Mild ovarian stimulation with clomiphene citrate launch is a realistic option for in vitro fertilization

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Objective: To validate the use of clomiphene citrate in IVF when mild stimulation approaches are chosen to reduce patient discomfort, risk, and cost.
Design: Prospective cohort study.
Setting: Private IVF clinic.
Patient(s): A total of 163 patients undergoing IVF and with a good prognosis (defined as $\leq$38 years old with normal ovarian reserve and normovulatory cycles, body mass index $<$29 kg/m^2, no previous assisted reproductive technology cycles, no severe endometriosis, no history of recurrent miscarriage, no endocrine/autoimmune diseases, and no surgical semen extraction).
Intervention(s): Mild stimulation using a fixed protocol of clomiphene citrate (100 mg/d from cycle days 3 to 7) in combination with low doses of gonadotropins (150 IU of recombinant FSH on cycle days 5, 7, and 9) and GnRH antagonist.
Main Outcome Measure(s): The cumulative delivery rate per patient after three fresh and/or frozen embryo transfers and time to pregnancy.
Result(s): No dropouts were observed. The cumulative delivery rate was 70%, and the mean time to pregnancy was 2.4 months.
Conclusion(s): Mild stimulation using clomiphene citrate in combination with low doses of gonadotropins can be considered a realistic option for good-prognosis patients undergoing IVF. (Fertil Steril® 2015;104:333–8. ©2015 by American Society for Reproductive Medicine.)
Key Words: Mild stimulation, clomiphene citrate, IVF, dropout

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In 1999, Fauser et al. (1) first developed the strategy of using mild ovarian stimulation in IVF, and a distinct definition regarding this concept was proposed in 2007 (2). Use of the lowest effective medication dosage for ovarian stimulation reduces patient discomfort and risk of ovarian hyperstimulation syndrome (OHSS) and lowers costs for the patients and society (3). These factors help patients tolerate repeated treatment, limit the dropout rate, and shorten time to pregnancy (4). Milder stimulation may also increase the relative proportion of genetically normal oocytes (5, 6). In contrast, excessive gonadotropin use may adversely influence clinical pregnancy rate (PR) (7), and excessive FSH stimulation may increase P production in follicular fluid (6).

Despite these potential benefits of mild stimulation for IVF, however, a 2010 update showed that this approach was not sufficiently applied in clinical practice (8). One reason seems to be a fear that use of milder stimulation would negatively influence results (9). When IVF is offered in competitive commercial environments, clinicians are under pressure to achieve the highest PR per stimulation cycle (10); thus, they are resistant to shifting from a classic, successful procedure to a novel and uncertain one (9). For this reason mild stimulation is often reserved for patients who are considered poor responders (11), although the concern that using mild ovarian stimulation could lower PRs per treatment cycle seems to be unjustified (12).

In March 2004, Italy passed a law (Law 40/2004) restricting all women to the insemination of a maximum of

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three eggs, mandating the transfer of all obtained embryos, and banning embryo cryopreservation (13). These restrictions motivated use of the lowest possible doses of agents for ovarian stimulation, limiting the number of recovered oocytes. Furthermore, the aim has been to reduce cost and discomfort, allowing patients to continue treatment for up to three cycles. The selected form of mild stimulation was a fixed protocol called "Lite IVF" that involves clomiphene citrate (CC) and low doses of FSH. This approach has been compared with conventional ovarian stimulation in a randomized prospective trial evaluating the primary endpoint of cumulative ongoing pregnancy rate over a period of 12 months (14). The minimal stimulation approach used at that time in Italy resulted in a similar outcome per started cycle compared with conventional stimulation protocols and produced significantly more pregnancies during the study period (14).

On April 1, 2009, the limitations on the number of eggs to inseminate and the cryopreservation of surplus embryos were lifted by a Sentence of the Supreme Court (Sentence no. 151, 2009). However, the results obtained in the previous study encouraged practitioners in our center to continue using the mild approach as the first-line intervention in good-prognosis patients. Here we present the results of 4.5 years of experience with mild stimulation involving CC.

MATERIALS AND METHODS

The present study was conducted in a private IVF clinic from May 1, 2009, until December 31, 2013. This study included only patients with a good prognosis, defined as follows: age $\leq$38 years, with a normal ovarian reserve and normovulatory cycles, body mass index $<$29 kg/m^2, no previous assisted reproductive technology (ART) cycles, no severe endometriosis, no history of recurrent miscarriage, no endocrine/autoimmune diseases, and no surgical semen extraction.

The Lite IVF program included three cycles of fresh and/or cryopreserved embryo transfers, at a reduced cost of 50% compared with the cumulative cost of three conventional IVF cycles. Stimulation was applied using a fixed protocol of CC (100 mg/d from cycle days 3 to 7) and 150 IU of recombinant FSH on cycle days 5, 7, and 9. The first ultrasound examination and E_2 assay were performed on cycle day 9. A cycle was canceled if there were fewer than three follicles. Otherwise, a GnRH antagonist was initiated on cycle day 9, with one or two more monitoring visits planned before hCG administration, depending on the ovarian response. An additional 150 IU recombinant FSH was administered on cycle day 11, if needed. Egg retrieval was performed 34 hours after hCG administration (5,000 IU). Up to six oocytes were inseminated by IVF or intracytoplasmic sperm injection, followed by transfer of a maximum of two embryos 3 to 5 days later. The luteal phase was supported with P in oil (50 mg/d) from day +3 until serum β-hCG evaluation or, in the event of conception, until the seventh week of pregnancy. Surplus oocytes were donated for research or cryopreserved according to the patient's decision. Surplus embryos were cryopreserved by vitrification for future transfer in conventional hormonal replacement therapy cycles. The Lite IVF program was considered complete in the event of delivery or after three fresh and/or thawed embryo transfers.

The primary study endpoint was the cumulative delivery rate per patient. The secondary endpoints were the dropout rate, clinical pregnancy rate per ET, implantation rate, and time to delivery. The Lite IVF approach was approved by the institutional review board of the S.I.S.Me.R. Clinic in 2007.

Data are presented as total number, mean $\pm$ SD, and percentages. Comparisons were performed using the χ^2 test. The clinical pregnancy rate was calculated on the basis of the presence of at least one fetal heartbeat per ET. The implantation rate was expressed as the number of fetal heartbeats per embryos transferred, and the cumulative delivery rate as the number of deliveries per patient after fresh and frozen cycles. Time to pregnancy was calculated as the time interval between the first egg retrieval and the occurrence of an ongoing pregnancy.

RESULTS

A total of 192 couples entered the Lite IVF program during the study period. Of these, 29 patients (15%) who showed a poor response (fewer than three follicles) in two stimulation cycles were advised to shift from the Lite IVF program to conventional stimulation. The remaining 163 couples completed the Lite IVF program, and none dropped out. The female mean age was 33.1 $\pm$ 3.9 years. The indications for IVF were tubal factor infertility with or without mild endometriosis in 48 cases, male factor infertility in 61 cases, male and female factor infertility in 33 cases, and idiopathic infertility in 21 cases. The mean duration of infertility was 3.2 $\pm$ 1.8 years.

Table 1 presents the results obtained in the fresh cycles. Of the 163 patients undergoing the first egg retrieval, 94 underwent a second egg retrieval and 46 a third one. The mean levels of E_2 at the moment of hCG injection, the mean numbers of recovered oocytes per patient, and the proportion of mature oocytes were similar across the three retrievals, which was expected because all cycles used the same fixed stimulation protocol. Likewise, the fertilization and cleavage rates did not differ, and a similar number of good-quality embryos were transferred. Overall, patients underwent a total of 303 egg retrievals (1.8 egg retrievals per patient), in which a mean of 5.6 $\pm$ 3.0 oocytes per patient were recovered. Only 57 oocytes from 12 cycles were cryopreserved or donated for research. Insemination was performed by IVF in 96 cycles and by intracytoplasmic sperm injection in 207 cycles. A total of 559 fresh embryos were transferred in 299 procedures (1.9 embryos/ET), and 127 surplus embryos from 60 cycles were vitrified.

A total of 106 clinical pregnancies were achieved after fresh replacements (PR/ET 35%), and the overall implantation rate was 23.5%. The rates of clinical pregnancy and implantation decreased significantly from the first and second cycles to the third cycle. Only one pregnancy ended in an early miscarriage, resulting in a fresh cumulative delivery rate of 64.4% (105 deliveries per 163 patients).

Of the 60 patients with frozen embryos, 26 achieved a pregnancy in the fresh cycles, and the remaining 34