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Review

Ovarian stimulation protocols for IVF: is more better than less?

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KEY MESSAGE

Conventional IVF stimulation protocols aim to maximize oocyte yields; mild stimulation protocols address the need for reduced patient discomfort and risk of ovarian hyperstimulation syndrome; both are associated with benefits and disadvantages. Physicians should consider individual patient clinical characteristics, medical history and IVF goals when determining the best treatment options.

A B S T R A C T

Conventional ovarian stimulation protocols for IVF are designed to achieve maximum oocyte yields. Conventional protocols, however, are associated with patient discomfort, increased risk of ovarian hyperstimulation syndrome and higher costs. In recent years, mild stimulation protocols have risen in popularity. These protocols typically use lower doses (≤150 IU/day), shorter duration of exogenous gonadotrophins, or both, compared with conventional protocols, with the goal of limiting the number of retrieved oocytes to less than eight. The pregnancy rate per cycle (fresh embryo transfer only) is lower with mild stimulation compared with conventional stimulation; however, the cumulative pregnancy rate seems to be comparable between the approaches. Reports are conflicting on the effects of mild versus conventional stimulation on embryo quality. This article expands on a live debate held at the American Society for Reproductive Medicine 2015 Annual Meeting to compare the advantages and disadvantages of the 'more is better' (conventional protocol) versus 'less is best' (mild protocol) approaches to ovarian stimulation. Both protocols are associated with benefits and challenges, and physicians must consider the needs of the individual patient when determining the best treatment options. Further prospective studies comparing a variety of outcomes with conventional and mild stimulation are needed.

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Introduction

The use of gonadotrophin for ovarian stimulation plays a central role in the treatment of infertility. Studies characterizing pituitary regulation of gonadal function in the early 1900s laid the foundation for the development of gonadotrophin preparations for ovarian stimulation (Lunenfeld, 2004; Practice Committee of American Society for Reproductive Medicine, 2008). In natural cycles, GnRH stimulates the secretion of FSH and LH from the anterior pituitary gland (Baerwald et al., 2012). Follicle development in the ovary and the selection of a dominant follicle is regulated by FSH and LH. Ovulation is then induced by a mid-cycle surge of LH. In the 1940s, HMG, which contains a 1:1 mixture of FSH and LH activity, was first extracted from postmenopausal urine and became commercially available a decade later (Leao and Esteves, 2014; Practice Committee of American Society for Reproductive Medicine, 2008). In the 1960s, HMG began to be used to treat infertility in anovulatory women, and in the 1980s HMG was used in anovulatory women for the stimulation of multiple follicles in IVF cycles (Macklon et al., 2006; Practice Committee of American Society for Reproductive Medicine, 2008). In the mid-1990s, antibody-based purification techniques led to the development of highly purified urinary FSH from HMG, and advances in recombinant DNA technology were used to develop recombinant FSH (rFSH) (Practice Committee of American Society for Reproductive Medicine, 2008; Leao and Esteves, 2014). Both highly purified urinary and recombinant gonadotrophin products demonstrate superior quality and performance compared with earlier crude urinary preparations (Practice Committee of American Society for Reproductive Medicine, 2008).

Today, the most commonly used gonadotrophins in controlled ovarian stimulation protocols are highly purified urinary HMG and rFSH (Fatemi et al., 2012). The administration of exogenous gonadotrophins maintains FSH and LH levels above a critical threshold needed to stimulate the development of many follicles, thus allowing the retrieval of multiple oocytes in a single IVF cycle (Fatemi et al., 2012). Concomitant administration of a GnRH agonist or antagonist is used to prevent a premature LH surge, which may occur with the development of multiple dominant follicles. Final oocyte maturation and ovulation is typically triggered with a bolus of GnRH agonist, HCG (a hormone that is biologically similar to LH but has a longer half-life), or both (Humaidan and Alsbjerg, 2014).

Conventional ovarian stimulation protocols aim to maximize the number of oocytes collected to obtain more embryos, thus enabling the selection of the best quality embryos for transfer and the generation of surplus embryos that can be cryopreserved for use in additional, unstimulated cycles (Fauser et al., 2010). Although conventional protocols are associated with good clinical outcomes, the high dose of gonadotrophins administered tends to increase patient discomfort, costs, the likelihood of required frequent hospital visits to monitor ovarian response and the risk of complications, such as ovarian hyperstimulation syndrome (OHSS), ovarian torsion and increased bleeding after excessive punctures to remove a large number of oocytes (>30) (Bodri et al., 2008; Steward et al., 2014; Verberg et al., 2008).

In recent years, mild stimulation protocols, which offer more affordable and safer options for patients, have risen in popularity. As with standard stimulation protocols, what has been considered 'mild stimulation' has varied widely; mild stimulation protocols typically use lower doses (≤150 IU/day), shorter duration of exogenous gonadotrophins, or both, compared with conventional protocols, with the goal of limiting the number of retrieved oocytes to less than eight (Fauser et al., 2010). Studies have shown that the pregnancy rate per cycle is lower with mild stimulation compared with conventional stimulation, which may be of particular concern to older patients; however, the cumulative pregnancy rate (from fresh and frozen transfers from a single cycle, or from cumulative IVF cycles) was shown to be comparable with both approaches (Fatemi et al., 2013; Heijnen et al., 2007). Reports are also conflicting on the effects of mild versus conventional stimulation on embryo quality (Arce et al., 2014; Ata et al., 2012; Baart et al., 2007; Labarta et al., 2012).

A debate was recently held at the American Society for Reproductive Medicine (ASRM) 2015 Annual Meeting to compare and contrast the advantages and disadvantages of the 'more is better' (conventional protocol) versus 'less is best' (mild protocol) approaches to ovarian stimulation based on published studies. Here, we provide a comprehensive overview of both sides of the debate to discuss the benefits and challenges associated with conventional and mild stimulation protocols (**Table 1**).

More is better: conventional stimulation protocols

With this approach, the optimal number of oocytes is the most that can be safely retrieved, thereby increasing the number of embryos available for cryopreservation, with the goal of helping patients complete their family in the least number of stimulated cycles. Compared with secondary frozen embryo transfers, i.e., with residual embryos frozen from an initial fresh transfer cycle, repetitive fresh cycles are

Table 1 – Advantages and disadvantages of conventional and mild stimulation protocols.

Conventional stimulation	Mild stimulation
Advantages	**Advantages**
Maximizes the number of oocytes retrieved	Minimizes treatment burden and reduces risk of complications
Greater number of embryos for cryopreservation	Lower doses of gonadotrophins and fewer injections
May help patients complete their family in fewer stimulated cycles	Possible association with better embryo quality
Higher pregnancy rates per cycle	Lower per-cycle drop-out rates
Disadvantages	**Disadvantages**
Greater patient discomfort and increased risk of complications, including OHSS[a]	Higher per-cycle cancellation rate; may require multiple stimulated cycles to achieve a pregnancy
Increased per-cycle costs associated with higher gonadotrophin dosage	Few embryos available for cryopreservation
Higher per-cycle drop-out rates	Increased cumulative costs associated with multiple fresh cycles

[a] When used with a traditional HCG trigger. OHSS, ovarian hyperstimulation syndrome.

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associated with greater cumulative risks and costs, including injectable medications, patient monitoring, anaesthesia and surgical risks, patient stress, higher drop-out rates, risk of OHSS and other healthcare-related costs. When comparing conventional and mild ovarian stimulation protocols, physicians and patients must consider whether obtaining higher egg yields (defined as more than 15 oocytes) has an effect on the number of embryos available for freezing, embryo quality, pregnancy rates per cycle, and cumulative pregnancy rates, as well as potential risks to the patient. Cumulative pregnancy rate is an important outcome for consideration, as a UK study found that per-cycle live birth rates were nearly 30% in the first cycle and remained over 20% through cycle four and over 15% through cycle nine (Smith et al., 2015). Additionally, evaluation of cumulative pregnancy rates removes discrepancy in the reporting of per-cycle outcomes based on embryo transfer compared with initiated ovarian stimulation, which would include fresh and subsequent frozen transfers as one cycle (Smith et al., 2015). Caution should be exercised in the application of IVF data obtained in Europe compared with the USA, however, owing to differences in the health systems. For example, European patients tend to use intracytoplasmic sperm injection (ICSI) less often and have higher rates of elective single embryo transfer (Myers, 2015; Smith et al., 2015).

The effects of high egg yields on embryo cryopreservation and embryo quality

As expected, studies have shown that high egg yields result in a greater number of embryos available for freezing. It has been reported that about 70% of cycles yielding over 16 oocytes had embryos for cryopreservation compared with about 40% of cycles yielding six to 10 oocytes (**Figure 1**) (Baker et al., 2015; Briggs et al., 2015). To date, high egg yield has not been shown to compromise embryo quality. A retrospective study of women undergoing IVF or ICSI in The Netherlands reported similar fertilization rates and implantation rates with high egg yields (11–20 and over 20 oocytes) and lower yields (≤10 oocytes) (Kok et al., 2006). A separate retrospective cohort study of over 400,000 IVF cycles found that retrieving a higher number of oocytes was not associated with an increased risk of miscarriage (Sunkara et al., 2014). Furthermore, ovarian stimulation has not been shown to affect embryo aneuploidy rates. A prospective cohort study reported similar aneuploidy rates (assessed using fluorescent in situ hybridization [FISH]) in stimulated versus natural IVF cycles) (Labarta et al., 2012); however, FISH is an older technique, and again caution should be exercised in interpreting these results. A separate study using a more comprehensive and accurate method of genetic screening (array comparative genomic hybridization) also found no association between aneuploidy rate and the number of embryos generated (Ata et al., 2012). Therefore, findings from these studies suggest that higher doses of gonadotrophins used in conventional stimulation protocols are not likely to have a negative effect on embryo quality.

The effects of high egg yields on pregnancy and live birth rates

Studies have shown that, among women with normal ovarian reserve, live birth rates peak with about 15 retrieved oocytes in fresh IVF cycles and remain relatively constant with about 16–20 oocytes retrieved (Steward et al., 2014; Sunkara et al., 2011; van der Gaast et al., 2006) (**Figure 2**); this trend is observed across age groups (Yih et al., 2005). Fewer studies have reported the effects of high egg yields on cumulative, i.e. fresh plus frozen transfers, pregnancy outcomes. A retrospective study of over 7500 IVF cycles conducted in Australia reported no decrease in live birth rates with high egg yields; however, the authors cautioned that data were sparse for retrievals with over 15 oocytes (Briggs et al., 2015). Data from a prospective randomized trial that included patients from Europe and North America (ENGAGE; *n* = 1506) showed that high egg yields (>18 oocytes) were associated with more good-quality embryos, comparable live birth rates and increased cumulative pregnancy rates compared with lower oocyte yields (**Figure 3**) (Fatemi et al., 2013). A large retrospective cohort analysis (*n* = 1099) in Belgium found that cumulative live birth rate significantly increased with ovarian response and the number of retrieved oocytes (zero to three oocytes versus four to nine oocytes versus 10–15 oocytes versus over 15 oocytes) (Drakopoulos et al., 2016). A similar finding was reported in a large retrospective cohort study in Chinese women (*n* = 2455) undergoing their first IVF cycle (Ji et al., 2013). It is notable that, in both studies, high responders had significantly better cumulative live birth rates compared with poor and suboptimal responders and women with normal response (Drakopoulos et al., 2016; Ji et al., 2013). Taken together, data from

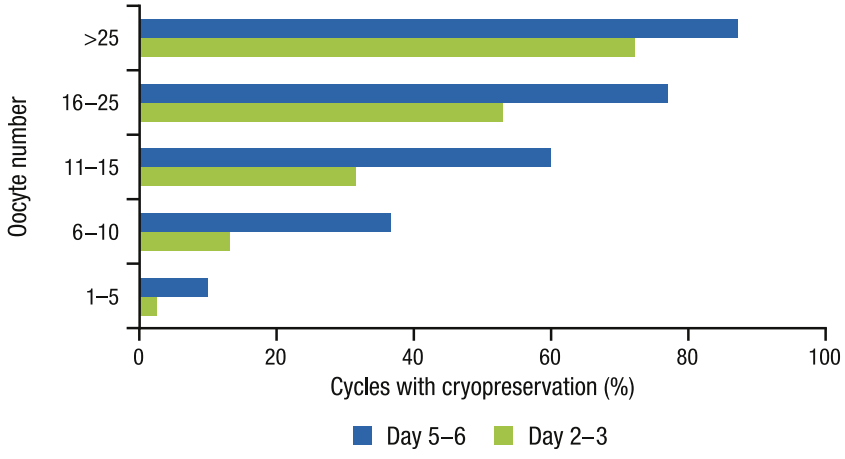

Figure 1 – Percentage of cycles with cryopreservation and increasing oocyte yield (Baker et al., 2015). Based on Society for Assisted Reproductive Technology (SART) data from 2004–2010.

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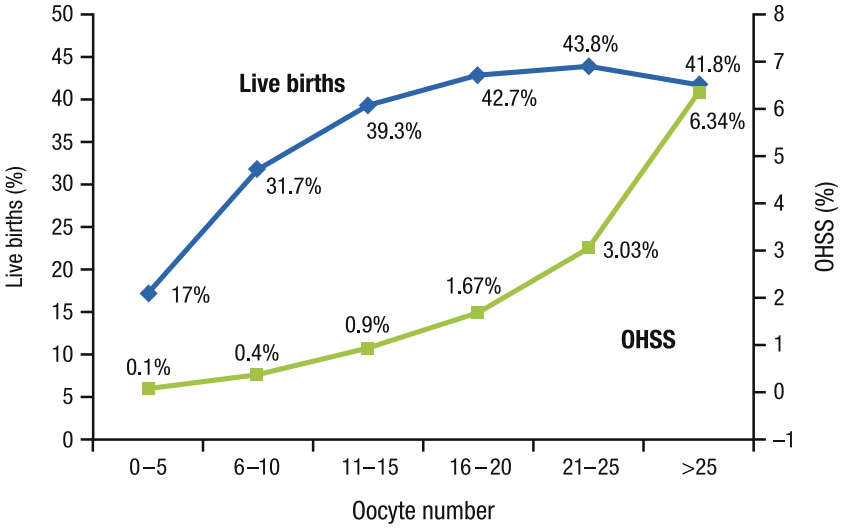

Figure 2 – Rates of live birth and ovarian hyperstimulation syndrome with increasing oocyte yield (Steward et al., 2014). Based on Society for Assisted Reproductive Technology (SART) data from 2008–2010. Figure reprinted from *Fertility and Sterility*, Vol. 101, Steward RG, et al., Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth; an analysis of 256,381 in vitro fertilization cycles, pp 967–973, ©2014 with permission from Elsevier and the American Society for Reproductive Medicine. OHSS, ovarian hyperstimulation syndrome.

these studies suggest that high egg yields do not adversely affect pregnancy and live birth outcomes.

Association of high egg yields with OHSS

Ovarian hyperstimulation syndrome is a serious complication of ovarian stimulation and is characterized by enlarged ovaries, abdominal distention and discomfort, ascites, nausea and vomiting, and, in severe cases, oliguria, i.e. reduced urine output, liver dysfunction and respiratory distress syndrome (Aboulghar and Mansour, 2003). The incidence of OHSS has been shown to increase with the number of oocytes retrieved. On the basis of the Society for Assisted Reproductive Technology (SART) data from 2008–2010, the incidence of OHSS was 0.37% in fresh cycles with six to 10 oocytes and 1.67% in fresh cycles with 16–20 oocytes (**Figure 2**) (Steward et al., 2014). A large retrospective cohort study (n = 2455) of Chinese women undergoing their first IVF cycle found a similar trend, although the incidence of moderate to severe OHSS was higher among all patient groups (2.07% in fresh cycles with six to 10 oocytes and 7.05% in fresh cycles with ≥16 oocytes) (Ji et al., 2013). The risk of OHSS must be balanced with the risks and costs of another cycle; however, physicians should keep in mind that most patients do not develop OHSS. Moreover, OHSS is becoming less of a concern owing to strategies developed to manage and prevent OHSS. For patients receiving a conventional GnRH an-

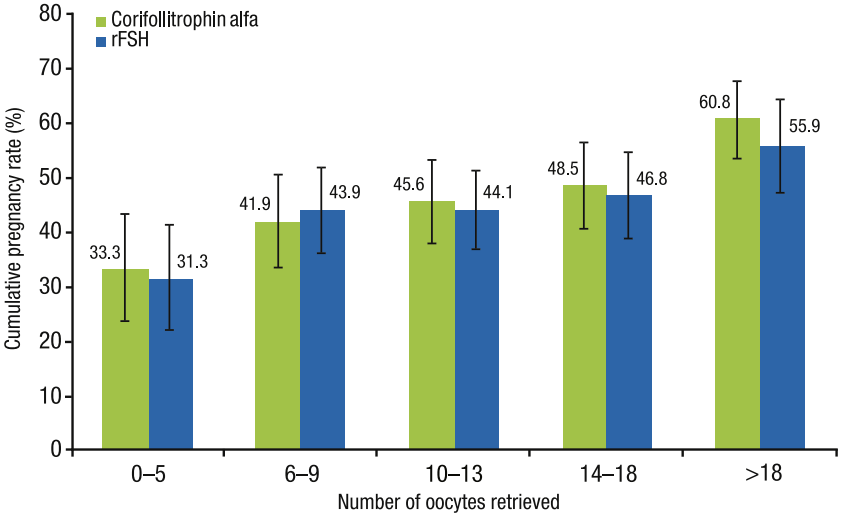

Figure 3 – Cumulative pregnancy rate with increasing oocyte yield (Fatemi et al., 2013). Figure reproduced from Fatemi HM et al., High ovarian response does not jeopardize ongoing pregnancy rates and increases cumulative pregnancy rates in a GnRH-antagonist protocol, *Human Reproduction* 2013;28(2):442–452 by permission of Oxford University Press and the European Society of Human Reproduction and Embryology. rFSH, recombinant follicle-stimulating hormone.

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tagonist protocol, the use of a GnRH agonist trigger seems to substantially reduce (but not eliminate) the risk of OHSS (Babayof et al., 2006; Engmann et al., 2008; Fatemi et al., 2014; Humaidan et al., 2005, 2013). A retrospective study of 2253 cycles identified a threshold of 24 or more retrieved oocytes to recommend a freeze-all cycle, a strategy in which a fresh transfer is avoided to allow the ovaries to return to a normal state before attempting pregnancy in order to prevent OHSS (Verwoerd et al., 2008). Other strategies that have been successfully used to minimize OHSS risk include lowering the dose of HCG, cabergoline treatment, coasting, i.e., withholding gonadotrophin therapy, aggressive use of paracentesis, and, as a last resort, no trigger (Aboulghar, 2010).

In conclusion, data suggest that high egg yields result in more embryos available for cryopreservation without compromising embryo quality. The generation of more frozen embryos may increase the chances of completing the family in fewer stimulated cycles, resulting in a higher cumulative chance of pregnancy per oocyte retrieval and lower overall risk and cumulative costs by reducing the need for additional stimulated cycles.

Less is best: mild stimulation protocols

With the mild stimulation approach, physicians focus on optimizing patient care rather than obtaining the highest yield of oocytes. The goal of all IVF is to achieve the birth of a healthy singleton baby, and mild stimulation protocols aim to do so while minimizing treatment burden and risk of complications. 'Controlled ovarian stimulation' is a misnomer, as the starting dose of gonadotrophin is the only controlled aspect of ovarian stimulation; once the initial dose is administered, ovarian response can be variable and difficult to predict or ultimately control. Outcomes are entirely dependent on the individual patient's response and resultant embryo quality. For example, data from a study by Sunkara et al. (2011) in over 400,000 IVF cycles in the UK has shown a wide variability in the number of oocytes retrieved (range of one to 40 oocytes per cycle). Furthermore, a meta-analysis of three randomized controlled trials showed the optimal number of oocytes retrieved per cycle is dependent on the stimulation protocol (Verberg et al., 2009a), suggesting that lower stimulations that produce lower numbers of oocytes may not necessarily negatively affect outcomes. Physicians should therefore get away from the 'per number' paradigm, as the optimal number of oocytes to retrieve is a surrogate outcome.

The effects of mild stimulation on embryo quality

Evidence suggests that mild stimulation protocols may be associated with better quality embryos compared with conventional protocols (Reindollar and Goldman, 2012; Revelli et al., 2011). A higher daily dose of FSH was found to be associated with errors in meiotic cell division in IVF embryos (Katz-Jaffe et al., 2005), and a separate study found that a shorter duration of stimulation and, consequently, a lower total dose of gonadotrophin, produced better quality embryos than protocols with a longer duration of stimulation (Hohmann et al., 2003). A prospective randomized trial comparing mild and conventional stimulation protocols in patients undergoing IVF ($n = 111$) showed that milder ovarian stimulation was associated with a lower oocyte yield (8.3 versus 12.1 oocytes), but significantly fewer aneuploid embryos per patient (45% versus 63%) (Baart et al., 2007); however, aneuploidy was assessed using an old method (FISH) that is no longer frequently used. Lastly, a more recent study in patients undergoing IVF or ICSI ($n = 265$) reported a dose-response relationship with oocyte yield and rFSH, yet the number of good-quality blastocysts was similar across all doses of rFSH despite higher doses generating more oocytes (Arce et al., 2014). Therefore, mild stimulation may have a beneficial effect on embryo quality, enabling similar outcomes to conventional stimulation. Many of the studies that have evaluated this topic, however, used older techniques for assessing embryo quality, and further studies are therefore needed, including studies that use advanced methods of genetic screening (Revelli et al., 2011).

The effects of mild stimulation on pregnancy and live birth rates

One of the main barriers to the use of mild stimulation protocols in clinical practice is the concern that decreased ovarian response will reduce pregnancy rates (Verberg et al., 2009b). Cycle cancellation rates do tend to be higher with mild stimulation protocols, resulting in a need for additional IVF cycles (Fauser et al., 1999; Verberg et al., 2009b). A meta-analysis of 10 studies (about 2000 IVF cycles), however, showed that lower doses of rFSH (100–150 IU/day) yielded slightly fewer oocytes, but similar ongoing pregnancy rates and a reduced risk of OHSS compared with higher doses of rFSH (200–250 IU/day) (Sterrenburg et al., 2011). Furthermore, a retrospective analysis of more than 650,000 IVF cycles found that higher FSH doses were associated with lower live birth rates (Baker et al., 2015). As we have described, the best way to evaluate success is to consider cumulative, i.e. multiple IVF cycles, outcomes, rather than outcomes per IVF cycle with fresh embryo transfer (Heijnen et al., 2004). Indeed, recent modifications to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for infertility treatments recommend that both live birth rate and cumulative live birth rate be reported as primary outcomes in trials with multiple treatment cycles (Legro et al., 2014). A large randomized trial in patients undergoing IVF ($n = 404$; over 750 cycles) showed that cumulative live birth rates were similar in patients assigned to a mild stimulation protocol with single embryo transfer and those assigned to standard stimulation with double embryo transfer; the mean number of cycles was 2.3 with mild stimulation and 1.7 with conventional stimulation (**Figure 4**) (Heijnen et al., 2007). In this study, the mild stimulation protocol was also shown to significantly reduce the rate of multiple pregnancy and overall costs per live birth (Heijnen et al., 2007). When interpreting clinical data, the patient populations of many studies tend to have more favourable characteristics, e.g. normal ovarian reserve or relatively young, compared with the general real-world IVF population.

Mild stimulation protocols help reduce the physical, emotional and financial burden of IVF

Physicians must consider the effect of IVF treatment from a patient's perspective, including the risks, per cycle costs, and patient discomfort associated with higher stimulation protocols. High egg yields are associated with an increased risk of OHSS and patient discomfort related to high doses of gonadotrophins and increased number of injections (**Figure 2**) (Mahajan, 2013; Steward et al., 2014). Although newer approaches, such as the use of a GnRH agonist trigger in conventional GnRH antagonist protocols, also minimize the incidence of OHSS, mild stimulation protocols still represent an important approach for some patients. An analysis of 470,000 IVF cycles in the

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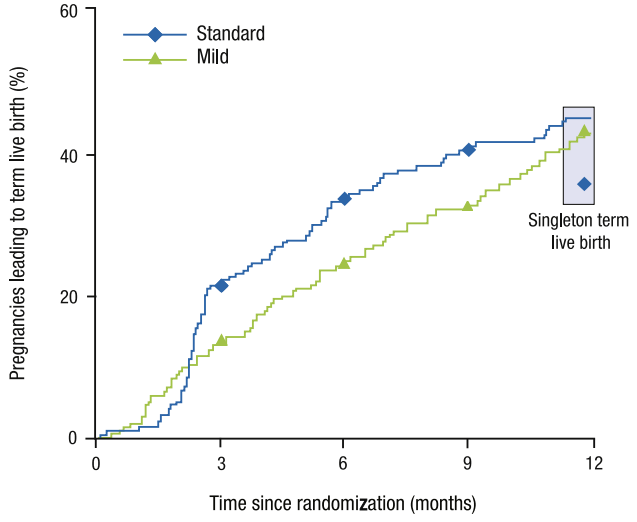

Number of patients

Standard	199	152	123	106	97
Mild	205	174	149	130	109

Figure 4 – Cumulative live birth rates after 12 months of treatment with conventional and mild stimulation protocols (Heijnen et al., 2007). Mild protocol: mild ovarian stimulation with GnRH antagonist and single embryo transfer; standard protocol: standard ovarian stimulation with GnRH antagonist and dual embryo transfer. Figure reprinted from *The Lancet*, Vol. 369, Heijnen EMEW et al., A mild treatment strategy for in-vitro fertilization: a randomized non-inferiority trial, pp 743–749, ©2007 with permission from Elsevier.

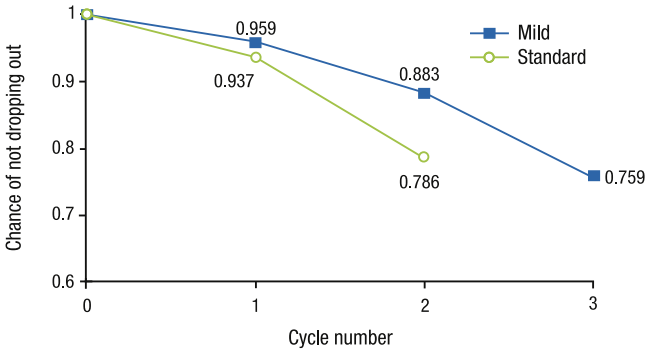

Figure 5 – Kaplan–Meier plot of drop-out rate per cycle for patients treated with conventional and mild stimulation protocols (Verberg et al., 2008). The maximum planned number of cycles was three for conventional stimulation and four for mild stimulation. Patients were considered as treatment drop-outs if they did not return for another IVF cycle within 1 year after the failure of the previous cycle. Figure reproduced from Verberg MFG et al., Why do couples drop out form IVF treatment? A prospective cohort study, *Human Reproduction* 2008;23(9):2050–2055 by permission from Oxford University Press and the European Society of Human Reproduction and Embryology.

USA reported a cumulative discontinuation rate of about 40%, primarily attributed to patient discomfort (Luke et al., 2012). Variation is seen in reported discontinuation rates between studies; however, the drop-out rate has been reported as significantly lower among patients undergoing IVF with mild stimulation compared with those treated with a standard stimulation protocol (**Figure 5**) (Heijnen et al., 2007; Verberg et al., 2008). Mild stimulation protocols have been associated with a reduction in anxiety and treatment-related stress (Verberg et al., 2008). In addition, a randomized controlled study demonstrated that women had fewer depressive symptoms after IVF failure with mild stimulation compared with failure after conventional stimulation (de Klerk et al., 2007). Mild stimulation protocols are also associated with a lower cost per fresh IVF cycle than conventional stimulation protocols (Baker, 2013; Verberg et al., 2009b), although cumulative costs may be higher for some patients owing to the greater average number of stimulated cycles required to achieve a pregnancy.

Improved IVF techniques have reduced the need for high egg yields

Over the past 30 years, IVF success rates have significantly improved. Over the past decade, SART registry data indicate that live birth rates per IVF cycle have noticeably increased, particularly for patients younger than 35 years (37.5% in 2003 versus 40.1% in 2013) using the transfer of multiple embryos in a distinct proportion of women (Society for Assisted Reproductive Technology, 2013). In the USA, IVF results are better than Europe; possible reasons for this discrepancy include more well-trained embryologists, higher use of ICSI, better incubators (e.g., closed system, low oxygen), more embryo quality assessments (i.e., time-lapse monitoring), preimplantation genetic screening, and greater use of day 5 cultures (Gleicher et al., 2006; Baker et al., 2010; Kupka et al., 2016; Society for Assisted Reproductive Technology, 2013). The continued development of improved genetic screening techniques and their increasing use in IVF cycles may help to further improve outcomes. The costs associated with fresh transfer IVF cycles, however, are more than two-fold higher in the USA compared with Europe (Connolly et al., 2010). Higher IVF success rates in the USA should offer more incentive to retrieve fewer oocytes, although clinicians must ensure that a sufficient number of oocytes are retrieved if procedures such as day 5 culture, preimplantation genetic screening, or both, are to be used. Furthermore, findings from a retrospective analysis of over 23,000 ICSI cycles in good-prognosis patients showed that only one out of every 20 retrieved oocytes resulted in a live birth (Stoop et al., 2012), suggesting that the additional oocytes obtained with higher stimulation may be wasteful and redundant. Therefore, obtaining a high egg yield may no longer be necessary to achieve successful outcomes.

In summary, instead of focusing on obtaining the highest possible pregnancy rates per cycle, regardless of consequences, physicians should take a more holistic approach, recognizing the broader endpoint of a healthy singleton gestation while taking into account paradigms that are relevant to the patient, such as minimization of treatment burden and complications. With milder protocols, however, patients must be willing to accept the potential of a longer time to pregnancy, as a greater average number of stimulated cycles are required to achieve a pregnancy compared with conventional stimulation protocols.

Conclusions

Conventional stimulation protocols are designed to achieve maximum oocyte yields, but are also associated with patient discomfort, in-

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creased risk of OHSS and higher costs. Mild stimulation protocols have been developed to address these patient concerns, yet widespread use remains limited owing to reports of lower pregnancy rates compared with conventional stimulation. Older patients may not be willing to accept the potential of a longer time to pregnancy. Other patients may prefer to generate more embryos for cryopreservation in an attempt to limit the number of stimulated cycles needed to achieve their family goals. A variety of alternative stimulation protocols and ovulation triggers have also been evaluated and can be used to meet patients' needs. Physicians must therefore consider the needs of the individual patient when determining the best treatment options. Many patients may benefit most from an individualized protocol that considers the patient's unique characteristics, needs, and treatment history and combines elements from standard protocols to maximize the chances of becoming pregnant by obtaining oocyte quantities relative to the burden of treatment. Further prospective studies comparing a variety of outcomes between different stimulation protocols are needed to better guide stimulation decisions.

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