Progesterone and the Luteal Phase

A Requisite to Reproduction

Tolga B. Mesen, MD*, Steven L. Young, MD, PhD

KEYWORDS

• Progesterone • Luteal phase • Luteal phase deficiency • Luteal phase support • ART

KEY POINTS

- Luteal phase deficiency is a disease without a reliable diagnostic test, impairing clinical research and patient care.
- Exogenous progesterone is the primary agent for luteal support during assisted reproductive technology treatment; however, the best delivery method, protocol, and formulation are not yet known.
- Vaginal or intramuscular progesterone seem to be equivalent in terms of pregnancy outcomes after in vitro fertilization.
- The best route of progesterone supplementation after frozen embryo transfer is not yet established.

INTRODUCTION

The normal menstrual cycle can be divided into two phases: follicular and luteal, which are separated by ovulation and bookended by the first day of menstrual bleeding. The follicular phase is dominated by the development of the preovulatory follicle, resulting in estrogen-stimulated endometrial proliferation, whereas the corpus luteum (CL) of its namesake luteal phase produces progesterone, which inhibits endometrial proliferation and determines endometrial receptivity. Without both phases working in series, natural reproduction is not possible. This article focuses on the normal physiology of the luteal phase, investigates the controversy surrounding luteal phase defect, and describes the role of luteal phase support in assisted reproductive technology (ART).

The authors have nothing to disclose.
Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, CB 7570, Chapel Hill, NC 27599, USA
* Corresponding author.
E-mail address: tolga_mesen@med.unc.edu

Obstet Gynecol Clin N Am 42 (2015) 135–151
http://dx.doi.org/10.1016/j.ogc.2014.10.003 **obgyn.theclinics.com**
0889-8545/15/$ – see front matter

LUTEAL PHASE PHYSIOLOGY

In the natural menstrual cycle, the follicular phase culminates with the maturation of the dominant follicle. Increasing estradiol, secreted from the granulosa cells inside the dominant follicle, triggers a surge of luteinizing hormone (LH) from the anterior pituitary. The LH surge propagates a series of events, beyond the scope of this article, that result in the breakdown of the connections of granulosa cells comprising the cumulus oophorous, reentry of the oocyte into the diplotene stage of prophase I of meiosis, and eventual rupture of the follicle and extrusion of the oocyte into the pelvis. While the oocyte is captured by the fimbria and possibly fertilized in the fallopian tubes, the postovulatory, deflated, and eggless follicle can easily be forgotten. However, the remaining follicular cells play an essential role in facilitating reproduction and maintaining normal menstrual cyclicity by forming the CL.

Before ovulation, the granulosa cells of the dominant follicle begin their transformation into the CL by enlarging and becoming vacuolated.[1] The vacuoles take up the pigment lutein (from the Latin *luteus*, meaning "yellow") giving developing CL its characteristic yellow color. Before ovulation the granulosa cells are separated from the circulation by the basal lamina, necessitating nutrients and communications travel through gap junctions. With luteinization, the basal lamina regresses and the theca cells migrate into the forming CL. In addition, there is prompt neovascularization of the developing CL,[2] mainly under the control of vascular endothelial growth factor and fibroblast growth factor, which are upregulated in the luteinized granulosa cells.[3] The result of the impressive neovascularization is one of the highest blood flows per unit mass in the body,[1] a fact clinically apparent to a gynecologist managing a hemorrhagic CL.

Although the CL secretes many different hormones, the sex steroid, progesterone, is of primary importance because it is necessary and sufficient to transform the endometrium to a state receptive to blastocyst implantation and to maintain early pregnancy.[1] The production of progesterone by the luteal cells depends on the availability of its circulating cholesterol substrate and is facilitated by a low-level LH stimulation.[4] To accomplish steroidogenesis, the luteal cells develop into 2 morphologic appearances, small and large cells, with distinct functions.[5] The small cells, likely derived from the theca cells,[6] contain LH and human chorionic gonadotropin (HCG) receptors.[7] The LH receptor regulates low-density lipoprotein cholesterol receptor binding and internalization of the cholesterol.[1] The large luteal cells are thought to arise from the granulosa cells.[6] These cells have a greater steroidogenic capacity but lack the LH and HCG receptors needed to stimulate growth and provide cholesterol substrate.[8] The small and large cells are linked by gap junctions facilitating rapid transport of signals between cells, providing a mechanism by which the large luteal cells, devoid of LH receptors, respond to LH stimulation and provide the primary source of progesterone.

Multiple experimental designs and clinical experience in patients undergoing ART treatment illustrate the importance of tropic LH secretion to progesterone production from the CL. In one classic experiment, rhesus monkeys with an obliterated median basal hypothalamus, and, therefore, absent gonadotropin-releasing hormone (GnRH) secretion, were given exogenous GnRH pulses of a uniform amplitude and frequency via a mechanical pump. When the GnRH pump was active during the luteal phase, LH and progesterone were secreted. Within hours of discontinuing GnRH pulses, LH and progesterone levels were undetectable.[9] In women, lacking GnRH due to hypophysectomy, progesterone from the CL can be maintained with LH infusion.[10] In women undergoing in vitro fertilization (IVF) with pituitary downregulation