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Mild ovarian stimulation for in vitro fertilization: one perspective from the USA

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Abstract
Purpose To provide a perspective regarding mild ovarian stimulation, taking into account particular issues relevant in the United States
Methods Literature review and editorial commentary
Results Mild ovarian stimulation for IVF has some proven and some theoretical advantages over conventional stimulation, such as lower risk of ovarian hyperstimulation syndrome and lower cost per fresh IVF cycle. However, cumulative live birth rate, including transfers from fresh and frozen embryos, is likely to be lower with mild stimulation. The cost-effectiveness of mild stimulation IVF in the United States has not been established.
Conclusions Mild ovarian stimulation is an appropriate option to consider for certain patient groups or based on patient preference. However, significant potential disadvantages limit its widespread acceptability for patients in the United States at this time.

Keywords Assisted reproductive technology · In vitro fertilization · Mild ovarian stimulation

Capsule Although mild ovarian stimulation has some advantages, concerns regarding lower cumulative live birth rate and unproven cost-effectiveness currently limit its use in the United States.

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Defining mild ovarian stimulation

Although there is no consistent definition of mild-ovarian stimulation for in vitro fertilization (IVF) in the medical literature, the International Society for Mild Approaches in Assisted Reproduction (ISMAAR) consensus group has proposed that the number of oocytes retrieved with "mild IVF" protocols be in the range of 2 to 7 and "conventional IVF" be the term utilized when the goal is to collect 8 or more oocytes [1]. Some authors have suggested that minimal stimulation be the term used when there is an aim to retrieve approximately 5 oocytes whereas mild simulation be the term used when the goal is 10 oocytes maximum [2]. The general principle is that mild ovarian stimulation is less aggressive than may be considered typical for IVF.

Mild stimulation typically involves lower doses and/or shorter duration of exogenous gonadotropin than would typically be used with a conventional stimulation protocol for IVF [3]. Follicle stimulating hormone (FSH) or human menopausal gonadotropin (HMG) are typically administered at a dose no higher than 150 IU/day [1]. Gonadotropin releasing hormone antagonists (GnRH antagonists) are now used routinely in mild stimulation protocols for the prevention of ovulation. Mild stimulation protocols often include the use of oral medications such as clomiphene citrate or aromatase inhibitors, either alone or in combination with gonadotropin. Modified natural cycle IVF, with use of GnRH antagonist and FSH add-back in the late follicular phase, is an option that can also be utilized [4, 5].

In contrast to the protocols just described, natural cycle IVF can also be performed without the use of human chorionic gonadotropin (hCG), GnRH antagonist, gonadotropin, or oral medication. Natural cycle IVF without use of any medications is associated with high rates of unexpected

ovulation, retrieval of no mature oocyte, and low rates of success [4]. For these reasons, this treatment is utilized infrequently and will not be discussed further. Perhaps the focus of discussion should be on "mild ovarian response" as a goal rather than "mild stimulation," as the latter term implies an emphasis on the type and dose of medications used for ovarian stimulation [6]. This review will focus on the mild stimulation protocols that are used with a goal of retrieving 2–7 oocytes.

Reasons to consider mild stimulation

There are multiple sound reasons for including the option of mild stimulation in discussions with patients who are undergoing in vitro fertilization (Table 1). Proposed advantages of mild stimulation include patient preference, reduced risk of ovarian hyperstimulation syndrome, decreased cost per fresh IVF cycle, and possibly improved pregnancy outcome. Mild stimulation may be a particularly good choice to consider for certain patient populations. Patient preference is an important consideration in choosing an ovarian stimulation protocol. Some patients may express concern about the side effects associated with conventional controlled ovarian stimulation for IVF.

It is expected that mild ovarian stimulation may be associated with fewer psychosomatic side effects compared with conventional stimulation, particularly if the conventional stimulation is aggressive. However, there was no difference between the mild and conventional stimulation groups with respect to anxiety, depression, physical discomfort or sleep disturbances in a randomized trial, perhaps because only a slight higher mean number of oocytes was retrieved with standard treatment compared with mild treatment (8.5 vs 6.9) [7]. But in this same trial, the rate of drop-out was significantly lower with mild treatment [8].

Another issue related to patient preference is that some patients desire few or no embryos for cryopreservation. Although these patients could inseminate a minimal number of oocytes and cryopreserve the remainder as oocytes rather than embryos, retrieval of a minimal number of oocytes is a valid alternative approach. Some patients may wish to avoid the high numbers of injections associated with conventional ovarian stimulation protocols for IVF. Mild stimulation protocols are typically simpler for patients because they involve fewer injections per day and lower total number of days of ovarian stimulation [7]. On the other hand, mild stimulation cycles without the use of pre-treatment oral contraceptives may be more difficult to program, an inconvenience that may an issue for both IVF centers and some patients. Alternative methods for programming of the IVF cycle with mild stimulation need to be studied [6].

Another consideration for future study is the possibility of using semi-quantitative urine pregnancy tests in the initial follow-up of IVF cycles, an option which some patients may appreciate to reduce the number of office visits and blood draws required [9]. Overall, it is apparent that attention is being paid to how IVF treatment can be made more "patient-friendly." Severe ovarian hyperstimulation is a rare but serious complication of superovulation [10]. The risk of thromboembolism and adnexal torsion are increased in IVF complicated by ovarian hyperstimulation syndrome. Mild ovarian stimulation is associated with a greatly reduced incidence of ovarian hyperstimulation syndrome [6].

Supraphysiologic levels of hormones may adversely affect endometrial receptivity [11, 12]. With mild stimulation, potentially detrimental effects of high levels of ovarian hormones such as estradiol and progesterone are minimized. If high levels of estradiol and progesterone are avoided, implantation rate could potentially improve. However, the potential association of reduced endometrial receptivity with more aggressive ovarian stimulation is not conclusive [3]. Supraphysiologic levels of estradiol and progesterone could also in theory adversely affect early placentation and fetal development. There has been concern that even among singletons, IVF cycles are associated with an increased risk of low birth weight [13, 14] as well as an increased risk of pre-eclampsia [14].

Although there are likely multiple contributing factors, adverse outcomes may at least in part be iatrogenic and attributable to ovarian stimulation. It is possible that high circulating levels of products of the corpus luteum, such as

Table 1 Principle advantages and disadvantages of mild ovarian stimulation for IVF

Advantages	Disadvantages
Less patient discomfort	Fewer embryos available for cryopreservation
Fewer injections	Lower livebirth rate per cycle in some studies
Lower cost per fresh IVF cycle	Probable lower cumulative live birth rate (including fresh and frozen transfers from a single oocyte retrieval)
Lower risk of ovarian hyperstimulation syndrome	Cost-effectiveness not proven
Possible improvement in endometrial receptivity (not proven)	
Possible improvement in embryo quality (not proven)	

relaxin, may negatively affect placentation and increase the risk of pregnancy complications such as pre-eclampsia and low birth weight [15]. This hypothesis is currently being tested by our group and others. One observation in support of this hypothesis is that ovarian hyperstimulation syndrome has been associated with a higher risk for low birth weight [16]. In addition, the percentage of low birth weight infants was recently found to be positively correlated with a higher number of oocytes retrieved [17]. Such data suggest that mild ovarian stimulation has the theoretical potential to reduce the risk of low birth weight infants associated with IVF.

As recently reviewed [18], it is important that we adopt an individualized approach to controlled ovarian stimulation. Biomarkers such anti-Mullerian hormone and antral follicle count can help to identify special populations of patients and allow us to match patients with the most appropriate protocol. Mild stimulation protocols are associated with a low risk of ovarian hyperstimulation syndrome and thus may be a good choice for women who are at particular risk for ovarian hyperstimulation syndrome, such as those with polycystic ovarian syndrome [4]. On the other hand, some patients may have a poor ovarian response even if high doses of gonadotropins are administered. These patients may benefit from the cost-savings associated with mild stimulation such as a modified natural cycle IVF protocol [5]. There are limited data regarding the use of mild stimulation for women over age 38. In one large case series reporting on the use of clomiphene-based mild ovarian stimulation, a mature oocyte was retrieved in 68 % of cycles for women aged 40–44 compared with 71 % of women aged 30–34 [19].

Fertility preservation, with cryopreservation of oocytes or embryos, is an important option to offer to women with cancer who are about to undergo potentially gonadotoxic therapy [20]. Avoidance of high estradiol levels may be particularly important for patients with estrogen-dependent cancers who are banking oocytes or embryos. On the other hand, for women about to undergo gonadotoxic treatment, it is also important to obtain as many eggs as safely possible, and mild stimulation may thus not be appropriate if a woman's cancer is not estrogen-dependent.

Other issues that must be considered

Although data are not entirely consistent and many different versions of mild stimulation IVF have been described, a review of the literature raises concern about the efficacy of minimal stimulation IVF compared with conventional IVF [3, 4]. The largest retrospective study analyzed 43,433 cycles completed from 2001 to 2005 in women aged 27–47 years [21]. This study included a protocol in which clomiphene citrate was administered from cycle day 3 until the day before maturation of the follicles was triggered with GnRH agonist, with the addition of 150 IU of FSH or HMG every other day beginning on cycle day 8. In the youngest age group (ages 27–29), the live birth rate was 14.6 % per fresh cycle. The live birth rate dropped steadily with age, such that for the 39–41 year old age group, the live birth rate per fresh cycle was 3.1 %. All rates were much lower than numbers published by the CDC for this timeframe [22].

It is difficult to be certain why live birth rates in the United States appear to be higher than in some other areas of the world, even with conventional IVF. One contributing factor may be differences in gonadotropin dosing [23]. Expectations regarding an appropriate target for egg number may be on average higher in the United States. As noted in the CDC report, 11 % out of 102,478 cycles using fresh non-donor eggs were discontinued before egg retrieval [22]. Among the cancelled cycles, 82.9 % were cancelled for inadequate follicle development whereas 4.2 % were cancelled because of over-response to ovarian stimulation. With mild ovarian stimulation, it is possible that the number of developing follicles will drop below a threshold that is deemed adequate by some patients or IVF centers, an issue that may lead to cancellation, particularly if it is thought that a higher dose of medication has the potential to lead to a more acceptable number of developing follicles in a subsequent cycle. Thus it is important that patients have clear expectations regarding the projected number of follicles that will develop with mild stimulation, and that treatment is individualized to achieve an acceptable ovarian response whenever possible. It is also important to note that although a low egg number with conventional IVF is associated with a poorer prognosis, a modest number of oocytes after mild ovarian stimulation is expected. One study found that optimal implantation rate was noted with 5 oocytes retrieved following mild stimulation versus 10 oocytes with conventional stimulation [24].

In a randomized controlled trial of over 400 patients with a mean age of approximately 33 years, a mild stimulation protocol utilizing low doses of FSH, a GnRH antagonist and transfer of one embryo had a lower live birth rate per cycle compared to conventional stimulation and transfer of two embryos [7]. The live birth rate per initiated cycle was of 15.8 % vs 24.0 %. However, in an intention-to-treat analysis, the cumulative live birth rate per year was similar between the two groups (43.4 % vs 44.7 %, $n=86$ term live births in each group over 1 year), with 11 vs 4 spontaneous pregnancies occurring during non-treatment cycles in the mild stimulation group vs the conventional IVF groups. Although this study is important and intriguing, it is not clear that the conventional IVF group in this study is truly comparable to typical practice in the USA. The live birth rate per cycle, even for the conventional group, appears to

be lower than that in the United States (41.2 % live birth per cycle in 2009 for women under 35, including both term and preterm deliveries) [22].

The issue of embryo cryopreservation is important to consider during discussion of the pros and cons of mild stimulation. Although live-birth rates have traditionally been reported per cycle of IVF treatment, more attention is now being given to the cumulative live birth rate from a course of treatment including multiple fresh and frozen embryo transfers [25]. Some authors have used the term "total reproductive potential" to describe the chance of live birth from a single fresh IVF cycle, including all fresh and frozen embryo transfers which utilized eggs from one fresh cycle [26]. In the randomized trial just described [7], the mean number of embryos cryopreserved per cycle was under 1 (0.9 for mild treatment, 0.6 for standard treatment), despite a mean age of under 33 years. This low number of embryos available for cryopreservation is an important consideration. Frozen non-donor embryos were used in approximately 18 % of all ART cycles performed in the USA in 2009 (26,069 cycles) [22]. In the same year, the live birth rate per frozen embryo transfer cycle was 35.2 % for women under 35 transferring embryos created from non-donor oocytes, 30.8 % if all frozen cycles using non-donor embryos are considered [22]. If mild ovarian stimulation is associated with a low number of embryos available for cryopreservation, this will significantly reduce the "total reproductive potential" of any fresh IVF cycle.

The economic cost of treatment is an important consideration in making a decision about what ovarian stimulation to choose. The cost per fresh IVF cycle is lower with minimal stimulation [7]. However, when all fresh and frozen embryo transfers associated with one oocyte retrieval are considered, it is not clear that mild stimulation IVF is cost-effective in the United States. In many centers, the high cost of oocyte retrieval and embryo culture may outweigh the advantage of reduced cost of the fresh IVF cycle associated with mild IVF. If the success rate with mild stimulation is significantly lower than a program's conventional IVF protocol, the total cost per pregnancy may be higher with mild stimulation [27].

Patients in the United States may have coverage for a limited number of IVF cycles or no IVF coverage at all. Even if couples have insurance coverage for IVF, often no more than 3 cycles are covered. A strategy that results in a reduced live birth rate per cycle may be difficult for patients to accept given these economic constraints. In addition, there is an economic cost with respect to time lost from work for IVF treatment, and this time lost from work would be expected to be greater for a fresh IVF cycle with oocyte retrieval compared with a frozen embryo transfer cycle. Any assessment of economic cost should also take into account the cost of multiple gestations, but the rate of multiple gestation does not necessarily have to be higher with conventional IVF stimulation if elective single embryo transfer is chosen. Although the economic cost of a fresh IVF cycle with mild stimulation is reduced compared with a fresh IVF cycle using conventional ovarian stimulation, the overall cost-effectiveness of mild stimulation has not been proven in the United States.

Some special considerations are relevant for cycles of oocyte donation. It is particularly important to prevent ovarian hyperstimulation syndrome for oocyte donors. Although in the US financial compensation of oocyte donors is permitted, oocyte donors otherwise receive little benefit from the process and the risk to donors must be minimized. On the other hand, there are reasons to retrieve more than just 7 oocytes from an oocyte donor when possible. The risk of severe ovarian hyperstimulation syndrome would be expected to be reduced by virtue of the fact that the donors will not become pregnant in the cycle of controlled ovarian stimulation.

The cost of oocyte donation in the USA is quite high for many reasons including the need to comply with strict FDA screening [28], routine genetic screening [29], compensation to donors, agency fees, and the medical costs for procedures that are charged by individual IVF programs. Given the high cost of oocyte donation, some programs will split oocytes between two recipient couples. This split reduces the cost of screening, monitoring of follicle development, and oocyte retrieval. If few oocytes were retrieved using a minimal stimulation protocol, this strategy of splitting eggs between recipients would not be feasible. Banks of cryopreserved eggs are beginning to provide another option. If few oocytes are retrieved, the costs associated with an oocyte retrieval would be shared by fewer recipients. Finally, if few oocytes are retrieved, recipient couples who are receiving all oocytes from a single donor will have fewer embryos available for cryopreservation, likely a lower cumulative chance of conceiving from a single cycle of oocyte donation, and a lower chance of having the potential to have a genetically related sibling if the fresh donor egg cycle is successful.

Competition between IVF centers is often intense, particularly in some geographic areas within the United States. It is important that we consider how this competition could influence care. On the one hand, competition could drive programs to use aggressive ovarian stimulation, even when patients may prefer a milder approach, in order to maximize success rates. On the other hand, some centers in the United States are using variations of mild stimulation IVF as a marketing tool, with trademarked names being used to appeal to patients and invoke the feeling of a more gentle, natural approach. Patients need to be aware of the full spectrum of advantages and disadvantages of mild ovarian stimulation, and physicians have an obligation to carefully explain these issues and put the needs of the patient first.

For the past several years, 4–5 % of the cycles in the United States have been performed using preimplantation genetic diagnosis [30, 31]. Indications in the United States include screening for aneuploidy, unbalanced translocations, single gene disorders, and sex selection [30]. The percentage of PGD cycles could increase in the coming years as there have been significant advances regarding comprehensive screening of the entire karyotype, rapid return of results, and trophectoderm biopsy [32]. The prevailing wisdom has been that there is an advantage to having as many embryos as possible available for biopsy for couple undergoing PGD. A well-known randomized controlled trial challenged that assumption. The rate of detected aneuploidy (as detected by day 3 embryo biopsy for 10 chromosomes) was higher with a long agonist protocol and FSH 225 IU daily compared with a milder protocol utilizing FSH 150 IU daily and GnRH antagonist [33]. The mean number of embryos without detected aneuploidy (1.8) was similar between the two groups, suggesting that the higher dose protocol led to retrieval of some additional oocytes that were not chromosomally normal. While intriguing, it is difficult to be certain if these findings will be replicated in the US population undergoing IVF with comprehensive chromosome screening using current methodologies and trophectoderm biopsy.

Conclusions

Mild ovarian stimulation for IVF has some proven and some theoretical advantages. It is an appropriate option to consider for certain patient groups or based on patient preference. However, cumulative live birth rate, including transfers from fresh and frozen embryos, is likely to be lower with mild stimulation. The cost-effectiveness of mild stimulation IVF in the United States has not been established.

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