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Review Article

Segmented ART – The new era in ART?

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ABSTRACT

Currently up to 4% of infants born in developing countries are conceived through assisted reproductive technology (ART). Even though most of these conceptions occur and progress without complications, ART procedures and processes may increase iatrogenesis through complications in - and after conception. We herein review and discuss the clinically and scientific implications and evidence of iatrogenesis, and show how the evolution in ART technologies and procedures has led to the current presumption that frozen embryo transfer might be a more optimal strategy than fresh embryo transfer, in terms of not only reproduction, but also of maternal and fetal outcomes. There is increasing scientific evidence to support the notion that controlled ovarian stimulation could induce significant changes to the endocrine profile of a reproductive cycle, especially to the reproductively important early luteal phase. These changes may not only have a negative effect on implantation and early placentation, but also on the mother, the fetus, and the infant. The overt consequences of controlled ovarian stimulation include ovarian hyperstimulation syndrome, reduced embryo implantation, increased ectopic pregnancy, and altered placentation and fetal growth. The cumulative scientific evidence from this review suggests that GnRHa trigger in segmented ART might constitute the future routine treatment regimen for IVF patients, providing a safe, effective, and patient friendly treatment.

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1. Introduction

The use of ART has increased significantly since its inception, with up to 4.0% of infants currently conceived through ART. The aspirational mission of ART is unquestionably to use 'safe' technologies that deliver healthy infants to infertile couples. Although the vast majority of ART infants are believed to be healthy, some epidemiological studies have identified significant differences between the reproductive outcomes of ART and those of spontaneous conceptions [1,2]. Critically, these differences have the potential to increase perinatal morbidity and postnatal systemic and metabolic disease [3,4]. Definitive research, therefore, is crucially required to identify the molecular and/or cellular mechanisms underlying these adverse outcomes inherent to ART.

The moral and ethical aversion to iatrogenic complications, such as, multiple pregnancy, luteal phase insufficiency,

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impaired embryo implantation, ovarian hyperstimulation syndrome (OHSS), and perinatal and long-term health issues have been the motivation behind many of the major changes that ART has undergone since its inception. While for most of these complications there were always apparent solutions, the implementation of the solutions have had to wait for evolutions in the medical, surgical, and laboratory technologies of ART to eliminate certain inadequacies. After nearly half-a-century of ART there may be more than a glimmer of hope that many of these solutions may now have become feasible to implement. Ultimately, only ART that is completely free of iatrogenesis has the potential to deliver truly healthy infants to infertile couples.

Segmented-IVF has become a feasible treatment option to routine-IVF through major changes in controlled ovarian stimulation (COS), ovulation trigger, and embryo cryopreservation. Optimally implemented it may have the potential to limit a number of the current iatrogenic complications [5]. Currently, only the ''OHSS-free-clinic'' concept motivates the implementation of segmented-IVF. However, there are outcomes such as improved implantation, placentation, fetal growth, neonatal and long-term health, and lower ectopic pregnancy rates that are being found to be associated with frozen embryo transfer (FET), that in the future may become the most compelling motivation. If, IVF with fresh embryo transfer (ET) is to be replaced with segmented-IVF, however, it is imperative that there is no increase in treatment-related risks and stress, and that infant health remains paramount [5].

In this review, we discuss the scientific and clinical evidence of IVF treatment iatrogenesis, the evolutions that may limit this iatrogenesis, and whether segmented-IVF with FET is the ultimate solution.

2. ART iatrogenesis

2.1. *Controlled ovarian stimulation*

At this point of time in the history of ART, the collective evidence suggests that COS is responsible, directly and indirectly, for most of the significant iatrogenesis in IVF. Its ubiquitous use in IVF also means that all patients are more or less affected. Conventionally, COS involves the administration of serial doses of exogenous gonadotropins (i.e., follicle stimulating hormone – FSH) to induce multi-follicular recruitment and sustain development and the trigger (i.e., human chorionic gonadotropin – hCG) of final oocyte maturation at predetermined follicular developmental stages (i.e., follicular size by ultrasound measurement). While COS in most cases may achieve its goal in terms of oocyte number its follow-on consequences have been assumed and in some measure shown to include outcomes such as OHSS, reduced implantation, increased ectopic pregnancy, and increases in adverse perinatal and longterm developmental outcomes. The supraphysiological and irregulated endocrine conditions during the late follicular and early luteal phases are the main reasons for these adverse outcomes, because they result in altered endometrial development and function, and intrauterine conditions that may effect receptivity, implantation and placentation. In addition, the daily and total doses of gonadotropins used may have a significant negative impact, with increasing doses found to be associated with reducing live birth outcomes [6].

In the majority of IVF treatment cycles ovaries contain large numbers of developing follicles at the end of the follicular phase as the result of COS, with the supraphysiological levels of estrogen and progesterone on the day of trigger depending on the actual number of follicles [7,8]. Serum estrogen levels might reach levels 10 times greater than those found during a natural cycle. Cycles with exaggerated responses to ovarian stimulation were assumed to be at greater risk of iatrogenesis, however, recent studies have failed to show any significant independent adverse effect on reproductive outcomes [9–11]. Moreover, increasing and increased serum estrogen levels a function of gonadotropin dose and follicular number were found to be associated with increasing serum progesterone levels (≥1.5 ng/mL) on the day of trigger [12–14]. Premature progesterone rises occur in 8–40% of cycles, despite the use of gonadotropin releasing hormone (GnRH) analogs to maintain pituitary suppression during COS. Generally, the lower the progesterone level on the day of hCG trigger, the higher the chance of pregnancy [12]. The clinical effect of premature progesterone rise on the day of trigger was confirmed in a meta-analysis on more than 60 000 cycles, which showed significant reduction in pregnancy rates [14–16]. Progesterone levels, in the presence of estrogen, play a pivotal and determining role in endometrial (i.e., induction of maturation, morphology, activity and ultimately the timing of receptivity) and corpus luteal function, which have a direct impact on pregnancy outcomes [17,18].

In addition to the supraphysiological estrogen and progesterone levels during the late-follicular-early-luteal phase and as the result of the conventional use of a bolus hCG trigger, the early luteal phase is characterized by significantly reduced endogenous LH levels, caused by aberrant hypothalamic–pituitary–gonadal feedback control [19]. Luteal endogenous LH plays a crucial role in the induction and maintenance of the corpus luteum, the stimulation of implantation promoting factors (i.e., cytokines and growth factors), and, to a lesser extent, in the maturation and function of the endometrium [17–21]. Because of the biological and structural similarities between hCG and LH, a bolus of hCG can be used as a surrogate for the mid-cycle endogenous LH surge. However, the half-life of hCG is significantly longer than that of LH, resulting in sustained luteogenesis (>5 days) [20,21].

In the last decade, the introduction of GnRH antagonist co-treatment has provided the opportunity to use GnRH agonist rather than hCG for final oocyte maturation. The displacement of GnRH antagonist from the pituitary GnRH receptor elicits a surge of LH and FSH similar to that observed in natural cycles, inducing the required oocyte maturation and corpus lutea development [20]. Although, the GnRHa-induced surge of LH was found to be sufficient to secure optimal oocyte maturation, its shorter duration (24 vs. 36–48 h, respectively) [20] as compared to that of natural cycles, resulted in early luteolysis and consequently in high early pregnancy loss rates in fresh ET cycles with standard luteal phase support [19,20]. Using the combination, GnRH antagonist co-treatment, GnRH agonist trigger, and fresh ET cycles, therefore, requires effective modified luteal phase support, including LH activity supplementation to ensure ongoing pregnancies [19].

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