Advanced Drug Delivery Reviews 61 (2009) 871–882

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Drug delivery for *in vitro* fertilization: Rationale, current strategies and challenges ☆

Margit M. Janát-Amsbury, Kavita M. Gupta, Caroline D. Kablitz, C. Matthew Peterson *

Department of Obstetrics and Gynecology, Health Science Center, University of Utah, 30 North 1900 East, Suite 2B200, School of Medicine, Salt Lake City, Utah 84132, USA

ARTICLE INFO

Article history:
Received 8 October 2008
Accepted 28 April 2009
Available online 5 May 2009

Keywords:
In vitro fertilization (IVF)
Luteal phase support
Controlled ovarian hyperstimulation
Gonadotropins
Progesterone
GnRH analogues

ABSTRACT

In vitro fertilization has experienced phenomenal progress in the last thirty years and awaits the additional refinement and enhancement of medication delivery systems. Opportunity exists for the novel delivery of gonadotropins, progesterone and other adjuvants. This review highlights the rationale for various medications, present delivery methods and introduces the status of novel ideas and possibilities.

Contents

1. Introduction

In vitro fertilization (IVF) is increasingly pursued as a treatment for infertility that affects nearly 70 million couples globally [1]. Three million babies have been born worldwide through IVF treatment cycles [2] since the first successful IVF in 1978 [3]. The IVF procedure involves stimulated development and maturation of multiple oocytes through exogenous hormonal stimulation, transvaginal retrieval of oocytes from the follicles, fertilization of the eggs *in vitro* with sperm collected from the male counterpart, transfer of the *in vitro* fertilized embryo(s) into the patient's uterus or fallopian tube (zygote intrafallopian tube transfer-ZIFT) and finally, hormonal support post-implantation for 30–70 days to sustain the pregnancy.

Numerous advancements have been made in IVF including surgical techniques, protocols and in development of synthetic/recombinant hormonal analogues [2]. However, approaches for long duration delivery of peptide and steroidal hormones to meet the demands of IVF treatment cycles remain as major technological gaps. IVF protocols

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "The Role of Gene- and Drug Delivery in Women's Health – Unmet Clinical Needs and Future Opportunities".

* Corresponding author. Tel.: +1 801 587 8303 fax: +1 801 585 9295.
E-mail address: c.matthew.peterson@hsc.utah.edu (C.M. Peterson).

0169-409X/$ – see front matter © 2009 Published by Elsevier B.V.
doi:10.1016/j.addr.2009.04.019

entail daily injections of multiple agents that extend for weeks to months; yet the majority of delivery methods utilized for IVF procedures are limited to often-painful intramuscular (i.m.) or subcutaneous (s.c.) injections. Furthermore, IVF treatments are expensive due to the high cost of medications used and the necessity for frequent monitoring. Novel delivery systems that will minimize patient-to-patient variation, improve efficacy of embryo implantation and live birth rates, reduce the dose and frequency of medications required, eliminate injections and complex monitoring, and overall decrease the cost of IVF treatments will be welcomed by IVF patients and physicians.

This review attempts to provide a background and rationale for the various pharmacological agents and treatment protocols utilized in IVF. Emerging delivery technologies applied in IVF procedures are briefly discussed and potential areas that would benefit from more extensive research endeavors focusing on more efficient and patient friendly drug delivery strategies are highlighted.

2. Hormone interplay in the natural menstrual cycle

The natural female reproductive endocrinology involves a delicate balance and an intricate interplay of hormones (see Figs. 1 and 2) resulting in cyclic changes in the endometrium along with the development of a mature oocyte each cycle [4–7]. The hypothalamus secrets gonadotropin releasing hormone (GnRH), a decapeptide, in a pulsatile manner to stimulate the pituitary to secrete the gonadotropins: luteinizing hormone (LH) and follicle stimulating hormone (FSH) (Fig. 1) [7]. GnRH has a short half-life of 2–5 min due to rapid cleavage by serum proteases. The frequency of GnRH pulses contributes to modulation of LH and FSH released and hence the LH: FSH ratio in blood (Fig. 2) [8].

LH and FSH synergistically regulate the menstrual cycle through stimulating production of estrogen and progesterone from the ovarian follicles. FSH stimulates the granulosa cell compartment and is essential for the development of mature oocytes capable of fertilization. While higher amounts of FSH in the early follicular phase promotes growth of 6–8 follicles (follicular cohort), the diminished levels occurring in the late follicular phase usually restrict the number of fully developed preovulatory follicles to a single follicle with highest sensitivity to FSH among the cohort [6]. The growing follicle secretes high levels of estrogens, which is produced by conversion of cholesterol to androgens in theca cells followed by aromatization of androgens to estrogen in granulosa cells. When elevated estrogen levels persist for more than 2 days, a positive feedback signal to the hypothalamus and pituitary initiates a preovulatory LH surge (Figs. 1 and 2). The LH surge initiates resumption of meiosis in the oocyte up to metaphase II, causes extrusion of the ovum from the follicle and results in luteinization of the follicle to form corpus luteum.

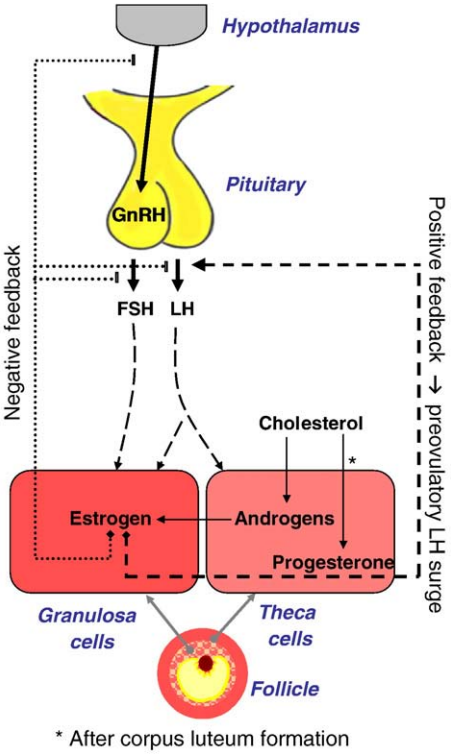

Fig. 1. Hormonal interplay in natural menstrual cycle.

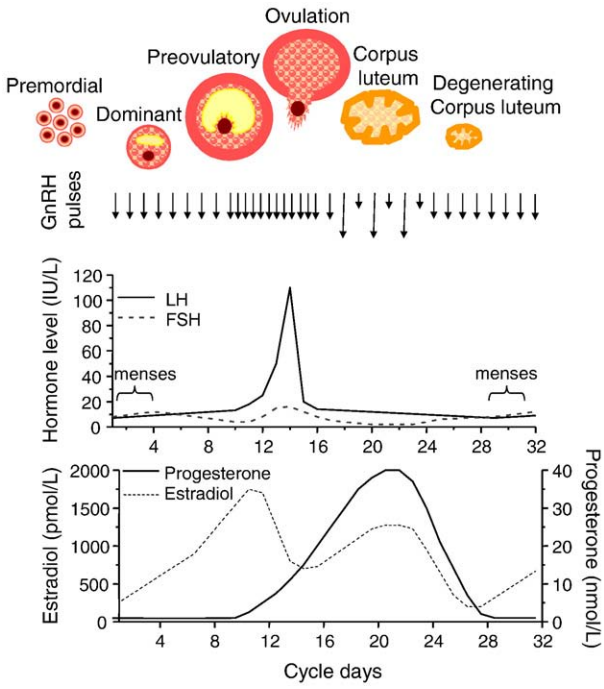

Fig. 2. Hormone levels in natural menstrual cycle and the corresponding states of follicular development.

The luteal phase is characterized by transformation of the follicle into a corpus luteum post-ovulation in response to the LH surge. The secretory cells of the follicle are converted to mainly progesterone secreting cells. The progesterone secretion in the luteal phase increases dramatically from 1 mg/day in the follicular phase to 25 mg/day in the luteal phase and promotes changes in the endometrium that are essential to sustain pregnancy [9]. The corpus luteum secretes estrogen and mainly progesterone and is responsible for sustaining pregnancy in the first trimester. If fertilization occurs, the growing embryo and placenta start secreting human chorionic gonadotropin (hCG) that prolongs the life of corpus luteum [9]. Human chorionic gonadotropin has molecular structure and function similar to LH and is secreted by the embryo and the placenta after conception [10].

FSH, LH and hCG are about 40 kD dimeric glycoproteins with identical α subunits consisting of 92 amino acids. The unique β subunits that determine the specific biological activity vary between 118 (FSH), 121 (LH) and 152 (hCG) amino acids. The initial and terminal half-life's vary depending on the degree of glycosylation of the glycoprotein hormones (LH: 1 h and 12 h [11]; FSH: 2 h and 17 h [12]; and hCG: 5 h and 30 h [13]).

3. Stimulated cycles in IVF

In early IVF treatments, including the first successful IVF in 1978 [3], a single mature oocyte retrieved from the patient's natural