

Effect of dydrogesterone drug on physiological parameters in women with recurrent pregnancy loss

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ABSTRACT

Three successive pregnancy losses before 20 weeks have passed since the last menstrual cycle are considered Recurrent Pregnancy Loss (RPL). Progesterone is crucial for the initiation and maintenance of pregnancy. Due to its well-established safety profile, hormonal therapy with dydrogesterone (Duphaston) is used globally to support luteal function and lower the risk of pregnancy loss in women with URPL.

Aim. Estimate the concentration of progesterone, estradiol, progesterone induce blocking factor and epithelial - cadherin in women's with RPL compared to control (fertile women) and known the correlation between them.

Methods. Blood samples obtained from (70) women with RPL (35 RPL without treatment and 35 RPL with treatment) from different infertility clinics in Iraq. Also, 36 fertile women's as control. All groups are matched in BMI and age.

Result. The concentration of these hormones were significantly decrease ($p < 0.05$) between RPL patients without treatment and controls. While, shown increase of all parameters level in RPL patients with treatment compared with RPL patients without treatment. Regarding the results of correlation were positive correlations between these parameters in patients with treatment and without treatment.

Conclusion. This study indicates the importance of dydrogesterone and their positive role in an increasing of hormones level in blood and then lead to increase of other proteins concentrations in patients.

Keywords: recurrent pregnancy loss, RPL, progesterone, P4, estradiol, dydrogesterone, PIBF, E-Cadherin

INTRODUCTION

Recurrent pregnancy loss, or RPL, is a serious pregnancy problem that affects 2-3% of pregnancies that are otherwise healthy [1]. RPL is a multifactorial condition that is defined as the loss of three or more pregnancies before the 20th week of gestation. It can be categorized based on the reasons that affect the mother and the embryo. The second group mostly consists of chromosomal abnormalities, while the former group

includes uterine anomalies, endocrine disorders, thrombophilic disorders, placental malformations, infection, genetics, immunological dysfunction, and exposure to environmental factors [2,3]. For almost half of the patients, the precise reason of RPL is still unknown [4]. The endometrium needs to be prepared for decidualization and ready to blastocyst invasion in order for a pregnancy to properly begin. Hormonally controlled molecular mechanisms that allow pregnancy establishment during the window of receptivity make this conceivable [5].

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The main mechanisms via which the progesterone receptor (PR) and estrogen receptor (ER), respectively, of their respective nuclear receptors are stimulated are the progesterone and estradiol responsive signaling pathways, which are essential for the success of pregnancy. In the endometrium, these pathways are controlled differently in the stromal and epithelial compartments [6].

During the proliferative phase of the menstrual cycle, estradiol stimulates epithelial proliferation to create endometrial thickness; during the secretory phase, progesterone suppresses estradiol-induced proliferation and permits stromal cells to start decidualization [7]. Progesterone-induced blocking factor (PIBF) is a downstream mediator that contributes to many of the immunological effects of progesterone. A recent study demonstrated the importance of PIBF in immune regulation during pregnancy, showing increased decidual and peripheral NK activity in PIBF-deficient mice, as well as down- and up-regulated T cell activation genes in CD4+ T cells and Th1 cell differentiation in CD8+ T cells. Compared to mice with normal PIBF activity, PIBF-deficient animals exhibit higher rates of fetal loss and lower rates of implantation [8]. It has been demonstrated that pregnant women's peripheral blood mononuclear cells and peripheral T cells contain nuclear progesterone receptors [9].

Transcription of the CDH1 gene produces the trans-membrane glycoprotein precursor of epithelial cadherin (E-cadherin, cadherin1, or E-cad), (135 kDa) molecular weight, that serves as a cell adhesion molecule (CAM) that binds to unlike cell types and is essential for the normal morphogenesis and development of animal tissues. The CDH1 is located on chromosome 16 q22 [10]. Mature E-cadherin, a 120 kDa Ca²⁺-dependent trans-membrane glycoprotein, forms adhesion junctions (AJs) at the lateral surface to connect polarized and unpolarized epithelial cells [11,12]. Cells switch to express different Cadherin during cadherin switching, a physiological process. Organ morphogenesis and tissue differentiation are controlled by cadherin switching [13]. E-cadherin has 3 different domains: a cytoplasmic domain that is highly conserved, transmembrane domain (TMD), and an extracellular domain. E-cadherin's cytoplasmic tail has 2 parts: the catenin-binding domain and juxta-membrane domain [14]. Additionally, α -catenin, β -catenin, γ -catenin, and p120 catenin combine to form a complex with E-cadherin [15]. The global morphogenetic mechanisms that result in prototypical tissues and organs fulfilling their roles throughout embryonic development as well as the adaptive processes of adult tissues are based on changes in cell size, shape, and relative cell motions. The remodeling of the E-Cad complexes and AJs is closely linked to these alterations in cell size, shape, and mobility [16]. In trophoblasts from humans, E-cadherin has been discovered, and it is

assumed that this protein mediates homophilic contacts between cytotrophoblasts and endometrium. This may imply that E-cadherin was involved in the embryo's implantation process at the attachment stage [17]. Patients who have spontaneous miscarriage had lower levels of E-cadherin in villi of placental through the primary stages of gestation. Reduced E-cad expression during villous development was observed in patients with missing and impending miscarriages, as was demonstrated by western blotting in a prior study [18].

Progesterone supplementation is a direct method to increase levels of this hormone when secretion from the corpus luteum is insufficient. Duphastone, an analog of progestogen, closely resembles endogenous the structure of progesterone and function. It has found wide application in threatened abortion treatment and assisted reproductive technology support with positive results [19]. Progesterone-like effects and a faster metabolism of natural progesterone when taken orally led to the development of synthetic progestin. These structurally diverse compounds exhibit varying effects on various cell types, receptors, and signaling pathways based on their chemical structure. These effects are contingent upon exposure patterns, dosages, and relative concentrations of receptors and enzymes involved in and prior to steroid metabolism at the target tissue level, tissue exposure to activators of un-ligated receptors and priming factors [20]. To ensure accuracy when studying the effects of primary gestation medications like Duphastone, it is an important to consider and account for potential sources of confounding factors and bias. These may include external influences, such as exposure to chemicals, without counter medications, infections, behavioral aspects such as smoking and genomic causes from mother and father. When, investigating the use of progestin's in the first trimester of pregnancy in women who are at risk of recurrent abortion [21]. Dydrogesterone used to treat various disorders associated with deficiency of progesterone. It is notable for being the only retro-steroid commercially available. While it's molecular structure closely resembles natural progesterone [20].

METHODS

Subject

A total samples (70) with at least two or more recurrent pregnancy loss before 20 week of pregnancy (35 with treatment, 35 without treatment) were recruited from clinics of infertility, in Kerbala province. As well as a control group (36) composed of women with no history of miscarriage that had previously given birth to at least one child. Patients were excluded from the study based on medical history and physical and biochemical examination (history of smoking, drinking

alcohol, toxoplasmosis, cytomegalovirus, thyroid gland problems, antiphospholipid syndrome, anticardiolipin, endocrine or metabolic disorders, Autoimmune diseases, and anatomic abnormalities and polycystic ovaries. Data collection took place from February 2022 to July 2023. All participants were similarly matched in terms of age (ranging from 25 to 38 years) and body mass index.

Ethical Issues

The study received approval from the Department of Biology and Scientific Committee of the Science College at Karbala University. Additionally, permission was obtained from the Department of Development and Research of the Health Directorate in Kerbala government. All participants provided orally informed consent after receiving a thorough explanation regarding the objectives and potential advantages associated with their involvement in this research project.

Venous blood sample obtained from all subject by disposable syringe (5 mL). Then, blood is gradually drained into single-use, disposable test tubes without anticoagulant. After allowing the blood to coagulate for 15 to 30 minutes at 37°C, the sample was centrifuged for five minutes at 10000xg. Protein levels (human progesterone, human estradiol, PIBF, and E-Cadherin) were measured using serum that had been separated by ELISA device.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) 24 program was used to analyze the data that had been collected. Data were presented as (mean \pm SD). ANOVA and the T-test were employed. Statistical significance was defined as P values <0.05 .

RESULTS AND DISCUSSIONS

In our study present, 35 RPL patients without treatment, 35 RPL patients with treatment and 36 controls (fertile women) were contributed. Table 1 shown no significant difference between all groups ($p < 0.05$) of the clinical and demographic features (body mass index and age).

Progesterone, estradiol, PIBF and E-Cadherin levels were significant decrease in RPL patients without treatment compared to the control group (Table 2). In addition the concentration of progesterone, estradiol, PIBF and E-Cadherin were significantly increased in RPL patients with treatment in comparison to the RSA patients without treatment. The results of correlation find positive correlation between Progesterone and estradiol concentration and PIBF in RPL patients without treatment. Also find same results in RPL patients with treatment as show in Figures 1-5.

Previous research [22], which was in line with our findings, revealed that the URPL group's serum progesterone expression levels were lower than those of the fertile women, but they considerably increased following dydrogesterone treatment. The meta-analysis agrees with our study that found after treating RPL patients with dydrogesterone, the levels of progesterone in RPL patients were notably higher than those in the fertile women. These results indicated that after using dydrogesterone, RPL patients could become pregnant again [23]. Progesterone levels, according to experts, may reveal information about prognosis and show how well medication works in target-oriented treatment. Nevertheless, little is known about the mechanisms behind variations in progesterone secretion capability and intero-placental shift placental. Experts have all agreed that using dydrogesterone as a treatment is safe. They

TABLE 1. Demographic features of subjects

Group	Age (years)	Number of abortion	Number of children	BMI (kg/m ²)
RPL patients with treatment (n=35)	31.46 \pm 2.81	2.49 \pm 0.51	NC	25.13 \pm 1.13
RPL patients without treatment (n=35)	31.60 \pm 2.75	2.31 \pm 0.47	NC	25.34 \pm 1.35
Control (n=36)	\pm 2.95	NA	2.47 \pm 1.08	25.60 \pm 1.03

p. value <0.05 is significant.

Data are represented as mean+SD

TABLE 2. Comparison of Progesterone, Estradiol, PIBF and E-Cadherin concentrations between RPL groups and Control

Groups Parameters	Control	RPL patients without treatment	RPL patients with treatment	p. value
Progesterone (ng/ml)	10.41 \pm 1.33	9.31 \pm 1.31	10.57 \pm 1.25	0.000
Estradiol (pg/ml)	139.55 \pm 8.34	133.99 \pm 7.45	137.62 \pm 5.75	0.020
PIBF (ng/L)	12.14 \pm 1.04	6.87 \pm 1.45	12.03 \pm 1.16	0.001
E-Cadherine (ng/dl)	21.60 \pm 2.09	16.96 \pm 2.11	20.27 \pm 2.47	0.001

p. value <0.05 is significant

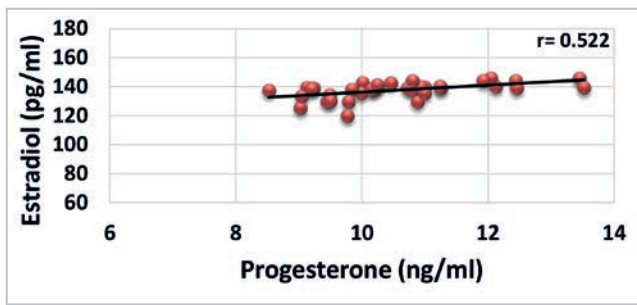


FIGURE 1. Correlation coefficient between progesterone concentration (ng/ml) and estradiol concentration (pg/mL) in RPL patients without treatment

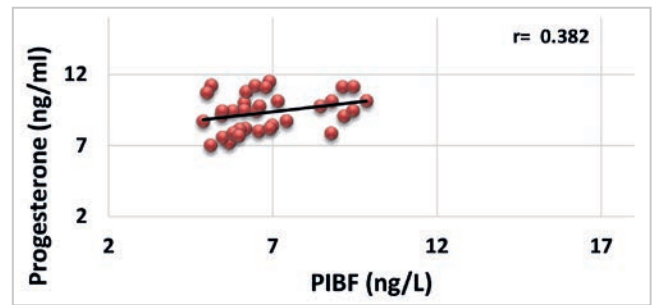


FIGURE 2. Correlation between progesterone concentration (ng/ml) and PIBF (ng/L) in RPL patients without treatment

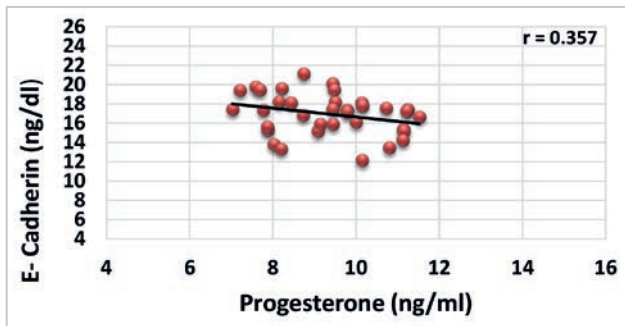


FIGURE 3. Correlation between progesterone (ng/ml) and E-Cad concentration (ng/dl) in RPL patients without treatment

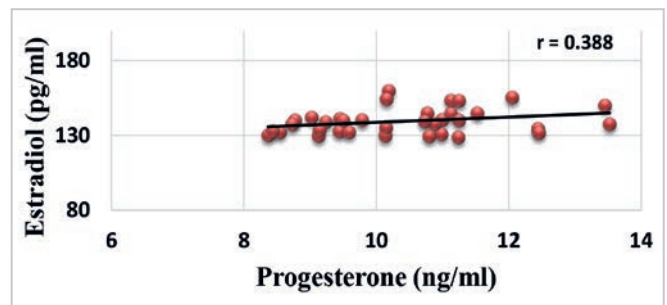


FIGURE 4. Correlation between progesterone concentration (ng/ml) and Estradiol concentration (pg/ml) in RPL patients with treatment

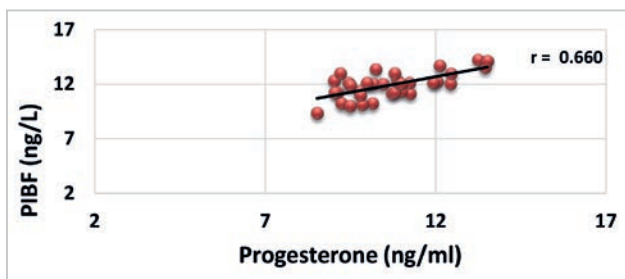


FIGURE 5. Correlation between PIBF concentration (ng/ml) and progesterone concentration (ng/ml) in RPL patients with treatment

cited respected organizations' recommendations, which state that Dophastone should be used to treat RPL and threatening patients [24]. One of the previous studies was consistent with our study, as it showed a significant decrease in the results of progesterone estradiol levels in the serum of recurrent miscarriage women versus control [25]. Numerous studies have demonstrated the role of estrogen in several aspects of immunological control during the implantation and development of embryos. For growth and development, the placenta and fetus require an adequate supply of nutrients and oxygen. Blood supply to the uterus and placenta must therefore gradually rise. Research has indicated that estrogen is crucial for the remodeling and dilatation of uterine arteries [26].

Progesterone-induced blocking factor (PIBF), which has been demonstrated in mice to suppress NK cell activity and have anti-abortive properties, is produced by

γ DT cells in response to progesterone [27]. According to some researchers, the fetus induces lymphocytes to make more PR, which binds P and results in the production of PIBF [28]. Progesterone can regulate T-cell activation by PIBF and LIF production, controlling it via membrane progesterone receptors. It is well known that a sharp rise in the intracellular concentration of free calcium is linked to T-cell activation. Progesterone is known to regulate the intracellular free calcium level, and this process is assumed to be linked to membrane progesterone receptors [29]. Progesterone inhibits this calcium ion signaling pathway by activating PGRMC1 (progesterone receptor membrane component 1), which lowers the Ca²⁺-dependent NFAT1 nuclear accumulation. This mechanism linked to progesterone and PRGMC1 is likely able to inhibit T-cell activation [27].

Progesterone levels in the blood may not always correspond to levels at the fetal-maternal interface or levels of progesterone receptors, even in women with URPL. Moreover, research indicates that stress causes a precipitous drop in progesterone levels [30]. It is well known that estrogen and progesterone affect the expression of several genes and have a major impact on the endometrium. The dynamic fluctuations in E-Cad sorting in the endometrial epithelium are not known to be regulated by steroid hormones [31]. The previous study exhibit that steroid hormones directly affect Epithelium- Cadherin organizing in the epithelium of endometrial, but the dynamic changes are unknown [32,33]. Previous studies have shown that dydrogesterone can

stimulate lymphocytes to progesterone production, which upregulates Th2 cytokines in T helper cells and down-regulates Th1 cytokines to stimulate blocking antibodies to protect against miscarriage [23,35]. The results of other studies revealed that dydrogesterone effectively regulated and promoted the production of progesterone-induced blocking factors by lymphocytes to regulate the immune function of the maternal-fetal interface, thereby increasing the pregnancy success rate of URPL women [23,34].

One benefit of dydrogesterone from a safety standpoint is that it does not inhibit ovulation at recommended doses, has no androgenic or estrogenic properties, and does not cause metabolic side effects. This could be the reason for the lack of an increase in estrogen concentration after using dydrogesterone compared to control [36] additionally: the synthesis of IL-17 [26], a powerful chemotactic and pro-inflammatory cytokine, is inhibited by dydrogesterone. In fact, IL-17 has been linked to miscarriage in humans as well as embryonic loss in animal studies. It has been demonstrated that injecting IL-17 into pregnant mice causes embryonic loss [37]. Women who experience successive abortions have been found to have elevated levels of IL-17 in their decidua and peripheral blood [38,39]. Duphas-ton has been found to be an effective treatment method for RPL, with an even better clinical efficacy than progesterone [40]. Because cellular immune effect is closely related to the development of RPL, pro-inflammatory and anti-inflammatory cytokines have a crucial influence on the success or failure of pregnancy. dydrogesterone able to increase the production of PIBF, Interlukin-10 and decrease the IFN- γ production [41]. This result agrees with [42], findings which suggested a prospective role of Epithelial-cadherin in the mechanism of embryo implantation and different expression in women with reproductive failure and low level of E-cad association with RPL. Also the results agree with [43], have showed a significant difference in E-cadherin concentration between RPL patients and fertile women. Additionally, Wu et al. hypothesized that placental syncytiotrophoblast produces hormones for fetal development and upholds immunological tolerance in addition to

being in charge of transporting oxygen, nutrients, and wastes. When cytotrophoblasts fuse, E-cadherin undergoes dynamic alterations, and its down regulation occurs simultaneously with cell fusion [44]. Likewise, [45] have demonstrated that E-cadherin expression is crucial for embryonic growth. E-cadherin knockout mice are unable to survive during implantation, because they are unable to develop functioning trophoblast. Also, when extravillous trophoblasts (EVTs) move or enter into the cell column during epithelial-mesenchymal transition (EMT), trophoblast cells have been shown to express less E-cadherin levels [34]. During implantation, uterine cells' e-cadherin levels rise, making them more receptive to the attachment of developing embryos. However, as trophoblasts breach the uterine wall, e-cadherin levels in implanting embryos may fall. It has been observed that e-cadherin is down-regulated by estrogen in a number of reproductive organs, including the uterus [43]. A risk factor for a stable pregnancy and subsequent effects on the embryonic adhesion process may be a low serum level of E-cadherin in the RPL group. One of the primary physical forces that interact with other primary forces in the embryo is adhesion, which is one of the forces that act between the cells of the embryo. By bringing cell surfaces together and establishing the first anchoring point, E-cadherin is believed to start this adhesive process [46]. Lacking both maternal and zygotic E-cadherin prevents embryos from compacting or becoming blastocysts, and instead makes them appear as loose clumps of cells [47].

CONCLUSION

The concentration of progesterone, estradiol, PIBF and E-Cadherin in RPL patients without treatment and the positive correlation between these parameters is expected to participate to the etiology of RPL. In addition; the concentration of progesterone, estradiol, PIBF and E-Cadherin in RPL patients with treatment increased in RPL patients with treatment.

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