The role of steroid hormone supplementation in non–assisted reproductive technology treatments for unexplained infertility

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Fertility treatment strategies are evolving, with a more rapid transition to assisted reproductive technology (ART) treatments after unsuccessful non-ART treatments. This trend increases the potential importance of adjuvant treatments in non-ART cycles, such as steroid hormone supplementation. It has been established that success rates of ART treatments are increased with the use of luteal support with progesterone. In the setting of non-ART cycles, however, the evidence is less clear, and clinical practices vary widely between providers and clinics. In this review, we aimed to provide an overview of the current evidence for the use of steroid hormone supplementation, including progesterone for luteal support, estrogens, androgens, and mineralocorticoids, in the setting of non-ART treatments for ovulatory women. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

Key Words: Unexplained infertility, intrauterine insemination, luteal supplementation, steroid hormones, progesterone

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The evaluation and treatment of unexplained infertility is evolving (1, 2). The diagnosis is made in ~10%–30% of couples presenting with infertility, when no etiology is identified after assessment of ovulatory function, tubal patency, and semen (2–4). Treatment paradigms for this diagnosis have typically involved ovarian stimulation (OS) with intrauterine insemination (IUI), first with oral agents such as clomiphene citrate (CC), then with injectable gonadotropins (GND) with IUI (2). For those unsuccessful in achieving pregnancy with OS-IUI, this is followed by treatments involving assisted reproductive technology (ART) such as in-vitro fertilization (IVF) (5). According to the definition by the Centers for Disease Control and Prevention based on the 1992 Fertility Clinic Success Rate and Certification Act (6), ART includes "all fertility treatments in which both eggs and sperm are handled," not treatments involving ovarian stimulation without the intention of egg retrieval, or those in which only sperm are handled.

Recent prospective studies have cast doubt on the above traditional strategy of progressing from CC + IUI to GND + IUI followed by IVF for couples with unexplained infertility, given low per-cycle pregnancy rates (7) and alarming multiple pregnancy rates (7–9) in patients treated with GND + IUI. Per-cycle live birth rates for OS-IUI treatments with the use of oral agents were similar to those conducted with the use of injectable agents in several prospective randomized clinical trials (7, 10), with lower associated multiple pregnancy rates. Although the Reproductive Medicine Network's Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) clinical trial demonstrated higher live birth rates following GND-IUI treatments compared with CC- or letrozole-IUI, the majority of the additional pregnancies were multiple gestations (8). In addition to concerns regarding multiple gestations associated with GND-IUI treatment, a cost-effectiveness analysis in the Fast Track and Standard Treatment (FASTT) trial has suggested that proceeding directly from CC-IUI treatment to IVF is associated with cost savings and a shorter time to delivery (7). Given these findings, practice patterns are shifting

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toward a faster transition from relatively low-cost low-intervention non-ART treatments to high-cost high-intervention ART treatments including IVF. With this trend in mind, even small improvements in per-cycle pregnancy rates in non-ART treatments including CC-IUI become more clinically relevant.

Luteal phase abnormalities have been described in women undergoing treatment with GND in the setting of ART, including treatment cycles involving GnRH agonists and antagonists and those involving no down-regulation (11–13). Randomized studies have demonstrated that luteal support with the use of progesterone (P) significantly improves outcomes in IVF cycles (13). It is hypothesized that P supplementation corrects the luteal phase abnormalities found in ART cycles that may result from suppression of GnRH activity, loss of granulosa cells associated with follicle aspiration, suppression of GND associated with supraphysiologic levels of E_2 and/or P, or a combination of the above factors.

Multiple studies suggest luteal phase alterations also occur in non-ART ovulation stimulation treatments with the use of GND and CC, with reported prevalence rates of 13%–50% (14–18). Even though there is a significant amount of controversy surrounding the diagnosis of "luteal phase defects" (discussion of which is beyond the scope of this review), these findings lead to the question: Does luteal-phase P treatment improve outcomes of OS-IUI treatment cycles?

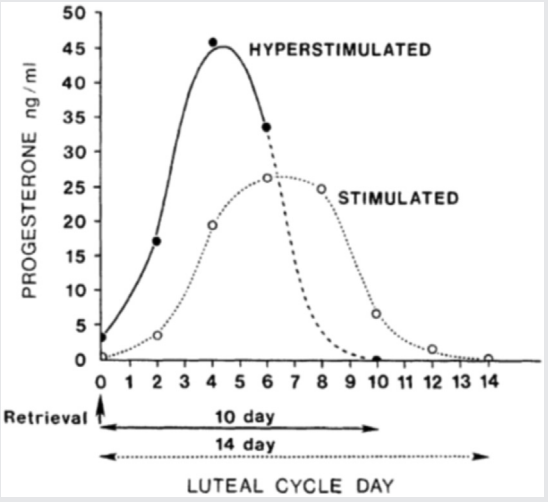
In addition to the effect of P supplementation, little is known about the impact of supplementation with the use of other steroid hormones, such as estrogens, androgens, and mineralocorticoids in the setting of non-ART fertility treatments. The role of steroid hormone supplementation in non-ART treatment cycles, particularly as it relates to OS-IUI treatment in the setting of unexplained infertility, is covered in this review.

LUTEAL-PHASE PROGESTERONE SUPPLEMENTATION IN GONADOTROPIN–INTRAUTERINE INSEMINATION TREATMENT CYCLES FOR UNEXPLAINED INFERTILITY

Duffy et al. reported that 13.9% of women undergoing OS with the use of hMG experienced luteal phase deficiencies (15). Similarly, Olson et al. documented altered luteal phases as assessed by serum steroid levels, luteal phase length, or both in 18.4% of women following hMG treatment for ovulation induction (18). OS with ovulation-inducing agents can result in significantly higher concentrations of E_2 and P than would be experienced in a natural cycle (11, 19). It has been hypothesized that these high concentrations of sex steroids in the late follicular and early luteal phases may result in negative feedback on the hypothalamic-pituitary axis, thus inhibiting the secretion of luteal LH necessary for continued progesterone production from the corpora lutea (Fig. 1) (19–21).

Multiple investigations have addressed the impact of luteal-phase P supplementation in GND-IUI treatments. A prospective randomized study that included 200 couples

FIGURE 1



Luteal-phase progesterone trajectory according to degree of ovarian stimulation. Adapted from (21), with permission.

Quaas. Steroid supplementation in non-ART treatments. Fertil Steril 2016.

undergoing up to four treatment cycles with the use of FSH-IUI identified significant differences in clinical pregnancy rates (CPRs) and live birth rates (LBRs) in women treated with luteal-phase P (39.4% and 35.8%, respectively) compared with untreated control women (23.8% and 18.1%, respectively) (22). That study was neither placebo controlled nor double blinded. Similarly, a prospective study by Maher that included 71 patients reported a higher LBR per treatment cycle after OS with the use of FSH-IUI for women who were treated with the use of luteal-phase P supplementation (18.9%) than for women who did not receive supplemental P (5.5%) (23).

In contrast, a prospective randomized study from Spain by Romero Nieto et al. which included 398 patients undergoing a total of 893 GND-IUI cycles, did not find significant differences in LBR (10.2% vs. 8.3%; $P=.874$), CPR (13.8% vs. 11.0%; $P=.248$), and early miscarriage rate (3.6% vs. 2.7%) between cycles supported with the use of micronized vaginal P (200 mg once daily) and unsupported cycles (24). Those authors stated that lack of homogeneity existed between the different studies on this topic, and that varying stimulation characteristics may have been responsible for different results and conclusions. When studying subgroups of cycles, it appeared that the difference in CPR between intervention and control groups was correlated with the degree of ovarian stimulation, as demonstrated by stimulation characteristics and multiple pregnancy rates. The studies showing a difference in outcomes (22, 23, 25) were associated with a higher number of dominant follicles on the day of hCG trigger and a higher multiple pregnancy rate than the studies that did not show a difference (24, 26, 27). Similarly, in a prospective study of 149 patients with unexplained infertility, Seckin et al. demonstrated no difference in outcomes following OS-IUI with the use of GND with and