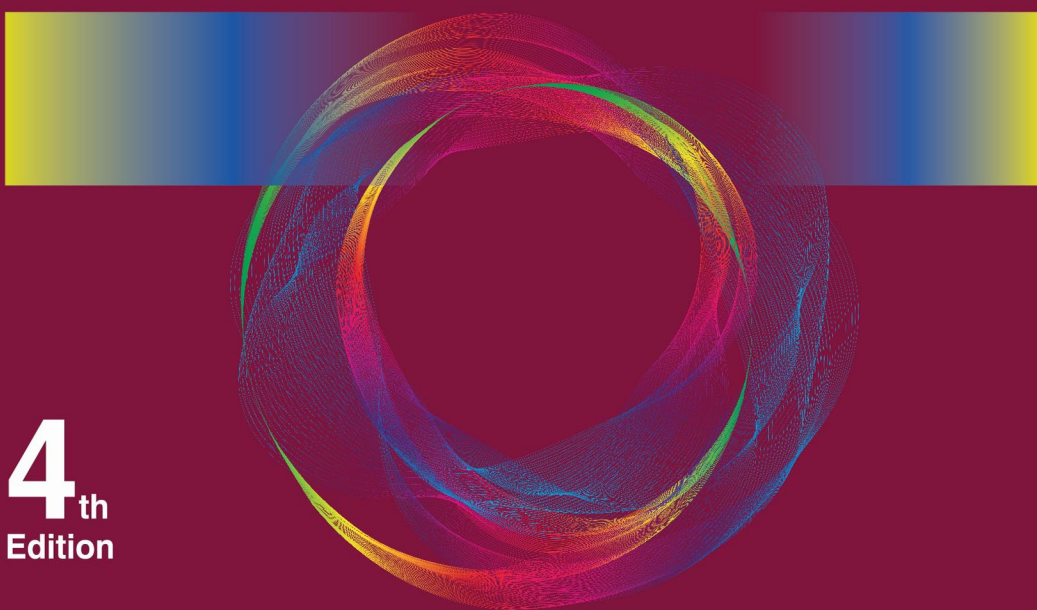
Manual of Ovulation Induction & Ovarian Stimulation Protocols



4th Edition

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CHAPTER 33

Induction of Monofolliculogenesis in Patients with Polycystic Ovary Syndrome

Raoul Orvieto, Roy Homburg

ABSTRACT

Chronic low-dose (CLD) follicle-stimulating hormone (FSH) regimens for induction of ovulation for women with polycystic ovary syndrome (PCOS) result in reduced ovarian hyperstimulation syndrome (OHSS) rate to almost zero, with pregnancy rates of 40% and multiple live birth rates of 5.1%. This has been achieved without compromising the success rate when compared to conventional treatments. The latest evidence-based guidelines on infertility treatment related to PCOS concluded that low-dose FSH protocols are effective in achieving ovulation in women with PCOS, but refinement to better control the safety of the low-dose FSH protocols can be achieved if ovulation is only triggered when there are fewer than three mature follicles and canceled if there are more than two mature follicles. Many strategies have been suggested in an attempt to improve CLD FSH protocol outcomes, such as using a step-down instead of a step-up protocol, reducing the starting dose, and substituting FSH with human menopausal gonadotropin (hMG). While none of these strategies has proved successful in improving results, the most crucial factor in determining the rate of monofollicular ovulation and improving results appears to be the size of the dose increment. The currently available recombinant human FSH (recFSH) pens allow a dose adjustment in increments of 8.3 or 12.5 IU with one "click" on the dial, at intervals of 7 days, as necessary. This chronic ultralow-dose regimen is more compatible with Brown's FSH threshold concept. By employing these ultralow doses, the FSH threshold can be accurately found without being exceeded thereby considerably reducing the chance of multifollicular development and its associated risks. Additionally, this chronic ultralow-dose approach significantly reduces the amount of gonadotropin needed and has a low cycle cancelation rate.

INTRODUCTION

Chronic low-dose (CLD) follicle-stimulating hormone (FSH) regimens for induction of ovulation for women with polycystic ovary syndrome (PCOS) have been a breakthrough, resulting in reduced ovarian hyperstimulation syndrome (OHSS) rate to almost zero, with pregnancy rates of 40% and multiple live birth rates of 5.1%.[1] This has been achieved without compromising the success rate when compared to conventional treatments that report a 34% rate of multiple pregnancies and a 4.6% occurrence of severe OHSS.[2]

The low-dose FSH therapy is based on Brown's FSH threshold concept, which suggests that follicular development begins only once a specific FSH threshold level is achieved.[3] Moreover, only a minor elevation of FSH concentrations (10–30% above the threshold level) is sufficient to stimulate normal follicle development, whereas a further increase might cause excessive stimulation.

In contrast to conventional therapy that consists of supraphysiological doses of FSH which stimulate a large cohort of follicles and rescue also those destined for atresia, the low-dose regimen aims to reach but not exceed the threshold level of FSH. This principle is achieved by employing the classic low-dose FSH regimen[4] that uses a low starting dose of gonadotropin (usually 50–75 IU FSH) for 7–14 days without alteration and followed, if necessary, by a weekly small FSH dose increment of 50% of the initial or previous FSH dose, until follicular development starts. The effective dose is then maintained until human chorionic gonadotropin (hCG) administration criteria are met.

- Using this low-dose protocol, mono-ovulation is achieved in a remarkably consistent figure of around 70% of treatment cycles,[1,5-7] resulting in the aforementioned acceptable outcomes.
- The latest evidence-based guidelines on infertility treatment related to PCOS[8] concluded that low-dose FSH protocols are effective in achieving ovulation in women with PCOS, but refinement to better control the safety of the low-dose FSH protocols can be achieved if ovulation is only triggered when there are fewer than three mature follicles and canceled if there are more than two mature follicles.

Many strategies have been suggested in an attempt to improve CLD FSH protocol outcomes, such as using a step-down instead of a step-up protocol,[9-11] reducing the starting dose to 37.5 [12] or 52.5 IU,[5] substituting FSH with human menopausal gonadotropin (hMG),[13] or shortening the initial dose duration by cutting down the initial dose duration of administration from 14 to 7 days without a change of dose.[1] None of these strategies has proved successful in improving results. However, the most crucial factor in determining the rate of monofollicular ovulation and improving results appears to be the size of the dose increment. In a large randomized controlled trial (RCT) of low-dose step-up protocol, smaller weekly increments of 25 IU in the daily dose were proven more effective and efficient than larger ones (50 IU).[14]

With the introduction of recombinant human FSH (recFSH) pens, an incremental dose rise of just 8.3 or 12.5 IU (16.6% of the initial FSH dose) could be achieved. This increment is significantly lower than the up-to-then widely used and accepted 50% increment and is more compatible with Brown's FSH threshold concept.

In 2009, we demonstrated[15] that using a weekly incremental dose as small as 8.3 IU of FSH in a chronic ultralow-dose step-up protocol for anovulatory

PCOS produced very good clinical results with an excellent safety profile. While utilizing a significantly lower incremental (16.6% of the initial dose) and total (622+286 IU) gonadotropin dose, as compared to the widely used and accepted low-dose gonadotropins regimen, a clinical pregnancy rate of almost 30% per started cycle has been achieved with just one twin gestation and no case of even mild OHSS.

The currently available recFSH pens allow a dose adjustment in increments of 8.3 or 12.5 IU with one "click" on the dial. The incremental dose rise of this order, at an interval of 7 days, as necessary, is applied until the initiation of follicular development. The secret of success in low-dose gonadotropin protocols is to achieve a high rate of mono-ovulation. The use of minimal incremental dose rise helps to attain this goal. By employing an incremental dose rise of just 8.3 or 12.5 IU, the FSH threshold can be accurately found without being exceeded thereby considerably reducing the chance of multifollicular development and its associated risks. Additionally, this chronic ultralow-dose approach significantly reduces the amount of gonadotropin needed and has a low cycle cancelation rate.

CONCLUSION

Using a minimal and manageable dose increase of 8.3 or 12.5 IU when required proves to be effective. It achieves nearly a 30% clinical pregnancy rate per cycle, with a negligible rate of multiple gestations and no cases of even mild OHSS.

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Manual of
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Manual of Ovulation Induction and Ovarian Stimulation Protocols is a concise monograph that aims to deliver everything the reader needs to know for performing a risk-free ovarian stimulation for medically assisted reproduction (MAR) and get a favorable outcome. Review of crucial issues such as the significance of monitoring ovarian stimulation, advantages and disadvantages of controlled ovarian hyperstimulation versus minimal stimulation, and the use of various drug regimens and stimulation protocols for various patient sub-sets, will help clinicians in selecting evidence-based and more appropriate protocols. The contributors of this book have leading scientific and clinical backgrounds, with years of experience to support their views. The book serves as a handy practical guide, targeting and settling clinical dilemmas that gynecologists commonly experience in their clinics while providing a window to the newer developments. This book will also be useful to practicing reproductive endocrinologists by way of continuing medical education.

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