

---

### Abstract

Minimal stimulation IVF was utilized in the early IVF experiences. It is proposed now as a solution for the unwanted consequences and costs of current conventional IVF protocols. Minimal stimulation IVF is thought to be a means to achieve some of the fertility-enhancing effects of IVF while minimizing discomforts, risks (especially of ovarian hyperstimulation syndrome), and costs. An additional benefit is a marked reduction in the likelihood of unused embryos. In aggregate, these advantages should increase the access to and acceptability of IVF for many potential patients. While the per cycle pregnancy rate in minimal stimulation IVF is lower than that of conventional protocols, proponents of this method cite increased patient tolerance and access that allow multiple efforts, with a cumulative success rate that can approach that of a single cycle of conventional IVF (Curr Opin Obstet Gynecol 22:189–192, 2010). Minimal stimulation IVF is now being offered in many fertility clinics both to young patients with good prognosis and to poor responders and women of advanced age as an alternative to conventional protocols. The renewed interest in minimal stimulation IVF is largely a result of improved outcomes in the IVF laboratory that have led to higher likelihoods of viable embryos and better success rates with single embryo transfer.

---

### Keywords

IVF • Hyperstimulation • Gonadotropins • Minimal stimulation • Embryo transfer

---

A.O. Hammoud (✉)  
Utah Center for Reproductive Medicine,  
Department of Obstetrics and Gynecology,  
University of Utah School of Medicine,  
Salt Lake City, UT, USA  
e-mail: ahmad.hammoud@hsc.utah.edu

## 2.1 Classification and Terminology

The field of minimal stimulation IVF is becoming popular and several recent publications have described the success with various stimulation protocols [1–4]. It is not uncommon to refer to minimal stimulation IVF as mild stimulation IVF or low-dose IVF. The various protocols and terminology used in this field make the comparison between studies challenging (Table 2.1). An interested group of experts from the International Society for Mild Approaches in Assisted Reproduction (ISMAAR) met and proposed the following classifications [5].

### 2.1.1 Natural Cycle IVF

The term Natural cycle IVF should be used when IVF is carried out with oocytes collected from a woman's ovary or ovaries in a spontaneous menstrual cycle without administration of any medication at any time during the cycle. The aim of this cycle is to collect a naturally selected single oocyte at the lowest possible cost.

### 2.1.2 Modified Natural Cycle IVF

The term Modified natural cycle should be applied when exogenous hormones or any drugs are used when IVF is being performed during a spontaneous cycle with the aim of collecting a naturally selected single oocyte, but with a reduction in chance of cycle cancellation. Modified natural cycle IVF employs hCG triggering of ovulation,

with or without concomitant GnRH antagonist for suppression of the endogenous LH surge.

### 2.1.3 Mild IVF

A mild IVF cycle is defined by use of oral agents (antiestrogens or aromatase inhibitors) and/or low-dose gonadotropins to modestly increase oocyte yields (2–7 oocytes). LH surge suppression with GnRH antagonist and triggering with hCG or GnRH agonist is followed by luteal support.

### 2.1.4 Conventional IVF

This term is used to define scenarios in which conventional gonadotropin dosing is employed to achieve maximum controlled ovarian hyperstimulation below the threshold for significant risk of OHSS. In all such scenarios, endogenous LH is suppressed with GnRH agonist in long or flare protocols, or with GnRH antagonist, triggering employs hCG or GnRH agonist, and luteal support is given.

## 2.2 Adoption of Minimal Stimulation IVF

There are currently several proposed indications for minimal stimulation IVF, including young patients with male factor or tubal factor infertility, poor responders, and patients with prior implantation failures [6, 7]. The rationale for its use in poor responders is that comparable oocyte yields

**Table 2.1** Different protocols of minimal stimulation IVF

	Ovarian stimulation	Prevention of premature LH surge	Ovulation trigger	Luteal phase support
Natural cycle IVF	None	None	None	None
Modified natural cycle IVF	None	None	hCG	Yes
	Gonadotropins add back	GnRH antagonist	hCG	Yes
Mild IVF	Clomiphene, letrozole, early or late low-dose gonadotropins	GnRH antagonist	hCG, or GnRH agonist	Yes
Conventional IVF	High-dose gonadotropins	GnRH agonist or antagonist	hCG, or GnRH agonist	Yes

are obtained without the costs and intrusiveness of high-dose conventional dosing, but success of this approach for these patients has been mixed [7]. Adoption of minimal stimulation IVF has been slow, particularly in the United States where it is not offered in most centers. The slow acceptance of minimal stimulation IVF is thought in part to be due to reluctance of clinics to use protocols that might adversely affect their published success rates in a competitive marketplace. Other factors include the often smaller margin of profitability, reduced number of embryo available for cryopreservation, and health plans that limit the benefits to a certain number of IVF cycles [6].

## 2.3 Comparison of Different Protocols for Minimal Stimulation IVF

### 2.3.1 Modified Natural Cycle IVF

Natural Cycle IVF was the protocol used in the early publications describing IVF [8]. Since then, several changes were introduced to the normal cycle IVF, mainly the control of the LH surge and modified oocyte retrieval methods. Natural IVF cycles have an inherently high cancellation rate because of premature LH surge, premature ovulation, and increased risk of failed oocyte retrieval [4]. Because of the unpredictable nature of the natural LH surge, early natural IVF cycles required intense and frequent monitoring and around the clock availability of the IVF team and laboratory to achieve a successful retrieval [2]. Controlling the timing of ovulation was one of the main achievements that improved the feasibility of natural cycle IVF. This was achieved with the administration of hCG to trigger the ovulation and later the introduction of GnRH antagonist to suppress the endogenous LH surge. Other less known methods to prevent a premature LH surge include endomethacin and clomiphene use [9, 10].

The introduction of hCG injection to trigger ovulation helped reduce the cancellation rates with natural IVF. In a study that included 35 women with infertility and tubal damage and 17 women with reduced ovarian reserve, a total of

202 natural cycle IVFs were performed [4]. All women who participated in this study had normal menstrual function and normal semen parameters in the male partner. The median age was 34 years with a range of 24–40 years. The protocol for natural cycle IVF in this study included initiating follicular scan on day 8 or 9 of a natural cycle, ultrasound monitoring was repeated as appropriate, and hCG 5,000 IU was administered when the follicular diameter reached 16–18 mm. There was no follicular growth documented in 21 cycles. In the 181 cycles where oocyte retrieval was attempted, pregnancy rate per cycle was 12.7% and live birth rate was 8.8%. After four cycles, the cumulative pregnancy rate was 46% and cumulative birth rate was 32% [4]. A subgroup of this cohort received Indomethacin 50 mg three times daily which was administered from Friday until Monday morning to allow delaying hCG administration so that all retrievals could occur on week days. Of these subjects, the rate of oocyte retrieval was 90.4%, oocyte fertilization 71%, and pregnancy rates per cycle 9.6% [4].

McDougall et al. compared modified natural IVF to IVF after stimulation with clomiphene 100 mg daily from day 3–7. The cancellation rate in the modified natural IVF cycle (4/14) was higher than that in the group stimulated with clomiphene (0/16). The clinical pregnancy rate was lower in modified natural IVF group (0%) when compared to that after clomiphene stimulation (18% per transfer) [11]. In a later study, Ingerlev et al. compared modified natural cycle IVF to clomiphene stimulation. This study included good prognosis young patient (<35 years), with unexplained, tubal, or severe male factor infertility and regular cycles. The proportion of cycle that resulted in embryo transfer (53.2%) was higher in the clomiphene group when compared to that in the modified natural cycle IVF group (25.4%). The clinical pregnancy rates in the clomiphene group (18% per cycle and 33.9% per transfer) were higher than those in the modified natural IVF group (3.5 and 13.8%, respectively) [12]. In women with previous poor response (less than four follicles), modified natural cycle IVF had higher implantation rates (14.9%) when compared to the GnRH agonist microflare protocol (5.5%); however, the ongoing pregnancy rates

were similar (6.1% in the natural cycle group and 6.9% in microflare protocol) [13].

While natural IVF cycle with utilization of hCG to trigger ovulation is classified as modified natural IVF, true modified natural IVF cycle refers mainly to the utilization of GnRH antagonists to prevent premature LH surge. The administration of gonadotropins helps supplement the natural gonadotropins expected to fall after the administration of GnRH antagonist, which helps maintain the follicular growth and the estradiol levels [14].

Pelinck et al. described a protocol for modified natural IVF cycle as follows: During spontaneous unstimulated cycles, follicular scans were initiated on cycles days 3 or 8, then repeated daily or every other day. A mean follicular diameter of 14 mm was used to determine the need to start the GnRH antagonist to prevent premature LH surge. At the same day, 150 IU of recombinant FSH (rFSH) was also started. The GnRH antagonist and rFSH were continued daily until the day of triggering of ovulation. The follicular growth was monitored with daily or every other day morning follicular scans, LH, and estradiol levels. hCG 10,000 IU was given when a mean follicular diameter of 18 mm and or an estrogen levels of 0.8 nmol/L (218 pg/dL) were reached. Cycle cancellation occurred if there was premature LH surge documented by an elevated LH levels  $\geq 20$  IU/L (if the mean follicular diameter was less than 15 mm), or regardless of the follicular diameter, if the LH levels were  $\geq 30$  IU/L. Oocyte retrieval occurred 34 h after hCG injection. Analgesia was only given at patient's request. In this protocol, embryo transfer occurred on day 3 and luteal support was provided through hCG injections of 1,500 IU days 5, 8, and 11 after oocytes retrieval [15]. The rate of oocyte retrieval was 76.9% and the rate of 2PN fertilization was 68.2% per oocytes. The rate of transfer was 43.7% per initiate cycle. The success rates of this protocol were initially reported as a birth rate of 13.4% per initiated cycles and 30.8% per embryo transfer [15]. In a later study, the cumulative live birth rate with this protocol after three cycles in a cohort of 350 patients was reported as 20.8% per patient [3]. The same group published a study that looked at the cumulative pregnancy rate after

an average of nine cycles of modified natural cycle (using GnRH antagonist) and reported a modest 8% ongoing pregnancy rate per cycle in a cohort of 268 patients aged 18–36 with regular ovulatory function [14]. In patient with previously poor response with conventional IVF, the success of modified natural IVF cycle was reported to be between 0 and 14% [2].

### 2.3.2 Mild IVF

Mild stimulation IVF can be done using antiestrogens for ovulation induction such as clomiphene or letrozole or using low-dose gonadotropins. Typically, endogenous LH is suppressed by addition of GnRH antagonist once folliculogenesis is underway. Proponents of milder stimulation propose several advantages to this protocol including: the possibilities of a more receptive endometrium and better quality embryos as well as less stress for patient and lower overall costs [16]. This approach may be most effective in young patients with normal ovarian function and good prognosis. Advantages of oral antiestrogen when compared to gonadotropins includes oral administration, lower costs, and wider availability [2].

A mild stimulation cycle using clomiphene can start with 100 mg of clomiphene from day 3 to day 7 of the cycle. Gonadotropins (HMG or rFSH) are given at a dose of 150 IU at day 9 of the cycle. Ultrasound monitoring starts at day 9 of the cycle and then frequently after that. GnRH antagonist is started when the lead follicle reaches 14 mm in diameter and is continued until the day of ovulation induction. hCG is used to trigger ovulation and retrieval occurs 35 h after the hCG injection. Luteal support is given as IM progesterone injection or vaginal suppositories [17].

When compared to conventional IVF, mild IVF using clomiphene (with or without the GnRH antagonist) showed similar clinical pregnancy rate in a retrospective controlled study (37% for minimal stimulation and 41% for conventional IVF) [17]. Weigert et al. compared the success of mild IVF using clomiphene followed by gonadotropins to conventional IVF in a randomized

controlled study. The pregnancy rate per initiated cycle in the mild stimulation cycle (35.1%) was not statistically different from that in the conventional IVF group (29.3%) [18]. Another study compared the clomiphene /gonadotropins protocol with the GnRH antagonist to conventional long stimulation IVF, in patients undergoing their first IVF ICSI for male factor infertility. They found similar pregnancy rates in both treatment groups (41.7 and 40%) [19].

An alternative protocol for mild stimulation IVF was developed to alleviate some of the concerns associated with the utilization of GnRH antagonist including a low LH environment and the requirement of a relatively high dose of gonadotropins [9]. This protocol relies on continuation of clomiphene to inhibit the LH surge. A Japanese group reported their experience with this protocol in 44,345 cycles. Clomiphene was administered at a dose of 50 mg daily until the day before triggering ovulation using a GnRH agonist. If the patient was found to have multifollicular growth, gonadotropins were added at a dose of 150 IU every other day (urinary HMG or rFSH) until the day before the GnRH agonist trigger. GnRH agonist was administered when the follicular diameter reached 18 mm or the estradiol level was  $\geq 300$  pg/mL. Follicular scans were started at day 8. Oocyte retrieval occurred 32–35 h after the ovulation trigger. The rate of premature LH surge with this protocol was 5.1%. Among this small subset of women with detected LH surges, Oocyte retrieval was scheduled immediately when LH levels indicated an imminent ovulation by reaching its peak value and documentation of a drop in 4 h. Oocyte retrieval was delayed 24 h if LH levels suggested the onset of LH surge by documenting increased levels in 4 h. Luteal phase support was provided using dydrogesterone at a dose of 30 mg daily. The embryo transfer occurred at either the four cells or the blastocyst stages. The use of birth control in the preceding month increased the number of oocytes and embryos available. The live birth rate for the fresh embryo transfer of four cell stage embryos was 5.2%, the frozen four cell embryo transfer 0.2%, and for the frozen blastocyst transfer 5.6% [9].

Aromatase inhibitors have been suggested as another way of reducing the total requirement of gonadotropins in ovarian stimulation protocols for mild IVF [20]. The role of aromatase inhibitors in IVF remains poorly studied. Grabia et al. studied letrozole (2.5 mg) as an alternative to clomiphene in minimal stimulation IVF in good prognosis patients. A clinical pregnancy rate of 27% was reported [21].

Gonadotropins may be used without prior oral agents in low doses with the intent to reduce the costs of medications and avoid complications associated with standard controlled ovarian hyperstimulation. They may be initiated on day 2–3 of cycle or in the second half of the follicular phase, although early starts more consistently achieve multifollicular responses [22]. Fernandez-Shaw et al. reported the efficacy of the low gonadotropins IVF protocol in 79 young women with a good prognosis. Patients with polycystic ovarian syndrome, severe endometriosis, ovarian failure, or elevated early follicular FSH or estradiol were excluded. The stimulation starts similar to the traditional long stimulation protocol utilizing GnRH agonist in the luteal phase of the previous cycle. Pituitary suppression is evaluated on day 3 by vaginal ultrasound and estradiol levels ( $< 50$  pg/mL). Gonadotropins were started on day 3 at a low dose of 100 IU rFSH. After 5–6 days of stimulation, the dose is increased if needed. hCG 10,000 IU was given when 1–3 follicles reached 18 mm. Oocyte retrieval was performed 35 h after hCG injection. Luteal support was given in the form of intravaginal micronized progesterone at a dose of 200 mg TID starting the day of oocytes retrieval. The protocol resulted in lower number of embryo when compared to conventional dose gonadotropins (150 IU); however, the pregnancy rates were not different (51.8 vs. 50.7%) [16].

---

## 2.4 Minimal Stimulation IVF and Single Embryo Transfer

One goal of minimal stimulation IVF is to reduce the number of multiple pregnancies as well as the cost of care. The overall number of embryos transferred should be, in theory, lower than that

during conventional IVF, and if combined with single embryo transfer, the cost saving could be considerable [23]. Heijnen et al. compared, in a randomized controlled study, the success of four cycles of mild IVF (gonadotropins started mid follicular phase) with single embryo transfer to three cycles of conventional IVF with transfer of two embryos [24]. Participants were good prognosis women who either had one birth through IVF or did not have IVF before. The patients were younger than 38 and had regular cycles and BMIs. The duration of stimulation, total dose of medication, number of oocyte retrieved, and number of embryo transferred were lower in the mild IVF group when compared to the conventional IVF group. The rate of live birth per started fresh mild IVF cycle with single embryo transfer (15.8%) was lower when compared with that of conventional IVF with dual embryo transfer (24%). Cumulative pregnancy rate and term delivery were calculated by adding the rates of pregnancy of the fresh and frozen cycle that originated from the same treatments. The 1-year cumulative term live birth rate per couple (43.4%) in the mild IVF group was not inferior to that of the conventional IVF group (44.7%). The proportion of multiple pregnancy rates per couple in 1 year in the mild IVF group (0.5%) was significantly lower than that in the conventional IVF group (13.1%) [24].

---

## 2.5 Follicular Flushing

In protocols where few mature follicles are present, optimal yield of oocytes per follicle is critical [25]. Follicular flushing has been advocated as a way to improve the yield of oocytes during oocyte retrieval in the hope of increasing the number of good quality embryos available for transfer. Follicular flushing is thought to have a role in patients undergoing conventional IVF with poor response or in patients undergoing minimal stimulation IVF [26]. The technique of follicle flushing can vary between centers. The most common technique involves the utilization of double lumen needles that can be used to aspirate the follicular fluid. The follicle is then injected with a sterile

solution (such as sterile phosphate-buffered saline) and the fluid is reaspirated. The procedure can be repeated. In one study, the optimal number of flushing was found to be four, and beyond this, the yield of oocyte retrieval is low [25]. Another study showed that only 4.3% of oocytes can be retrieved with the second flushing [27].

A recent randomized controlled trial compared follicular flushing to direct follicular aspiration in poor responders to conventional IVF stimulation. Poor responders were defined as patients who on the day of oocytes retrieval had a cumulative follicle count of 4–8 follicle  $\geq 12$  mm and at least two follicles  $\geq 16$  mm. There was no difference in the total number of oocytes or number of mature oocytes between the study groups. However, retrieval time was two times longer in patients undergoing follicular flushing when compared to direct aspiration technique. Follicular flushing did not improve the fertilization, implantation, or pregnancy rates [28]. Other observational studies did not show any benefit from follicular aspiration in the context of conventional IVF [26, 29].

In the context of minimal stimulation IVF, follicle flushing may be more important because of the expected low number of oocytes retrieved [30]. The competence of oocyte retrieved through flushing in the context of minimal stimulation IVF was studied by Lozano et al. In this study, 271 minimal stimulation IVF cycles were included. The oocytes retrieved were divided into two groups: retrieved with the first aspiration or retrieved through flushing. Embryo morphology and implantation rates were higher in the oocytes retrieved through flushing; however, the fertilization rate and clinical pregnancy rates were comparable in both groups [31, 32].

---

## 2.6 Cost Considerations

Cost of fertility treatment and IVF are under strict scrutiny and often cited as the reason for the absence of insurance coverage of fertility care in the United States [33, 34]. Economic considerations remain the main barrier to increased IVF availability and utilization in the United States [35].



Minimal stimulation IVF is thought to reduce the overall cost of fertility treatment. The cost reduction results from the reduced dose of gonadotropins and the presence of fewer embryos which can reduce the variable costs of IVF laboratories and may permit lower fees for IVF procedures (retrieval, fertilization, and culture fees). The cost of natural IVF cycle based on the cost of limited ultrasound scans, oocyte retrieval, cost of embryo transfer, and cost of medication is thought to be 23% of that of conventional IVF [4]. However, with lower pregnancy rates, cumulative costs incurred to achieve likelihoods of pregnancy rivaling those seen with conventional IVF may not offer savings relative to conventional IVF [7]. Another proposed cost reduction with minimal stimulation IVF occurs if associated with single embryo transfer [24, 36]. Although single embryo transfer may be common with minimal stimulation IVF because of limited numbers of oocytes and viable embryos, it is not by any means within the exclusive domain of minimal stimulation IVF and can be employed with the same benefits in conventional IVF. Single embryo transfer results in an overall reduction in the cost of care of infertility patients by reducing multiple pregnancy rates. When minimal stimulation IVF was associated with single embryo transfer, the incremental cost per additional pregnancy leading to live birth in the conventional IVF was €185,000 when compared to minimal stimulation IVF [24]. It is predicted that with increasing success of single embryo transfer, the option of minimal stimulation IVF in good prognosis patient would reduce the number of multiple pregnancies and the overall cost of care [36].

## 2.7 Conclusion

In conclusion, minimal stimulation IVF is gaining more ground because of increased concern regarding the complications of conventional IVF. Clinical pregnancy rates per cycle are lower with minimal stimulation IVF when compared to conventional IVF. However, with better tolerance of minimal stimulation protocols, cumulative pregnancy rates may be similar. Ideal candidates for minimal stimulation IVF are young patients with

good prognosis or patients who failed conventional IVF. Minimal stimulation IVF has the potential of reducing the side effects of IVF as well as the overall cost of care.

## References

1. Moragianni VA, Penzias AS. Cumulative live-birth rates after assisted reproductive technology. *Curr Opin Obstet Gynecol*. 2010;22:189–92.
2. Verberg MF, Macklon NS, Nargund G, et al. Mild ovarian stimulation for IVF. *Hum Reprod Update*. 2009;15:13–29.
3. Pelinck MJ, Vogel NE, Hoek A, et al. Cumulative pregnancy rates after three cycles of minimal stimulation IVF and results according to subfertility diagnosis: a multicentre cohort study. *Hum Reprod*. 2006;21:2375–83.
4. Nargund G, Waterstone J, Bland J, Philips Z, Parsons J, Campbell S. Cumulative conception and live birth rates in natural (unstimulated) IVF cycles. *Hum Reprod*. 2001;16:259–62.
5. Nargund G, Fauser BC, Macklon NS, Ombelet W, Nygren K, Frydman R. The ISMAAR proposal on terminology for ovarian stimulation for IVF. *Hum Reprod*. 2007;22:2801–4.
6. Heng BC. Reluctance of medical professionals in adopting natural-cycle and minimal ovarian stimulation protocols in human clinical assisted reproduction. *Reprod Biomed Online*. 2007;15:9–11.
7. Kolibianakis E, Zikopoulos K, Camus M, Tournaye H, Van Steirteghem A, Devroey P. Modified natural cycle for IVF does not offer a realistic chance of parenthood in poor responders with high day 3 FSH levels, as a last resort prior to oocyte donation. *Hum Reprod*. 2004;19:2545–9.
8. Steptoe PC, Edwards RG. Birth after the reimplantation of a human embryo. *Lancet*. 1978;2:366.
9. Teramoto S, Kato O. Minimal ovarian stimulation with clomiphene citrate: a large-scale retrospective study. *Reprod Biomed Online*. 2007;15:134–48.
10. Nargund G, Wei CC. Successful planned delay of ovulation for one week with indomethacin. *J Assist Reprod Genet*. 1996;13:683–4.
11. MacDougall MJ, Tan SL, Hall V, Balen A, Mason BA, Jacobs HS. Comparison of natural with clomiphene citrate-stimulated cycles in in vitro fertilization: a prospective, randomized trial. *Fertil Steril*. 1994;61:1052–7.
12. Ingerslev HJ, Hojgaard A, Hindkjaer J, Kesmodel U. A randomized study comparing IVF in the unstimulated cycle with IVF following clomiphene citrate. *Hum Reprod*. 2001;16:696–702.
13. Morgia F, Sbracia M, Schimberni M, et al. A controlled trial of natural cycle versus microdose gonadotropin-releasing hormone analog flare cycles in poor responders undergoing in vitro fertilization. *Fertil Steril*. 2004;81:1542–7.

14. Pelinck MJ, Knol HM, Vogel NE, et al. Cumulative pregnancy rates after sequential treatment with modified natural cycle IVF followed by IVF with controlled ovarian stimulation. *Hum Reprod.* 2008;23:1808–14.
15. Pelinck MJ, Vogel NE, Hoek A, Arts EG, Simons AH, Heineman MJ. Minimal stimulation IVF with late follicular phase administration of the GnRH antagonist cetrorelix and concomitant substitution with recombinant FSH: a pilot study. *Hum Reprod.* 2005;20:642–8.
16. Fernandez-Shaw S, Perez Esturo N, Cercas Duque R, Pons Mallol I. Mild IVF using GnRH agonist long protocol is possible: comparing stimulations with 100 IU vs. 150 IU recombinant FSH as starting dose. *J Assist Reprod Genet.* 2009;26:75–82.
17. Williams SC, Gibbons WE, Muasher SJ, Oehninger S. Minimal ovarian hyperstimulation for in vitro fertilization using sequential clomiphene citrate and gonadotropin with or without the addition of a gonadotropin-releasing hormone antagonist. *Fertil Steril.* 2002;78:1068–72.
18. Weigert M, Krischker U, Pohl M, Poschalko G, Kindermann C, Feichtinger W. Comparison of stimulation with clomiphene citrate in combination with recombinant follicle-stimulating hormone and recombinant luteinizing hormone to stimulation with a gonadotropin-releasing hormone agonist protocol: a prospective, randomized study. *Fertil Steril.* 2002;78:34–9.
19. Lin YH, Hwang JL, Seow KM, Huang LW, Hsieh BC, Tzeng CR. Comparison of outcome of clomiphene citrate/human menopausal gonadotropin/cetrorelix protocol and buserelin long protocol—a randomized study. *Gynecol Endocrinol.* 2006;22:297–302.
20. Mitwally MF, Casper RF. Aromatase inhibition reduces gonadotrophin dose required for controlled ovarian stimulation in women with unexplained infertility. *Hum Reprod.* 2003;18:1588–97.
21. Grabia A, Papier S, Pesce R, Mlayes L, Kopelman S, Sueldo C. Preliminary experience with a low-cost stimulation protocol that includes letrozole and human menopausal gonadotropins in normal responders for assisted reproductive technologies. *Fertil Steril.* 2006;86:1026–8.
22. de Jong D, Macklon NS, Fauser BC. A pilot study involving minimal ovarian stimulation for in vitro fertilization: extending the “follicle-stimulating hormone window” combined with the gonadotropin-releasing hormone antagonist cetrorelix. *Fertil Steril.* 2000;73:1051–4.
23. Ledger WL. Favourable outcomes from “mild” in-vitro fertilisation. *Lancet.* 2007;369:717–8.
24. Heijnen EM, Eijkemans MJ, De Klerk C, et al. A mild treatment strategy for in-vitro fertilisation: a randomised non-inferiority trial. *Lancet.* 2007;369:743–9.
25. Bagtharia S, Haloob AR. Is there a benefit from routine follicular flushing for oocyte retrieval? *J Obstet Gynaecol.* 2005;25:374–6.
26. Hill MJ, Levens ED. Is there a benefit in follicular flushing in assisted reproductive technology? *Curr Opin Obstet Gynecol.* 2010;22:208–12.
27. El Hussein E, Balen AH, Tan SL. A prospective study comparing the outcome of oocytes retrieved in the aspirate with those retrieved in the flush during transvaginal ultrasound directed oocyte recovery for in-vitro fertilization. *Br J Obstet Gynaecol.* 1992;99:841–4.
28. Levens ED, Whitcomb BW, Payson MD, Larsen FW. Ovarian follicular flushing among low-responding patients undergoing assisted reproductive technology. *Fertil Steril.* 2009;91:1381–4.
29. Knight DC, Tyler JP, Driscoll GL. Follicular flushing at oocyte retrieval: a reappraisal. *Aust N Z J Obstet Gynaecol.* 2001;41:210–3.
30. Lozano DH, Fanchin R, Chevalier N, et al. Optimising the semi natural cycle IVF: the importance of follicular flushing. *J Indian Med Assoc.* 2006;104:423–7.
31. Mendez Lozano DH, Fanchin R, Chevalier N, et al. [The follicular flushing duplicate the pregnancy rate on semi natural cycle IVF]. *J Gynecol Obstet Biol Reprod (Paris).* 2007;36:36–41.
32. Mendez Lozano DH, Brum Scheffer J, Frydman N, Fay S, Fanchin R, Frydman R. Optimal reproductive competence of oocytes retrieved through follicular flushing in minimal stimulation IVF. *Reprod Biomed Online.* 2008;16:119–23.
33. Philips Z, Barraza-Llorens M, Posnett J. Evaluation of the relative cost-effectiveness of treatments for infertility in the UK. *Hum Reprod.* 2000;15:95–106.
34. Jain T, Harlow BL, Hornstein MD. Insurance coverage and outcomes of in vitro fertilization. *N Engl J Med.* 2002;347:661–6.
35. Hammoud AO, Gibson M, Stanford J, White G, Carrell DT, Peterson M. In vitro fertilization availability and utilization in the United States: a study of demographic, social, and economic factors. *Fertil Steril.* 2009;91:1630–5.
36. Nygren KG. Single embryo transfer: the role of natural cycle/minimal stimulation IVF in the future. *Reprod Biomed Online.* 2007;14:626–7.



Biennial Review of Infertility

Volume 2, 2011

Racowsky, C.; Schlegel, P.N.; Fauser, B.C.J.M.; Carrell, D.  
(Eds.)

2011, XIV, 296 p. 37 illus., 25 illus. in color., Hardcover

ISBN: 978-1-4419-8455-5