

**GEORGE EMIL PALADE" UNIVERSITY OF MEDICINE, PHARMACY,
SCIENCE, AND TECHNOLOGY OF TÂRGU MUREŞ
DOCTORAL SCHOOL OF MEDICINE AND PHARMACY**

Summary of PhD thesis

Title: "EFFECTIVENESS OF PROGESTINS FOR PITUITARY SUPPRESSION DURING OVARIAN STIMULATION IN ASSISTED REPRODUCTIVE TECHNOLOGY"

PhD student: Alexandru-Crişan Polexa

PhD coordonator: Prof. Angela Borda Ph.D., Prof. Baris Ata M.D., M.Sc.

INTRODUCTION

According to the World Health Organization, infertility is a global health issue that affects 15 per cent of reproductive-aged couples worldwide. Ever since its innovative introduction in 1978, in vitro fertilization has been a significant point of interest in the scientific community and has become one of the most sought-after interventions in the field of tubal infertility.

GENERAL METHODOLOGY

The fundamental step of in vitro fertilization is controlled ovarian hyperstimulation, which involves the use of medication to induce ovulation by multiple ovarian follicles. Ovarian stimulation consists of three major elements: stimulation of the development of multiple follicles, suppression of the pituitary gland to prevent ovulation before egg harvest, and a trigger for the final maturation of oocytes. The suppression of gonadotropin production in the pituitary is currently performed using GnRH analogues, most often GnRH antagonists. GnRH analogues, however, may have several side effects, are only available as subcutaneous injections, and they can also entail higher costs, being more inconvenient for patients. In recent years, progesterone and its synthetic derivatives, called progestins, have emerged as more convenient alternatives to GnRH analogues for pituitary suppression. They can be administered orally, are less expensive, and are able to prevent the endogenous LH surge that leads to ovulation. **The aim** of this thesis was to explore the benefits, drawbacks, and future perspectives of progestin-primed ovarian stimulation.

In the first study from the personal contribution, we assessed the effectiveness of progestins for pituitary suppression during ovarian stimulation in

assisted reproductive technology, by comparing progestins to the current standard, GnRH analogues. As part of the co-tutorship with Prof. Baris Ata and in collaboration with his team of researchers from the Assisted Reproduction Unit of Koc University Hospital, Istanbul, Turkey, we conducted a systematic review of the literature and presented the results in a meta-analysis. Prof. Baris Ata extended the literature search to include more recent studies and presented the results in a second meta-analysis. Performing two literature searches at two different points in time has made it possible to include additional, more recent studies and to consolidate the results by combining the data from the two meta-analyses. The thesis evaluates the results of both meta-analyses in detail.

The meta-analyses assess the quality of available evidence presented in randomized clinical trials and cohort studies published on this topic until April 2020. The first literature search yielded seven studies, and the second one yielded 22 studies comparing the effectiveness of progestins and GnRH analogues. A wide range of parameters were analyzed, including live birth rates, numbers of retrieved oocytes, duration of stimulation, gonadotropin consumption, as well as the incidence of adverse events, comparing progestins to GnRH antagonists, progestins to GnRH agonists, different progestins, or the same progestin in different doses. The quantitative analyses also evaluate the impact of progestins on oocyte development potential and embryo euploidy and the cost-effectiveness of progestin-primed ovarian stimulation and reflect on the future perspectives of this treatment method.

The results of the meta-analyses and literature review suggest that progestins are similarly effective as GnRH antagonists in suppressing the LH surge and preventing premature ovulation in women undergoing controlled ovarian hyperstimulation in assisted reproductive technology, and they have a similar safety profile to GnRH analogues.

The second study from the personal contribution focuses on a special patient population, women with diminished ovarian reserve. The study was carried out at the Assisted Reproduction Unit of Koc University Hospital, Istanbul, Turkey, and its objective was to compare the effectiveness of the flexible progestin-primed ovarian stimulation protocol with that of the flexible GnRH antagonist protocol in women with diminished ovarian reserve undergoing controlled ovarian hyperstimulation for oocyte cryopreservation. These patients represent a challenge in assisted reproductive technology due to reduced pregnancy and live birth rates and the fact that they are more prone to premature ovulation.

The study compared 36 women receiving progestin with 36 women receiving a GnRH antagonist. One-to-one propensity score matching allowed the direct comparison of the outcomes of the two stimulation protocols and increased the precision of the results. The results have shown that the flexible progestin-primed

ovarian stimulation protocol has similar effectiveness to the flexible GnRH antagonist protocol in suppressing the LH surge and preventing premature ovulation in women with diminished ovarian reserve, with no significant negative effect on the number of oocytes retrieved or metaphase-two oocytes. If confirmed by larger studies, the flexible progestin-primed ovarian stimulation protocol has the potential to become a standard protocol for this specific patient population.

CONCLUSION

Based on the results of this thesis, progestins represent a safe, affordable, and patient-friendly alternative to GnRH analogues, being similarly effective in suppressing the LH surge and preventing premature ovulation in women undergoing controlled ovarian hyperstimulation, and yielding a similar number of metaphase-two oocytes. For these reasons, progestins have the potential to become a standard protocol in stimulation cycles where a fresh embryo transfer is not intended, such as oocyte cryopreservation or preimplantation genetic testing.