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Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) Trial: Baseline Characteristics

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Abstract

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Objective—To identify baseline characteristics of women with unexplained infertility to determine whether treatment with an aromatase inhibitor will result in a lower rate of multiple gestations than current standard ovulation induction medications.

Design—Randomized, prospective clinical trial

Patients—900 couples with unexplained infertility Interventions: Ovarian stimulation with gonadotropins, clomiphene citrate, or letrozole in conjunction with intrauterine insemination.

Setting—Multicenter University based clinical practices.

Main Outcome Measures—Demographic, laboratory, imaging, and survey characteristics.

Interventions—Collection of baseline demographics, blood samples, and ultrasonographic assessments.

Results—Demographic characteristics of women receiving clomiphene citrate, letrozole, or gonadotropins for ovarian stimulation were very consistent. Their mean age was 32.2 ± 4.4 years and infertility duration was 34.7 ± 25.7 months, with 59% primary infertility. More than 1/3 of the women were current or past smokers. The mean BMI was 27 and mean AMH level was 2.6; only 11 women (1.3%) had antral follicle counts of less than 5. Similar observations were identified for hormonal profiles, ultrasound characterization of the ovaries, semen parameters, and quality of life assessments in both male and female partners.

Conclusion—The cause of infertility in the couples recruited to this treatment trial is elusive, as the women were regularly ovulating and had evidence of good ovarian reserve both by basal FSH, AMH levels, and antral follicle counts; the male partners had normal semen parameters. The three treatment subgroups have common baseline characteristics, thereby providing comparable patient populations for testing the hypothesis that use of letrozole for ovarian stimulation can reduce the rates of multiples from that observed with gonadotropin and clomiphene citrate treatment.

Keywords

Unexplained Infertility; aromatase inhibitors; letrozole; gonadotropins; clomiphene citrate; multiple gestations

INTRODUCTION

In regularly ovulating women with unexplained infertility, a frequently chosen option that has been shown to enhance the likelihood of conception is empiric ovulation induction (1–4). A major challenge of ovulation induction in the United States has been the increased incidence of multiple births associated with the administration of fertility promoting agents, including gonadotropins and clomiphene citrate (CC)(5, 6) Multiple gestations following the use of these agents are associated with increased risk for preterm labor, preterm delivery, antepartum maternal hospitalization, and neonatal morbidity and mortality associated with preterm delivery (7–10) A direct result of the prolonged maternal and neonatal hospitalizations (including multiple babies from the multi-fetal gestations) is the marked increase in expense related to this intensive care,(11, 12) and an overall increased risk for lifelong morbidity for these babies.

Recently, there have been numerous reports of the use of aromatase inhibitors (AIs) for ovarian stimulation as an alternative to gonadotropins and CC, for treatment of both women with anovulation/oligo-ovulation with polycystic ovary syndrome (PCOS), and of unexplained infertility, in which the woman is ovulatory but infertile.(13–18) Taken together, these reports have suggested that AIs may be useful agents to reproducibly stimulate ovarian follicular development, leading to unifollicular ovulation with resultant singleton pregnancy. If accurate, the use of AIs would lead to both a reduction in multi-fetal pregnancies and the potential maternal and long-term neonatal morbidity associated with them, and a decrease in the significant, short-term morbidity associated with ovarian hyperstimulation syndrome (OHSS).

To examine these major clinical issues, the Eunice Kennedy Shriver National Institute of Child Health and Human Development Cooperative Reproductive Medicine Network (RMN) conducted the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) clinical trial. (4) Specifically, the objective of this study was to examine whether treatment of women with unexplained infertility with an aromatase inhibitor, letrozole, would result in a lower rate of multiple gestations than the current standard ovarian stimulation medications, CC or gonadotropins. The central hypothesis was that prescribing AIs to infertile ovulatory women undergoing ovarian stimulation and intrauterine insemination (IUI) will result in a clinically acceptable (noninferior) rate of pregnancy, while significantly reducing the number of multiple gestations associated with the current standard treatments. This report summarizes the baseline demographic, biomedical, and quality of life survey characteristics of nine hundred male and female partners who participated in the AMIGOS trial.

MATERIALS & METHODS

Study Design

This was a multicenter, randomized, prospective clinical trial of an aromatase inhibitor (letrozole) vs. clomiphene citrate vs. gonadotropins in nine hundred couples with unexplained infertility. Women were regularly ovulating, and received gonadotropin (Menopur®, Ferring Pharmaceuticals) by subcutaneous injection, or clomiphene citrate by oral ingestion of overcoated pills, or letrozole by oral ingestion of overcoated pills. Assignment of clomiphene citrate or letrozole was in a double blinded fashion under IND (#107705) from the US FDA for administration of letrozole for ovarian stimulation in women with unexplained infertility. All medications were initiated on cycle days 3–5. Treatment assignments were randomized within each site, with further randomization within age groups (18–34 or 35–40) using a varying block-size design. Women who conceived were followed through pregnancy and delivery, with additional assessments of the offspring during the first 3 years of childhood through the RMN's Pregnancy Registry. The protocol was reviewed and approved by an NIH/NICHD appointed Advisory Board and Data Safety Monitoring Committee, with informed written consent provided by all participants (females and males) of an IRB approved protocol from each participating institution.

Inclusion/Exclusion Criteria

The overall goal of the inclusion/exclusion criteria has been previously described.

(4) Briefly, the goal was to identify healthy, infertile couples with unexplained infertility in which the female partner was ovulating regularly. This included women 18 to 40 years of age, with one or more years of infertility history, desirous of conceiving, regularly ovulating (defined as 9 or more menses per year), at initiation of participation with a normal uterine cavity and at least one patent fallopian tube.

Study Conduct

Following provision of informed, written consent, female study participants underwent a physical exam, including height, weight and abdominal circumference, and Pap smear as necessary per current ACOG guidelines. Subjects also underwent Ferriman-Gallwey hirsutism scoring, an acne assessment, and sebum measurements. Blood was obtained for inclusion/exclusion criteria, core laboratory studies, and fasting safety labs, and if desired by the participant, determination of rubella and varicella immunity, and HIV status. Demographic and quality of life surveys were also conducted.

Fasting blood work was obtained for hormone and metabolite assays, which were conducted by the University of Virginia Ligand Assay and Analysis Core Laboratories, as was done for the RMN's Pregnancy in Polycystic Ovarian Syndrome (PPCOS) I and II studies. See supplemental table 1 for assay kit and manufacturer, as well as assay sensitivity, range, and inter- and intra- assay coefficient of variation.

A semen specimen was obtained from the male partner and processed for semen analysis and future genetic and RNA-seq analysis. Blood was obtained from the male for the baseline characteristics.

Standardized Questionnaires

Quality of Life Measures (QOL)—Mood, quality of life, and sexual function were assessed at baseline and at the end of the study visit. Quality of life was assessed by the Medical Outcomes Survey (Prime MD-PHQ), (19, 20) Short Form 36 (SF-36). (20–22) Female sexual function was assessed by the Female Sexual Function Inventory (FSFI) (23) along with the Female Sexual Distress Scale (FSDS). (24) Male sexual response was assessed by the International Index of Erectile Function (IIEF), a multidimensional scale for assessment of erectile dysfunction. (25) This measure addresses the relevant domains of male sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction). (25) We also assessed the quality of life relating to infertility with the FertiQoL survey. (26, 27) The Sleep Habits questionnaire, the standard instrument used to collect data for the 10-year long multi-center NHLBI Sleep Heart Health Study was administered. (28) Male partners completed the RMN standardized demographic questionnaire, as well as the SF-36, Prime MD, and other QOL surveys.

DATA MANAGEMENT AND ANALYSIS

The Data Coordinating Center (DCC) for this study was the Collaborative Center for Statistics in Science at Yale University in New Haven, Connecticut. The DCC was

responsible for data management (including data entered at each participating center) and data analysis. Data are presented as frequency and percentage for categorical variables for each treatment group. Differences between treatment groups are assessed by Chi-square analysis, with application of Fisher's exact test if any expected frequencies were less than 5. Data are expressed as mean $\pm$ SD for continuous variables within each treatment group, with Wilcoxon rank sum test used for testing differences between two groups, and a Kruskal-Wallis test used for testing differences among groups of three or more. Data are expressed in box plots for the three treatment groups. Analyses were performed utilizing the Statistical Analysis System, version 9.2 (SAS Institute, Cary, NC). Significance was defined as $P < 0.05$.

RESULTS

Female Partner Characteristics

Female partners of the infertile couples had a mean age of 32.2 ± 4.4 years and a BMI of 26.9 ± 6.6 kg/m². A previous formal diagnosis of infertility by a physician had been made in 36.9% of the women (Table 1). The mean duration of attempting to conceive was 34.7 ± 25.7 months (Table 2). A total of 41.4% had conceived previously, with 30.4% having had a prior pregnancy loss, and 20.3% having a prior live birth. 55.4% had received prior infertility medications; 37.8% had been treated previously with clomiphene alone, 1.9% with letrozole alone, and 0.8% with gonadotropin alone. Within this group of 900 infertile women, 12.3% had received two or three of these agents; only 6.3% had previously received letrozole alone or in combination with clomiphene or gonadotropins (Table 1). None of these parameters varied significantly among the three individual treatment arms. Demographic characteristics, race, ethnicity, and medical history were comparable among the couples in each treatment arm (Table 1; Supplemental Table 2). Past medical history of the female and male participants is presented in Supplemental Table 2. The only significant difference was in the incidence of a history of problems affecting the heart among the female partners, which was slightly greater in women randomized to gonadotropins (6.3% versus 3.3 and 2.3% in the clomiphene and letrozole groups, respectively).

Clinical characteristics at baseline were comparable in all treatment groups (Table 1). The mean systolic and diastolic blood pressures were 115.8 ± 13.2 mm Hg and 74.6 ± 9.8 mm Hg respectively (Table 1). Regarding hirsutism, mean Ferriman-Galloway score was 7.5 ± 5.8 with 53.4% having Ferriman-Galloway scores below 8, and another 39.2% having scores 8–16 (Table 1). Mean acne scores were 2.7 ± 6.3 ; 82.2% had scores ≤ 5 , and 10.7% had scores 5–10. There was a wide range in the mean sebum score of 90.8 ± 48.9 mcg/cm²; 68.0% had scores less than 100 mcg/cm², and another 28.8% had scores < 200 mcg/cm² (Table 2). Tubal patency was assessed by hysterosalpingogram in 61.1% of women, by sonohysterogram in 31.2% of women, and by laparoscopy in 7.2%. Six women (0.7%) had an intrauterine pregnancy within the previous year and had tubal patency testing deferred (Table 1).

Only two women did not have both ovaries visualized on baseline ultrasound exams, and only 17 ovaries were not individually visualized. Left and right ovarian volumes averaged 8.4 ± 8.3 cm³ and 9.4 ± 7.4 cm³ respectively (Table 2). Regarding ovarian morphology,

individual ovaries were identified as normal appearing, PCO appearing, or hyperthecotic in 52.1%, 41.3%, and 6.6% respectively. Interestingly, nearly equal proportions of women had neither ovary polycystic (37.1 %), one ovary normal and one ovary appearing polycystic (30.2 %), or both ovaries appearing polycystic (32.6%). Considering individual ovaries, antral follicle counts (AFC) were < 5, 5–10, 10–15, and > 15 in 13.9%, 54.3%, 22.1%, and 11.4% of all ovaries visualized respectively. When the combined AFC of both ovaries together were assessed using the same groupings, only 11 women (1.3%) had AFC of < 5, 132 (15.2%) had an AFC of 5–10, 181 (20.8%) had AFCs of 10–15, while nearly two thirds (62.8%) had combined AFC > 15.

Mean testosterone levels, as measured at the central laboratory, were 25.3 ± 21.6 ng/dl; 839/876 (96.1 %) had levels < 50 ng/dl, 29 (3.3 %) had levels 50–100 ng/dl, with five women with levels > 100 ng/dl (Table 2; Supplemental Figure 1). The mean sex hormone binding globulin level was 59.2 ± 28.1 nmol/L with levels being < 25, 25–50, 50–75, and > 75 nmol/L in 7.7%, 35.1%, 31.7%, and 25.5% respectively. The mean calculated free androgen index was 2.1 ± 5.5 . None of these parameters varied significantly among the three treatment groups.

The mean serum LH and FSH levels on cycle day 3 were 5.1 ± 2.9 and 7.0 ± 2.7 mIU/ml; there were no differences among the treatment groups (Table 2). Similarly, mean estradiol (32.9 ± 30.9 pg/ml), progesterone (0.8 ± 0.6 ng/ml), and TSH (1.9 ± 1.0 μ IU/ml) were comparable in the three treatment arms. Baseline AMH levels were 2.6 ± 2.1 ng/ml overall and the mean was identical for each treatment arm.

Fasting glucose levels averaged 85.2 ± 11.9 mg/dl, with 93.1% having levels < 100 mg/dl, 6.5% with levels 100–125 mg/dl, and only 0.3% with levels > 125 mg/dl (Table 2; Supplemental Figure 1). Fasting insulin levels averaged 9.7 ± 15.5 uIU/ml, with 73.1% having values < 10 uIU/ml, 17.5% having values 10–20 uIU/ml, 7.0% having values 20–50 uIU/ml, and 2.4% having levels > 50 uIU/ml. Insulin action, as assessed by HOMA, revealed a mean level of 2.1 ± 3.6 , with 20.9% having values < 2.6. There were no significant differences in the mean levels of proinsulin (12.9 ± 8.6 pmol/L) among the three treatment arms.

Levels of hsCRP, total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol are presented in Table 2. Mean values were within the normal range and comparable among the three treatment groups.

Male Partner Characteristics

The male partners of the couples with unexplained infertility had a mean age of 34.3 ± 5.6 year, with a mean BMI of 28.9 ± 5.8 kg/m². 18.6% of the men had received a graduate degree, 63.0% had attended college or completed college, and 18.4 % had attended or completed high school (Table 1). There was no difference between treatment arms for these parameters, or for ethnicity, race, or past medical history (Table 1; Supplemental Table 2). 38.8% had achieved a pregnancy with a partner (Table 1).

Mean semen volume in the male partners was 2.9 ± 1.4 ml, with a mean sperm concentration of 66.4 ± 61.8 million/ml. Mean sperm motility was 56.2 ± 14.8 with no differences in normal sperm morphology between the three groups (WHO 3rd Edition, $n = 163$, mean 24.8 ± 14.7 ; WHO 4th Edition Kruger $n = 607$, mean $= 9.8 \pm 12.4$). The mean number of total motile sperm was 107.0 ± 128.3 million/ejaculate, with 50 million total motile sperm in 61.3% of men, 20–50 million/ml in 25.1%, and 5–20 million/ml in 13.6% of men.

Impact of BMI

Two hundred forty-one women (26.8%) had a BMI of 30 or greater. When assessing phenotypic characteristics by BMI categories of <25, 25–<30, 30–<35, and ≥ 35 , increasing BMI was positively associated with increasing age, waist circumference, systolic blood pressure, and diastolic blood pressure (Table 3). There were no differences in DHEAS concentration, hirsutism score, sebum, ovarian volume, antral follicle count of both ovaries or endometrial thickness as a function of BMI. BMI was negatively correlated with AMH level, SHBG concentration, LH/FSH ratio, HDL cholesterol, and positively correlated with total testosterone, fasting glucose, fasting insulin, and triglyceride (Table 3). The percentage of women with Metabolic Syndrome increased markedly with increasing BMI, being present in 0.7%, 13.4%, 27.4%, and 47.1% of women, respectively in the BMI categories noted above.

Quality of Life Assessments

There was no significant difference between the three treatment groups in any component of the SF36 Score at baseline in the females, with the only significant difference in the males being an increase in panic syndrome in partners of letrozole recipients. There were no significant differences between the groups for sleep habits (difficulty falling asleep, sleepy during the day, snoring, or stopping breathing during snoring), or in any component of the Ferti QoL score (Supplemental Table 3). Interestingly, compared to women, the incidence of snoring was nearly twice as high in men (74.4% vs 44.7%), and seven fold more men reported stopping breathing during snoring (10.2% vs 1.4%)

DISCUSSION

Couples participating in the AMIGOS trial shared similar demographics with other infertile populations (see Table 4), but had a more heterogeneous racial distribution, a higher BMI, and relatively longer duration of infertility than prior reports of women with unexplained infertility.(2, 3, 10, 29, 30) The randomization was successful in achieving consistent distribution of women in the three AMIGOS treatment arms (gonadotropins, clomiphene citrate, and letrozole). There were no significant differences in each of the treatment groups for key parameters known to influence pregnancy outcome including age of the female partner, length of infertility, BMI, cycle day 3 FSH level, AMH level, history of smoking, and male partner sperm count, motility, and morphology. Thus, given the number of parameters that we examined, the subgroups have consistent characteristics for testing of the hypothesis that use of an aromatase inhibitor can reduce the rate of multiples from those observed with gonadotropin and clomiphene citrate treatment, without detrimentally altering the live birth rate.

Of note, while not differing among the three treatment arms, it was observed that slightly over a third of the women had a history of smoking with 7.9% still smoking, and 55% of the women had previously received fertility medications. Thus this patient population may not be representative of other clinical practice-based samples of women with infertility.

Importantly, the AMIGOS baseline data also present a large cohort of couples with unexplained infertility, comprised of 900 women and 900 men, which is now available for examination and comparison with patient populations of future studies. In addition to the large amount of demographic information collected, psychosocial variables assessed in standardized, validated questionnaires, and biomarkers already measured, the AMIGOS trial created a biorepository of serum and genetic samples which will be available for future analysis by both RMN and independent investigators. Significantly, the AMIGOS trial design parallels that of the RMN's recently completed Pregnancy in Polycystic Ovary Syndrome (PPCOS) II Study, thereby providing a future opportunity for contemporary comparative cohort comparisons of infertile couples with unexplained infertility and polycystic ovary syndrome.

Over half of the female partners of this population of couples with unexplained infertility were overweight (BMI ≥ 25 kg/m²), and over one quarter were obese (BMI ≥ 30 kg/m²). As expected, increasing BMI in this population was associated with increasing waist circumference, systolic and diastolic blood pressure, fasting glucose and insulin, triglyceride, and the incidence of metabolic syndrome. Hormonally, increasing BMI was associated with a small but significant increase in serum testosterone, a pronounced reduction in SHBG, and small but significant reductions in the LH/FSH ratio and AMH. Increasing obesity was not associated with alterations in ovarian volume, antral follicle count, endometrial thickness, hirsutism, sebum measurements, and DHEAS levels. Collectively, these observations suggest that obesity was associated with metabolic changes, but did not manifest pathophysiologic manifestations of the polycystic ovary syndrome. (30)The cause of the infertility in these regularly ovulating women and their male partners is elusive; they may truly be characterized as having unexplained infertility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Subject demographic and biometric characteristics by treatment arm

	Clomiphene Female		Letrozole		Gonadotropin		All		Clomiphene Male		Letrozole		Gonadotropin		All	
Age (yr)																
N	300		299		301		900		297		292		294		884	
Mean(SD)	32.0 (4.6)		32.2 (4.3)		32.3 (4.1)		32.2 (4.4)		34.1 (5.3)		34.3 (5.6)		34.6 (6.0)		34.3 (5.6)	
BMI (kg/m ²)																
N	300		299		301		900		290		289		285		865	
Mean(SD)	26.7 (6.4)		27.3 (6.5)		26.8 (6.7)		26.9 (6.6)		28.6 (5.8)		29.3 (5.8)		28.8 (5.8)		28.9 (5.8)	
Waist circumference (cm)																
N	300		299		300		899									
Mean(SD)	85.9 (15.6)		87.5 (16.0)		85.9 (15.8)		86.5 (15.8)									
Blood pressure (mmHg)																
Systolic																
N	300		299		301		900									
Mean(SD)	116.3 (13.8)		116.2 (13.0)		114.8 (12.7)		115.8 (13.2)									
Diastolic																
N	300		299		301		900									
Mean(SD)	74.9 (9.9)		74.6 (9.6)		74.2 (9.8)		74.6 (9.8)									
Level of education																
High school graduate or less	26/300 (8.7%)		25/299 (8.4%)		22/301 (7.3%)		73/900 (8.1%)		53/297 (17.8%)		64/292 (21.9%)		45/292 (15.4%)		162/882 (18.4%)	
College graduate or some college	193/300 (64.3%)		195/299 (65.2%)		201/301 (66.8%)		589/900 (65.4%)		181/297 (60.9%)		178/292 (61.0%)		196/292 (67.1%)		556/882 (63.0%)	
Graduate degree	81/300 (27.0%)		79/299 (26.4%)		78/301 (25.9%)		238/900 (26.4%)		63/297 (21.2%)		50/292 (17.1%)		51/292 (17.5%)		164/882 (18.6%)	
Annual household income																

	Clomiphene Female	Letrozole	Gonadotropin	All	Clomiphene Male	Letrozole	Gonadotropin	All
<\$50,000	45/300 (15.0%)	49/299 (16.4%)	58/301 (19.3%)	152/900 (16.9%)				
>=\$50,000	195/300 (65.0%)	195/299 (65.2%)	200/301 (66.4%)	590/900 (65.6%)				
Wish to not answer	60/300 (20.0%)	55/299 (18.4%)	43/301 (14.3%)	158/900 (17.6%)				
Ethnicity								
Not Hispanic or Latino	270/300 (90.0%)	264/299 (88.3%)	272/301 (90.4%)	806/900 (89.6%)	268/297 (90.2%)	271/292 (92.8%)	263/294 (89.5%)	803/884 (90.8%)
Hispanic or Latino	30/300 (10.0%)	35/299 (11.7%)	29/301 (9.6%)	94/900 (10.4%)	29/297 (9.8%)	21/292 (7.2%)	31/294 (10.5%)	81/884 (9.2%)
Race								
White	241/300 (80.3%)	243/299 (81.3%)	238/301 (79.1%)	722/900 (80.2%)	248/297 (83.5%)	233/291 (80.1%)	239/294 (81.3%)	721/883 (81.7%)
Black	31/300 (10.3%)	30/299 (10.0%)	23/301 (7.6%)	84/900 (9.3%)	29/297 (9.8%)	34/291 (11.7%)	25/294 (8.5%)	88/883 (10.0%)
Asian	17/300 (5.7%)	14/299 (4.7%)	28/301 (9.3%)	59/900 (6.6%)	13/297 (4.4%)	13/291 (4.5%)	21/294 (7.1%)	47/883 (5.3%)
American Indian or Alaska Native	4/300 (1.3%)	3/299 (1.0%)	3/301 (1.0%)	10/900 (1.1%)	1/297 (0.3%)	2/291 (0.7%)	3/294 (1.0%)	6/883 (0.7%)
Native Hawaiian or other Pacific Islander	0/300 (0.0%)	0/299 (0.0%)	0/301 (0.0%)	0/900 (0.0%)	0/297 (0.0%)	3/291 (1.0%)	0/294 (0.0%)	3/883 (0.3%)
Mixed race	7/300 (2.3%)	9/299 (3.0%)	9/301 (3.0%)	25/900 (2.8%)	6/297 (2.0%)	6/291 (2.1%)	6/294 (2.0%)	18/883 (2.0%)
Pregnancy history								
Prior conception	133/300 (44.3%)	119/299 (39.8%)	121/301 (40.2%)	373/900 (41.4%)				
Prior live birth	67/300 (22.3%)	52/299 (17.4%)	64/301 (21.3%)	183/900 (20.3%)				
Prior loss	99/300 (33.0%)	94/299 (31.4%)	81/301 (26.9%)	274/900 (30.4%)				
Have ever created a pregnancy with partner					126/297 (42.4%)	103/292 (35.3%)	114/294 (38.8%)	343/884 (38.8%)
Infertility history & factors								

	Clomiphene Female	Letrozole	Gonadotropin	All	Clomiphene Male	Letrozole	Gonadotropin	All
Patient had a diagnosis of infertility	112/300 (37.3%)	101/299 (33.8%)	119/301 (39.5%)	332/900 (36.9%)				
Patient had prior therapy for infertility	175/300 (58.3%)	157/299 (52.5%)	167/301 (55.5%)	499/900 (55.4%)				
How long has the patient been attempting conception (months)?								
N	298	294	299	891				
Mean(SD)	34.2 (24.1)	35.2 (26.8)	34.8 (26.2)	34.7 (25.7)				
HSG								
Both Tubes Patent	168/189 (88.9%)	160/182 (87.9%)	160/179 (89.4%)	488/550 (88.7%)				
Only one Tube Patent	21/189 (11.1%)	22/182 (12.1%)	19/179 (10.6%)	62/550 (11.3%)				
Laparoscopy/Surgery								
Both Tubes Patent	21/23 (91.3%)	21/26 (80.8%)	15/16 (93.8%)	57/65 (87.7%)				
Only one Tube Patent	2/23 (8.7%)	5/26 (19.2%)	1/16 (6.3%)	8/65 (12.3%)				
SHG								
At least one Tube Patent	88/88 (100.0%)	89/89 (100.0%)	104/104 (100.0%)	281/281 (100.0%)				
Having an IUP within the last three years	1/1 (100.0%)	2/2 (100.0%)	3/3 (100.0%)	6/6 (100.0%)				
Semen volume (mL)								
N					300	299	301	900
Mean(SD)					2.9 (1.4)	2.9 (1.4)	3.0 (1.5)	2.9 (1.4)
Sperm motility (%)								
N					300	299		
Mean(SD)					55.2 (15.0)	57.3 (14.0)	56.0 (15.5)	56.2 (14.8)

	Clomiphene			Letrozole			Gonadotropin			All		
	Female											
	Male											
Sperm concentration (million/mL)												
N	300			299			301			900		
Mean(SD)	64.9 (62.6)			64.5 (57.4)			70.0 (65.2)			66.4 (61.8)		
Morphology (% normal) WHO 3rd Ed)												
N	48			55			60			163		
Mean(SD)	23.7 (13.8)			23.4 (13.5)			26.9 (16.5)			24.8 (14.7)		
Morphology (% normal) WHO 4th Ed-Kruger)												
N	201			202			204			607		
Mean(SD)	9.2 (12.0)			9.3 (9.9)			10.7 (14.7)			9.8 (12.4)		
Total motile sperm (million)												
N	300			299			301			900		
Mean(SD)	107.0 (151.4)			104.5 (113.7)			109.4 (116.6)			107.0 (128.3)		
5–20	38/299 (12.7%)			45/299 (15.1%)			39/301 (13.0%)			122/899 (13.6%)		
20–50	80/299 (26.8%)			74/299 (24.7%)			72/301 (23.9%)			226/899 (25.1%)		
>50	181/299 (60.5%)			180/299 (60.2%)			190/301 (63.1%)			551/899 (61.3%)		
Total score of IIEF												
N	287			285			286			859		
Mean(SD)	68.2 (7.9)			67.6 (9.6)			68.5 (6.8)			68.1 (8.1)		
Erection (time)												
N	285			285			286			900		
Mean(SD)	4.8 (0.7)			4.7 (0.8)			4.8 (0.6)			107.0 (128.3)		
Previous study drug exposure												

	Clomiphene Female	Letrozole	Gonadotropin	All	Clomiphene Male	Letrozole	Gonadotropin	All
None	131/300 (43.7%)	149/299 (49.8%)	145/301 (48.2%)	425/900 (47.2%)				
Clomiphene only	119/300 (39.7%)	99/299 (33.1%)	122/301 (40.5%)	340/900 (37.8%)				
Letrozole only	5/300 (1.7%)	7/299 (2.3%)	5/301 (1.7%)	17/900 (1.9%)				
Gonadotropin only	3/300 (1.0%)	3/299 (1.0%)	1/301 (0.3%)	7/900 (0.8%)				
Letrozole and Clomiphene	11/300 (3.7%)	13/299 (4.3%)	11/301 (3.7%)	35/900 (3.9%)				
Clomiphene and gonadotropin	25/300 (8.3%)	23/299 (7.7%)	14/301 (4.7%)	62/900 (6.9%)				
Letrozole and gonadotropin	0/300 (0.0%)	1/299 (0.3%)	1/301 (0.3%)	2/900 (0.2%)				
Letrozole and clomiphene and gonadotropin	6/300 (2.0%)	4/299 (1.3%)	2/301 (0.7%)	12/900 (1.3%)				
Total score of FSFI								
N	288	290	288	867				
Mean(SD)	29.8 (4.7)	29.9 (5.6)	29.8 (4.7)	29.8 (5.0)				
Sexual dysfunction	52/288 (18.1%)	55/290 (19.0%)	59/288 (20.5%)	166/867 (19.1%)				
Total score of FSDS								
N	286	289	285	861				
Mean(SD)	5.7 (7.3)	5.5 (8.0)	5.5 (7.3)	5.6 (7.5)				

Table 2

Transvaginal ultrasound results and Baseline Lab Measurements in female participants by treatment arm

	Clomiphene	Letrozole	Gonadotropin	All
Left ovary not visualized	4/300(1.3%)	4/298(1.3%)	2/301(0.7%)	10/899(1.1%)
Right ovary not visualized	3/300(1.0%)	1/298(0.3%)	3/301(1.0%)	7/899(0.8%)
Neither ovary visualized	2/300(0.7%)	0/298(0.0%)	0/301(0.0%)	2/899(0.2%)
Morphology				
Left: Normal	160/295(54.2%)	147/294(50.0%)	174/299(58.2%)	481/888(54.2%)
>12 follicles < 10 mm	116/295(39.3%)	133/294(45.2%)	104/299(34.8%)	353/888(39.8%)
Hyperthecotic	19/295(6.4%)	14/294(4.8%)	21/299(7.0%)	54/888(6.1%)
Right: Normal	142/297(47.8%)	150/297(50.5%)	154/298(51.7%)	446/892(50.0%)
>12 follicles < 10 mm	135/297(45.5%)	133/297(44.8%)	115/298(38.6%)	383/892(42.9%)
Hyperthecotic	20/297(6.7%)	14/297(4.7%)	29/298(9.7%)	63/892(7.1%)
Both ovaries: Neither ovary				
>12 follicles less than 12 mm	104/294(35.4%)	106/293(36.2%)	118/296(39.9%)	328/883(37.1%)
>12 follicles less than 12 mm /normal combination	93/294(31.6%)	84/293(28.7%)	90/296(30.4%)	267/883(30.2%)
>12 follicles less than 10 mm bilaterally	97/294(33.0%)	103/293(35.2%)	88/296(29.7%)	288/883(32.6%)
Left ovarian volume(cm ³)				
N	294	294	297	885
Mean(SD)	8.7(11.0)	8.8(7.8)	7.6(5.0)	8.4(8.3)
Right ovarian volume(cm ³)				
N	295	297	295	887
Mean(SD)	9.4(6.7)	9.7(8.4)	9.1(7.1)	9.4(7.4)
Patients with at least one follicle/cyst>10 mm diameter	126/296(42.6%)	119/296(40.2%)	122/300(40.7%)	367/892(41.1%)
Size of largest follicle/cyst (cm ³)				
N	118	112	109	339
Mean(SD)	6.6(16.0)	4.0(7.3)	3.7(9.5)	4.8(11.7)
Antral follicle count: right ovary				
<5	42/293(14.3%)	38/294(12.9%)	37/294(12.6%)	117/881(13.3%)
5–10	131/293(44.7%)	136/294(46.3%)	143/294(48.6%)	410/881(46.5%)
10–15	71/293(24.2%)	68/294(23.1%)	61/294(20.7%)	200/881(22.7%)
>15	49/293(16.7%)	52/294(17.7%)	53/294(18.0%)	154/881(17.5%)
Antral follicle count: left ovary				
<5	38/292(13.0%)	37/291(12.7%)	53/294(18.0%)	128/877(14.6%)
5–10	142/292(48.6%)	132/291(45.4%)	140/294(47.6%)	414/877(47.2%)
10–15	67/292(22.9%)	68/291(23.4%)	54/294(18.4%)	189/877(21.6%)
>15	45/292(15.4%)	54/291(18.6%)	47/294(16.0%)	146/877(16.6%)
Antral follicle count: both ovaries				
N	291	289	290	870
Mean(SD)	20.3(11.3)	21.2(11.2)	20.6(12.6)	20.7(11.7)

	Clomiphene	Letrozole	Gonadotropin	All
<5	4/291(1.4%)	5/289(1.7%)	2/290(0.7%)	11/870(1.3%)
5–10	43/291(14.8%)	39/289(13.5%)	50/290(17.2%)	132/870(15.2%)
10–15				
>15	60/291(20.6%)	55/289(19.0%)	66/290(22.8%)	181/870(20.8%)
Reproductive Hormones	184/291(63.2%)	190/289(65.7%)	172/290 (59.3%)	546/870 (62.8%)
Total Testosterone (ng/dL)				
N	293	287	293	873
Mean(SD)	24.7(16.6)	24.9(15.5)	26.4(29.7)	25.3(21.6)
<=50	284/293(96.9%)	274/287(95.5%)	281/293(95.9%)	839/873(96.1%)
50–100	8/293(2.7%)	10/287(3.5%)	11/293(3.8%)	29/873(3.3%)
100–150	0/293(0.0%)	3/287(1.0%)	0/293(0.0%)	3/873(0.3%)
>150	1/293(0.3%)	0/287(0.0%)	1/293(0.3%)	2/873(0.2%)
Calculated Free Androgen Index				
N	292	285	292	869
Mean(SD)	2.4(9.1)	1.9(2.0)	2.0(2.2)	2.1(5.5)
<=5	280/292(95.9%)	269/285(94.4%)	276/292(94.5%)	825/869(94.9%)
5–10	9/292(3.1%)	13/285(4.6%)	13/292(4.5%)	35/869(4.0%)
10–20	1/292(0.3%)	3/285(1.1%)	2/292(0.7%)	6/869(0.7%)
>20	2/292(0.7%)	0/285(0.0%)	1/292(0.3%)	3/869(0.3%)
SHBG (nmol/L)				
N	294	285	292	871
Mean(SD)	59.3(29.0)	60.0(28.2)	58.4(27.0)	59.2(28.1)
<=25	24/294(8.2%)	22/285(7.7%)	21/292(7.2%)	67/871(7.7%)
25–50	99/294(33.7%)	95/285(33.3%)	112/292(38.4%)	306/871(35.1%)
50–75	101/294(34.4%)	92/285(32.3%)	83/292(28.4%)	276/871(31.7%)
>75	70/294(23.8%)	76/285(26.7%)	76/292(26.0%)	222/871(25.5%)
DHEAS (ug/dL)				
N	294	287	293	874
Mean(SD)	128.4(65.2)	131.4(68.9)	134.2(63.4)	131.3(65.8)
Androstenedione (ng/mL)				
N	292	284	289	865
Mean(SD)	2.4(1.0)	2.4(1.0)	2.4(1.0)	2.4(1.0)
Estradiol (pg/mL)				
N	295	287	293	875
Mean(SD)	32.4(21.5)	32.7(28.0)	33.7(40.4)	32.9(30.9)
Progesterone (ng/mL)				
N	294	286	293	873
Mean(SD)	0.8(0.3)	0.8(0.5)	0.8(0.8)	0.8(0.6)
FSH(mIU/mL)				
N	295	287	293	875
Mean(SD)	7.2(2.8)	7.0(2.9)	6.9(2.4)	7.0(2.7)
LH (mIU/mL)				

	Clomiphene	Letrozole	Gonadotropin	All
N	295	284	292	871
Mean(SD)	5.0(2.5)	5.4(3.4)	4.9(2.5)	5.1(2.9)
TSH(uIU/mL)				
N	295	285	292	872
Mean(SD)	2.0(1.0)	1.8(1.0)*	2.0(1.1)	1.9(1.0)
AMH (ng/mL)				
N	295	287	292	874
Mean(SD)	2.6(2.1)	2.6(1.9)	2.6(2.1)	2.6(2.1)
Metabolic Hormones				
Fasting glucose (mg/dL)				
N	295	287	293	875
Mean(SD)	85.9(11.6)	85.4(11.9)	84.2(12.2)	85.2(11.9)
<=100	273/295(92.5%)	267/287(93.0%)	275/293(93.9%)	815/875(93.1%)
100–125	20/295(6.8%)	19/287(6.6%)	18/293(6.1%)	57/875(6.5%)
>125	2/295(0.7%)	1/287(0.3%)	0/293(0.0%)	3/875(0.3%)
Fasting insulin (uIU/mL)				
N	295	286	293	874
Mean(SD)	11.1(18.6)	9.4(15.5)	8.7(11.3)	9.7(15.5)
<=10	209/295(70.8%)	217/286(75.9%)	213/293(72.7%)	639/874(73.1%)
10–20	54/295(18.3%)	43/286(15.0%)	56/293(19.1%)	153/874(17.5%)
20–50	23/295(7.8%)	20/286(7.0%)	18/293(6.1%)	61/874(7.0%)
>50	9/295(3.1%)	6/286(2.1%)	6/293(2.0%)	21/874(2.4%)
HOMA-IR				
N	295	286	293	874
Mean(SD)	2.57(4.3)	2.0(3.7)	1.9(2.7)	2.1(3.6)
Proinsulin (pmol/L)				
N	293	282	293	868
Mean(SD)	13.7(8.7)	12.9(9.4)	12.1(7.1)	12.9(8.6)
hsCRP (mg/L)				
N	295	284	293	872
Mean(SD)	3.4(5.5)	3.4(5.1)	3.2(4.1)	3.3(4.9)
Total cholesterol(mg/dL)				
N	284	277	283	844
Mean(SD)	170.3(29.0)	169.0(33.0)	168.3(32.5)	169.2(31.5)
Triglycerides(mg/dL)				
N	284	277	283	844
Mean(SD)	96.6(54.3)	92.0(45.6)	95.7(56.7)	94.8(52.4)
HDL cholesterol(mg/dL)				
N	284	277	283	844
Mean(SD)	46.3(11.4)	45.5(11.0)	45.9(11.0)	45.9(11.1)
LDL cholesterol(mg/dL)				
N	284	277	283	844

	Clomiphene	Letrozole	Gonadotropin	All
Mean(SD)	109.9(35.3)	108.3(27.6)	108.9(36.6)	109.0(33.4)
>15	184/291(63.2%)	190/289(65.7%)	172/290(59.3%)	546/870(62.8%)

*
P-value between 0.05 and 0.1.

Table 3

Phenotypic characteristics by BMI category

Category	Parameter	BMI<25	BMI 25–29	BMI 30–34	BMI 35	P value *
Demographic	Age (yr)					
	N	433	226	146	95	
	Mean(SD)	31.9(4.1)	32.1(4.7)	32.3(4.3)	33.1(4.6)	0.04
	>=35	122/433(28.2)	76/226(33.6)	49/146(33.6)	41/95(43.2)	0.032
	Caucasian (%)	350/433(80.8)	182/226(80.5)	111/146(76.0)	79/95(83.2)	0.522
	Black (%)	25/433(5.8)	23/226(10.2)	26/146(17.8)	10/95(10.5)	<0.001
	Asian (%)	44/433(10.2)	12/226(5.3)	1/146(0.7)	2/95(2.1)	<0.001
Biometric	Latino (%)	36/433(8.3)	34/226(15.0)	16/146(11.0)	8/95(8.4)	0.053
	Body Mass Index (kg/m ²)					
	N	433	226	146	95	
	Mean(SD)	21.8(2.0)	27.3(1.5)	32.3(1.5)	41.0(4.4)	<0.001
	Waist circumference(cm)					
	N	433	226	145	95	
	Mean(SD)	75.7(8.3)	87.7(9.1)	98.3(9.1)	114.3(14.7)	<0.001
	Systolic					
	N	433	226	146	95	
	Mean(SD)	111.4(11.2)	117.7(12.9)	120.3(11.7)	124.4(16.2)	<0.001
	Diastolic					
	N	433	226	146	95	
	Mean(SD)	71.3(9.3)	76.0(9.6)	78.1(8.6)	80.6(8.5)	<0.001
	Hirsutism					
	N	428	226	146	93	
	Mean(SD)	7.2(5.5)	8.0(6.1)	7.2(6.4)	7.8(5.4)	0.517
	Sebum(mcg/cm ²)					
Imaging	N	425	215	140	91	
	Mean(SD)	91.9(50.7)	89.5(46.8)	84.8(42.8)	97.9(53.1)	0.914
	Total ovarian volume(cm ³)					
	N	423	218	142	94	

Category	Parameter	BM<25	BMI 25–29	BMI 30–34	BMI 35	P value*
Laboratory	Mean(SD)	17.5(12.8)	17.2(9.3)	17.8(9.6)	18.2(10.7)	0.29
	Antral Follicle Count: Both Ovaries					
	N	421	219	138	92	
	Mean(SD)	20.5(11.6)	21.4(11.2)	20.2(11.7)	20.5(13.7)	0.626
	Endometrial Thickness(mm)					
	N	429	225	146	95	
	Mean(SD)	6.6(3.3)	6.7(2.9)	7.0(3.1)	6.8(3.2)	0.106
	AMH(ng/mL)					
	N	417	222	143	92	
	Mean(SD)	2.8(2.2)	2.5(1.8)	2.6(2.1)	2.0(1.4)	0.03
	Total Testosterone(ng/dL)					
	N	418	221	142	92	
	Mean(SD)	24.2(26.2)	24.5(11.9)	27.3(21.4)	29.0(15.5)	<0.001
	SHBG(nmol/L)					
	N	417	222	142	90	
LH to FSH ratio	Mean(SD)	70.8(27.8)	56.0(24.7)	44.8(22.1)	36.2(16.6)	<0.001
	DHEAS(ug/dL)					
	N	418	222	143	91	
	Mean(SD)	127.6(62.6)	136.3(65.5)	132.7(71.5)	133.8(71.6)	0.379
	Fasting glucose(mg/dL)					
	N	416	222	143	90	
	Mean(SD)	1.0(3.6)	0.7(0.4)	0.7(0.3)	0.7(0.3)	<0.001
	Fasting insulin(uIU/mL)					
	N	418	222	143	92	
	Mean(SD)	82.8(11.8)	86.2(10.8)	87.6(11.7)	90.0(13.0)	<0.001
	HDL cholesterol(mg/dL)					
	N	418	222	143	91	
	Mean(SD)	5.9(8.8)	9.6(15.3)	13.9(17.8)	21.0(25.9)	<0.001
	HDL cholesterol(mg/dL)					
	N	405	216	136	87	
	Mean(SD)	48.8(11.2)	44.8(10.4)	43.2(11.3)	39.3(7.5)	<0.001

Category	Parameter	BMI<25	BMI 25–29	BMI 30–34	BMI 35	P value*
QoL	Triglycerides(mg/dL)					
	N	405	216	136	87	
	Mean(SD)	80.3(36.8)	97.4(54.7)	112.4(57.1)	128.2(73.2)	<0.001
	Metabolic syndrome (%)	3/405 (0.7)	29/216 (13.4)	37/135 (27.4)	41/87(47.1)	<0.001
	SF36 score					
	Physical component					
	N	415	219	137	86	
	Mean(SD)	57.4(4.3)	56.4(5.3)	55.5(5.3)	55.4(5.0)	<0.001
	Mental component					
	N	415	219	137	86	
	Mean(SD)	53.2(6.3)	53.1(7.2)	55.0(5.4)	53.0(7.8)	0.03

* Spearman correlation test was used for continuous variables and chi-square test was used for categorical variables.

Table 4
 Characteristics of Reports of Infertile Couples in Comparison to Previously Published Infertility Study Populations

	Diamond AMIGOS	Reindollar ²⁶ FASST Trial		Steures ²⁷		Guzick ²⁸	Legro ²⁹ PPCOS I	Legro ³⁰ PPCOS II
		Conventional	Fast Track	Expectant	COH			
Female	Age (years)	33	33	33	33	32	28	29
	Female Age 35 years (%)	36%	36%					
	Caucasian (%)	85%	89%			88%	70%	79%
	Hispanic (%)	4%	9%				26%	17%
	BMI	24	25				35	35
	CD 3 FSH (mIU/ml)	6.6	6.7	6.7	7.0			6.2
	Duration of Subfertility (months)			23	24	43	40	41
	Primary Infertility			76%	78%	59%	67%	64%
	Current of Past smoking (%)	27%	29%				40%	42%
	Age (years)	34	35					32
Male	Caucasian (%)	86%	89%					
	Hispanic (%)	2%	5%					
	Sperm Concentration (M/ml)	89	85					
	Sperm Motility (%)	63%	62%			43%		78%
	Total Motile Count	56	53	60	68	50		19%
	Current or Past smoking (%)	27%	29%					52%