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REDUCED FSH AND LH ACTION: IMPLICATIONS FOR MEDICALLY ASSISTED REPRODUCTION

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Introduction

Folliculogenesis is tightly controlled by a complex neuroendocrine interaction among the hypothalamus, anterior pituitary gland, and ovaries, mediated by the synergistic actions of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Historically, gonadotropin-related subfertility was attributed primarily to deficient hormone production. However, contemporary evidence highlights that diminished gonadotropin action driven by advanced reproductive age, variable glycosylation, and receptor-level polymorphisms is a critical factor in reproductive failure. In medically assisted reproduction (MAR), the transient pituitary suppression induced by GnRH analogue protocols can compound this baseline resistance. This interaction culminates in unexpected ovarian hypo-responsiveness and suboptimal clinical outcomes, even in women with normal baseline ovarian reserves, necessitating innovative, highly targeted therapeutic modifications.

Material and Methods

This thesis utilizes a comprehensive review of molecular, genetic, and clinical trials to evaluate the biological determinants of impaired FSH and LH action. A systematic search of major electronic databases, including PubMed, Embase, and Web of Science, identified relevant clinical trials and prospective cohorts investigating controlled ovarian stimulation (OS), in vitro fertilization (IVF) outcomes, and hypothalamic-pituitary-gonadal (HPG)-axis genetic variants. Evaluated primary clinical endpoints included cumulative oocyte yield, embryological parameters, and ongoing pregnancy rates. Furthermore, individual response dynamics were assessed via the follicle output rate (FORT) and follicle-to-oocyte index (FOI) to measure receptor-level sensitivity relative to patient-specific baseline ovarian reserve, allowing precise identification of unexpected hypo-responders.

Results

Molecular data demonstrate that advanced maternal age (>35 years) shifts circulating gonadotropin profiles toward highly sialylated, more acidic, and less sulfonated isoforms, which exhibit significantly reduced receptor binding affinity, altered intracellular signaling cascades, and decreased bioactivity. This age-dependent decline in action is further exacerbated by single nucleotide polymorphisms (SNPs). Specifically, carriers of the FSHR Ser680 allele (rs6166) and LHCGR Ser312 allele (rs2293275) receptor variants display lowered receptor sensitivity, requiring significantly higher cumulative FSH doses and longer stimulation durations during OS. Clinical and translational trials show that combining therapeutic recombinant human FSH with recombinant LH (r-hFSH:r-hLH co-treatment) in older cohorts (ages 35–39) and unexpected hypo-responders significantly rescues steroidogenesis in theca and granulosa cells, enhances oocyte maturation, downregulates follicle apoptosis, enhances fertilization potential, and improves clinical pregnancy, implantation rates, and overall embryo quality compared to r-hFSH monotherapy.

Conclusion

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Impaired FSH and LH action represents a distinct clinical entity that compromises standard ovarian stimulation protocols in MAR. Dynamic clinical indices like FORT and FOI provide a far more precise measure of individual receptor-level sensitivity than absolute oocyte counts. Proactively identifying patients with genetic or age-related gonadotropin resistance enables clinicians to transition from empirical stimulation regimens to personalized, precision-medicine protocols. Ultimately, utilizing targeted, evidence-based r-hFSH and r-hLH co-treatment represents a highly crucial clinical strategy to overcome receptor-level resistance and optimize clinical live birth rates in low-prognosis patients.

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