Combination therapeutic options in the treatment of the luteal phase deficiency

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ABSTRACT

Luteal phase deficiency (LPD) is described as a condition of insufficient progesterone exposure to maintain a normal secretory endometrium and allow for normal embryo implantation and growth. There is evidence that both follicular and luteal phase abnormalities can result in LPD cycles. The aim of this randomized prospective noncomparative study is to evaluate the effectiveness of combination therapy in patients with LPD. This prospective study included 35 women of the reproductive age. They were diagnosed with LPD with sonographically and laboratory-verified methods. The age of patients was 36±0.46 years. The results of the study sonographically demonstrated an increase in the diameter of the corpus luteum from 1.36±0.32 (initially) to 2.16±0.21 mm after combination therapy. In addition, there was a statistically significant increase in the level of estrogens and progesterone in the corresponding phases of the menstrual cycle. Thus, the combination therapy for patients with LPD contributes to the recovery of cyclic events in the hypothalamic-pituitary-gonadal system, which determines the restoration of the endocrine function of the ovaries and promotes adequate secretory rearrangement of the endometrium in women of reproductive age.

Introduction

Luteal phase deficiency (LPD) is a condition of insufficient progesterone exposure to maintain a normal secretory endometrium and allow for normal embryo implantation and growth [1]. Most of these controversies derive from too much confusion existing in the knowledge of corpus luteum function, progesterone production, implantation window and endometrial competence and, consequently, about luteal phase deficiency (LPD) and support.

LPD is sometimes clinically manifest by a shortened luteal phase lasting less than 9 days, from the day of ovulation to menstrual bleeding [1–3].

LPD is also suspected when spotting begins many days before menstruation without a structural or infectious cause. LPD has been implicated as a cause of irregular menstrual bleeding, infertility and recurrent pregnancy loss [3–8]. However, despite the repeated association, a 2012 American Society for Reproductive Medicine (ASRM) committee opinion reminds readers that LPD has yet to be proven as a cause of infertility [9]. Pathophysiological theories of luteal phase deficiency include two mechanisms that have been proposed as causes of clinical LPD. The first and likely more common cause relates to the impaired function of the CL resulting in insufficient progesterone and estradiol secretion [10]. Impaired function can be the result of improper development of the dominant follicle destined to become the CL or aberrant stimulation of a normally developed follicle. Both mechanisms result in a CL with deficiencies in progesterone production. The second theory suggests an inability of the endometrium to mount a proper response to appropriate estradiol and progesterone exposure [11].

LPD is described as a condition of insufficient progesterone exposure to maintain a normal secretory endometrium and allow for normal embryo implantation and growth [12]. This definition has been sustained during years from its first description [13].

The human endometrium undergoes a complex series of organized proliferative and secretory changes in each menstrual cycle and exhibits only a short period of receptivity, known as the ‘implantation window’ [14]. Endometrial receptivity during the implantation window requires a close cooperation of an extremely large number of different factors; unfortunately, the individual role of each factor in the network of endometrial development is still not completely understood [15]. The corpus luteum is derived from the transformation of granulosa and theca cells into luteal cells in response to the mid-cycle surge of gonadotropins or to an exogenous human chorionic gonadotropin (hCG) bolus administration. The most important function of the corpus luteum is progesterone secretion, which is necessary to obtain a secretory transformation of the endometrium and to sustain the early pregnancy. Progesterone prepares the endometrium for pregnancy by stimulating proliferation in response to hCG. This occurs in the luteal phase of the menstrual cycle.

During the mid-luteal phase of a normal cycle, progesterone is involved in the modulation process of the expression of ultrastructural hallmarks of secretory transformation, such as giant mitochondria, subnuclear glycogen deposits, pinopodes and nucleolar channel system (NCS) [8]. With the aim of inducing endometrial competence/receptivity, progesterone can also act by stimulating the immune system to produce non-inflammatory T-helper 2 cytokines and C3–C4, as shown in patients with...
autoimmune diseases [16,17], increasing nitric oxide production, with improvement of the blood flow and oxygen to the endometrium [18]. Progesterone is also able to reduce the contractility of the myometrium at the time of the implantation [19].

In consideration of the LPD definition, histological evaluation of the endometrium has been considered the gold standard procedure to study endometrial competence. The histological method is based on a careful examination of an endometrial biopsy, and on the definition of the histologic characteristics of a secretory endometrium and describing the temporal responses to progesterone, that is, endometrial dating. An endometrium is considered out of phase when there is a lag of more than two days [20].

Ultrasound assessment is still used to evaluate endometrial competence though no significant correlation has been seen between endometrial measurement (>7 mm) and the pregnancy rate; moreover, the triple-layered pattern is visible in the same rate in infertile and fertile women (91% vs. 90%, respectively) [21]. In order to increase accuracy of the ultrasound method and to find a predictor sign of pregnancy during IVF treatment, the power-Doppler was proposed as the instrument for evaluating endometrial competence, but no statistically significant differences in the vascularization indexes of endometrial and subendometrial blood flows were found between pregnant and non-pregnant groups [22].

Several molecular markers of endometrial competence have been discovered in blood and uterine fluid analysis and endometrial biopsy, such as estradiol, progesterone, pinopodes, glycodelin, IL-1 system, cytokines, integrons and HOXA genes [23]. Serum progesterone assay has been proposed as surrogate of endometrial competence, but it has been observed that no minimum progesterone levels can define a ‘fertile’ luteal phase [24] because progesterone concentrations may fluctuate up to eightfold within 90 min [25] and its levels peak 6–8 days after the ovulation [26].

Classical therapy of choice in the treatment of luteal phase failure of the menstrual cycle is the use of hormonal drugs, primarily, gestagens, sometimes in combination with estrogens.

Dydrogesterone, a stereoisomer of progesterone, appears to be a highly selective progestin which, due to its retrostructure, binds almost exclusively to the progesterone receptor. Dydrogesterone has a good safety and tolerability profile. It is structurally and pharmacologically similar to natural progesterone and has good oral bioavailability with few side effects. After oral administration, it is generally absorbed reaching a maximum serum concentration within 2–5 h and displays stable plasma level [27].

In recent years, taking into account the involvement of several factors in the development of LPD (hypothalamic–pituitary level of regulation; metabolic disorders associated with it; state of receptivity of the endometrium, excessive free radicals, hypoxia, acidosis, depletion of energy resources of cells), nevertheless, in gynecological practice, the use of drugs of ‘metabolic’ therapy, with new mechanisms of action and levels of influence is widely introduced.

The mechanisms of the action of the human placental hydrolysate are the ability to enhance the energy potential of cells, promoting the stabilization of cell membranes, the normalization of the functional activity of mitochondria, the synthesis of nucleic acids, proteins and other intracellular structures, which leads to optimization of cellular metabolism in general and inhibits the formation and progression of pathological processes at the cellular level due to direct action on the link of the gonads themselves and the body as a whole.
Statistical processing of data was carried out on a personal computer using the Biostatistics (version 4.03) package for Windows. The arithmetic mean (M) and mean error of the arithmetic mean (m) were calculated. The differences between the groups were established taking into account Student’s t-test. The statistical index was considered reliable at \( p < .05 \).

### Results

Before the start of treatment, the presence of a dominant follicle was determined by sonography only in 23 patients (65.7%), after combination therapy a dominant follicle was detected in 33 women (94.4%).

The inclusion of ovulation was confirmed by a statistically significant change in the diameter of the corpus luteum (Figure 1) and the performance of the hypothalamic-pituitary-ovarian system, which are reflected by cyclic changes in the level of hormones. So, an increase in the diameter of the corpus luteum was noted from \( 1.36 \pm 0.32 \) (initially) to \( 2.16 \pm 0.21 \) mm against the background of the maintained combination therapy. In addition, there was a statistically significant increase in the level of estrogens and progesterone corresponding to the phases of the menstrual cycle (Figure 2).

These changes reflect the restoration of the cyclic regulation of the ovarian-menstrual cycle and provide the formation of a morphological substrate of the endometrium for successful implantation.

Confirmation of this conclusion is a positive dynamics of the endometrial thickness index verified sonographically, which before the treatment was \( 6.0 \pm 0.54 \) mm, and after combination therapy it increased to \( 10.0 \pm 0.27 \) mm.

In the verified histological study of the endometrial biopsy (obtained by the paypel –biopsy method), the early stage of the secretion phase was detected in 13.6% of women, the average stage of the secretion phase was diagnosed in 68.4% of women, thus indicating that after the treatment a full secretory transformation of the endometrium was observed in the overwhelming majority of cases.

### Discussion

The clinical manifestations of LPD depend on the form of LPD which develops in the patient. As per today, several forms of LPD are basically distinguished: the hypo-progesterone form which is characterized by a violation of the formation of the corpus luteum, consequence of which is decrease of progesterone production and the deficiency of the luteal phase of the menstrual cycle [28]. The result of such changes is a decrease in the endometrium thickness and a decrease in the secretory activity of the uterine glands with a violation of the receptivity of the endometrium [29]. The second form of LPD is associated with hyperproduction of estrogens [30]. In this case, the corpus luteum and endometrium may have normal characteristics, but the imbalance between estrogen and progesterone leads to a disruption of the mechanisms of endometrial receptivity, and the result is infertility or recurrence miscarriage [31]. The hypoestrogeny variant can also be the cause of the LPD development - at the stage of selection of the dominant follicle hypoestrogenesis leads to a decrease in the ovulatory peak of LH and a decrease in the level of estradiol, a slowdown in the development of the preovulatory follicle, premature induction of meiosis, intra-follicular overmaturity and degeneration of the oocyte. The level of estradiol decreases, this leads to inferior production of progesterone and, due to it, proper secretory transformation of the endometrium and, as a feedback, to a high level of LH [32].

LPD is a controversial disorder, viewed as predisposing to failed or delayed implantation, infertility, and early pregnancy loss. The prevalence and clinical importance of LPD have not been established, because there is no validated diagnostic test for the disorder. Common measures of luteal function and endometrial receptivity, mid-luteal phase serum progesterone concentrations and endometrial histological dating, have limitations. Serum progesterone levels fluctuate due to pulsatile corpus luteum P secretion.

### Conclusions

Thus, the combination therapy of dydrogesterone and metabolic correction with placental hydrolyzate for patients with LPD contributes to the recovery of cyclic events in the hypothalamic-pituitary-gonadal system, which determines the restoration of the endocrine function of the ovaries and promotes adequate secretory rearrangement of the endometrium in women of reproductive age.

### Disclosure statement

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