A personalized medicine approach to ovulation induction/ovarian stimulation: development of a predictive model and online calculator from level-I evidence

Irene Souter, M.D.,[a] Fangbai Sun, M.P.H.,[b] Heping Zhang, Ph.D.,[b] Michael P. Diamond, M.D.,[c] Richard S. Legro, M.D.,[d] Robert A. Wild, M.D., Ph.D.,[e] Karl R. Hansen, M.D., Ph.D.,[e] and Nanette Santoro, M.D.,[f] for the *Eunice Kennedy Schriver* National Institute of Child Health and Human Development Reproductive Medicine Network

[a] Department of Obstetrics/Gynecology and Reproductive Biology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [b] Collaborative Center for Statistics, Department of Biostatistics, Yale University School of Public Health, New Haven, Connecticut; [c] Department of Obstetrics and Gynecology, Augusta University, Augusta, Georgia; [d] Department of Obstetrics and Gynecology, Pennsylvania State University, Hershey, Pennsylvania; [e] Department of Obstetrics and Gynecology, University of Oklahoma Health Schiences Center, Oklahoma City, Oklahoma; and [f] Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora, Colorado

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San Diego, California; Invited Speaker, Obesity Week, Las Vegas, Nevada; Visiting Professor and Invited Speaker, Seminars in Obstetrics, Gynecology and Reproductive Biology; and Grand Rounds Obstetrics and Gynecology, University of Kansas Medical Center, Kansas City, Kansas; Invited Webinar Speaker, Human Reproduction Update Chinese Edition Young Editor Meeting; Invited Webinar Speaker, Obesity and Women's Health Webinar: NIH Obesity Research Task Force Seminar Series; and Advisor, A metabolomic approach to redefine diagnostic criteria and classification of polycystic ovary syndrome (principal investigator: Professor Chi Chui Wang, Chinese University of Hong Kong). 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Correspondence: Irene Souter, M.D., Department of Obstetrics/Gynecology and Reproductive Biology, Massachusetts General Hospital Fertility Center, Harvard Medical School, 55 Fruit Street, Yawkey 10A, Boston, Massachusetts 02114 (E-mail: isouter@mgh.harvard.edu).

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Objective: To estimate the probability of clinical or multiple pregnancy during ovulation induction (OI)/ovarian stimulation (OS).
Design: Secondary analysis of two multicenter randomized clinical trials (combined).
Setting: Multicenter.
Patients: A total of 750 women with polycystic ovary syndrome and 900 women with unexplained infertility.
Interventions: Ovulation induction/OS with either timed intercourse (polycystic ovary syndrome) or intrauterine insemination.
Main Outcome Measures: Clinical and multiple pregnancy rates/cycle, cumulative pregnancy rates. Age, body mass index, parity, diagnosis, medication, markers of ovarian reserve, and ovarian response were considered in multivariable regression models for clinical, multiple, and cumulative pregnancy rates. Receiver operating characteristic curves were created for clinical and multiple pregnancy rates.
Results: Younger patient and partner age, treatment type, lower body mass index, and medication dose were all associated with clinical pregnancy. Variables associated with multiple pregnancy included the abovementioned variables (except age), in addition to diagnosis, parity, higher antral follicle count, antimüllerian hormone levels, and ovarian response. Gonadotropin use was associated with multiple pregnancy, with progressively increasing odds ratios (cycles 1–4). Receiver operating characteristic curves indicated the model's predictive power to be fair for clinical pregnancy (areas under the curve [95% confidence interval {CI}]: 0.78 [0.75–0.81] for cycle 1 and 0.70 [0.64–0.75] for cycle 4) and good-to-excellent for multiple pregnancy (areas under the curve [95% CI]: 0.78 [0.72–0.84] for cycle 1 and 0.86 [0.78–0.93] for cycle 4). Partner age, lower medication dose, parity, antimüllerian hormone levels, and diagnosis were associated with cumulative pregnancy rates.
Conclusions: Using the majority of the factors known to predict the outcome of OI/OS cycles, we constructed an easy-to-use formula that may predict individualized chances of clinical and multiple pregnancy for commonly used fertility treatments (https://pregnancyprediction.medicine.yale.edu/CalDirect.html).
Clinical Trial Registration Numbers: Assessing Multiple Intrauterine Gestations after Ovulation Stimulation NCT 1044862; PPCOSII NCT00719186. (Fertil Steril® 2022;117:408–18. ©2021 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Ovulation induction, ovarian stimulation, probability of clinical pregnancy, probability of multiple pregnancy, individualized prediction models

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Ovulation induction (OI) and controlled ovarian stimulation (OS) with intrauterine insemination (IUI) are often the first-line treatment for many couples with infertility. Historically, and depending on the diagnosis, the age of the partners, and the cost and insurance coverage status, treatments may start with oral agents (clomiphene citrate [CC] or letrozole [LTZ]) coupled with either timed intercourse (TIC) or IUI and subsequently progress in a stepwise fashion through gonadotropin/IUI to more aggressive and efficient but expensive treatments such as in vitro fertilization (IVF). For IVF, counseling of infertile couples regarding relevant success and complications is greatly facilitated by the availability of an annually updated registry produced by the Society of Assisted Reproductive Technology (SART). In contrast, counseling about the potential success of OI and/or OS/IUI treatments seems to rely on results from isolated studies from specific patient populations, such as those with unexplained infertility (UI) or polycystic ovary syndrome (PCOS). Quoted pregnancy rates/cycle range from 8.3% to 9.6% for CC/IUI and 14% to 17.1% for gonadotropin/IUI (1–3) to cumulative live birth rates as high as 32.2%, 23.3%, and 18.7%, for gonadotropin, CC, and LTZ treatments, respectively (4, 5).

Over the last decade, the advent of precision medicine has rapidly permeated all areas of medicine. It is now an expectation that counseling and treatment planning be individualized and hopefully accurate. In the case of OI and/or OS/IUI, whether with oral agents or gonadotropins, the incorporation of a wide variety of individual data (such as demographics, biomarkers of ovarian reserve, and clinical and treatment characteristics) can be used to develop algorithms to successfully predict the likelihood of success for each patient, thus guiding decisions toward the most effective treatments. The eventual clinical goal is to identify the subgroup of patients who will benefit most from specific types of treatment. This spares those who may not benefit from a nonspecific algorithm, the expense, the time commitment, side effects, and complications. For IVF, SART developed an easy-to-use online calculator based on N>5,00,000 cycles of therapy (available at https://www.sartcorsonline.com/Predictor/Patient) (6). This tool helps patients and physicians predict a particular patient's individual chances of pregnancy (singleton or multiple) after one or two IVF cycles when transferring one or more embryos, thus facilitating individualized decision making. Yet, despite the fact that clinical studies have identified some individual patient factors and predictors of clinical and multiple pregnancy among OI and/or OS/IUI cycles (7–10), a tool for effective counseling and individualized treatment planning, similar in magnitude to the SART calculator, is not widely available.

The goal of the present study was to help develop an individualized prediction model for the probability of pregnancy (singleton or multiple) after OI and/or OS among women with either PCOS or UI using readily available databases. Our aims were to identify patient and cycle-specific characteristics associated with success in the abovementioned populations, to calculate the probability of clinical and/or multiple pregnancy per OI/OS cycle as well as the cumulative chances of pregnancy, based on the previously identified success-predictive factors. Our ultimate goal was to build a predictive

model and implement it in an easy-to-use calculator that can be applied to patient counseling to guide clinical decision making.

MATERIALS AND METHODS

Design and Study Population

Data collected from 1,650 patients participating in two multicenter, randomized controlled trials (RCTs) (Pregnancy in Polycystic Ovary Syndrome II [PPCOSII] and Assessing Multiple Intrauterine Gestations after Ovulation Stimulation [AMIGOS], clinicaltrials.gov: NCT00719186 and NCT1044862, respectively) performed by the Reproductive Medicine Network of the *Eunice Kennedy Shriver* National Institute of Health and Human Development were used for this secondary analysis. The study included 750 and 900 participants from PPCOSII and AMIGOS trials, respectively. Details regarding the trials' design, interventions, and participants' characteristics have been previously published (AMIGOS [4, 11], PPCOSII [5, 12]). At each participating site, institutional review board approval was obtained for both trials. All participants signed an informed consent.

Briefly, PPCOSII trial included women diagnosed with PCOS (according to modified Rotterdam criteria [anovulation with either hyperandrogenism or polycystic ovaries] [13]) who were randomized to either CC or LTZ to determine which treatment was more likely to result in a live birth. Assessing Multiple Intrauterine Gestations after Ovulation Stimulation trial included couples with UI and was originally designed to determine whether treatment with LTZ would result in a lower multiple pregnancy rate than standard OS regimens for UI in use at the time (either CC or gonadotropins). In both studies, the participating women were aged ≥ 18 and ≤ 40 years and had a normal uterine cavity and at least one patent fallopian tube. Women in the AMIGOS trial also had evidence of regular ovulation and normal ovarian reserve. Male partners had semen parameters that permitted either IUI or TIC (at least 5 and 14 million motile sperm per milliliter for AMIGOS and PPCOSII, respectively). Other diagnoses, not in conflict with the above inclusion/exclusion criteria, assigned to these patients through previous fertility evaluations and recorded at study enrollment were included in the current analysis and referred to as "other diagnoses" and considered "historic" compared with the primary diagnoses. Couples were monitored for up to four (AMIGOS trial) or five (PPCOSII trial) cycles of treatment and throughout pregnancy to determine outcomes. In summary, 750 women with PCOS were randomized to up to five cycles of OI/TIC using either LTZ or CC (PPCOSII), and 900 women with UI were randomized to LTZ, CC, or gonadotropins for up to four OS/IUI cycles. For the purpose of this article, the terms OI and OS are used as suggested by the American Society for Reproductive Medicine (14). The former term refers to the pharmacologic treatment of anovulatory women to induce a mono-ovulatory response, whereas the latter is reserved for the pharmacologic treatment of ovulatory women with the intent of inducing multifollicular development.

Outcomes

Outcomes of interest for this study were clinical and multiple pregnancy rates per treatment cycle, as well as cumulative rates of clinical pregnancy. The decision to estimate both individual (per cycle) and cumulative probabilities of success was based on the fact that both outcomes are of interest to the couple and counseling clinician.

Clinical pregnancy was defined as an intrauterine pregnancy with cardiac motion identified by the early first trimester ultrasonography (at approximately six weeks of gestation).

Multiple pregnancy was defined as an intrauterine pregnancy with more than one fetal pole with cardiac activity detected via the first trimester ultrasonography. To define the number of fetuses in a multiple pregnancy, the highest number of identified fetal heartbeats was used.

Cumulative pregnancy included any intrauterine pregnancy with cardiac motion achieved by either the fourth (AMIGOS) or fifth (PPCOSII) treatment cycle.

Statistical Analysis

The Collaborative Center for Statistics in Science at Yale University provided oversight for both RCTs, was responsible for data entry and management, and performed all analyses.

Baseline characteristics were compared between cycles, between clinical pregnancies, and between multiple pregnancies. Student's t test, χ^2 test, and Fisher's exact test were performed to compare outcome measures with the putative predictors depending on the data type (continuous or categorical) and distribution (normal or not) of a predictor. Analysis of variance was used as appropriate. A multivariable logistic regression model was created using baseline characteristics considered as putative predictor variables. Variables included patient's and partner's age, body mass index (BMI), prior parity, infertility diagnosis, treatment type (CC, LTZ, or gonadotropins), ovarian reserve measures (serum levels of antimüllerian hormone [AMH], basal follicle-stimulating hormone and estradiol [E_2] levels, and antral follicle count [AFC]), endometrial thickness, medication dose and maximum daily dose (MaxMed), peak E_2 levels (when available), total number of preovulatory follicles (≥ 14 mm, when available), and total number of treatment cycles. Peak E_2 levels and total number of preovulatory follicles (≥ 14 mm) were not introduced into the multivariable logistic regression analysis as these two variables were available only for the patients in AMIGOS trial. Variables were introduced to a multivariable logistic regression analysis in a stepwise fashion, with a univariate analysis P value of $<.30$ to enter, and were retained in the multivariable model when the P value was $<.35$ (the latter P value was used to be as inclusive as possible of all potential determinants of pregnancy outcomes). Tables are presented with odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for the predictors in the adjusted logistic regression analysis (Supplemental Tables 1–4, available online). Of note, in the treatment cycle 5, none of the variables had a P value of $<.05$. Therefore, in the cycle 5, these variables were not predictive of the chance of having clinical or multiple pregnancy.

TABLE 1

Baseline and cycle characteristics of the 1,650 patients stratified by pregnancy outcome.

Variable	Clinical pregnancy (N = 457)	Without clinical pregnancy (N = 1,193)	*P* value[b]	Multiple pregnancy (N = 61)	Without multiple pregnancy (N = 1,589)	*P* value[b]
Participant's age (y)	30.24 ± 4.44 (457)	30.85 ± 4.60 (1,193)	.016	30.18 ± 4.09 (61)	30.70 ± 4.58 (1,589)	.384
Partner's age (y)	32.36 ± 5.46 (448)	33.27 ± 5.83 (1,160)	.004	32.69 ± 5.26 (59)	33.03 ± 5.76 (1,549)	.660
BMI (kg/m^2)	29.58 ± 8.37 (457)	31.08 ± 9.04 (1,193)	.002	26.70 ± 8.07 (61)	30.81 ± 8.88 (1,589)	< .001
Prior parity	108/457 (23.6)	231/1,193 (19.4)	.055	19/61 (31.1)	320/1,589 (20.1)	.037
Ovarian reserve measures						
Baseline AMH (ng/mL)	5.03 ± 5.10 (452)	5.12 ± 5.84 (1,170)	.750	3.58 ± 3.40 (60)	5.15 ± 5.70 (1,562)	.001
Baseline FSH (IU/L)	6.84 ± 2.40 (452)	6.60 ± 3.09 (1,171)	.105	6.72 ± 2.40 (60)	6.67 ± 2.93 (1,563)	.858
Baseline E_2 (pg/mL)	42.11 ± 39.41 (452)	43.61 ± 33.91 (1,171)	.476	34.51 ± 17.10 (60)	43.53 ± 36.00 (1,563)	< .001
Antral follicle counts[c]	20.57 ± 9.64 (344)	20.95 ± 9.50 (888)	.526	18.75 ± 9.09 (53)	20.94 ± 9.55 (1,179)	.103
Peak E_2 (pg/mL) (AMIGOS only)	728.73 ± 630.19 (257)	753.78 ± 755.57 (629)	.613	954.46 ± 698.71 (51)	733.81 ± 721.00 (835)	.034
Total number preovulatory follicle (AMIGOS only)	4.83 ± 2.68 (253)	4.52 ± 2.59 (627)	.117	6.12 ± 3.25 (50)	4.52 ± 2.55 (830)	.001
Infertility diagnosis			.283			< .002
Unexplained infertility	259/457 (56.7)	641/1,193 (53.7)		51/61 (83.6)	849/1,589 (53.4)	
Polycystic ovary syndrome	198/457 (43.3)	552/1,193 (46.3)		10/61 (16.4)	740/1,589 (46.6)	
Treatment			.002			< .001
Clomiphene	166/457 (36.3)	510/1,193 (42.7)		14/61 (23.0)	662/1,589 (41.7)	
Letrozole	184/457 (40.3)	489/1,193 (41.0)		13/61 (21.3)	660/1,589 (41.5)	
Gonadotropin	107/457 (23.4)	194/1,193 (16.3)		34/61 (55.7)	267/1,589 (16.8)	
Maximum medication dose			< .001			< .001
1 tablet clomiphene	38/446[a] (8.52)	69/1,157 (5.96)		3/61 (4.92)	104/1,542 (6.74)	
2 tablets clomiphene	97/446[a] (21.75)	178/1,157 (15.38)		10/61 (16.39)	265/1,542 (17.19)	
3 tablets clomiphene	24/446[a] (5.38)	246/1,157 (21.26)		1/61 (1.64)	269/1,542 (17.44)	
1 tablet letrozole	49/446[a] (10.99)	65/1,157 (5.62)		1/61 (1.64)	113/1,542 (7.33)	
2 tablets letrozole	96/446[a] (21.52)	186/1,157 (16.08)		7/61 (11.48)	275/1,542 (17.83)	
3 tablets letrozole	35/446[a] (7.85)	219/1,157 (18.93)		5/61 (8.20)	249/1,542 (16.15)	
Gonadotropin ≤ 250 IU	100/446 (22.42)	166/1,157 (14.35)		31/61 (50.82)	235/1,542 (15.24)	
Gonadotropin > 250 IU	7/446 (1.57)	28/1,157 (2.42)		3/61 (4.92)	32/1,542 (2.08)	

Note: Data are presented as mean ± SD (total number) or number of subjects/total number (percentage). AMH = antimüllerian hormone, AMIGOS = Assessing Multiple Intrauterine Gestations after Ovulation Stimulation, BMI = body mass index, E_2 = estradiol, FSH = follicle-stimulating hormone.

[a] In 11 clinical pregnancies, no dose data were available.

[b] Student's *t* test was used to test for differences between the two groups for continuous variables; χ^2 test or Fisher's exact test was used for categorical variables.

[c] Antral follicle counts refer to only those patients with the antral follicle count of ≤40.

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TABLE 2

Baseline demographic and cycle characteristics and outcomes, stratified by treatment cycle number.

Variables	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	*P* value[b]
Number of subjects	1,600[a]	1,347	1,129	919	380	
Participant's age (y)	30.71 ± 4.55 (1,600)	30.66 ± 4.55 (1,347)	30.67 ± 4.51 (1,129)	30.67 ± 4.44 (919)	29.15 ± 4.10 (380)	< .001
Partner's age (y)	33.05 ± 5.72 (1,565)	33.01 ± 5.67 (1,317)	33.07 ± 5.65 (1,103)	33.11 ± 5.61 (899)	31.92 ± 5.42 (370)	.016
BMI (kg/m^2)	30.58 ± 8.85 (1,600)	30.86 ± 8.94 (1,347)	31.17 ± 9.10 (1,129)	31.28 ± 9.12 (919)	35.81 ± 9.15 (380)	< .001
Prior parity	333/1,600 (20.81)	269/1,347 (19.97)	217/1,129 (19.22)	178/919 (19.37)	75/380 (19.74)	.857
Ovarian reserve measures						
Baseline AMH (ng/mL)	5.05 ± 5.65 (1,580)	5.25 ± 5.87 (1,331)	5.34 ± 5.82 (1,114)	5.39 ± 5.92 (907)	8.13 ± 7.32 (379)	< .001
Baseline FSH (IU/L)	6.68 ± 2.86 (1,581)	6.61 ± 2.82 (1,331)	6.55 ± 2.85 (1,114)	6.54 ± 3.01 (907)	6.21 ± 3.54 (379)	.001
Baseline E_2	42.53 ± 34.09 (1,581)	42.75 ± 31.44 (1,331)	43.18 ± 31.54 (1,113)	43.75 ± 32.45 (914)	52.94 ± 38.90 (431)	< .001
Antral follicle counts[d]	20.84 ± 9.49 (1,194)	21.13 ± 9.55 (993)	21.38 ± 9.51 (828)	21.49 ± 9.38 (663)	25.08 ± 9.76 (192)	< .001
Peak E_2 (pg/mL) (AMIGOS only)	531.5 ± 531.3 (886)	545.18 ± 528.81 (709)	503.08 ± 442.47 (579)	553.96 ± 647.72 (460)	(-)[c]	.762
Total number preovulatory follicles (AMIGOS only)	4.47 ± 3.71 (886)	4.69 ± 3.62 (709)	4.57 ± 3.83 (579)	4.80 ± 3.61 (460)	(-)[c]	.177
Infertility diagnosis						< .001
Unexplained infertility	886/1,600 (55.4)	709/1,347 (52.6)	579/1,129 (51.3)	460/919 (50.0)	(-)[c]	
Polycystic ovary syndrome	714/1,600 (44.6)	638/1,347 (47.4)	550/1,129 (48.7)	459/919 (50.0)	380/380 (100.0)	
Treatment type						< .001
Clomiphene	652/1,600 (40.75)	560/1,347 (41.57)	482/1,129 (42.69)	407/919 (44.29)	204/380 (53.68)	
Letrozole	651/1,600 (40.69)	563/1,347 (41.80)	479/1,129 (42.43)	393/919 (42.76)	176/380 (46.32)	
Gonadotropin	297/1,600 (18.56)	224/1,347 (16.63)	168/1,129 (14.88)	119/919 (12.95)	(-)[c]	
Maximum medication dose						< .001
1 tablet clomiphene	107/1,599 (6.69)	73/1,347 (5.42)	49/1,129 (4.34)	41/919 (4.46)	33/380 (8.68)	
2 tablets clomiphene	275/1,599 (17.20)	217/1,347 (16.11)	170/1,129 (15.06)	128/919 (13.93)	36/380 (9.47)	
3 tablets clomiphene	270/1,599 (16.89)	270/1,347 (20.04)	263/1,129 (23.29)	238/919 (25.90)	135/380 (35.53)	
1 tablet letrozole	114/1,599 (7.13)	73/1,347 (5.42)	53/1,129 (4.69)	35/919 (3.81)	28/380 (7.37)	
2 tablets letrozole	282/1,599 (17.64)	236/1,347 (17.52)	181/1,129 (16.03)	141/919 (15.34)	48/380 (12.63)	
3 tablets letrozole	254/1,599 (15.88)	254/1,347 (18.86)	245/1,129 (21.70)	217/919 (23.61)	100/380 (26.32)	
Gonadotropin ≤ 250 IU	262/1,599 (16.39)	190/1,347 (14.11)	137/1,129 (12.13)	93/919 (10.12)	(-)[c]	
Gonadotropin > 250 IU	35/1,599 (2.19)	34/1,347 (2.52)	31/1,129 (2.75)	26/919 (2.83)	(-)[c]	
Outcome						
Live birth (%)	133/1,600 (8.31)	94/1,347 (6.98)	79/1,129 (7.00)	58/919 (6.31)	25/380 (6.58)	.354
Clinical pregnancy (%)	150/1,600 (9.38)	110/1,347 (8.17)	95/1,129 (8.41)	63/919 (6.86)	28/380 (7.37)	.246
Multiple pregnancy (%)	19/1,600 (1.19)	20/1,347 (1.48)	13/1,129 (1.15)	8/919 (0.87)	1/380 (0.26)	.324

Note: Data are presented as mean ± SD (total number) or number of subjects/total number (percentage). AMH = antimüllerian hormone, AMIGOS = Assessing Multiple Intrauterine Gestations after Ovulation Stimulation, BMI = body mass index, E_2 = estradiol, FSH = follicle-stimulating hormone.

[a] In 50 subjects, no cycle data were available.

[b] One-way ANOVA was used for testing differences between groups for continuous variables; χ^2 test or Fisher's exact test was used for categorical variables.

[c] Only women in the Pregnancy in Polycystic Ovary Syndrome II trial underwent the fifth cycle; patients in the AMIGOS trial were randomized up to a maximum of four cycles.

[d] Antral follicle counts refer to only those patients with the antral follicle count of ≤40.

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Finally, to assess the predictive power of the final models, receiver operating characteristic (ROC) curves were created for both clinical and multiple pregnancy rates, and the areas under the curve (AUC) were calculated (an area of 1.0 represents a perfect test, and areas of 0.9–0.99, 0.8–0.89, and 0.7–0.79 represent an excellent, good, and fair test, respectively). For all analyses, SAS 9.4 (Cary, NC) was used. A P value of $<.05$ was considered statistically significant.

RESULTS

The baseline demographic and treatment cycle characteristics of the study population are shown in Table 1, stratified by outcome (clinical pregnancy and/or multiple pregnancy). Table 2 shows the demographic and cycle characteristics, as well as pregnancy outcomes, stratified by cycle number (cycles 1 through 5). Patients with PCOS were younger and had a higher BMI than patients with UI (mean ± SD: 28.9 ± 4.3 years vs. 32.2 ± 4.3 years, respectively, $P<.001$; 35.2 ± 9.3 kg/m^2 vs. 26.8 ± 6.4 kg/m^2, respectively, $P<.001$). Patients with UI reported a higher level of education and household income than patients with PCOS, and African American and Hispanic race was more commonly reported among patients with PCOS ($P<.001$ for all comparisons). The percentage of patients conceiving clinical pregnancy was comparable between patients with UI and PCOS (28.8% and 26.4%, $P=.29$, for UI vs. PCOS, respectively). However, a significantly higher proportion of multiple pregnancies was noted among women with UI (5.7% vs. 1.34%, $P<.0001$, for UI vs. PCOS, respectively) probably due to the use of gonadotropins only in patients with UI (AMIGOS trial). The majority (1,349/1,650; 81.7%) of the patients were treated with oral agents (41.0% and 40.8% for CC and LTZ, respectively), whereas the remaining 18.2% received gonadotropins (Table 1). Most pregnancies (79.6%) occurred within the first three cycles of treatments (Table 2).

Clinical Pregnancy

Four hundred and fifty-seven patients (27.7%) conceived a clinical pregnancy with 40.3%, 36.3%, and 23.4% of the conceptions resulting from LTZ, CC, and gonadotropins, respectively. As expected, patients who conceived were younger ($P=.016$), had a lower BMI ($P=.002$), and were more likely to have a younger partner ($P=.004$). The mean serum AMH levels and AFCs ($\leq$40) were comparable between patients who conceived and those who did not ($P=.750$ and $P=.526$, respectively, Table 1). Among patients with extremely high AFC (>40), those conceiving had lower mean values than those not achieving pregnancy ($P=.026$; data not shown in Table 1). Overall, diagnosis was not related to the chance of pregnancy (except in the first cycle, in which patients with PCOS had a lower chance to achieve a clinical pregnancy than patients with UI) (Supplemental Table 1); however, the type of treatment and medication doses were related to the chance of pregnancy. At least one-half of the patients undergoing the fourth or fifth cycle (49.5% [455/919] and 61.8% [235/380], respectively, Table 2) were at the maximum dose for either CC or LTZ (150 mg or 7.5 mg, respectively). However, most patients who conceived on either CC (135/159; 84.9%) or LTZ (145/180; 80.6%) did so with either one or two tablets per day (50 and 100 mg or 2.5 and 5 mg, for CC and LTZ, respectively). A significantly lower proportion of women conceived with three tablets of either medication (Table 1). This finding was most prominent in the second cycle in which the odds of achieving a pregnancy were significantly reduced on either three tablets of CC or LTZ compared with one (OR [95% CI]: 0.040 [0.011, 0.151], $P<.001$; and 0.028 [0.006, 0.134], $P<.001$; for CC and LTZ, respectively) and evident in the third cycle for three tablets of CC compared with one (OR [95% CI]: 0.2 [0.051, 0.787], $P=.021$; Supplemental Tables 2 and 3). The adjusted OR (and 95% CI) for all predictors of clinical pregnancy were calculated per cycle, and the results are summarized in Supplemental Tables 1–4. Of note, in the treatment cycle 5, none of the predictor variables had a P value of $<.05$ (data not shown). Predictor variables were associated with clinical pregnancy but were inconsistent across all cycles. For example, in the treatment cycle 1, women with a diagnosis of PCOS had significantly lower odds of a clinical pregnancy (OR [95% CI]: 0.43 [0.29, 0.62], $P<.001$) but not in cycles 2 through 4 (Supplemental Tables 1–4).

Figure 1 depicts the ROC curves and AUCs of the final model for each cycle for the outcome of clinical pregnancy. In the case of clinical pregnancy, the ROC curves and AUC demonstrate that the model is fair for predicting clinical pregnancy rates for cycles 1 through 4.

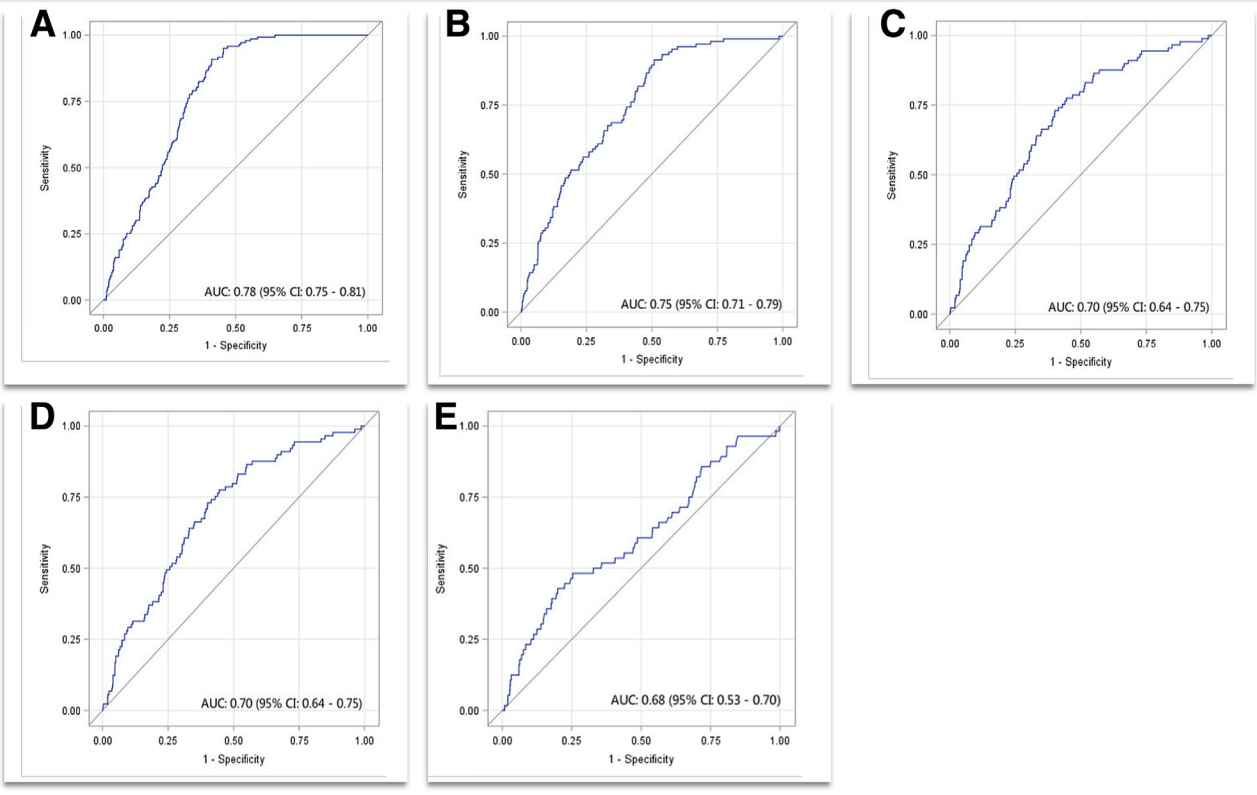
Multiple Pregnancy

Sixty-one pregnancies (13.4%) involved multiples. More than half of those (55.7%) were conceived in gonadotropin-stimulated cycles, whereas 23.0% and 21.3% resulted from either CC or LTZ treatments, respectively. The majority of patients conceiving multiples on gonadotropins did so at a maximum daily dose of $\leq$250 IU and not >250 IU (50.8% vs. 4.9%, respectively). Variables including prior parity ($P=.037$) and infertility diagnosis ($P=.002$), as well as the patient's BMI ($P<.001$), baseline AMH levels ($P=.001$), AFCs ($P<.001$, data not shown in Table 1), the type of treatment ($P<.001$), maximum daily medication dose ($P<.001$), peak E_2 levels ($P=.034$), and the total number of preovulatory follicles ($P=.001$), were all associated with whether the participant conceived a multiple pregnancy (Table 1).

A few of the predictor variables were significantly associated with the outcome of multiple pregnancy (i.e., age, prior parity, etc.) for one or more cycles; however, gonadotropin use had the strongest association and this persisted through cycles 1–4. Overall, the odds of conceiving multiples were higher with gonadotropins than with CC. The ORs increased progressively from the first to fourth cycle (OR [95% CI]: 4.6 [1.2, 17.2], $P<.02$; 6.2 [1.2, 21.0], $P=.003$; 6.3 [1.7, 24.2], $P=.007$; and 8.5 [1.4, 50.5], $P=.019$; for cycles 1 through 4, respectively).

Supplemental Figure 1 (available online) depicts the ROC curves and AUCs of the final model for each cycle for the outcome of multiple pregnancy. In the case of multiple pregnancy, ROC curves and AUCs suggested the model's fair-to-good association for cycles 1 and 2 and good-to-excellent

FIGURE 1



Receiver operating characteristic curves and areas under the curve of the final model for each cycle in clinical pregnancy. Top panel shows cycles 1–3, and the bottom panel shows cycles 4 and 5. AUC = areas under the curve, CI = confidence interval.

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association for cycles 3 through 4 with the model's ability increasing with a higher number of cycles (AUC [95% CI]: 0.78 [0.72–0.84] for cycle 1 and 0.86 [0.78–0.93] for cycle 4].

Cumulative Pregnancy Rate

Most variables associated with clinical and multiple pregnancy rates per cycle were also associated with cumulative pregnancy rates across the trials. Partner age ($P<.001$), prior parity ($P=.003$), AMH levels ($P=.037$), lower medication dose, and a diagnosis of UI as opposed to PCOS ($P=.001$) were all associated with a higher cumulative pregnancy rate (Supplemental Table 5, available online).

Finally, using the putative predictors and the models described earlier, we associated the probability of having a clinical or multiple pregnancy from the assessed variables and constructed an easy-to-use calculator.

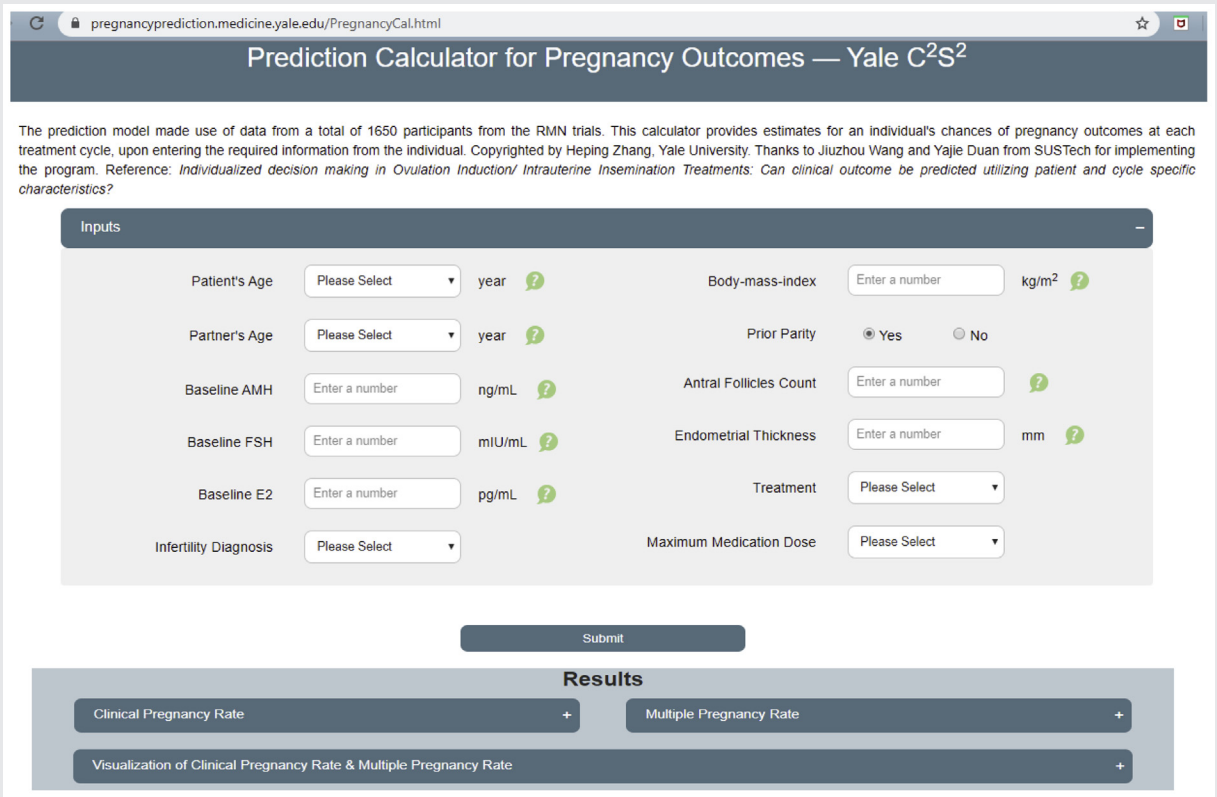
The calculator is available on the following website: https://pregnancyprediction.medicine.yale.edu/CalDirect.html (Fig. 2). For example, in the case of a 26-year-old female parous woman with the diagnosis of PCOS, whose BMI was 36.5 kg/m^2 and who had an AMH level of 5.0 ng/mL, AFC of 29, the day-3 follicle-stimulating hormone level of 5.5, baseline E_2 level of 62 pg/mL, and endometrial thickness of 5 mm, with a 26-year-old partner, who is undergoing her first cycle of LTZ at a daily dose of 2.5 mg/d, the probability of a clinical pregnancy is estimated to be 21.4% and the risk of multiple pregnancy is 2.0%.

DISCUSSION

Using clinically available, prospectively derived, patient-specific data, we demonstrated that the probability of a clinical pregnancy and the risk of a multiple pregnancy can be estimated for patients undergoing treatment with LTZ, CC, or gonadotropins. Partner's age, patient's age and BMI, the type of treatment, and maximum medication dose were all predictive of a clinical pregnancy, whereas BMI, AMH levels, AFC, parity, diagnosis, treatment type, maximum medication dose, peak E_2 levels, and the total number of preovulatory follicles were all predictive of multiple pregnancy.

For multiple pregnancy, the most consistent predictor among all considered factors was gonadotropin use (AMIGOS trial only). By combining data from the two multicenter Reproductive Medicine Network RCTs, we created an easy-to-use calculator that may predict with reasonable accuracy, among patients with either UI or PCOS, the chances of clinical or multiple pregnancy, taking into consideration patient-

FIGURE 2



Pregnancy calculator for pregnancy outcomes. All variables are based on baseline or screening values from the two studies.

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specific characteristics. This hypothesis needs to be tested further in additional diagnoses.

With the advent of precision medicine, the advances in bioinformatics, artificial intelligence, and the availability of large biomedical data, the concept of delivering more individualized treatments by integrating the characteristics (demographic, diagnostic, genetic, psychosocial, lifestyle, treatment, etc.) that distinguish one patient from another has gained ground in reproductive medicine. Recognizing the need for the availability of such tools in the field of reproduction, SART created an easy-to-access, online calculator that can individualize predictions for pregnancy (singleton and/or multiple) and live birth after IVF treatments. Similarly, recent efforts are focusing on integrating emerging assisted reproductive technology, time-lapse imaging, and -omic technologies (genomics, transcriptomics, proteomics and metabolomics) to improve outcomes (15). Despite recognizing the need for the availability of similar predictive models in OI/OS and/or IUI treatments, no such tools are widely available in reproductive medicine. Patient counseling and treatment planning are based on the results of the previously published studies (2, 4, 7–9); however, efforts to integrate this information and provide predictive models with individual patient data have either been isolated or are rudimentary (9).

The current project is an attempt to bridge this gap by developing an easy-to-use, individualized prediction model to estimate the probability of pregnancy (singleton or multiple) after OI/OS and/or IUI for women with either PCOS or UI. Using a well-characterized patient sample drawn from multiple sites throughout the United States, we suggest that it is possible to create a tool that can aid in the counseling and clinical decision making of patients with these types of infertility who are weighing treatment options. We believe that this is an improvement over current practice, which seems to rely on the previously published data, most of which are single-site or internal, with clinic-specific metrics that can suffer from smaller numbers and time-related variations in outcomes. More precise estimation of the odds of pregnancy based on pooling data can be used to identify subpopulations likely to benefit the most from a given proposed treatment or those who may fare better by moving earlier to IVF, sparing expenses, side effects, and psychological stress.

Our finding that baseline ovarian reserve did not differ between patients achieving pregnancy and those who did not is likely explained by the inclusion of a large number of patients with PCOS with expected high AMH values, which potentially masked an existing difference in prognosis (16). Supporting this, a significantly higher percentage of patients with very high AFCs (>40) was found among patients who did

not achieve a clinical pregnancy. Furthermore, patients with a diminished ovarian reserve diagnosis were not included in the study. On the other hand, another study showed that AMH level alone is not predictive of reproductive success (defined as the cumulative probability of conception) in a population-based sample of regularly cycling women followed until conception (17).

Strengths of this study include the combination of data sets and their multicenter designs that recruited patients from nine different sites with a broad geographic and socioeconomic distribution across the United States. Our sample contained sufficient racial and ethnic diversity to allow for extrapolation to most subpopulations of the United States. A large number of identified variables allowed for further input into the model to improve the prediction. The prediction model and calculation formula take into consideration most factors known to predict cycle-specific outcomes. We opted to estimate individual (per cycle) and cumulative probabilities of success as both outcomes are of interest to the couple and counseling clinician.

However, random population-based sampling was not performed. Patients for both studies were selected based on specific criteria recruited by convenience sampling. Limitations, of note, include the following: the study population by design was limited to PCOS or UI in a multisite study; the logistic regression model used took into consideration the diagnosis but combined both populations; and other diagnoses, recorded at study enrollment and not in conflict with the two RCTs' inclusion/exclusion criteria, were considered "historic" compared with the primary diagnoses (UI or PCOS) as they were assigned to the participating patients though previous fertility evaluations. Future validation of the model in subpopulations with other diagnoses is required. In the meantime, the calculator should only be used in patients with the diagnosis of UI or PCOS, as those were defined in the two RCTs. The present version of the calculator is not built to predict the outcomes of the fifth cycle, although when data are available in the future, an extension is possible. Outcomes observed here were based on strict study protocols and specific center- and study-related variables. Patients who participated in either clinical trial might have otherwise differed from those who did not, thus limiting the generalizability of the findings. Identification and inclusion of genomic data that may further characterize patient's response to treatment may prove to be useful and should be considered in future predictive models.

The ability to weigh the estimated chance of clinical pregnancy against the risk of a multiple pregnancy for each individual cycle in real-time may help guide decisions related to aborting a particular cycle, if risks seem to outweigh the benefits. Predictions can be made before the initiation of medication and used for counseling. This may inform medication choice, aid in estimating the cumulative probability of a clinical pregnancy, and facilitate decisions regarding when IVF is likely a better option.

Before the initiation of the cycle, the predictive model may be used to counsel the patient regarding the risk of a multiple pregnancy, and this risk can be balanced against the overall probability of achieving clinical pregnancy in a shared decision-making paradigm.

CONCLUSION

In summary, we observed that partner's age, patient's age and BMI, their type of treatment, and the maximum medication dose were all predictors of a clinical pregnancy. Body mass index, AMH, AFC, parity, diagnosis, the type of treatment, maximum medication dose, peak E_2 level, and the total number of preovulatory follicles were all predictors of having a multiple pregnancy. For multiple pregnancies, the most consistent predictor was gonadotropin use for OS. Our model combines the abovementioned predictors in an easy-to-use calculator to predict individual chances of clinical pregnancy and the risks of having a multiple pregnancy with common fertility treatments among patients with either PCOS or UI. Hopefully, this tool, when further modified to include other diagnoses, can assist in counseling and provide more precise therapeutic strategies "tailored" to each patient's individual needs.

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Abordaje médico personalizado en inducción de la ovulación/estimulación ovárica: Desarrollo de un modelo predictivo y una calculadora en línea desde nivel I de evidencia.

Objetivo: Estimar la probabilidad de embarazo clínico o múltiple durante una inducción de la ovulación (IO)/estimulación ovárica (EO).

Diseño: Análisis secundario de dos estudios clínicos multicéntricos aleatorizados (combinados).

Lugar: Multicéntrico.

Pacientes: Un total de 750 mujeres con síndrome de ovario poliquístico y 900 mujeres con infertilidad inexplicable.

Intervenciones: Inducción de la ovulación/EO con relaciones programadas (síndrome de ovario poliquístico) o con inseminación intrauterina.

Resultado principal medible: Tasa de embarazo clínico y múltiple por ciclo, tasa acumulada de embarazo. Edad, índice de masa corporal, paridad, diagnóstico, medicación, marcadores de reserva ovárica y respuesta ovárica fueron considerados en modelos de regresión multivariable para tasas de embarazo clínico, múltiple y acumulada. Se crearon curvas de características operadas por el receptor para tasas de embarazo clínico y múltiple.

Resultados: Paciente jóven y edad de su pareja, tipo de tratamiento, menor índice masa corporal, y dosis de la medicación se asociaron con embarazo clínico. Las variables asociadas con embarazo múltiple incluyeron las variables anteriormente mencionadas (excepto la edad), además del diagnóstico, paridad, conteo mayor de folículos antrales, niveles de la hormona antimulleriana, y la respuesta ovárica. El uso de gonadotropinas se asoció con embarazo múltiple, con una razón de probabilidad incrementada progresivamente (ciclos 1-4). Las curvas de características operadas por el receptor indicaron que el poder predictivo del modelo era favorable para embarazo clínico (áreas bajo la curva [95% de intervalo de confianza {CI}]: 0.78 [0.75-0.81] para el ciclo 1 y 0.70 [0.64-0.75] para el ciclo 4) y de bueno-a-excelente para embarazo múltiple (áreas bajo la curva [95% CI]: 0.78 [0.72-0.84] para el ciclo 1 y 0.86 [0.78-0.93] para el ciclo 4. La edad de la pareja, menor dosis de medicación, paridad, niveles de hormona antimulleriana, y el diagnóstico se asociaron con las tasas acumuladas de embarazo.

Conclusiones: Usando la mayoría de los factores conocidos para predecir el resultado de los ciclos de IO/EO, elaboramos una fórmula fácil de usar que puede predecir las oportunidades individuales para embarazo clínico y múltiple en los tratamientos de fertilidad comunmente utilizados. (https://pregnancyprediction.medicine.yale.edu/CallDirect.html).