Stimulation for low responder patients: adjuvants during stimulation

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Growth hormone, letrozole, and clomiphene citrate do not have US Food and Drug Administration approval for their use in in vitro fertilization (IVF) cycles. However, despite this fact, they often are used to augment the IVF cycle in women considered "low responders." Unfortunately, because of the problems inherent to recruiting women who have undergone several unsuccessful IVF treatment cycles, and their inevitable low live birth rate, studies involving adjuvants for women considered low responders to ovarian stimulation often are underpowered. This is compounded further by the difficulty in recruiting vulnerable women to a study with a placebo arm. Consequently, the evidence base for their use as adjuncts to IVF treatment may be limited, and consequently their use may be empirical rather than evidence based. This short narrative review describes the evidence for these "add-ons" for a patient with a low response to ovarian stimulation. It suggests that a woman with a low ovarian response will derive benefit from using growth hormone; with a reduction in the ovarian stimulation required for oocyte retrieval, collection of a greater number of oocytes, and improvement in the clinical pregnancy rate. Although there currently is insufficient evidence to state categorically that it leads to an increased chance of a live birth. In the same situation, clomiphene citrate and letrozole lead to a reduced requirement for gonadotropins before oocyte retrieval, but with no improvement in live birth rate for their use. (Fertil Steril® 2022;117:669–74. ©2022 by American Society for Reproductive Medicine.)

Key Words: Growth hormone, IVF, poor responder, clomiphene citrate, letrozole

In the field of infertility, it is common that clinicians, patients, and the media alike refer to adjuvant treatments used in assisted reproduction as "add-ons," often in a derogatory manner (1, 2). Because the majority of these interventions are not licensed for such use, and the evidence for their use may be lacking, and in some situations these interventions may be expensive, this occasionally has led to the vilification of some clinicians or clinics within the infertility industry for using nonstandard treatment purportedly for their own gain (3). Consequently, it is essential to examine the effectiveness of such interventions before the widespread adoption of these interventions. However, this often is limited in the field of infertility as the intervention groups often have a very low chance of conception. Hence, many studies are underpowered for a primary outcome of live birth. Furthermore, if the intervention is relatively inexpensive, it often is challenging to recruit patients into a study with a placebo control arm, as patients potentially may insist on taking the unproven intervention off-label and remain outside the trial, despite counseling to the contrary. Certainly, this was our experience with recruitment for the Australian LIGHT study, where despite the fact that the intervention being tested was growth hormone (GH), a relatively expensive drug, we had substantial difficulty recruiting patients (4). This ultimately led to the premature cessation of the study. Consequently, before rushing to vilify clinicians prescribing "add-on" interventions, we must acknowledge the limitations and the challenges inherent in the current literature, and encourage clinicians to recruit patients to further studies and ensure that the evidence base, or lack-there-of, is explained fully to the patient before their treatment commences.

On this background, the following review provides a narrative overview of 2 of the oldest interventions in the field of infertility treatment; GH and clomiphene citrate (CC), and one of the more recent additions to our armamentarium commonly used for ovulation induction, letrozole (5). The literature review was performed on November 1, 2021 and was limited to

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a Medline search of English language literature from 2016 onward using the Medical Subject Heading terms: "growth hormone" OR "GH" OR "clomiphene" OR "clomid" OR "mL" OR "letrozole" AND "poor" OR "low" OR "slow" OR "inadequate" OR "suboptimal" AND "response" OR "responder" OR "ovarian reserve," with a view to report the most recent meta-analyses of the literature and randomized controlled trials.

GROWTH HORMONE

Growth hormone has been used as an adjunct to assist follicular development and recruitment in ovulation induction for many years (6). However, its place in in vitro fertilization (IVF) treatment cycles for women with a low response to ovarian stimulation still is keenly debated 30 years later (4, 7–24). The rationale for the use of GH is that GH is believed to act on the oocyte and augment folliculogenesis via insulin-like growth factor 1 (IGF-1), or by a direct action of GH itself, as IGF-1 receptors are present within the oocyte and in granulosa and theca cells (25). Furthermore, GH stimulates serum and follicular IGF-1 and hepatic production of IGF-1 (20, 26). Studies using animal models suggest that GH improves the maturation of the oocyte cytoplasm and nucleus, and promotes granulosa cell steroidogenesis, whereas IGF-1 suppresses follicular apoptosis and assists acquisition of follicle-stimulating hormone (FSH) responsiveness (27–29). In humans GH appears to promote the maturation of denuded oocytes in women undergoing in vitro maturation treatment, and intrafollicular GH concentrations correlate with the chance of conception in IVF cycles (30, 31). Consequently, this provides the rationale for use of GH to assist the "low responder" by increasing their recruitment of preantral and antral follicles, and potentially improving embryonic development (14, 32).

The potential interest in the use of GH for "low responders" undergoing IVF treatment was given substantial momentum in 2009 with the publication of the meta-analysis by Kolibianakis et al. (22) and the review by Kyrou et al. (23), which led to a renewed interest in the role of GH in this setting. They reported significant increases in the live birth rates in women randomized to GH. The subsequent Cochrane review, assessing the evidence for the use of GH in this setting, suggested that there was substantial heterogeneity between the studies, and potential for bias in the trials analyzed, tempering the enthusiasm for GH as an intervention (24).

Hopefully, the heterogeneity between future studies will diminish as an accepted defined "poor responder" definition exists (33). In addition, all future studies should be presented with intention-to-treat analysis, as many patients do not proceed to oocyte retrieval because of a poor response, leading to a potential for bias when live-births are quoted per oocyte retrieval or per embryo transfer, not per cycle initiated.

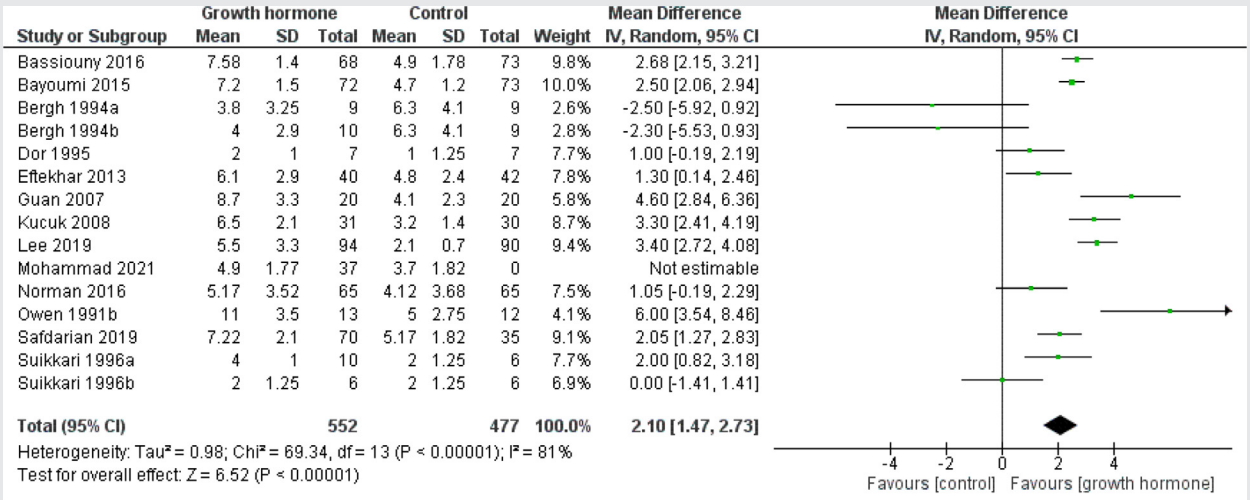
Since the 3 meta-analyses described were performed, several further randomized controlled trials (RCTs) have been performed and several further meta-analyses of the literature have been published (15, 16, 34–37). The most recent meta-analyses by Zhang et al. (37), Cozzolino et al. (16) and Yang et al. (15), all published in 2020, performed searches to July 2018, September 2019, and February 2020, respectively. All 3 analyses demonstrate significant increases in the number of oocytes collected, less requirement for medication before oocyte retrieval, and an improvement in the clinical pregnancy rates, but with differing conclusions with respect to live birth rates, for RCTs comparing GH to placebo. Zhang et al. (37) performed a rigorous network meta-analysis of the literature using the Bologna criteria (33) to define poor responders. They concluded that dehydroepiandrosterone, coenzyme Q10, and GH were the top 3 agents that improved the probability of achieving pregnancy, and these treatments also had lower cycle cancellation rates in patients with a poor ovarian response, although live birth was not the primary outcome measure (37). Twelve RCTs of 1,139 patients were included in the Cozzolino et al. (16) review, which determined no increase in the live birth rates from the addition of GH during ovarian stimulation in poor responder patients (odds ratio [OR] 1.34, 95% confidence intervals [CIs] 0.88–2.55) (16). Finally, the meta-analysis by Yang et al. (15) was the largest review, including 15 studies of 1,448 patients. This review did report a significant increase in the live birth rate from their included studies for the use of GH (relative risk 1.74; 95% CI, 1.19–2.54; $P=.004$), with no heterogeneity observed between the studies. Since the publication of these 3 meta-analyses, a further randomized study has been reported, although the primary outcome was clinical pregnancy (17). Including this study, an update of our previous meta-analysis (34) is provided in Figures 1 and 2, which demonstrates a significant increase in the number of oocytes retrieved (OR 2.10, 95% CI 1.47–2,73, $P<.0001$) with the addition of GH, but a nonsignificant increase in live birth (OR 1.71; 95% CI 0.97–3.01, $P=.06$) (7–9, 10, 11, 13, 17–19, 38–40).

Consequently, in summary, there exists good evidence that GH increases the number of oocytes retrieved and the clinical pregnancy rate achieved. However, with a limited number of studies reporting live birth as the primary outcome, the jury is still out with respect to the robustness of data for the outcome live birth, and any enthusiasm for the use of GH must be tempered by the consideration of its cost to the patient. Furthermore, compounding the difficulty in establishing the role for, or against, the use of GH for women with a low response to ovarian stimulation is its cost. It is unclear as to when the treatment with GH should commence, or indeed what is the appropriate dose to use (up to 12 IU per day with gonadotropin stimulation), or even in which subgroup of patients it should be used as it may be more applicable for women with poor embryonic development, as opposed to a poor response to stimulation (32).

CLOMIPHENE CITRATE

Clomiphene citrate has been used in assisted reproduction for several decades (41). Because it is a selective estrogen receptor modulator, its action leads to increased pituitary gonadotropin secretion and consequent increased follicular stimulation. It usually is administered at a dose of 50–150 mg per day for a few days in the early follicular phase. However, its use

FIGURE 1



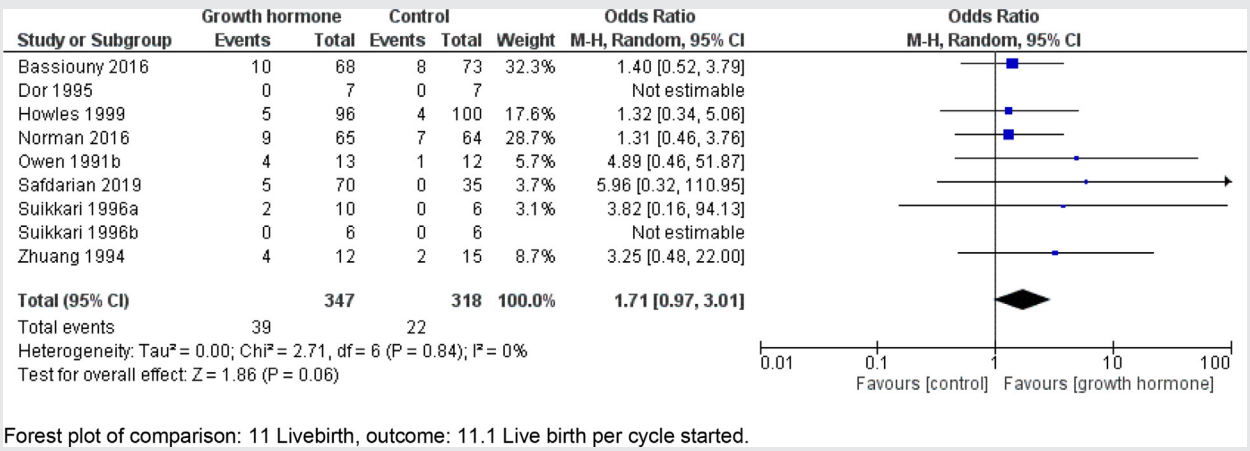
Forest plot of comparison: Oocytes collected per cycle started. (Not all patients reached oocyte retrieval).

Adjuvants during IVF stimulationForrest plot of RCTs on the use of GH versus placebo for the outcome oocytes retrieved (7–9, 10, 11, 13, 17–19, 38–40). CI = confidence interval; GH = growth hormone; RCT = randomized controlled trial.

Hart. Adjuvants during IVF stimulation. Fertil Steril 2022.

specifically to assist a woman with a previous low response to ovarian stimulation in an IVF cycle is more recent. The rationale for its use is that it may potentiate the early follicular phase recruitment of follicles by initiating a flare of endogenous FSH (42). The network meta-analysis of low responders to ovarian stimulation, undertaken by Zhang et al. (37) using the Bologna criteria, demonstrated that the protocol involving the use of CC had the lowest ranked score of the 9 potential interventions analyzed with respect to clinical pregnancy rate. After that review, only 1 RCT has reported on the use of CC for low responding patients (43). This trial of 114 patients performed by Moffat et al. (43) studied the use of CC or placebo, with a high (450 IU) and a low (150 IU) dosing regimen of FSH, with oocytes retrieved as the primary outcome. They did not determine a difference between the 4 arms of the study (43). However, it did show increased blastocyst development with CC, in combination with the low FSH dose, compared with the other arms, and with a thinner

FIGURE 2



Forest plot of comparison: 11 Livebirth, outcome: 11.1 Live birth per cycle started.

Forrest plot of RCTs on the use of GH versus placebo for the outcome live birth (7–9, 10, 11, 13, 17–19, 38–40). CI = confidence interval; GH = growth hormone; RCT = randomized controlled trial.

Hart. Adjuvants during IVF stimulation. Fertil Steril 2022.

endometrium. Consequently, there may be an economic benefit for the use of CC for the low responding patient, by reducing the requirement for gonadotropins, as proposed by Bechtejew et al. (44) in their review of CC and letrozole, and reported in a Cochrane review, although without an improvement in the live birth rate (45).

LETROZOLE

Because letrozole is an aromatase inhibitor, it acts to reduce the central negative feedback by estradiol leading to an increase in pituitary gonadotropin secretion, the presumed method of action employed for ovulation induction (5). A further mechanism of action has been proposed for low responders whereby intraovarian androgen concentrations are increased, by the inhibition of aromatization, leading to a potentiation of follicular response (similar to the proposed mechanism whereby androgens are administered to increase ovarian response [46]). Furthermore, proposed benefits of letrozole as an adjunct for healthy responders undergoing IVF treatment are that as it leads to a reduction in systemic estradiol concentrations, this may be more conducive to embryo implantation in the endometrium (47). In addition, the more physiologic estradiol concentrations achieved lead to less profound pituitary luteinizing hormone secretion suppression, and enhanced luteal phase progesterone secretion (47), which potentially could translate into improved implantation rates.

One of the first RCTs of the use of letrozole for low responders was published in 2004 (48), with most of the literature being in the last few years (49–57), with the most notable RCTS performed by Ebrahimi et al. (52) and Moini et al. (53), and meta-analyses performed by Bechtejew et al. (44), Qin (58), and Montoya-Botero et al. (57). The RCT reported by Ebrahami et al. (52) included 70 patients meeting the Bologna criteria, randomized to FSH (225 IU), and either placebo or letrozole (2.5 mg) for 5 days, and did not detect any differences in the outcomes of oocyte number and clinical pregnancy rates between the groups. The RCT reported by Moini et al. (53) included 160 patients meeting the Bologna criteria, randomized to FSH (150 IU) and either placebo or letrozole (5 mg) for 5 days, and despite an increase in the number of oocytes retrieved in the letrozole group there was no difference in the clinical pregnancy rates between the groups (53).

The meta-analysis undertaken by Montoya-Botero et al. (57) was focused on studying the approach of mild ovarian stimulation for poor ovarian responders with the addition of letrozole, rather than a more traditional approach to treating low responders with high doses of FSH. The meta-analysis by Qin (58) represents the most up-to-date review of the literature, with search date to July 2020. Their meta-analysis included studies with at least 1 clinical feature of being a low responder to stimulation and included 5 RCTs and 1 prospective controlled study. The clinical pregnancy rate per cycle started was greater with administration of letrozole, than that in the control groups, (risk rate 1.57; 95% CI, 1.00−2.44; P= .05), with a significant reduction in gonadotropin use with letrozole. In a subgroup analysis, there was no difference detected between 2.5 mg and 5 mg dosing regimens, with 3 studies in each group. Consequently, similarly to the potential use of CC for a patient with a low response to ovarian stimulation, there may be economic benefit for the use of letrozole, by reducing the requirement for gonadotropin, but not for a benefit of increase live birth.

DISCUSSION

In summary, GH, CC, and letrozole did not have strong evidence to support their use in the patient with a low response to ovarian stimulation regarding increasing the chance of a live birth. However, there is evidence to support the fact that the use of GH, CC, and letrozole leads to a reduction in total gonadotropins used before oocyte retrieval (15, 16, 34, 37, 45, 57, 58), and further studies to analyze any potential economic benefits for the use of CC and letrozole are encouraged. With respect to consistency with current guidelines, the American Society of Reproductive Medicine states, “In women considered to be poor responders, there is fair evidence that clinical pregnancy rates after IVF are not substantially different when comparing mild ovarian stimulation protocols using a combination of oral agents and low-dose gonadotropins (150 IU per day) to conventional-gonadotropin protocols” and “but there are no data about live-birth rates” (59). Similarly, the European Society of Human Reproduction and Embryology guidelines for ovarian stimulation for IVF state that “clomiphene citrate alone, or in combination with gonadotropins, and gonadotropin stimulation alone is equally recommended for predicted poor responders” and “the addition of letrozole to gonadotropins in ovarian stimulation protocols is probably not recommended” (60). With respect to GH, the European Society of Human Reproduction and Embryology guidelines state that “use of adjuvant GH before and/or during ovarian stimulation is probably not recommended for poor responders” (60). Hence, this review generally is consistent with these guidelines.

The investigator’s viewpoint, from an Australian perspective where the medication supplied for an IVF cycle is financially well supported and underpinned by Medicare, is that there is no benefit for the use of clomiphene citrate or letrozole as adjuncts for an IVF cycle for a woman with a suspected low response to ovarian stimulation with respect to live birth. Regarding the use of GH as an adjunct to an IVF cycle, which is not supported by Medicare, for a woman with a suspected low response to stimulation, there exists fair evidence for its use. As a low responder, she will have more oocytes retrieved, more blastocysts, a greater clinical pregnancy rate, and a reduced cycle cancellation rate, and will be required to use less gonadotropins and potentially will have a higher live birth rate as reported by the largest published meta-analysis (15). The studies to date on GH have been limited by too few having live birth rate as the primary outcome. Furthermore, the place of GH in IVF treatment also may relate to its perceived benefit with regard to favorable embryonic development (14, 32). Consequently, studies to date may have been focusing on examining the wrong population, as frequently populations of women with a low response to ovarian stimulation may overlap with those in a population of women with poor embryonic development. Hence, a

challenge for further studies is to tease out from the data whether GH plays a role, or not, for the low responder, or for the woman with poor embryonic development, or indeed women with both challenges.

If GH were to be used as an adjunct in an IVF cycle, it is my practice to use, after appropriate counseling, the dosing regimen that we used in the LIGHT study (4), of 12 IU daily from stimulation. The rationale for this regimen is that we analyzed the literature and debated for a considerable time the proposed protocol before embarking on the project, although subsequent publications from Mohammad et al. (17) and Li et al. (32) used 4 IU and 3 IU per day, respectively. Consequently, there is no "right" dosing regimen for the use of GH, and more studies are required to be performed. Furthermore, it could be argued that commencing the GH in the luteal phase of the previous cycle may be a more physiologic approach to its use in an IVF cycle (11, 13, 32, 61, 62).

In conclusion, the use of CC and letrozole in an IVF cycle, with a predicted low response to stimulation, may lead to a reduced requirement for gonadotropins before oocyte retrieval. However, there is no evidence to support a benefit with respect to an improvement in the live birth rate for their use. In contrast, the use of GH for an IVF cycle, with a predicted low response to ovarian stimulation, will lead to a reduction in the ovarian stimulation required, the collection of a greater number of oocytes, than a similar cycle without the use of GH, and potentially an increased chance of a live birth, although this latter assertion still requires further ratification.

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