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Review Article

Luteal Phase Defects: Review

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ABSTRACT

Luteal Phase Defects (LPD), also known as Corpus Luteum Insufficiency or Luteal Phase Insufficiency, are characterized by insufficient function of the corpus luteum, resulting in inadequate progesterone secretion. This can lead to a shortened luteal phase and poor endometrial secretion, which are critical for embryo implantation and pregnancy maintenance. During the menstrual cycle, women with LPD still experience normal follicular development and ovulation. However, due to early degeneration of the corpus luteum or insufficient progesterone, the luteal phase becomes dysfunctional. This can hinder the thickening of the endometrium, which is necessary for a fertilized egg to implant. Luteal Phase Defects are a common cause of female endocrine dysfunctions, impacting fertility and pregnancy outcomes. With advancements in Assisted Reproductive Technology (ART), LPD has become more prevalent, particularly among ART patients. The condition is often addressed through progesterone supplementation or other fertility treatments to improve the luteal phase function and enhance chances of conception. Management of LPD typically includes hormone therapy to correct progesterone deficiency and optimize the uterine environment for implantation.

KEYWORDS

• Corpus Luteum • Progesterone • Implantation • Uterus • Fertility

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INTRODUCTION

Luteal Phase Defects are synonymous with Corpus luteum Insufficiency, or Luteal phase insufficiency. It is defined as inadequate corpus luteal function, luteal hypoplasia or premature degeneration.[1] Women with LPD have follicular development and ovulation during the menstrual cycle. However, due to the premature decline of the luteum or insufficient progesterone secretion, these patients' luteal period is shortened, and their secretion of the endometrium is poor. The concept of LPD was first proposed by Jones in 1949. Luteal insufficiency is one of the most common causes of female endocrine dysfunctions. LPD is a common female reproductive endocrine defect. In the natural cycle, LPD in women of childbearing age was found to be 3%–10%, while the incidence was significantly increased in the ovulation stimulation cycle. With the development of assisted reproductive technology (ART) in recent years, the incidence of LPD is high among patients using ART.

ETIOLOGY

The etiology of luteal phase defect could be multifactorial.

- Inadequate development of the pre ovulatory follicle
- Inadequate development and/or vascularisation of the corpus luteum
- Inadequate HCG pulse secretion from the anterior pituitary
- Inadequate progesterone receptors on the endometrium
- Imbalance between estrogen and progesterone ratio and/or receptors.[1]

Pathological conditions that disrupt normal gonadotropin-releasing hormone (GnRH) and LH pulsatility can hypothetically lead to LPD. Conditions associated with luteal phase deficiency (LPD) include hypothalamic amenorrhea, eating disorders, excessive exercise, significant weight loss, stress, obesity, polycystic ovary syndrome (PCOS), endometriosis, and aging.

undiagnosed or inadequately treated 21-hydroxylase deficiency, thyroid dysfunction, hyperprolactinemia, ovarian stimulation alone and assisted reproductive technology use.[3]

Diagnostic criteria

- Short luteal phase of less than 10 days - This was first described by Strott. It has been observed that not all short luteal phases are inadequate.[4]
- Absent or Inadequate thermogenic Shift in Basal Body Temperature (BBT) levels. There is a poor correlation between BBT and hormonal levels.
- Low levels of Serum Progesterone on cycle day 21 in a 28 day cycle or 7 days post ovulation in a longer cycle. The cut off level is not precisely defined. Discriminatory values for normal cycles have ranged from 9.4-12.5ng/ml. Levels lower than 10 ng/ml are certainly pathognomonic. The variability in daily progesterone levels is quite wide. To reduce such variability, multiple estimations in the luteal phase have been suggested as a practical solution.
- Endometrial histology lagging behind by 2 days in the luteal phase.
- Ultrasonic evidence of poor endometrial echogenic change.
- Ultrasonic evidence of absent corpus luteum formation in the mid luteal phase and/or poor corpus luteal vascularisation.[5]

DISCUSSION

Luteal support using progesterone, human chorionic gonadotropin (HCG), estrogen, and GnRH agonists (GnRH-a) has become a crucial treatment in assisting pregnancies through ART. In cases of luteal insufficiency, the progesterone produced during the luteal phase is insufficient to fully transform the endometrium from the proliferative phase to the secretory phase,so the embryo implantation environment cannot be guaranteed. On the other hand, even if the embryo is successfully implanted, the progesterone secreted by the gestational luteum is not enough to maintain embryo development to placental formation. Luteal insufficiency can easily desynchronise the patient's endometrium with embryonic development, resulting in infertility or early pregnancy loss. Clinically, 35% of early pregnancy loss and 4% of recurrent pregnancy loss are caused by luteal insufficiency.[2]

Newer Diagnostic Modalities under investigation are as follows:

- Daily Salivary Progesterone measurements- The total progesterone output as measured by the area under the progesterone profile curve is significantly lower in LPD cycles than normal cycles. Since daily blood measurements are cumbersome, salivary measurements may be more acceptable.
- Progesterone associated endometrial protein The levels of this protein increase in the luteal phase. Measurement of this protein holds promise for the diagnosis of LPD but further study is required to determine its accuracy as a diagnostic test.
- Morphometric analysis of endometrium Morphometric analysis is superior to simple histology of the endometrium. However it is time consuming but with advances in computer technology and the use of image analysis this may become less of a problem.
- Ultrastructure of endometrial glandular epithelium Electron microscopy has been used to study the glandular epithelium. Since each of the above criteria when taken alone is not diagnostic, one has to take into account two or more of the above criteria i.e. endometrial histological dating more than 2 days out of phase coupled with low progesterone levels and/or short duration of progesterone secretion by the corpus luteum. Interestingly LPD has been shown to co-exist with Normal serum levels of progesterone. Hence progesterone levels alone do not reflect endometrial histology.[6]

MANAGEMENT

The treatment options available for the patient with luteal inadequacy leading to early pregnancy wastage are many. Every option has its proponents and critics and although in some circumstances a definitive treatment can be identified, in the majority of cases, the initial therapy is mostly a matter of preference. The various treatment options are clomiphene citrate (cc), Progesterone supplementation, hCG, bromocriptine and menotropins in addition to various synthetic progestational compounds.

Clinically diagnostic methods

- Luteal duration an 5 Research diagnostic methods
- Frequent assay of progesterone and gonadotropins
- Endometrial histology
- Decidual prolactin measurement
- Steroid hormone receptor analysis
- Analysis of novel substances[7]

Stimulation of Folliculogenesis

Clomiphene citrate (cc): The rationale for the use of clomiphene in the treatment of luteal phase deficiency is based on substantial evidence from the work by Di Zerega and Hodgen who have shown that the functional capacity of the Corpus luteum is dependant upon normal growth and maturation of the preovulatory follicle.[8] Emergence of the dominant ovarian follicle, proliferation of the granulosa layer, induction of the LH receptors, endometrial proliferation and Progesterone receptor (PR) induction and finally stimulation of the LH surge itself are all important prerequisites of the follicular phase for subsequent normal luteal function. All are directly dependent on the follicular phase FSH or the estrogen produced by FSH-induced aromatase activity, or both. During clomiphene administration peripheral serum levels of FSH rise as they do in the early follicular phase of the normal cycle. There are several studies which link a short or otherwise inadequate luteal phase to relative follicular phase FSH deficiency.[9] It follows therefore, that clomiphene would be considered as an appropriate means to correct or improve inadequate luteal function This treatment has been supported by the finding that luteal phase P concentrations are always higher in patients treated with clomiphene citrate.[10]

Ovulation induction

Ovulation induction medications play a key role in the development of dominant follicles and the growth of the endometrium. They also inhibit the conversion of androgens to estrogen, act as antagonists on estrogen receptors, aid in tissue insulin sensitization, and directly stimulate the hypothalamus via gonadotropins. Laparoscopic ovarian drilling is an adjunct second-line treatment.[7]

In the absence of an identifiable correctable underlying cause of LPD, progesterone replacement and clomiphene citrate are the usual treatment options for consideration. Combination therapy, gonadotropins, and other treatments are reserved for refractory cases. No data at present suggest a difference in efficacy between progesterone and clomiphene. When abnormal luteal endometrial biopsy is corrected, conception and live birth rates are high.[11]

CONCLUSION

Luteal Phase Defects (LPD) represent a significant cause of reproductive dysfunction, particularly in women experiencing infertility. Characterized by insufficient corpus luteum function and inadequate progesterone secretion, LPD can lead to a shortened luteal phase and an underdeveloped endometrial lining, both of which are crucial for embryo implantation and successful pregnancy. Although women with LPD may have normal follicular development and ovulation, the premature decline of the corpus luteum impairs the luteal phase, affecting fertility outcomes. With the increasing use of Assisted Reproductive Technology (ART), LPD has become more frequently recognized in clinical practice, highlighting the need for proper diagnosis and treatment. Management strategies, including progesterone supplementation, can help correct the hormonal imbalances and improve the uterine environment for implantation. Further research into the underlying mechanisms and more targeted treatments will be essential to improve fertility outcomes and minimize the impact of LPD on women's reproductive health. Addressing LPD effectively remains crucial for optimizing fertility treatments and supporting women through their reproductive journeys.

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