Predictors of participant retention in infertility treatment trials

Hongying Kuang, M.D., Ph.D.,[a,b] Susan Jin, M.P.H.,[b] Tracey Thomas, M.P.H.,[b] Lawrence Engmann, M.D.,[c] Karl R. Hansen, M.D., Ph.D.,[d] Christos Coutifaris, M.D., Ph.D.,[e] Peter Casson, M.D.,[f] Gregory Christman, M.D.,[g] Ruben Alvero, M.D.,[h] Nanette Santoro, M.D.,[h] Esther Eisenberg, M.D., M.P.H.,[i] Michael P. Diamond, M.D.,[j] Richard S. Legro, M.D.,[k] and Heping Zhang, Ph.D.,[b] for the Reproductive Medicine Network

[a] Department of Obstetrics and Gynecology, First Affiliated Hospital and Heilongjiang University of Chinese Medicine, Harbin, People's Republic of China; [b] Department of Biostatistics, Yale University School of Public Health, New Haven; and [c] Department of Obstetrics and Gynecology, University of Connecticut School of Medicine, Farmington, Connecticut; [d] Department of Obstetrics and Gynecology, University of Oklahoma College of Medicine, Oklahoma City, Oklahoma; [e] Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, Pennsylvania; [f] Department of Obstetrics and Gynecology, University of Vermont, Burlington, Vermont; [g] Department of Obstetrics and Gynecology, Shands Hospital, University of Florida, Gainesville, Florida; [h] Department of Obstetrics and Gynecology, University of Colorado, Aurora, Colorado; [i] *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, Maryland; [j] Department of Obstetrics and Gynecology, Georgia Regents University, Augusta, Georgia; and [k] Department of Obstetrics and Gynecology, Penn State College of Medicine, Hershey, Pennsylvania

Objective: To identify variables associated with retention (or dropout) in infertility clinical trials. Retention of subjects in randomized controlled clinical trials (RCTs) has received considerable attention, but there have been few consistent findings.
Design: Secondary analysis of data from RCTs.
Setting: Academic medical centers.
Patient(s): Women with polycystic ovary syndrome (PCOS) or couples with unexplained infertility, aged 18–40 years.
Intervention(s): This study is not an intervention study, but the patients in the original RCTs were treated with any or combination of metformin, clomiphene citrate (CC), letrozole, and gonadotropins.
Main Outcome Measure(s): Successful retention versus dropout during the RCTs.
Result(s): Race, ethnicity, body mass index (BMI), insurance coverage, history of smoking, and history of alcohol use were significantly associated with retention whether they were considered in bivariate analyses or a multivariable logistic model. Specifically, white race, higher income, having graduate degrees, normal weight, better insurance coverage, nonsmokers, and those who reported current use of alcohol at the start of the trial, had higher retention rates.
Conclusion(s): We identified several additive and persistent predictors of retention that can be used to guide the conduct of RCTs and improve the retention rate. Given the limitation of our association analysis, methodologically sound and theoretically grounded research are warranted so that high quality data can be collected to improve our understanding on the causes of dropout.
Clinical Trial Registration Number: NCT00068861 (PPCOS-I), NCT00719186 (PPCOS-II), and NCT01044862 (AMIGOS). (Fertil Steril® 2015;104:1236–43. ©2015 by American Society for Reproductive Medicine.)
Key Words: Randomized controlled clinical trial, dropout, logistic regression, retention

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Reprint requests: Heping Zhang, Ph.D., Department of Biostatistics, Yale University School of Public Health, New Haven, Connecticut 06520 (E-mail: Heping.Zhang@yale.edu).

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In randomized comparative effectiveness trials participants are recruited and randomly assigned to treatments, which are being evaluated by the investigators (1–3). Randomized controlled trials (RCTs) are the most accepted study design for providing robust evidence of the relative efficacy and safety of treatments (4). Important, RCTs form the basis for evidence-based medicine, although aspects of execution may affect the validity and generalizability of results.

It has been well recognized that many RCTs, including some of our own (5), fail to either be completed or achieve their goals because of difficulties with recruitment (6). Although there is no doubt regarding the critical importance of recruitment, retention of subjects and low dropout rates are a hallmark of a sound clinical trial (7). Acceptable recruitment, enrollment, engagement with the intervention, and retention of an appropriate sample from the population under study determines the feasibility and validity of an RCT, and excessive dropout limits the external validity of the trial (7). In fact, dropouts from a clinical trial bears similarity to dropouts from clinical practices, and understanding the causes for this may enhance compliance with treatment recommendations.

Randomization is fundamental to a RCT (8), and the intent-to-treat approach aims to obtain unbiased estimates of treatment effect (9). Yet, the randomization and intent-to-treat analysis cannot guarantee the validity of an RCT if the participants in the trial drop out in distinct predictable ways, violating the assumption that missing data are random (9). Hence, it is essential for any clinical trial to reduce dropouts (10). Although dropouts can be incorporated in the intent-to-treat power analysis, RCTs with high dropout rates are expected to yield smaller, more conservative, treatment differences because dropouts do not get the full intervention, resulting in a dilution of the treatment effect (10–12).

We evaluated potential factors that may impact retention in three RCTs conducted by the Reproductive Medicine Network (1–3). The Reproductive Medicine Network, established in 1990 and funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, is a cooperative effort of a number of geographically dispersed clinical sites, a data coordinating center, and the Fertility and Infertility Branch of the National Institute of Child Health and Human Development. We used data from three recent Reproductive Medicine Network trials—Pregnancy in Polycystic Ovary Syndrome (PPCOS-I) (3), Pregnancy in Polycystic Ovary Syndrome II (PPCOS-II) (2), and Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) (1). The primary outcome for these three large infertility trials was live birth; however, in the present report, we focus on participant retention, rather than the analysis of the primary outcome as already reported.

We hypothesized that certain data collected during the screening/baseline visit, including demographic variables, insurance coverage, and clinical characteristics (medical history, infertility history, family history, gynecological history, and obstetric history) will be predictive of successful retention among enrolled infertile couples. In particular, we predicted that women with lower income, no insurance coverage, and a shorter history of infertility would persist in the trial, thus having lower dropout rates because they had fewer alternatives for costly infertility treatment.

MATERIALS AND METHODS

Trials Included

Pregnancy in Polycystic Ovary Syndrome (3) was a double-blind, multicenter randomized trial, in which 626 infertile women aged 18–39 years with polycystic ovary syndrome (PCOS) were randomly assigned to receive clomiphene citrate (CC) plus placebo, extended-release metformin plus placebo, or a combination of metformin and CC for up to 6 months. Participants in the trial had evidence of a normal uterine cavity and at least one patent fallopian tube. Analysis of the semen of each woman's current partner was performed within 1 year of participation in the study, and a sperm concentration of at least 20 million/mL was required. Subjects with other causes of infertility were excluded.

Pregnancy in Polycystic Ovary Syndrome-II (2) was a double-blind, multicenter randomized treatment trial of letrozole versus CC (1:1 randomization) for up to five treatment cycles in 750 infertile couples. Women, aged 18–40 years, with a diagnosis of PCOS by Rotterdam criteria, had at least one patent fallopian tube and normal uterine cavity, had a male partner with sperm concentration of $\geq$14 million/mL, and who consented to regular intercourse during the study.

Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (1) was a prospective, multicenter, randomized clinical trial of 900 couples with unexplained infertility for up to four treatment cycles of letrozole versus CC versus gonadotropin with hCG triggering of ovulation in conjunction with IUI. Women were 18–40 years of age with regular ovulatory menstrual cycles ($\geq$9 cycles/year), had a normal uterine cavity with at least one patent fallopian tube, and a male partner with a semen specimen with a minimum of 5 million total motile sperm/mL. Women were randomly (1:1:1) assigned to receive either gonadotropin by SC injection, over-coated CC orally, or over-coated letrozole orally. All medications were initiated on days 3–5 of the menstrual cycle.

The three trials were approved by Institutional Review Boards at all participating sites. All participants signed informed consents.

Study Variables

For the present report we consider successful retention versus dropout as the outcome measure, although as stated, live birth was the original primary outcome for the three trials. Reasons for dropout include, but may not be limited to, loss to follow-up, medication side effect, lost interest, noncompliance, difficulty in access to clinic, relocation, and other personal constraints (1–3). Successful retention was when a participant remained in the study until her outcome was observed; namely, she did not drop out for any reason. We analyzed the data using dropout/retention as a dichotomous variable. Then we examined the specific reasons for dropout and their association with particular groups of participants. We consolidated the reasons into four major categories to