Endocrine Basis for Recurrent Pregnancy Loss

Raymond W. Ke, MD, HCLD

KEYWORDS

• Recurrent pregnancy loss • Luteal phase defect • Hyperprolactinemia
• Polycystic ovary syndrome • Thyroid disease • Thyroid antibodies

KEY POINTS

- Common endocrinopathies are a frequent contributor to both spontaneous and recurrent miscarriage.
- Although the diagnostic criteria for luteal phase defect is still controversial, treatment of patients with both recurrent pregnancy loss and luteal phase defect using progestogen in early pregnancy appears to be beneficial.
- With rising demand, an increase in thyroid gland function is critical in the maintenance of early pregnancy.
- Overt or subclinical hypothyroidism along with the presence of antithyroid antibodies is correlated with poor obstetric outcome.
- Women with polycystic ovary syndrome, the most common endocrinopathy of reproductive age women, have an increased risk of pregnancy loss.
- Management of hyperinsulinemia in polycystic ovary syndrome with normalization of weight or metformin appears to reduce the risk of pregnancy loss.

The human embryo enters the uterine cavity 4 days after ovulation. The process of implantation begins approximately 3 days later or typically between 19 and 23 days from the last menstrual cycle, a time period of high receptivity known as the *implantation window*.[1] It has been observed that the longer the ovulation-to-implantation interval, the higher the risk of early pregnancy loss.[2] Endocrine hormones play a critical role in the expression, modulation, and inhibition of various growth factors, cytokines, cell adhesions molecules, and decidual proteins. Estradiol and progesterone control the orderly growth and differentiation of the endometrium for implantation of the embryo. A receptive endometrium is characterized by growth and coiling of spinal arteries, secretory changes in the glands, and decidualization of the stromal compartment. Failure of the endometrium to respond to these hormonal signals can result in

The author has nothing to disclose.
Assisted Reproduction, Fertility Associates of Memphis, 80 Humphreys Center, Suite 307, Memphis, TN 38120, USA
E-mail address: rke@fertilitymemphis.com

Obstet Gynecol Clin N Am 41 (2014) 103–112
http://dx.doi.org/10.1016/j.ogc.2013.10.003 **obgyn.theclinics.com**
0889-8545/14/$ – see front matter

defective placentation resulting in a risk of miscarriage. Recurrent pregnancy loss (RPL), defined as 2 or more consecutive pregnancy losses before the 20th week of pregnancy, is a frequent obstetric complication. One of the pathogenetic mechanisms underlying RPL includes a dysfunction of the endocrine system.

LUTEAL PHASE DEFECT

Crucial to the development of the endometrium is adequate glandular growth primarily mediated by abundant estradiol during the proliferative phase. At a threshold value, estradiol signals the pituitary to release a large amount of luteinizing hormone (LH) into circulation. This surge of circulating LH triggers oocyte maturation and release and the formation of the corpus luteum from the granulosa cells of the ruptured follicular bed. The luteal phase begins with the LH surge and ideally lasts 14 days in a nonpregnant menstrual cycle ending when hormone withdrawal from the involuting corpus luteum results in endometrial sloughing and the start of another menstrual cycle. Unique to the luteal phase is a sharp increase in progesterone production from the corpus luteum that, along with estradiol, peaks during the implantation window. Primarily through the action of progesterone, the endometrium undergoes stromal decidualization, and the glands switch to a secretory role in preparation for implantation.[3,4] A normal luteal phase is characterized by estradiol-mediated glandular growth in the preceding proliferative phase, adequate LH surge triggering ovulation, followed by robust progesterone production with an appropriate endometrial response.

Accordingly, the dysfunctional mechanisms resulting in luteal phase defect (LPD), also known as *luteal phase insufficiency*, may include poor follicular growth, oligoovulation, inadequate corpus luteum function, or altered endometrial response to secreted progesterone.[3] These mechanisms may arise from a wide spectrum of endocrinopathies and comorbidities such as hyperprolactinemia or stress (**Box 1**).[5] LPD has long been suspected with miscarriage and RPL.[6] However, quantifying the risk has been hampered by the difficulty in defining diagnostic criteria for LPD.[3,4] Although histologic dating of the endometrium after timed biopsy has been the historical gold standard for the diagnosis of LPD, the accuracy and reproducibility of this modality is highly suspect given significant intra- and interobserver variation in interpretation.[5,7] In a study of timed endometrial biopsies from 130 fertile women, Murray and colleagues[8] found that histologic endometrial dating had neither the accuracy nor the precision to diagnose LPD and thus did not help in the clinical management of these patients. A criterion of luteal phase length less than 11 days can be difficult to measure reliably and document consistently but could be useful as a screening evaluation for LPD. Luteal phase hormone levels, especially progesterone concentration, are more

Box 1
Identified causes of luteal phase defect

- Hyperprolactinemia
- Polycystic ovary syndrome
- Hypogonadotropic hypogonadism
- Poor ovarian reserve
- Stress
- Exercise
- Extreme weight loss