction (6.4%).[12] We speculate that the higher rates in Australia might be due to an established national birth-defects registry with mandatory reporting of all anomalies detected at birth or within the neonatal period. We examined the pregnancy, birth, and neonatal records of all live births; in addition, almost three fourths of the neonates underwent physical examination by medical personnel trained in detecting congenital anomalies. Our data indicate that anomaly rates are similar with the two treatments we evaluated, and these rates are also similar to the rate in a population of healthy, fertile women who conceived without undergoing treatment for assisted reproduction (5.8%).[12]

The live-birth rate was higher with letrozole than with clomiphene among women with the polycystic ovary syndrome in our study. Prior trials appear to have been insufficiently powered to detect differences in live-birth rates, lacked adequate concealment of study-group assignments, or did not allow for repeated cycles to achieve an ovulatory response with an increased dose.[13] Two well-designed, industry-sponsored, multicenter, phase 2 studies, both of which were randomized, double-blind, dose-finding, noninferiority studies, compared anastrozole with clomiphene (the latter at a daily dose of 50 mg) in women with oligo-ovulation (most of whom had the polycystic ovary syndrome), with ovulation as the primary outcome.[14],[15] Both studies concluded that treatment with anastrozole was less effective than a 5-day course of clomiphene. The discrepant outcomes with similar drugs may reflect the greater suppression of aromatase with letrozole than with anastrozole.[16] When given to women with a history of breast cancer who were undergoing ovarian stimulation with gonadotropins, letrozole was associated with significantly lower estradiol levels during treatment than was anastrozole in an area-under-the curve analysis.

We attribute our findings of lower estradiol levels and higher progesterone levels during the midluteal phase with letrozole than with clomiphene to sustained aromatase inhibition into the luteal phase. This hormonal profile, against expectations,[6] probably led to a thinner endometrium during the midluteal phase. Our previous study[18] showed that a higher baseline level of sex hormone–binding globulin, as compared with a lower level, and a lower free androgen index at baseline, as compared with a higher index, were associated with an increased live-birth rate. Our observations with letrozole suggest that improvement in hyperandrogenism may not be necessary to increase ovulation and live-birth rates.

The proportion of obese patients in our study population was larger than the proportions in study populations in other countries,[19–21] but the mean BMI was reflective of the U.S. population of women with the polycystic ovary syndrome and nearly identical to that in our previous trial[2] and other U.S. multicenter trials,[22] despite slightly different diagnostic criteria for the polycystic ovary syndrome. There was no clear evidence that relative efficacy

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differed according to BMI tertile. Our current and previous data indicate that fecundity in women with the polycystic ovary syndrome may be greatly improved with an intervention that has little effect on BMI or other metabolic variables.

We did not require a lifestyle intervention before enrollment. Although such interventions are recommended by experts,[4] there is currently no evidence from high-quality clinical trials that they improve pregnancy outcomes in obese women.[23] We left the choice of inducing withdrawal bleeding after an anovulatory cycle to the site investigator's discretion and found no adverse effect of withdrawal bleeding on fecundity, in contrast to the findings in our previous study.[2],[24] Another potential weakness of the study is the relatively high dropout rate; however, it is similar to the dropout rate in the clomiphene group in our prior study (26%)[2] and to the rate in a similar multicenter trial involving 320 patients (19%).[21] We speculate that the dropout rates may be relatively high in such infertility trials because a woman or her male partner may individually discontinue participation. Cumulative failure after multiple treatment cycles may also breed discouragement and the desire to seek alternative infertility therapies.

In conclusion, our study showed that letrozole was superior to clomiphene as a treatment for anovulatory infertility in women with the polycystic ovary syndrome. Letrozole was associated with higher live-birth and ovulation rates. Further study with larger numbers of infants is needed to clarify the safety and teratogenic risks with letrozole relative to those with other infertility therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

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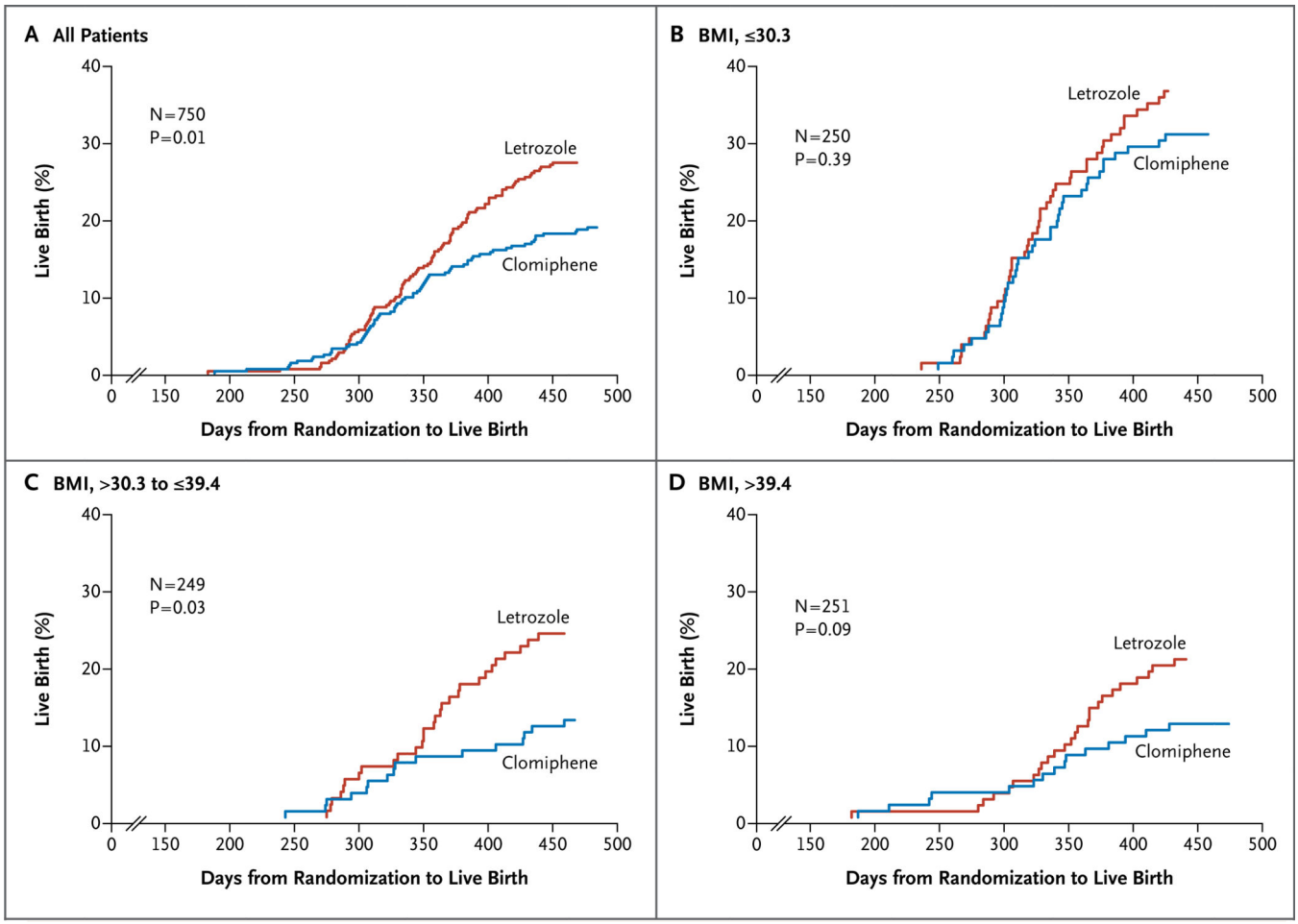

Figure 1. Kaplan–Meier Curves for Live Birth

Live-birth rates are shown according to treatment group in Panel A and according to treatment group and maternal body-mass index (BMI, the weight in kilograms divided by the square of the height in meters), in thirds, in Panels B, C, and D.

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Table 1

Baseline Characteristics of the Patients.*

Characteristic	Clomiphene Group (N = 376)	Letrozole Group (N = 374)
Age — yr	28.8±4.0	28.9±4.5
Body-mass index†	35.1±9.0	35.2±9.5
Ferriman–Gallwey hirsutism score‡	16.9±8.5	17.0±8.6
Race or ethnic group — no. (%)§		
White	302 (80.3)	288 (77.0)
Black	44 (11.7)	56 (15.0)
Asian	12 (3.2)	12 (3.2)
Mixed race	12 (3.2)	15 (4.0)
Hispanic or Latino	68 (18.1)	60 (16.0)
Fertility history		
Duration of time attempting to conceive — mo	42.5±37.6	40.9±38.0
Previous live birth — no. (%)	73 (19.4)	75 (20.1)
Ultrasonographic findings		
Antral follicle count in both ovaries	46.5±28.5	47.4±27.4
Polycystic ovaries according to modified Rotterdam criteria — no./total no. (%)¶	349/374 (93.3)	354/369 (95.9)
Endometrial thickness in sagittal plane — mm	6.7±2.9	6.8±3.0
Fasting serum biochemical values		
Total testosterone — ng/dl	56.3±30.1	53.8±27.4
Sex hormone–binding globulin — nmol/liter	33.2±23.7	34.5±22.4
Free androgen index. ‖	8.2±6.2	7.4±5.6
Estradiol — pg/ml	55.7±40.5	54.6±32.6
Progesterone — ng/ml	1.5±2.9	1.5±3.3
Antimüllerian hormone — ng/ml	8.1±6.9	8.0±7.1
Quality-of-life measures**		
Total score on PCOSQ	3.9±1.2	3.9±1.2
Body-hair score on PCOSQ	4.1±1.8	4.2±1.8

*Plus–minus values are means ±SD. There were no significant differences ($P<0.05$) between the two groups in any of the baseline characteristics. To convert the values for total testosterone to nanomoles per liter, multiply by 0.03467. To convert the values for estradiol to picomoles per liter, multiply by 3.671. To convert the values for progesterone to nanomoles per liter, multiply by 3.180.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡Scores on the Ferriman–Gallwey scale for hirsutism range from 0 to 44, with higher scores indicating a greater degree of hirsutism.

§Race or ethnic group was reported by the patients. Some patients chose more than one category, including Hispanic or Latino.

¶Polycystic ovaries were defined by an antral follicle count of 12 or more or by a volume of more than 10 cm^3 in at least one ovary.

‖The free androgen index was calculated according to the following formula: (total testosterone [nanomoles per liter] ÷ sex hormone–binding globulin [nanomoles per liter]) × 100.

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** Total scores on the PCOSQ, a questionnaire for measuring health-related quality of life in women with the polycystic ovary syndrome, range from 1 to 7, with higher scores indicating better function. Scores on the body-hair component of the PCOSQ range from 1 to 7, with higher scores indicating more satisfaction with body hair.

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Table 2

Outcomes with Regard to Live Birth, Ovulation, Pregnancy, Pregnancy Loss, and Fecundity.*

Outcome	Clomiphene Group (N = 376)	Letrozole Group (N = 374)	Absolute Difference between Groups (95% CI)†	Rate Ratio in Letrozole Group (95% CI)	P Value‡
Primary outcome					
Live birth — no. (%)	72 (19.1)	103 (27.5)	8.4 (2.4 to 14.4)	1.44 (1.10 to 1.87)	0.007
Singleton live birth — no./total no. (%)	67/72 (93.1)	99/103 (96.1)	3.1 (−3.9 to 10.0)	1.03 (0.96 to 1.11)	0.49
Twin live birth — no./total no. (%)§	5/72 (6.9)	4/103 (3.9)	−3.0 (−10.0 to 3.9)	0.56 (0.16 to 2.01)	0.49
Birth weight					
No. of infants	71	102			
Mean weight — g	3229.9±715.3	3232.3±657.4	2.4 (−205.6 to 210.4)		0.83
Sex ratio at birth (boys:girls)	0.88 (36:41)	0.65 (42:65)		0.74 (0.41 to 1.33)¶	
Duration of pregnancy					
No. of women	72	101			
Mean duration — wk	38.0±3.6	38.4±2.7	0.4 (−0.6 to 1.4)		0.59
Secondary outcomes					
Pregnancy					
Conception — no. of women (%)	103 (27.4)	154 (41.2)	13.8 (7.1 to 20.5)	1.50 (1.23 to 1.84)	<0.001
Pregnancy — no. of women (%)	81 (21.5)	117 (31.3)	9.7 (3.5 to 16.0)	1.45 (1.14 to 1.85)	0.003
Twin pregnancy — no. of women/total no. of pregnancies (%)	6/81 (7.4)	4/117 (3.4)	−4.0 (−10.6 to 2.6)	0.46 (0.13 to 1.58)	0.32
Time to pregnancy ‖					
No. of women	90	145			
Mean time — days	85.9±48.8	90.4±44.4	4.5 (−8.0 to 17.0)		0.27
Pregnancy loss					
Pregnancy loss among women who conceived — no./total no. (%)	30/103 (29.1)	49/154 (31.8)	2.7 (−8.7 to 14.1)	1.09 (0.75 to 1.60)	0.65
Loss in first trimester — no./total no. (%)	29/103 (28.2)	45/154 (29.2)	1.1 (−10.2 to 12.3)	1.04 (0.70 to 1.54)	0.85
Ovulation					
Women who ovulated — no. (%)	288 (76.6)	331 (88.5)	11.9 (6.5 to 17.3)	1.16 (1.08 to 1.24)	<0.001
No. of ovulations/total treatment cycles (%)	688/1425 (48.3)	834/1352 (61.7)	13.4 (9.7 to 17.1)	1.28 (1.19 to 1.37)	<0.001

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Outcome	Clomiphene Group (N = 376)	Letrozole Group (N = 374)	Absolute Difference between Groups (95% CI)†	Rate Ratio in Letrozole Group (95% CI)	P Value‡
Fecundity among women who ovulated — no./total no. (%)					
Conception	103/288 (35.8)	154/331 (46.5)	10.8 (3.1 to 18.5)	1.31 (1.07 to 1.58)	0.007
Singleton pregnancy	75/288 (26.0)	113/331 (34.1)	8.1 (0.9 to 15.3)	1.31 (1.03 to 1.58)	0.03
Singleton live birth	67/288 (23.3)	99/331 (29.9)	6.6 (−0.3 to 13.6)	1.29 (0.98 to 1.68)	0.06

* Plus–minus values are means ±SD. Live birth was defined by the delivery of a live-born infant. Conception was defined by a serum level of human chorionic gonadotropin of more than 10 mIU per milliliter. Pregnancy was defined by observation of fetal heart motion on ultrasonography. Ovulation was defined by a progesterone level of more than 3 ng per milliliter (10 nmol per liter).

† Differences are expressed as percentage points for all outcomes except birth weight, duration of pregnancy, and time to pregnancy, for which the absolute difference between mean values is shown.

‡ P values were calculated with the use of the chi-square test or Fisher's exact test for categorical data and the Wilcoxon rank-sum test for continuous data.

§ All twins were diamnionic and dichorionic.

¶ The odds ratio is shown.

‖ Time to pregnancy was the time between the first day that the patient took the study drug and the first day that a positive pregnancy test was recorded.

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Table 3

All Serious Adverse Events, plus Other Adverse Events with Significant Differences between the Treatment Groups.*

Event	Clomiphene Group	Letrozole Group
	no. of women/total no. (%)	
Event before conception in women who received a study drug		
Serious adverse event		
Ovarian torsion	1/355 (0.3)	0/359
Ruptured corpus luteum cyst	0/355	1/359 (0.3)
Hospitalization†	3/355 (0.8)	2/359 (0.6)
Other adverse event		
Hot flushes‡	117/355 (33.0)	73/359 (20.3)
Fatigue§	53/355 (14.9)	78/359 (21.7)
Dizziness§	27/355 (7.6)	44/359 (12.3)
Serious adverse event after conception in women who Discontinued the study drug		
First trimester		
Ectopic pregnancy	3/94 (3.2)	4/149 (2.7)
Heterotopic pregnancy	1/94 (1.1)	0/149
Pregnancy of unknown location	1/94 (1.1)	1/149 (0.7)
Hospitalization¶	2/94 (2.1)	4/149 (2.7)
Second and third trimester		
Hospitalization for premature labor	0/94	2/149 (1.3)
Hospitalization for other reasons. ‖	2/94 (2.1)	7/149 (4.7)
Postpartum anemia requiring transfusion after delivery	0/94	1/149 (0.7)
Serious adverse event after 20 wk of pregnancy in fetus through neonatal period in infant		
Congenital anomaly**	1/66 (1.5)	4/102 (3.9)
Fetal death	1/66 (1.5)	1/102 (1.0)
Neonatal death	2/66 (3.0)	1/102 (1.0)

* For more detailed information on adverse events, see Table S4 in the Supplementary Appendix.

† In the clomiphene group, hospitalization was due to a reported cancer at an unknown site, a stage III skin cancer, and a cholecystectomy in one patient each. In the letrozole group, hospitalization was due to nonadherence to the emergency department treatment plan in one patient and the drainage and removal of an ovarian cyst in another patient.

‡ $P<0.01$.

§ $P<0.05$.

¶ In the clomiphene group, one woman was hospitalized for cervical cerclage and one for vaginal bleeding. In the letrozole group, four women were hospitalized, one each for constipation, viral meningitis, chest pain, and an appendectomy.

‖ In the clomiphene group, hospitalization was due to Bell's palsy associated with preeclampsia and a subsequent diagnosis of multiple sclerosis in one woman and hypertension in another. In the letrozole group, seven women were hospitalized, one each for back pain, a methicillin-resistant *Staphylococcus aureus* abscess, preeclampsia, a ureteral stone, cholecystitis, a cholecystectomy, and the repair of an umbilical hernia.

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** In the clomiphene group, one infant had an atrial septal defect, a ventricular septal defect, and pulmonary stenosis. In the letrozole group, one infant had cerebral palsy with arrested hydrocephalus as well as polycythemia and neutropenia, one infant had an imperforate anus with perineal fistula and spina bifida with a tethered spinal cord, one infant had right hemimegalencephaly and dysgenesis of the left frontal and temporal lobes but no hydrocephalus, and one infant had a large ventricular septal defect requiring surgical repair. One minor birth defect (ankyloglossia) was detected on neonatal examination in an infant in the letrozole group. For a detailed description of the congenital anomalies, see Table S5 in the Supplementary Appendix.

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Table 4

Absolute Changes in Key Measures from Baseline to Last Midluteal-Phase Visit.*

Measure	Clomiphene Group	Letrozole Group	P Value†
Ultrasonographic findings			
Antral follicle count in both ovaries			
No. of women	321	325	
Mean change	−2.8±22.9	−5.2±21.9	
Median change (IQR)	−1.0 (−12.0 to 8.0)	−4.0 (−16.0 to 5.0)	0.04
Endometrial thickness in sagittal plane			
No. of women	351	352	
Mean change — mm	3.4±3.7	2.4±3.8	
Median change (IQR) — mm	3.0 (1.0 to 6.0)	2.0 (0.0 to 5.0)	<0.001
Fasting serum biochemical values			
Sex hormone–binding globulin			
No. of women	350	354	
Mean change — nmol/liter	13.7±19.5	−1.5±15.5	
Median change (IQR) — nmol/liter	9.9 (3.3 to 20.7)	−1.2 (−5.1 to 3.1)	<0.001
Free androgen index‡			
No. of women	350	354	
Mean change	−1.9±4.7	1.7±6.4	
Median change (IQR)	−1.5 (−4.0 to 0.2)	0.4 (−1.2 to 3.2)	<0.001
Estradiol			
No. of women	351	355	
Mean change — pg/ml	52.9±107.7	9.2±59.5	
Median change (IQR) — pg/ml	22.5 (−2.0 to 92.2)	−0.8 (−21.4 to 32.6)	<0.001
Progesterone			
No. of women	351	355	
Mean change — ng/dl	11.0±21.5	13.2±21.0	
Median change (IQR) — ng/dl	0.2 (−0.1 to 14.8)	2.7 (0.1 to 18.2)	<0.001
Antimüllerian hormone			
No. of women	350	355	
Mean change — ng/ml	0.1±5.1	−0.5±4.8	
Median change (IQR) — ng/ml	0.1 (−1.1 to 1.9)	−0.2 (−2.0 to 1.1)	0.02
Quality-of-life measures			
Body-hair score on PCOSQ§			
No. of women	272	271	
Mean change	0.4±1.0	0.2±1.1	
Median change (IQR)	0.3 (−0.2 to 1.0)	0.2 (−0.4 to 0.8)	0.03

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[*] Plus–minus values are means ±SD. If conception occurred, the last visit was the one before pregnancy was documented. IQR denotes interquartile range.

[†] Wilcoxon's rank-sum test was used to compare the difference in change from baseline between the two treatment groups. Shown are measures with a significant between-group difference ($P<0.05$).

[‡] The free androgen index was calculated according to the following formula: (total testosterone [nanomoles per liter] ÷ sex hormone–binding globulin [nanomoles per liter]) × 100.

[§] Scores on the body-hair component of the PCOSQ, a questionnaire for measuring health-related quality of life in women with the polycystic ovary syndrome, range from 1 to 7, with higher scores indicating more satisfaction with body hair.