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CASE REPORT

The use of corifollitropin alfa in overlapped doses, in a desogestrel-primed ovarian stimulation regimen, as a new protocol towards an extremely patient-friendly approach: a case report

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Abstract:

Objectives: To report the well-succeeded use of a new extremely patient-friendly COS protocol, using overlapping doses of corifollitropin alfa in a once-a-day pill desogestrel-primed regimen. **Methods:** Case report. **Results:** 37 years old nuligesta, attempting social egg freezing. **Conclusions:** Overlapping doses of corifollitropin alfa plus desogestrel-priming stimulation protocol yields a satisfactory number of mature oocytes, presenting an interesting and innovative option towards an improvement of comfort and a reduction in emotional and financial burdens for social egg freezing cycles.

Keywords: Assisted Reproductive Techniques, Ovulation Induction, Superovulation, Corifollitropin Alfa, Desogestrel

Introduction

Controlled ovarian stimulation (COS) protocols used in assisted reproductive technologies (ART) cycles are notorious for their complexity and side effects. In addition, economic, psychologic, and physical burden often associated with them commonly result in bad patient experiences and high dropout rates, even before completing all reimbursed cycles. The premature discontinuation should be regarded as an unfavorable outcome, as it deprives the couple of the cumulative chances of pregnancy, impacting the overall success rates.[1-3]

For those reasons, the very first concept of a patient-friendly ovarian stimulation protocol[4,5] has evolved in the last two decades. COS using corifollitropin alfa (CFA), a long-acting gonadotropin designed to reduce the injection burden on women, was probably the first step towards a real patient-friendly strategy, because of its pharmacokinetic ability to sustain follicle-stimulating action for an entire week with a single injection.[6] In other words, using CFA means to replace seven daily gonadotropin injections for one. However, the original protocol still involved pituitary suppression by daily subcutaneous doses of the GnRH antagonist ganirelix acetate from day 5, and continuity of COS by daily subcutaneous doses of follitropin beta from day 8, still limiting women everyday activities and maintaining concerns on how to proceed injections.[7,8]

Due to need to avoid spontaneous pre-ovulatory luteinizing hormone (LH) surge before triggering the final follicular maturation and the oocyte retrieval, progestin-primed COS protocols (PPOS) have been tested, focusing on the substitution of injectable GnRH antagonists for oral pills, and meaning the second step in the path of a patient-friendly approach.

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The first well-designed study investigating the use of medroxyprogesterone acetate (MPA) to suppress LH surge in COS cycles was published in 2015,[9] since then many authors have tested other molecules, i.e., dydrogesterone,[10,11] micronized progesterone (MP),[12-14] desogestrel (DSG),[15-17] and chlormadinone.[18]

In the context of ovarian stimulation protocols development, associating CFA to a one-pill-a-day PPOS seems to be an interesting and empathetic innovation. In this paper, we report an extremely patient-friendly PPOS protocol, using overlapping doses of CFA in desogestrel-primed regimen.

Case report

A healthy nuligesta, 37 years old, 57kg, body mass index 20.19 k/m^2, with regular menstrual cycles, sought the private clinic for social egg freezing. No alterations were identified in pre-treatment blood tests and the ultrasonographic exam revealed normal ovarian reserve, counting seventeen antral follicles. Considering comfort and costs, PPOS was proposed.

On the third day of the spontaneous menstrual cycle (D3), ovarian stimulation was initiated by subcutaneous administration of corifollitropin alfa (CFA) 100mcg (Elonva®, NV Organon Oss, Netherlands), and an overlapped dose of CFA 100mcg was administered on treatment day 5 (tD5). According to the initial pharmacokinetic studies of corifollitropin alfa,[6] it is on the fifth day that the maximum serum concentration drops by half, which is why the timing of administration of the second injection was determined.

Pituitary suppression was also initiated on tD5, using DSG, 75 mcg/day (Cerazette®, Organon Brasil). Although the PPOS protocols described to date recommend starting progestogen earlier, we have not identified a scientific rationale that would justify starting pituitary suppression at a different time than what is usually practiced for GnRH antagonists. On the contrary, studies demonstrate that suppression occurs in a very similar way for GnRH antagonists and progestins.[19,20]

Finally, on tD11, there were nine follicles with mean diameter ≥ 17mm, and follicular maturation was triggered with triptorelin acetate, 0.2mg (Gonapeptyl Daily®, Ferring GmbH Kiel, Germany). Follicular aspiration was performed 36 hours after the trigger (Figure 1), yielding twelve oocytes, of which ten were in metaphase II, and vitrified using the Cryotech® (Reprolife Inc, Shinjuku-ku, Tokyo) method. Immature eggs were discarded.

This case report was approved by the Research Ethics Committee of the Centro Universitario de Brasília, CEUB, Brasília, Distrito Federal, Brazil (certificate CAAE 69544423.0.0000.0023), and the patient signed a written informed consent form authorizing publication.

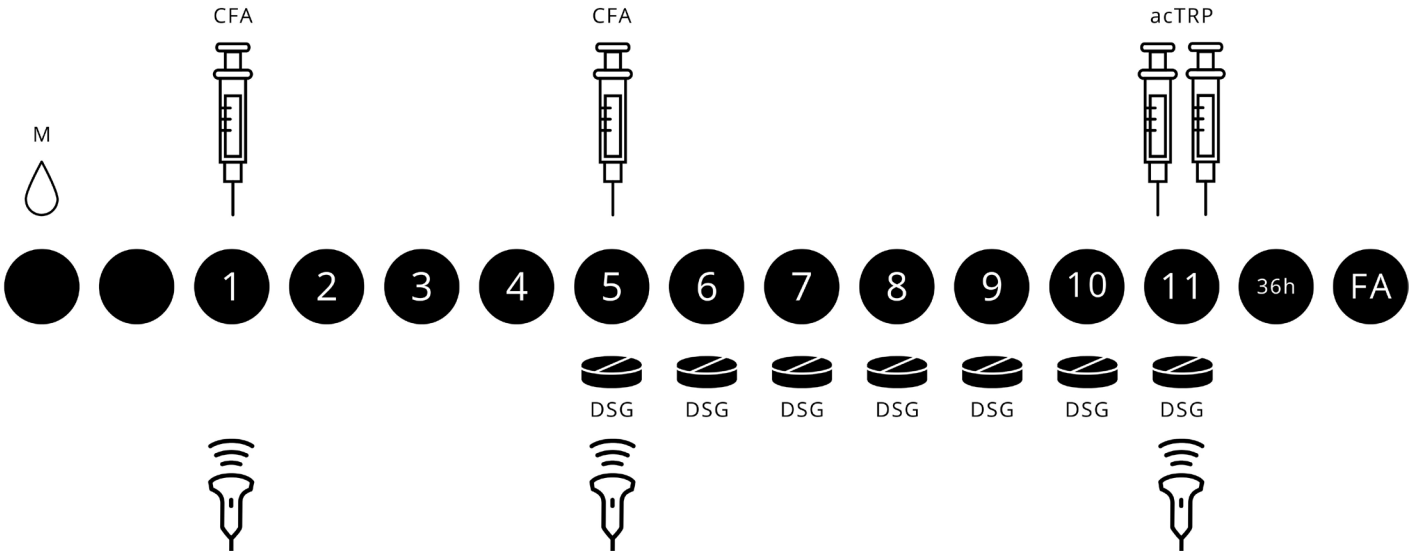

Figure 1. Diagram of the extremely patient-friendly protocol for controlled ovarian stimulation, using two overlapped doses of corifollitropin alfa (CFA) and oral desogestrel (DSG) for LH surge suppression. M, menses; acTRP, triptorelin acetate; FA, folicular aspiration

Discussion

In our double CFA plus DSG-priming stimulation protocol, the whole treatment included only four injections, and yielded a satisfactory number of mature oocytes, presenting an interesting and innovative option towards an improvement of comfort and a reduction in costs for social egg freezing cycles. This is the first report of the use of overlapped doses of CFA, and there are only three reports of the use of DSG for pituitary suppression.[15-17]

Although knowledge has evolved exponentially over the last few decades, little progress has been made in reducing the physical and emotional burden of assisted reproductive technologies (ART), which seem to be the main causes of treatment drop-out.[1,3] In parallel, patients' concerns about the correct administration and dosing of injections, the possibility of hitting a vessel, the fear of pain, and handling the needles are observed as cause of COS burden, as much as they are concerns related by physicians and nurses.[2]

In addition to the above mentioned, women undergoing ART were investigated and 75% of them stated to prefer replacing seven daily doses with one gonadotropin dose, indicating the possibility of reducing the emotional burden, better adherence to treatment, and less abandonment.[21] This is why we believe that there is sufficient data on ART burden to support strategies of reducing self-administered injections to possible minimum, as we present using overlapped doses of CFA.

Regarding the use of progestins for LH surge suppression during COS, MPA efficacy observed by Kuang and colleagues (2015)[9] has been reaffirmed for other progestins, with very low rates of premature LH surge, similar number of competent oocytes and embryos, lower rates of ovarian hyperstimulation syndrome, and similar pregnancy outcomes when compared to conventional stimulation protocols.[22,23] Recent evidence also suggests that PPOS may improve reproductive outcomes of women with diminished ovarian reserve,[24] with no negative effect on embryo ploidy.[25,26]

Although MPA is more potent than that observed for dydrogesterone, this molecule has been extensively studied in the last years, due to its wide access as well as the high selectivity for progesterone receptor, and reduced androgenic activity.[10] However, there is still the inconvenience of taking two pills/day, which is a disadvantage comparing to progestagens with similar suppressive action administered in one daily pill; as a matter of fact, oral MPA and chlormadinone are not available in Brazil, so that the one-pill-a-day options to Brazilian women are restricted to MP and DSG, among the molecules tested in literature.

DSG-primed CFA stimulation cycles have been previously tested. Martínez and colleagues (2019a)[16] studied 29 non-obese oocyte donors between 18 and 35 years old, with regular menses, who had received CFA and DSG, comparing with CFA and GnRH antagonist; fewer number of injections, lower total cost of medication, total number of oocytes retrieved were observed for cycles under DSG, and no cycle cancelation due to low ovarian response or premature LH surge, or cases of OHSS were observed. In addition, clinical pregnancy, miscarriage, or live birth rates were similar between donor and recipients for both LH surge suppression regimen.

In a subsequent analysis, the same group of researchers found similar serum LH levels after trigger between women treated with GnRH antagonist and DSG, and, despite serum progesterone was significantly lower in PPOS group, there was no difference in the number of mature oocytes retrieved[17] or in the clinical pregnancy rates between oocyte donors and recipients submitted to DSG LH surge suppression,[15,17] reassuring efficacy and safety of DSG for pituitary suppression in cycles for fertility preservation, total embryo cryopreservation or pre-implantation genetic testing for aneuploidies.

Based on the mentioned above, we have the conviction that future innovation in the field of ART must pass by an empathetic view of fertility treatments. Our extremely patient-friendly protocol using two overlapped doses of CFA in a DSG-primed regimen seems to be a feasible strategy for ovarian stimulation in cycles in which fresh embryo transfer is not planned or those intending egg freezing. The significant reduction of the number of injections and costs may reduce emotional burden associated to self-applied gonadotropins as much as the possibility of errors. Naturally, further well-designed studies are necessary to confirm our finding.

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Authors contribution

JKAF, BVAC, and MJFCMRC were responsible for writing the original draft; ETSR and NSS were responsible for review and editing the original draft; BRC was responsible for conceptualization, methodology, investigation, review and editing the final draft, and closing the definitive manuscript to be submitted.