LUTEAL PHASE DEFECT

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INTRODUCTION

Following ovulation, the mature ovarian follicle forms the corpus luteum, with the initiation of progesterone production which prepares the endometrium for implantation and maintenance of a pregnancy.

If pregnancy occurs, the production of progesterone from the corpus luteum continues for 7 weeks then the placenta takes over this function.

If pregnancy does not occur, menses begins with the demise of the corpus luteum.

In 1949, Georgeanna Jones, first described luteal phase deficiency (LPD) when the luteal phase is shorter than normal, progesterone levels during the luteal phase are below normal, or both, with inadequate secretory transformation of the endometrium, resulting from deficient progesterone production, with the implication of both infertility and recurrent pregnancy loss.

Since then LPD has been the subject of much debate among specialists in the field of reproductive endocrinology.

There is debate about its existence, there are also questions surrounding its impact on fertility and recurring miscarriage and how luteal phase defect can be diagnosed.

LPD has been diagnosed in 3-20% of infertile patients and in 5-60% of patients with recurrent pregnancy loss.

However, data show that 6-10% of women who are fertile demonstrate an inadequacy of the luteal phase.

Theoretically, a luteal phase defect may occur due to insufficient progesterone produced to develop the endometrium. This has led to many proposed methods for diagnosis including: measuring a progesterone level during the luteal phase, monitoring the number of days between ovulation and menses, or performing an endometrial biopsy. Unfortunately, none of these methods have been proven to accurately predict infertility.

PATHOPHYSIOLOGY

The following mechanisms can cause an inadequate endometrial response to hormonal stimulation during the luteal phase.

Abnormal follicular development: due to inadequate FSH and LH production with the resultant reduced granulosa cell growth and lower estradiol levels . The corpus luteum is not a de novo structure. It shows the effects of abnormal folliculogenesis with decreased progesterone production.

Abnormal luteinization: A suboptimal LH surge at ovulation causes deficient progesterone because of inadequate luteinization of the granulosa cells.

Uterine anomalies: can cause changes in vascularization of the endometrium despite normal progesterone levels. Myomas, uterine septa, and endometritis are responsible for poor secretory changes in the endometrium.

Hypocholesterolemia: cholesterol is the substrate responsible for initiation of the steroid pathway. A deficiency results in low-to-absent progesterone production and a luteal phase defect.

CLINICAL

PRESENTATION

A high level of suspicion that such a condition exists when seeing a patient with infertility or recurrent pregnancy loss is needed.

A menstrual cycles of less than 26 days or a luteal phase of less than 11 days by basal body temperatures are suggestive, but are not very effective and highly inaccurate however, and can not alone diagnose luteal phase defect.

Serum progesterone levels: studies confirmed that there is wide range of normal values for progesterone during the luteal phase because it is released in a pulsatile fashion, suggesting that a single sample is not sufficient for the diagnostic and confirmed the need for multiple samples to overcome the pulsatile nature of progesterone is expensive and inconvenient.

A Urinary LH kits provide a useful test to estimate the appropriate timing of an endometrial biopsy (EB). Following a positive test finding, ovulation occurs within 24-26 hours. The EB should be performed on the 12th day of a 14-day luteal phase.

Studies regarding cell adhesion molecules or integrins, growth factors, and cytokines are all in the experimental phase.

Studies measuring progestin endometrial protein (PEP) have not been conclusive in diagnosing LPD.

Imaging Studies: Ultrasound documentation of ovulation from follicular growth to collapse of the follicle is very accurate; however, this procedure is time consuming and expensive. Ultrasound measurement of endometrial thickness has not been shown to be effective in the prediction of luteal phase deficiency.

Endometrial Biopsy (EB): Noyes, and Rock established that the diagnosis of luteal phase deficiency is centered on histologic dating of the endometrium. However, the location and time of the biopsy can greatly influence the EB findings. Some authors believe that mid-luteal phase biopsy can give accurate diagnosis of LPD, however, endometrial samples are assessed with considerable variation and its poor ability to predict fertility has led some to prove against using this method.

Histologically, a luteal phase defect provides a biopsy that lags behind the date of actual endometrial sampling by 3 days or more. The biopsy should be performed in 2 consecutive cycles.

The basal body temperature (BBT) chart can aid in determining the length of the luteal phase. A luteal phase of less than 11 days may be associated with LPD however, temperature charts are not very effective and highly inaccurate when used to diagnose luteal phase defect. .

The BBT chart can also assist in timing the EB by observing the patient's cycle length and performing the biopsy 2 days prior to the expected menses.

TREATMENT

If luteal phase defect is suspected, treatments designed to increase luteal phase progesterone have been proposed and may help support implantation and pregnancy.

There are three methods of therapy that have been utilized to treat luteal phase defect:

--Controlled ovarian stimulation with clomiphene citrate or human menopausal gonadotropin (hMG) to produce more than one follicle and therefore more than one corpus luteum.

--Supplemental hCG to increase corpus luteum secretion of progesterone.

--Supplementation of progesterone after ovulation.

defect:

In women without hyperprolactinemia and hypothyroidism, vaginal progesterone is advocated to supplement endogenous progesterone production.

The vaginal suppository or gel is preferred over both the oral and intramuscular forms because of superior endometrial progesterone concentrations.

Vaginal suppositories are less expensive but are messier than the vaginal gel. Progesterone should be continued for 8-10 weeks to cover the time of the ovarian-placental shift.

A Cochrane review found that synthetic progesterone is preferred to micronized progesterone, and also other substances, such as human chorionic gonadotropin (hCG), did not improve outcomes. No specific route or duration was preferred.

Clomiphene citrate corrects LPD by improving folliculogenesis and the resultant luteal phase following ovulation. Successful treatment with gonadotropins and HCGs probably results from superovulation rather than from a correction of LPD.

Following any of these treatments, the patient should have a repeat endometrial biopsy to determine that LPD has been corrected.

Hyperprolactinemia and hypothyroidism cause luteal phase deficiency (LPD) through hypothalamic-pituitary dysfunction. Agents like Bromocriptine and levothyroxine are used to treat LPD in women with these conditions.

PROGNOSIS

The lack of double-blinded placebo-controlled studies prevents an accurate prognosis for this condition. A report by the Practice Committee of the American Society for Reproductive Medicine concluded that there is no significant evidence that LPD alone can cause infertility.

THANK YOU