ORIGINAL ARTICLE: INFERTILITY

Predictors of pregnancy and live-birth in couples with unexplained infertility after ovarian stimulation–intrauterine insemination

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Objective: To identify baseline characteristics of couples that are likely to predict conception, clinical pregnancy, and live birth after up to four cycles of ovarian stimulation with IUI in couples with unexplained infertility.

Design: Secondary analyses of data from a prospective, randomized, multicenter clinical trial investigating pregnancy, live birth, and multiple pregnancy rates after ovarian stimulation-IUI with clomiphene citrate, letrozole, or gonadotropins.

Setting: Outpatient clinical units.

Patient(s): Nine-hundred couples with unexplained infertility who participated in the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation clinical trial.

Intervention(s): As part of the clinical trial, treatment was randomized equally to one of three arms and continued for up to four cycles or until pregnancy was achieved.

Main Outcome Measure(s): Conception, clinical pregnancy, and live-birth rates.

Result(s): In a multivariable logistic regression analysis, after adjustment for other covariates, age, waist circumference, income level, duration of infertility, and a history of prior pregnancy loss were significantly associated with at least one pregnancy outcome. Other baseline demographic and lifestyle characteristics including smoking, alcohol use, and serum levels of antimüllerian hormone were not significantly associated with pregnancy outcomes.

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Conclusion(s): While age and duration of infertility were significant predictors of all pregnancy outcomes, many other baseline characteristics were not. The identification of level of income as a significant predictor of outcomes independent of race and education may reflect differences in the underlying etiologies of unexplained infertility or could reveal disparities in access to fertility and/or obstetrical care.

Clinical Trial Registration: NCT01044862. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

Key Words: Unexplained infertility, predictors, ovarian stimulation, intrauterine insemination, pregnancy

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Infertility is one of the most common medical problems affecting reproductive age adults (1). Although the estimated prevalence is between 10% and 15%, the true prevalence is likely greater owing to the social stigma associated with this diagnosis (2, 3). In couples experiencing infertility, it has been estimated that between 15% and 37% have infertility with no identifiable etiology (4, 5). Treatment paradigms for unexplained infertility typically involve ovarian stimulation (OS) with intrauterine insemination (IUI), subsequently followed by IVF for those unsuccessful in achieving pregnancy with OS-IUI (6). Unfortunately, less than one-third of couples will achieve a live birth after the most aggressive OS-IUI treatments involving gonadotropins and will therefore require IVF (7, 8).

Previous investigations have evaluated the relationship between lifestyle and socioeconomic factors and pregnancy outcomes after treatment in couples with unexplained infertility (9, 10). Many of these investigations have relied on retrospective data, have not included the outcome of live birth, or have focused on outcomes in the setting of IVF rather than OS-IUI (9,11–15). One of the largest investigations, which included 664 couples with unexplained infertility, 164 of whom underwent up to four cycles of OS-IUI treatment, has suggested that the former use of coffee, tea, and alcohol was associated with greater pregnancy and live-birth rates as compared with never and current users (10).

Since OS-IUI and IVF are personally demanding, resource intensive, and not without expense and risk, identification of patient characteristics associated with successful treatment outcomes after OS-IUI may allow for more effective counseling and treatment planning. Our hypothesis was that baseline characteristics of the couple, including lifestyle factors, would predict treatment outcomes. To this end, the present investigation sought to [1] identify risk factors associated with treatment outcomes and [2] develop prediction models of treatment outcomes after OS-IUI treatment applied to the Reproductive Medicine Network's Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) clinical trial. This trial, conducted at 12 clinical sites, randomized 900 couples with unexplained infertility to clomiphene, letrozole, or gonadotropins treatment for OS-IUI (8).

MATERIALS AND METHODS

Study Design

This secondary analysis included all 900 participants from the AMIGOS clinical trial. The trial design, analysis plan, and baseline characteristics of the participating couples as well as the trial outcomes have previously been published (8, 16). Briefly, the AMIGOS trial was a prospective, multicenter randomized clinical trial that evaluated the outcomes of conception, pregnancy, live birth, and multiple gestations associated with OS-IUI in couples with unexplained infertility. The trial was conducted at 12 clinical locations in the United States, with the clinicaltrials.gov number NCT01044862. Treatment arms included clomiphene citrate (300 couples), letrozole (299 couples), and gonadotropin (Menopur, Ferring Pharmaceuticals; 301 couples). Couples underwent OS-IUI treatment in the assigned arm until four cycles were completed or pregnancy occurred. Participating women were $\geq$18 to $\leq$40 years with regular menses, had a normal uterine cavity with at least one patent fallopian tube, and had a male partner with a semen specimen with at least 5 million motile sperm in the ejaculate. Institutional Review Board approval was obtained at each study site, and all participants gave written informed consent. The investigation was monitored by the Data and Safety Monitoring Board.

Methods

Baseline demographics as well as a complete medical and fertility history were obtained using standardized forms upon enrollment for all participants (16). Antimüllerian hormone (AMH) assays were completed on fasting samples, and batched samples were analyzed at the Ligand Assay and Analysis Core Laboratory at the University of Virginia (16). Intra- and interassay coefficients of variation were 3% and 7%, respectively.

Data Analyses

Outcomes of interest for this study are conception, pregnancy (clinical), and live birth. For the AMIGOS trial, conception was defined as having a rising serum level of hCG on two consecutive tests. Clinical pregnancy was defined as an intrauterine pregnancy with fetal heart motion as detected by