Mild/minimal stimulation for in vitro fertilization: an old idea that needs to be revisited

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Mild ovarian stimulation for in vitro fertilization usually refers to the use of low-dose gonadotropins in conjunction with a gonadotropin-releasing hormone (GnRH) antagonist whereas minimal stimulation refers to the use of a sequential administration of clomiphene citrate followed by low-dose gonadotropins and a GnRH antagonist. These protocols offer important cost and tolerability advantages to all patients but specifically to high and low responders. (Fertil Steril® 2011;95:2449–55. ©2011 by American Society for Reproductive Medicine.)

Key Words: Clomiphene citrate, IVF, mild stimulation, minimal stimulation

Louise Brown, the first baby born from in vitro fertilization (IVF) in the world in 1978, was conceived as a result of fertilization of a single preovulatory oocyte collected in the course of a natural cycle (1). Even though the natural cycle continued to be used for IVF in England, Australia, and the United States in the late 1970s and early 1980s, it was soon replaced by the concept of controlled ovarian stimulation to retrieve more than one oocyte and increase the possibility of success. The early stimulation protocols involved minimal fertility medications for fear of achieving supraphysiologic levels of estradiol (E_2) and progesterone that potentially could interfere with implantation. Dr. Georgeanna Seegar Jones and her colleagues in Norfolk, Virginia, employed a stimulation protocol consisting of 150 IU of human menopausal gonadotropin (hMG) daily starting on the third day of the cycle (2). This led to the birth of Elizabeth Carr, the first IVF baby in the United States on December 28, 1981. Later on, the Norfolk program reported on a large series of cycles (n = 325) using the same gonadotropin protocol, in which the average number of eggs retrieved was 3.7 (only 1.5 mature oocytes) and the pregnancy rate per transfer was 25% (3). In the same series, increasing the daily dosage of hMG to 225 IU did not result in an increase in the number of eggs retrieved or the rate of pregnancy per transfer. The addition of 150 IU of follicle-stimulating hormone (FSH) to 150 IU of hMG only on days 3 and 4 of the cycle resulted in an average of three preovulatory oocytes retrieved and a pregnancy rate per transfer of 27% (4). It is evident that in the early days of IVF the use of "minimal" gonadotropin daily doses, as compared with the current dosages used, resulted in very reasonable pregnancy rates despite a low number of preovulatory oocytes retrieved. In addition, multiple pregnancies were rather uncommon, and ovarian hyperstimulation syndrome (OHSS) was somewhat rare.

Clomiphene citrate (CC), a nonsteroidal triphenylethylene derivative used mostly to induce ovulation in euestrogenic anovulatory patients, was also used in the early days of IVF because of its simplicity of administration (oral), low cost, and acceptable success rates. In 1981, Trounson et al. (5) reported a live-birth rate per transfer of 4 (17%) of 23 with the use of CC alone for ovarian stimulation for IVF. In the United States, Marrs et al. (6) reported a pregnancy rate of 11% per laparoscopy with the use CC alone, with cycle day 5 as the best day to start the medication. Later, several investigators reported on sequential or combined use of CC and hMG with retrieval of a mean of 3.0 to 3.5 fertilizable oocytes and a pregnancy rate per transfer ranging from 20% to 30% (7–9). With time, most IVF centers in the world discontinued the use of CC in favor of multiple follicular recruitment for multiple reasons, including the low number of fertilizable oocytes retrieved (2, 3), the high incidence of premature luteinizing hormone (LH) surge (15% to 25%), the concern with its antiestrogenic effect on the endometrium, and the widespread use of gonadotropins alone for IVF.

In the late 1980s and early 1990s, a widespread increase in the daily dosage of gonadotropins was introduced for multiple reasons that included the attempt to increase the number of oocytes for low responders, the goal of retrieving excess oocytes for embryo cryopreservation, and the introduction of suppression protocols with gonadotropin-releasing hormone (GnRH) agonists that eliminated the premature LH surge but led to the increase in the dosage of gonadotropins required and the duration of treatment. An increase in the recruitment of multiple fertilizable oocytes definitely contributed to better success rates with IVF, but also resulted in an increased cost of treatment and an increased incidence of multiple pregnancies and OHSS. Today, with improvements in all aspects of the IVF methodology and the transfer of one or two embryos for the majority of the patients, the time has come to revisit some of the early "mild/minimal" stimulation protocols, which provide significant advantages to patients such as reduced cost, better tolerability, and a decreased risk of morbid complications.

MILD STIMULATION

Mild stimulation uses a low dosage of gonadotropins to produce a maximum of 10 oocytes. In contrast, the conventional long-stimulation protocol uses GnRH agonists for suppression of the anterior pituitary and its reproductive hormones. The agonist is usually started in the midluteal phase of the preceding menstrual cycle followed by stimulation after menses. The agonist protocol prevents the LH surge and leads to multifollicular recruitment. However, the agonist protocol has many side effects, including formation of ovarian cysts and symptoms of estrogen deprivation such as hot flushes, vaginal dryness, and headaches. Additionally, suppression necessitates an increase in the dosage of gonadotropins and in the duration

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of treatment. Dual suppression with oral contraceptives and a GnRH agonist requires an even higher dosage of gonadotropins. As success rates improved in the 1990s, the long GnRH-agonist stimulation protocol became accepted as the standard protocol. Simultaneously, improvements in IVF methodology also aided in improved implantation rates, leading to more high-order multiple pregnancies and a higher incidence of OHSS. These negative effects led many to question the continued need for aggressive stimulation and to encourage the reintroduction of mild stimulation protocols (10–14).

In mild stimulation, a dosage of 100–150 IU of gonadotropins is started in the early follicular phase with the prevention of an LH surge by the use of a GnRH antagonist after 5 to 7 days of stimulation. In distinction from GnRH agonists, the GnRH antagonist prevents the LH and FSH rise by blocking the GnRH receptors. The immediate blockade circumvents the issue of the initial surge of endogenous gonadotropins seen with GnRH agonists. Consequently, GnRH antagonists reduce the dosage and length of the exogenous gonadotropin treatment. Dose-finding experiments performed in the 1990s demonstrated a decrease in implantation rates with dosages higher than 0.25 mg/day (15). Thus, 0.25 mg/day is the accepted dosage for GnRH antagonists. In addition, prospective randomized trials showed that, compared with the agonist, the antagonist protocol required fewer injections of analog, fewer days of stimulation, and fewer doses of gonadotropins, but resulted in similar implantation and clinical pregnancy rates (16–18). The potential advantages include a simpler protocol, a reduced dosage of gonadotropins, fewer days of monitoring, lower cost, a lessened negative psychological impact on infertile couples, and a decrease in OHSS.

Compared with the standard dosage of 225 IU of gonadotropins per day, the lower dose of 150 IU used in mild stimulation cycles demonstrates equivalent, not lesser pregnancy rates (19–21). Hohmann et al. (22) demonstrated in a prospective randomized trial that although mild stimulation results in a lower number of oocytes, it is associated with a higher chance of conceiving. In this study, 142 patients were divided into three groups, A, B, and C. Using the standard protocol, group A was given 2 weeks of daily GnRH agonist started in the pretreatment cycle followed by ovarian stimulation with recombinant FSH ($n = 45$). The mild stimulation group was split into groups B and C. Group B was given 150 IU of recombinant FSH daily initiated on cycle day 2 ($n = 48$) with the addition of an GnRH antagonist, cetrorelix acetate (Cetrotide; Serono), when the dominant follicle was ≥ 14 mm. Group C ($n = 49$) received 150 IU of recombinant FSH starting on cycle day 5 with cetrorelix acetate started in a similar fashion as group B. A maximum of two embryos were transferred in all groups. Group C had 61% of embryos scored as the best grade compared with 29% and 37%, respectively, in groups A and B. Group C also demonstrated a 90% transfer rate per oocyte retrieval versus 68% in group A and 71% in group B. Pregnancy rates per embryo transfer were similar in all three groups, 39%, 40%, and 36% in groups A, B, and C, respectively.

In a prospective study by Pelinck et al. (23), 50 patients underwent a mild stimulation protocol. In this protocol, 150 IU of recombinant FSH was administered daily with the addition of daily injections of 0.25 mg of cetrorelix acetate when a 14 mm lead follicle was seen. The cumulative ongoing pregnancy rate after three cycles of mild stimulation was 34% (95% confidence interval [CI], 20.6–47.4%). Heijnen et al. (24), in a prospective, randomized, noninferiority trial, studied a total of 404 patients who were randomly assigned to a mild GnRH antagonist protocol or a standard long GnRH agonist protocol. In the standard protocol, 2 weeks of daily GnRH agonist was started in the pretreatment cycle with subsequent ovarian stimulation with recombinant FSH. In the mild stimulation group, a fixed dosage of 150 IU of FSH was administered starting on cycle day 5. Once at least one follicle ≥ 14 mm was observed, a daily dose of GnRH antagonist was added. In addition, only single-embryo transfers were allowed in the mild stimulation group whereas double-embryo transfers occurred in the standard long protocol group (24). The cumulative pregnancy rates resulted in a term live-birth rate of 43.4% for the mild treatment and 44.7% with the standard treatment. The multiple pregnancy rates per couple were 0.5% for the mild stimulation and 13.1% for the standard protocol. In the mild versus standard treatment, the number of days of ovarian stimulation was lower (8.3 vs. 11.5) as well as the number of injections (8.5 vs. 25.3). The cancellation rate per started cycle was higher with mild stimulation (18 vs. 8.3%). This randomized controlled trial demonstrated that mild stimulation with single-embryo transfer and a standard protocol with double-embryo transfer had equivalent pregnancy rates (24).

Ovarian stimulation with higher levels of stimulation can affect embryo aneuploidy. In a study by Munné et al. (25), donated embryos were evaluated for mosaicism, using preimplantation genetic screening. Increased mosaicism was suggested in higher stimulation conditions. Given that mild stimulation can mimic the physiologic follicular response better than the standard protocol, additional studies have demonstrated that there is an increase in embryo aneuploidy with the prolonged GnRH agonist standard protocol. In a prospective randomized trial by Baart et al. (26), embryo aneuploidy rates were measured in embryos retrieved after standard protocol (GnRH agonist and 225 IU of recombinant FSH) and mild stimulation (GnRH antagonist and 150 IU of recombinant FSH). Fluorescent in situ hybridization (FISH) was used to determine aneuploidy. A nine chromosome panel (1, 7, 13, 15, 16, 18, 21, 22, X, and Y) was used and interpreted by two independent reviewers who were blinded to the stimulation protocol. Fifty percent of the embryos were chromosomally normal in the mild stimulation group compared with 38% of the embryos in the standard protocol. No differences were seen in fertilization rates although more oocytes were obtained in the standard group. The ongoing pregnancy rates in the mild stimulation group and the standard group were 12 (34%) of 35 women and 7 (23%) of 31 women, respectively. Interim analysis during the study demonstrated that a statistically significant lower embryo aneuploidy rate was seen with the mild stimulation protocol. The study was terminated secondary to these findings.

Similarly, Haaf et al. (27) demonstrated that the chromosome error rate was higher when more oocytes were retrieved. Women underwent a long GnRH agonist protocol with 112.5–225.0 IU of FSH per day. Polar body biopsy was performed on both the first and second polar body. A FISH analysis was performed using a five chromosome panel (13, 16, 18, 21, 22) on the embryos. Women in the same age range were subdivided into three groups based on oocyte yield, ranging from low yield (one to five oocytes), to intermediate yield (6 to 10), to high yield (>10). In the high yield group, the oocyte aneuploidy rate was 10% higher compared with the intermediate group, particularly in women younger than 35 years old. This study demonstrated that a high oocyte yield resulted in more chromosomally abnormal embryos, particularly in younger women. Another study by Katz-Jaffe et al. (28) found similar results, demonstrating that the likelihood of segregation errors seen in early embryo cleavage states is reduced with mild stimulation.

A meta-analysis done by Verberg et al. (29) investigated whether the lower number of retrieved oocytes in mild stimulation cycles affected implantation rates. This meta-analysis searched randomized

controlled trials where a GnRH antagonist was used and a cotreatment with a mild dosage of gonadotropins was started on cycle day 5. The three studies that met these criteria were described earlier in detail (22, 24, 26). The meta-analysis included a total of 592 cycles, where a statistically significant reduction in retrieved oocytes was seen compared with the standard stimulation. The ongoing pregnancy rate per started cycle was 15% with mild stimulation and 29% in the conventional group. However, the embryo implantation rate after mild stimulation was 31% versus 29% for the standard protocol (29).

MINIMAL STIMULATION

"Minimal stimulation" usually refers to stimulation protocols that yield a maximum of five oocytes, with a range from one to five. Corfman et al. (30) reported in 1993, in a prospective nonrandomized study, a protocol consisting of CC, 100 mg orally on days 3 to 7, followed by a single injection of 150 IU of IM hMG on cycle day 9. In that report, the investigators introduced the term "minimal stimulation" to their novel protocol. The number of retrieved oocytes was statistically significantly fewer than the standard long GnRH agonist protocol (3.4 vs. 10.1), but there were no statistically significant differences in the pregnancy and implantation rates between the two protocols. In a follow-up article from the same institution, the investigators reported similar findings in a larger retrospective study (31). Subsequently, many investigators reported similar findings with a sequential or combined protocol of CC and gonadotropin.

Weigert et al. (32) reported on a combined protocol of CC and gonadotropin (gonadotropin administered on alternate days) and demonstrated similar pregnancy rates to the long GnRH-agonist protocol. Williams et al. (33) published a retrospective controlled study comparing a sequential protocol of CC and gonadotropin (100 mg of oral CC on days 3 to 7 and 150 IU of gonadotropin daily starting on day 9), with or without adding a GnRH-antagonist to suppress the LH surge, with the standard GnRH-agonist protocol; they reported similar pregnancy rates despite retrieving statistically significantly fewer oocytes (3.7 vs. 13.1) in the minimal stimulation protocol. Engel et al. (34) reported a sequential CC and gonadotropin (FSH or hMG) protocol, using a GnRH antagonist to suppress the LH surge, with a mean of 6.4 oocytes retrieved and a clinical pregnancy rate of 26% per transfer.

Hwang et al. (35) reported on a combined protocol of CC (100 mg on days 3 to 7) and gonadotropin (administered on alternate days) with a mean number of 8.0 oocytes retrieved and an ongoing pregnancy rate of 35% per started cycle. More recently, the largest study (43,433 cycles) was reported from Japan using a protocol of CC (100 mg on days 3 to 7) and gonadotropin (150 IU on alternate days starting on cycle day 8) with a mean number of 2.2 oocytes retrieved and a live-birth rate of 11% per started cycle (36). Zhang et al. (37), using a very similar protocol to the Japanese study, reported recently a pregnancy rate of 20% per fresh transfer, and a 41% rate by use of vitrification and cryopreserved-thawed embryo transfer.

During the last 2 years, we have been using a minimal stimulation protocol at our institution (the Muasher Center for Fertility and IVF) with encouraging success rates. This protocol is offered to all patients, mostly women with no insurance coverage for the treatment, to decrease the cost and improve the patient's tolerability and acceptance of the IVF treatment. No patients were excluded for elevated day-3 FSH levels (under 20 mIU/mL) or age (under 44 years). We administered 100 mg of oral CC on cycle days 3 to 7 followed by 150 IU of SC gonadotropin (FSH or hMG) daily starting on cycle day 8. Ganirelix acetate (Merck), 0.25 mg SC daily, was started on the morning of cycle day 11 and was continued daily for an average of three doses. We administered 10,000 IU of IM human chorionic gonadotropin (hCG) when at least two follicles were $\geq$17 mm on ultrasound. Figure 1 illustrates the minimal stimulation protocol used. The patients were monitored at the office for an average of three visits before oocyte retrieval. The mean number of total vials of gonadotropins used was 10.5 (75 IU per vial), the mean number of mature oocytes retrieved was 4.2, the mean number of embryos transferred was 2.4, and the clinical pregnancy rate per cycle initiated was 42%. Table 1 lists the stimulation characteristics and pregnancy results for 31 consecutive patients who underwent the minimal stimulation protocol.

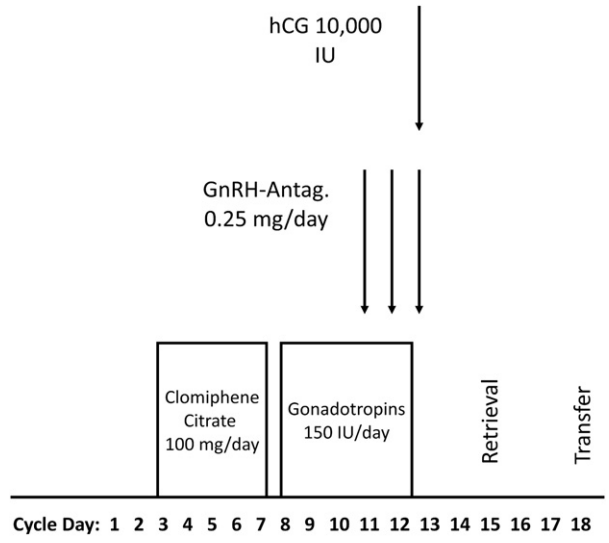
Minimal Stimulation for Low Responders

There is no universally accepted definition for low responders. The term is commonly applied to patients who have one or more of the following characteristics: poor ovarian reserve (measured by an elevated day-3 FSH level, low antral follicle count, and/or low antimüllerian hormone level), yield of a low number of mature follicles (less than six on a conventional IVF protocol), low peak E_2 level (less than 900 pg/mL), high gonadotropin dosage (>3,000 IU) used for the total stimulation, and prior canceled cycles with a standard IVF protocol due to poor response. During the early days of IVF, multiple studies reported no statistically significant differences in using a higher dosage of gonadotropins (six vials) compared with the standard dosages used at the time (two to four vials) in terms of the number of oocytes retrieved or pregnancy rates (38–41).

More recently, Klinkert et al. (42), in a prospective randomized study that used a long GnRH agonist protocol in patients with an antral follicle count less than five, reported no improvement in the mean number of oocytes or the ongoing pregnancy rates with a daily dosage of 300 IU of recombinant FSH when compared with 150 IU. Lekamge et al. (43) reported the same findings in a retrospective study. Kyrou et al. (44), in an elegant systematic review and meta-

FIGURE 1

Minimal stimulation protocol at The Muasher Center for Fertility and IVF.



Zarek. Mild/minimal stimulation for IVF. Fertil Steril 2011.

TABLE 1

Minimal stimulation protocol of clomiphene citrate, gonadotropin, and a gonadotropin-releasing hormone antagonist at the Muasher Center for Fertility and IVF, 2009–2010.

No. of patients	31
Age (y)	35.7 ± 4.4
Cancellations	1
Day-3 FSH (mIU/mL)	8.2 ± 3.8
E_2 at hCG pg/mL	1283 ± 802
Vials of gonadotropins	10.5 ± 3.2
Mature oocytes	4.2 ± 2.7
Embryos transferred	2.4 ± 0.9
Clinical pregnancy/cycle	42% (13/31)
Clinical pregnancy/transfer	43% (13/30)

Note: E_2 = estradiol; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin.

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TABLE 2

Minimal stimulation versus full stimulation in low responders at the Muasher Center for Fertility and IVF, 2009–2010.

	Stimulation protocol		
	Minimal	Full	*P* value
No. of patients	13	42	
Age (y)	38.7 ± 3.7	38.9 ± 2.9	NS
Day-3 FSH (mIU/mL)	12.1 ± 2.7	10.1 ± 3.7	NS
E_2 at hCG (pg/mL)	808 ± 353	1,082 ± 561	<.05
Vials of gonadotropins	9.7 ± 3.3	49.8 ± 7.4	<.01
Days of monitoring	3	6	
Mature oocytes	2.4 ± 1.6	3.8 ± 2.3	<.05
Embryos transferred	2.0 ± 1.1	2.1 ± 1.2	NS
Clinical pregnancy/cycle	38% (5/13)	36% (15/42)	NS
Clinical pregnancy/transfer	42% (5/12)	47% (15/32)[a]	NS

Note: E_2 = estradiol; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin.

[a] Four patients canceled before retrieval. Six patients had retrieval without transfer.

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analysis of 22 randomized controlled trials in low responders, drew the following comparisons in terms of interventions without statistically significant differences in pregnancy rates in low responders: short GnRH-agonist compared with long GnRH agonist protocol, sequential CC/FSH/GnRH antagonist compared with long GnRH-agonist protocol, GnRH antagonist compared with short GnRH-agonist protocol, short GnRH-agonist compared with a natural cycle protocol, and stop compared with nonstop long GnRH-agonist protocol. Based on this meta-analysis of only randomized studies in the literature, the investigators concluded that there was no superior protocol that significantly improved the success rates of low responders. D'Amato et al. (45) in a prospective randomized study of low responders with elevated basal FSH levels greater than 10 mIU/mL, compared a sequential protocol of CC/FSH/GnRH-antagonist with the standard long GnRH-agonist protocol and reported a lower cancellation rate, higher number of mature oocytes, and similar clinical pregnancy and implantation rates in the minimal stimulation group compared with the standard protocol.

At our institution, we compared the minimal stimulation protocol, described earlier, in low responders to the standard protocol in a properly matched group of patients treated at the same time. Our full standard protocol for low responders consists of administering 300 IU of FSH and 150 IU of hMG SC daily starting on the third day of the cycle with the addition of ganirelix acetate, 0.25 mg SC daily, starting on cycle day 8 for an average of five doses. We administer 10,000 IU of IM hCG when at least two follicles are ≥17 mm in diameter. The stimulation characteristics and pregnancy results are shown in Table 2. The full stimulation protocol used statistically significantly more vials of gonadotropins and had a higher number of mature oocytes retrieved, but the clinical pregnancy rate per cycle initiated and per transfer was similar to the minimal stimulation protocol. Of interest, more patients were canceled and more patients had no embryo transfer with the full stimulation protocol compared with the minimal stimulation protocol.

Minimal Stimulation for High Responders

In general, high responders are patients who respond to ovarian stimulation for IVF with peak E_2 levels greater than 3,000 pg/mL and retrieval of more than 15 oocytes. These patients usually have a very favorable prognosis for success in terms of live-birth rates but also have a greatly increased rate of OHSS. The usual suspects include, but are not limited to, patients with polycystic ovary syndrome, egg donors, young women with irregular cycles, patients with a high (more than eight) antral follicle count for each ovary, and patients with a relatively high antimüllerian hormone level. In a large retrospective study, Sharara and McClamrock (46) reported no detrimental effects on pregnancy and implantation rates in patients with a peak E_2 level of >3,000 pg/mL (compared with <3,000 pg/mL) and more than 15 oocytes retrieved (compared with less than 15) (46). Other investigators have reported similar findings (47, 48).

Although the incidence of severe OHSS is relatively low in IVF (2% to 3%), it is statistically significantly higher in high responders. There are no exact data in the literature on the incidence of OHSS proportional to the number of oocytes retrieved and the peak E_2 level, but in general it is believed from clinical experience that high responders are at a greatly increased risk of OHSS, with the complication being almost a certainty in patients whose peak E_2 concentrations are greater than 5,000 pg/mL and/or those with more than 20 oocytes retrieved. As such, prevention of OHSS should be the main goal in the treatment of high responders.

Multiple strategies have been reported in the literature to decrease the incidence of OHSS in high responders, but none of these strategies prevent OHSS completely. The strategies include, but are not limited, the use of minimal gonadotropin daily doses (100–150 IU), dual suppression with oral contraceptives and a GnRH-agonist protocol, withdrawal of gonadotropins for 1 to 4 days before hCG administration (coasting), reducing the hCG dose (3,000–5,000 IU), cryopreservation of all embryos, and use of GnRH-antagonist protocols with a GnRH-agonist for the ovulation trigger. In vitro maturation (IVM) of human oocytes can be attempted but is of limited use due to inadequate experience and suboptimal pregnancy results. Minimal stimulation with

TABLE 3

Minimal stimulation versus full stimulation in high responders at the Muasher Center for Fertility and IVF, 2009–2010.

	Stimulation protocol		
	CC + FSH + antagonist	Low-dose FSH + antagonist	*P* value
No. of patients	18	32	
Age (y)	33.7 ± 3.8	30.8 ± 3.5	NS
Day-3 FSH (mIU/mL)	5.6 ± 1.4	5.6 ± 1.6	NS
E_2 at hCG (pg/mL)	1,600 ± 807	2,028 ± 942	<.05
Vials of gonadotropins	11.1 ± 3.1	19.6 ± 7.3	<.05
Mature oocytes	5.4 ± 2.7	8.8 ± 4.0	<.05
Embryos transferred	2.7 ± 0.7	2.3 ± 0.7	NS
Clinical pregnancy/transfer	44%	50%	NS
Cycles with freezing	—	20%	
Mean embryos frozen	—	4.8 ± 3.1	

Note: CC = clomiphene citrate; E_2 = estradiol; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin.

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a sequential CC/gonadotropin/GnRH antagonist protocol seems to offer the best strategy to reduce or prevent the incidence of OHSS for the relatively low number of oocytes retrieved. At our center, we retrospectively compared the stimulation characteristics and IVF outcomes in 18 patients who were considered to be high responders with 32 matched control patients who were given a mild stimulation protocol (daily dose of 100–150 IU of gonadotropin) in conjunction with a GnRH antagonist. The results are shown in Table 3. It is clear that the IVF outcome of the high responders was equivalent with a minimal or mild stimulation protocol. The only negative finding was that the minimal stimulation protocol did not yield excess embryos that could be used for cryopreservation for future use.

CONCLUSION

Success rates with IVF have definitely increased over the last 30 years. This can be attributed to multiple factors, including refinement of the stimulation protocols, the introduction of GnRH-agonists and later antagonists, improvements in IVF culture conditions, the extension of the transfer to day 5 in the same patients, gentle transfer techniques with the use of ultrasonography, preimplantation genetic diagnosis with transfer of euploid embryos in the same patients, and other factors. However, for the most part, the IVF treatment process remains costly and unaffordable to a significant number of patients as well as being stressful due to the multiple office visits, injections, blood drawings, and ultrasound examination. It is also potentially complicated with increased risks of multiple pregnancy and OHSS in some patients. Studies have shown that the physical and/or psychological burden of treatment is the most common cause of dropout from IVF treatment programs (49). In the United States, lower rates of IVF use are correlated with lack of insurance coverage and a lower median income (50). In our opinion, minimal stimulation protocols offer significant advantages to patients by reducing the total cost of medications (savings of greater than $3,000), reducing the stress of treatment (average of three versus six office visits for a conventional protocol), and greatly reducing the number of injections, blood drawings and ultrasound. In addition, these protocols reduce the incidence of OHSS the most among all the strategies that have been proposed to treat high responders.

In the United States, there has been general resistance to use mild/minimal stimulation protocols because of the generally believed misconception that they will compromise pregnancy rates. Fauser et al. (51) recently studied the advantages, disadvantages, and the resistance to employing mild stimulation protocols over the last 10 years. There is no question that mild/minimal stimulation protocols have some disadvantages, including limiting the potential to obtain excess oocytes for cryopreservation, the lessening the ability to transfer one or two blastocysts (due to the lower number of embryos), and limiting the number of oocytes from egg donors that can be used to one or two recipients. Patients undergoing IVF treatment with preimplantation genetic diagnosis are best treated with a conventional protocol. However, not all patients undergoing treatment with a conventional protocol will have excess embryos for cryopreservation, and a sizable number of patients will elect not to cryopreserve excess embryos for multiple reasons. A minority but still sizable number of patients will elect to fertilize a limited number of oocytes due to religious, ethical, or moral beliefs, and minimal stimulation can be an attractive option for these patients.

During the last 10 years, a great deal of progress has been achieved toward decreasing the incidence of high-order (triplet or more) multiple pregnancy in the United States. We wish we could say the same about OHSS. We believe that OHSS is underreported and that not enough attention has been devoted to decreasing its incidence in high-risk patients. Mild/minimal stimulation offers an attractive option for patients who have experienced this complication in a previous treatment cycle, and it can reduce the incidence in high-responder patients.

It is true that mild/minimal stimulation may not be the optimal treatment protocol for all patients, but we believe that it can be an option for many patients and should not be dismissed because of misconceptions about lower success rates. For some patients, IVF does not need to be a costly, stressful process that involves multiple daily injections for a lengthy period of time with increased complications. We need to think outside the box, because there is another option.

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