ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Outcomes from a university-based low-cost in vitro fertilization program providing access to care for a low-resource socioculturally diverse urban community

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Objective: To report on outcomes from a university-based low-cost and low-complexity IVF program using mild stimulation approaches and simplified protocols to provide basic access to ART to a socioculturally diverse low-income urban population.
Design: Retrospective cohort study.
Setting: Academic infertility center.
Patient(s): Sixty-five infertile couples were enrolled from a county hospital serving a low-resource largely immigrant population.
Interventions(s): Patients were nonrandomly allocated to one of four mild stimulation protocols: clomiphene/letrozole alone, two clomiphene/letrozole–based protocols involving sequential or flare addition of low-dose gonadotropins, and low-dose gonadotropins alone. Clinical fellows managed all aspects of cycle preparation, monitoring, oocyte retrieval, and embryo transfer under an attending preceptor. Retrieval was undertaken without administration of deep anesthesia, and laboratory interventions were minimized. All embryo transfers were performed at the cleavage stage.
Main Outcome Measure(s): Sociomedical demographics, treatment response, and pregnancy outcomes were recorded.
Result(s): From August 2010 to June 2016, 65 patients initiated 161 stimulation IVF cycles, which resulted in 107 retrievals, 91 fresh embryo transfers, and 40 frozen embryo transfer cycles. The mean age of patients was 33.3 years, and mean reported duration of infertility was 5.3 years; 33.5% (54/161) of cycles were cancelled before oocyte retrieval, with 13% due to premature ovulation. Overall, cumulative live birth rates per retrieval including subsequent use of frozen embryos was 29.0%; 44.6% (29/65) of patients enrolled in the program achieved pregnancy.
Conclusion(s): Use of mild stimulation protocols, simplified monitoring, and minimized laboratory handling procedures enabled access to care in a low-resource socioculturally diverse infertile population. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Low-cost IVF, mild stimulation, simplified IVF, socioeconomic disparities, access to care

In vitro fertilization (IVF) is a remarkable technological achievement of medicine that has enabled millions of couples to conceive. Yet today, more than 35 years since the first live birth, IVF remains a highly complex and costly treatment with staggering disparities in access to therapy, both within the United States and abroad (1, 2). In the United States, the direction of IVF research and clinical practice has largely focused on the progressive development of more complex technologies. Relatively little attention has been focused on making assisted reproductive technologies (ART) available to a wider population through development of evidence-

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based approaches for lower-cost and -complexity in vitro fertilization (LCC-IVF).

Significant challenges limit the safe and effective provision of LCC-IVF in low-resource and underserved settings (3–7). Proposed approaches to lower cost of technology include low-cost hormonal stimulation and simplified laboratory protocols (8). Until the recent Food and Drug Administration approval of the INVOcell intravaginal culture device in November 2015, simplified embryo culture technologies remained largely experimental or with extremely limited experience in the United States (9–12). Mild stimulation has been proposed to achieve favorable outcomes at lower cost, with less need for monitoring and risk for complications (13–19). Limitations to mild stimulation approaches include lower pregnancy rates, less potential for embryo selection, and higher rates of cycle cancellation.

In 2010, a program was initiated within the University of California, San Francisco (UCSF), reproductive endocrinology and infertility (REI) fellowship program with a goal to provide safe, effective, and affordable access to ART for infertile patients from low-resource largely immigrant communities served by the university. We aimed to achieve this goal through the use of existing technology to simplify therapeutic interventions and laboratory procedures to minimize cost and invasiveness while striving to optimize outcomes within resource constraints. The overarching goal was to provide increased access to care and to create a replicable model that could be implemented within existing infrastructure at other university-based academic ART centers to provide a network for access to infertility care to low-resource populations.

MATERIALS AND METHODS

Patient Population

Patients were enrolled from the REI clinic at San Francisco General Hospital (SFGH), a large county-funded public hospital affiliated with UCSF (20). The REI clinic is staffed by UCSF obstetrics and gynecology residents under the preceptorship of an REI senior fellow. The clinic conducts basic infertility diagnostic evaluation and treatment, including semen analysis, saline-infusion sonohysterography, and hysterosalpingography. Clomiphene citrate is used for ovulation induction in anovulatory patients and for superovulation in patients with unexplained infertility. However, intrauterine insemination (IUI), superovulation with exogenous gonadotropins, and ART services are not available.

Criteria for inclusion into the LCC-IVF program were female age $\leq$37 years at the time of enrollment, in good health, and not able to successfully conceive with the use of infertility treatment available at SFGH. Exclusion criteria included need for donor oocytes and/or gestational surrogacy. Financial criteria required for entry into the program was an institutionally validated combined household income at or below 200% of the federal poverty level. Patients at SFGH enrolled in the LCC-IVF program were seen at UCSF for further counseling and ART treatment.

Patient fees for the LCC-IVF program at UCSF were determined by a cost calculation of material expenses and variable costs for the cycle. Fixed costs of supporting the laboratory were not included in the fees, because there was an assumption of limited oocyte numbers and therefore decreased use of laboratory time and resources. In that regard, the program operated to an extent through subsidization. Because the program was clinically managed by the REI fellow, under the supervision of a board-certified REI attending physician, the clinical operating costs and overhead regarding nursing and support staff were significantly reduced. The cost to the patient, including sonographic monitoring, oocyte retrieval, administration of mild intravenous sedation, conventional fertilization, embryo culture to cleavage stage, fresh embryo transfer, and embryo cryopreservation for 1 year, was set at $1,550. The use of ICSI was an additional fee of $270. Medications were not included in the fees, and patients purchased them separately. Some patients were eligible for medication discounts through pharmacy programs or received donated medications. Overall total per-cycle costs including medications per patient ranged from $1,750 to $2,500, depending on the stimulation protocol used. Patients were charged $543 for a subsequent frozen embryo transfer. This study was performed under the approval of the UCSF Institutional Review Board.

Treatment Protocol

All patients initiating treatment in the LCC-IVF program were included in the study. Patients were nonrandomly assigned to one of four different stimulation protocols: clomiphene or letrozole only, sequential clomiphene/letrozole with low-dose gonadotropins, flare clomiphene/letrozole with low-dose gonadotropins, and low-dose gonadotropins only (Fig. 1). In the first protocol, 100 mg clomiphene citrate or 5 mg letrozole was administered daily from cycle days 2 to 6. In the sequential clomiphene/letrozole with low-dose gonadotropin protocol, 75–150 IU recombinant FSH (rFSH) or hMG was added on cycle day 7 and continued until the day of trigger. In the flare-based protocol, 75–150 IU rFSH or hMG was added on cycle day 5 and continued until day of trigger. Patients on gonadotropins only (75–150 IU rFSH or hMG) started daily injections on cycle day 2 and continued until trigger day. For this and other gonadotropin-based protocols, selection to use rFSH versus hMG was largely based on cost and access.

Protocol selection was based on the clinical judgement of the REI fellow and supervising attending physician. At inception of the program only clomiphene/letrozole alone protocols were used; however, addition of low-dose gonadotropins was selectively instituted after a high rate of cycle cancellation due to monofollicular development, as well for anovulatory patients not responsive to oral agents. As a generalization, normo-ovulatory patients with less complex infertility diagnoses, including tubal factor, were preferentially assigned to clomiphene/letrozole alone protocols. Patients with clomiphene-resistant polycystic ovary syndrome (PCOS) were assigned to sequential or flare clomiphene/letrozole with low dose gonadotropin protocols. More complex forms of infertility, such as unexplained infertility, were typically assigned to flare protocols to optimize superovulation within constraints. A low-dose gonadotropin only