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Mini Review

Progesterone Protocol as An Alternative to Gonadotropin-Releasing Hormone Antagonist Protocol in IVF Programs

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Introduction

Over the past decades, In Vitro Fertilization (IVF) technologies have advanced significantly, improving outcomes and broadening the scope of indications for their use. One of the key aspects of a successful IVF program is the proper preparation of the endometrium for embryo implantation. This involves both ovulation stimulation and optimization of conditions for embryo attachment, achieved through hormonal therapy. Currently, Gonadotropin-Releasing Hormone (GnRH) antagonists are actively used to control ovulation and prevent premature Luteinizing Hormone (LH) surges. However, progesterone, the main hormone of the luteal phase, can also create favourable conditions for embryo implantation. In recent years, various protocols for pituitary suppression have been actively discussed in the context of IVF programs. One widely used method involves GnRH antagonists, which effectively reduce the risk of ovarian hyperstimulation and provide better control over ovarian stimulation (*Daya & Gunby*, 2002). Alternatively, protocols utilizing progesterone have been proposed to support the endometrium during ovarian stimulation (*Lessey & Plant*, 2005). This article explores the use of progesterone as an alternative to GnRH antagonists in IVF protocols, analysing its advantages and limitations.

IVF Protocols Using GnRH Antagonists

In traditional IVF protocols, GnRH antagonists play a crucial role in preventing premature ovulation and synchronizing follicular maturation. By blocking gonadotropins, these agents allow pre cise control over ovulation timing and oocyte retrieval schedules. However, GnRH antagonist use necessitates additional medications, typically progesterone, to support the luteal phase. Drugs such as ganirelix and cetrorelix offer rapid and effective ovulation control. However, their use requires incorporating luteal phase support with progesterone to ensure adequate hormonal therapy.

Progesterone as an Alternative to GnRH Antagonists

Progesterone, naturally produced during the luteal phase, is key for preparing the endometrium for embryo implantation. Recent studies suggest that progesterone alone can support the luteal phase and replace GnRH antagonists in IVF programs.

Mechanism of Action

Progesterone interacts with endometrial receptors, transforming it into a secretory form suitable for embryo implantation. It also prepares the uterus to receive the embryo, with deficiencies often leading to implantation failure.

Advantages of Progesterone Use

a) Reduced Medication Load: Using progesterone alone as supportive therapy reduces the number of medications a patient must take during IVF.

b) Minimized Side Effects: GnRH antagonists may cause side

effects such as reduced bone density, hot flashes, headaches, and irritability. Progesterone generally has fewer side effects.

c) Flexible Administration: Progesterone can be delivered via injections, vaginal suppositories, or capsules, allowing personalized administration based on patient preferences and clinical needs.

Limitations

a) Risk of Insufficient Ovulation: In women with ovarian dysfunction or elevated prolactin levels, progesterone may not be effective without prior ovulation stimulation.

b) Need for Additional Monitoring: Ensuring successful implantation requires careful endometrial monitoring, which may involve additional medical interventions and diagnostics.

Research and Clinical Data

Recent studies indicate that using progesterone as an alternative to GnRH antagonists can be effective in IVF protocols. A 2021 study found that progesterone administered in the first half of the cycle adequately prepared the endometrium for implantation, with outcomes comparable to therapy using GnRH antagonists.

Clinical trials also suggest that progesterone reduces hospitalizations and adverse side effects in patients undergoing IVF.

Study Aim and Methods

This study compares two approaches: traditional stimulation with GnRH antagonists and a protocol utilizing progesterone. The GnRH antagonist protocol avoids prolonged pituitary suppression and enables faster, more predictable follicular stimulation, reducing ovarian hyperstimulation risk (*Liu & Sunkara*, 2017). Conversely, progesterone-based support shows promising outcomes in late stimulation stages (*Samarajeewa, et al.,* 2021) [4-25].

Study Design

GnRH Antagonist Group: Patients received ganirelix acetate (Orgalutran) 0.25 mg daily subcutaneously when follicle size reached 13-14 mm, continuing until ovulation trigger day.

Progesterone Group: Patients took oral dydrogesterone (Duphaston) 10 mg twice daily from the third day of stimulation until ovulation trigger day.

Ovarian Response Monitoring: Transvaginal ultrasound and serum hormone analysis (estradiol and progesterone) were used to monitor ovarian response.

Ovulation Trigger: Human Chorionic Gonadotropin (hCG) 10,000 IU or GnRH agonist (triptorelin acetate 0.4 mg) was administered based on follicular maturity.

Oocyte Retrieval: Transvaginal ultrasound-guided oocyte retrieval occurred 36 hours post-hCG injection.

Statistical Analysis

Data were analyzed using SPSS software. Differences were considered significant at $p<0.05$.

Results

(Table 1).

Table 1:

Outcome	GnRH Antagonist Protocol (n=130)	Progesterone Protocol (n=196)	p-Value
Failed Transfers (%)	16.20%	27.60%	$p < 0.02$
Successful Transfers (1st Try)	71.50%	57.70%	$p < 0.02$
Successful Transfers (2nd Try)	10.80%	10.20%	$p > 0.05$
Successful Transfers (≥3 Tries)	1.50%	4.60%	$p > 0.05$
Total Successful Transfers	33.40%	43.60%	$p < 0.01$

Conclusion

i. The GnRH antagonist protocol demonstrated higher success in first attempts (71.5% vs. 57.7%, $p<0.02$).

ii. Progesterone proved more effective in long-term outcomes, with overall successful transfers at 43.6% compared to 33.4% ($p<0.01$).

iii. Differences in late-stage success rates were statistically insignificant ($p > 0.05$).

Discussion

Both protocols have unique advantages, and the choice should depend on patient-specific conditions and indicators. GnRH antagonists are better suited for initial cycles, while progesterone offers a safer alternative for extended IVF programs.

Conflict of Interest

None.

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