ORIGINAL ARTICLE

Role of Luteal Phase Steroids in Unexplained Recurrent Miscarriages

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Abstract

Recurrent pregnancy loss (RPL) is a dreadful reproductive health burden that affects around 5% of couples worldwide who are trying to conceive.

Luteal phase insufficiency is one of the factors that contribute to implantation failure and has been linked to miscarriages and unsuccessful assisted reproduction.

Before the placenta assumes control of progesterone synthesis, the corpus luteum produces enough progesterone that leads to secretory changes in the endometrium to maintain early pregnancy. A deficiency in corpus luteum function is linked with implantation failure and ends up in miscarriage. The optimum period for implantation is 6–10 days following the peak of luteinizing hormone (LH); any earlier or later than this is linked to an increased chance of miscarriage. Women with polycystic ovaries, thyroid, and prolactin disorders frequently have luteal phase defects. Women with a history of recurrent miscarriage (RM) have been found to benefit from the treatment of the underlying disease and the use of progestational hormones like progesterone and human chorionic gonadotrophin. There are more uterine and peripheral natural killer (NK) cells in women who experience RM than in control women, according to several publications. However, there is no evidence linking it to miscarriage.

The goal of the current study is to thoroughly assess luteal phase steroids in cases of unexplained miscarriage. The patients were split up into two groups for this study. Group I received progesterone with Deltacortril while group II received progesterone treatment.

Keywords: Deltacortril support, Luteal phase steroids, Natural killer cells, Progesterone support, Recurrent miscarriages.

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Introduction

Recurrent miscarriages (RMs), which affect about 1% of couples, are defined as the loss of three or more subsequent pregnancies occurring between the period of conception and 24 weeks of pregnancy.[1,2] Factors, including chromosomal anomalies, stress factors, environmental factors, coagulation protein deficiencies, anatomic endocrine problems, and the autonomic nervous system contribute about 60% of recurrent pregnancy loss (RPL). In the remaining 40% of instances, the causes of miscarriage are unclear and not well understood.[3] Progesterone is a crucial hormone that encourages endometrial secretory changes, which aid in the implantation and support of the pregnancy. One of the possible reasons for unsuccessful implantation and a potential cause of miscarriage is luteal phase insufficiency.[4] The corpus luteum and placenta are responsible for producing progesterone once pregnancy is achieved. If this occurs, the corpus luteum supports the fetus until roughly 8–12 weeks of gestation, and after that point placenta takes over and continues to produce progesterone for the rest of the pregnancy.[5]

Progesterone is also renowned for its functions in uterine contractility inhibition, endometrial decidualization, endometrial preparation for implantation, and cytokine production regulation during pregnancy. It also has an immunomodulatory impact by reducing T-cell activation.[6–8] Owing to these characteristics, it is frequently used to treat RPL. Because progesterone stimulates an adequate immunological response throughout the early stages of pregnancy, it is thus helpful in preventing abortions.[9] It is not clear exactly how progesterone contributes to the preservation of pregnancy. However, an increase in inflammatory mediators has been connected to progesterone deficiency.[10] Monocyte chemoattractant protein-1, cyclo-oxygenase-2, and proinflammatory interleukin 8 (IL-8) are among them.[11] Progesterone can be useful in this process since it is believed that controlling these inflammatory mediators is necessary to have a healthy pregnancy.[12]

Myometrial contractility is reduced by natural progesterone. While intramuscular progestogens avoid the liver and intestines' first-pass metabolism, they however produce extremely high levels of circulating progesterone that are longer-lasting than progesterone administered vaginally.[13–16] No compelling evidence suggests that the number of pregnancies succeeding is expanding.[17] How well the immune system supports healthy pregnancies is a matter of some debate. Naturally, the mother's immune system does not typically target foreign or paternally acquired fetal antigens because the uterus and the fetus are immunologically favorable.

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Regulatory T cells have a well-established involvement in miscarriage and loss of fetal tolerance, and several immunological changes have been linked to these events.[18]

When compared to healthy people, studies on women with idiopathic RM have shown a significant increase in natural killer (NK) cells in the peripheral and uterine circulation.[19] CD56-positive lymphocytes are known as NK cells. They exhibit a significant level of proliferative activity and produce immune regulatory cytokines. These cells' capacities for cytolysis and immunomodulatory regulation are modified by the various ways that CD56, CD16, and other surface receptors are expressed.[20]

Corticosteroids are synthetically produced steroid hormones that are naturally present in the adrenal cortex. They possess anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive properties.[21] In target cells, glucocorticoids (GCs) alter pre- and post-transcriptional mechanisms of gene regulation through their interaction with the cytosolic glucocorticoid receptor (cGCR). In addition to their numerous other effects, GCs inhibit the synthesis of cytokines that cause inflammation. The reduction of pro-inflammatory Th1 cells by preferential inhibition of type-I cytokines eventually causes a shift in the CD4+ T-lymphocyte profile toward a Th2 profile. Pro-inflammatory cytokines are suppressed and their impact on target cells is diminished by GC-mediated degradation of cytokine receptor signaling. It results in decreased T-cell activation and nitric oxide generation, as well as an increase in T-cell, thymocyte, and eosinophil apoptosis. Glucocorticoids also boost the synthesis of lipocortin-1, which reduces the production of prostaglandins and leukotrienes. Glucocorticoids decrease the body's natural inflammatory responses by inhibiting adhesion molecules on antigen-presenting cells (APCs).[22]

In this study, we established two groups: One that received steroids along with progesterone and the other that only received progesterone to evaluate the clinical impact of steroids in individuals with RM.

Methods

This experimental study was conducted in the Outpatient Department of Gynaecology and Obstetricts in Hamdard University Hospital, Karachi, Pakistan from October 2020 to September 2023.

The study was approved by the Ethics Board of Hamdard University Karachi.

Sample Size

The sample size was calculated by OpenEpi with the use of proportion which estimated the total sample size of group I ($n = 43$) and group II ($n = 45$).

Study Groups

A randomized controlled trial was done to compare two groups. Group I ($n = 50$) received progesterone plus steroid (Deltacortril) supplementation, while group II ($n = 50$) was given only progesterone.

Inclusion Criteria

The study included patients aged 18–40 years with a history of two or more consecutive unexplained miscarriages and gestational age 7 weeks onward up to 24 weeks.

Exclusion Criteria

The study excluded patients with medical problems like chronic hypertension, known cases of diabetes mellitus, thyroid diseases, polycystic ovarian syndrome disorders, maternal antiphospholipid antibody syndrome, systemic lupus erythematosus, and maternal thrombophilia along with gestational age <7 weeks and >24 weeks.

Informed consents were taken from all patients who participated in the study. A detailed history and examination was carried out on all participants. Ultrasonography imaging was carried out to confirm gestational age and fetal viability.

Analytical Statistics Version 26.0 of the Statistical Package for Social Science (SPSS) was used to analyze the data. Frequency and percentage were used to express the qualitative data.

The proportions of two qualitative factors were compared using the Chi-square test of significance. Note that p-value < 0.05 was considered significant.

Table 1: Demographics

	Frequency	*Percentages*
Age		
18–25 years	3	3
25.5–30 years	37	37
30.5–35 years	32	32
35.5–40 years	18	18
>40 years	10	10
Miscarriages		
2	14	14
3	65	65
>3	21	21
Ethnicity		
Urdu	20	20
Sindhi	20	20
Punjabi	10	10
Pathan	35	35
Balochi	15	15
Education		
Did not attend school	7	7
Class 6	13	13
Class 10	24	24
College	31	31
University	25	25
Working status		
Housewife	47	47
Working	40	40
Student	13	13
Socioeconomic status		
Low class	14	14
Middle class	75	75
Upper class	11	11

Results

A sample size of 100 patients was included in this study. Most of them were 30 years old, with a range of 25–35 years of age. There were approximately 65% of females with three miscarriages, (40%), and students were (13%). Those belonging to middle class socioeconomic backgrounds were 75% belongs to middle class while 14% lower class and 11% upper class (Table 1).

Table 2: Study groups and outcomes

Groups	*Healthy pregnancy at 3 months*	*Miscarriage*	*Abnormal laboratory tests (UCE, LFT)*	*p-value*
Group I (*n* = 50) Progesterone + Deltacortril	40	10	0	
Group II (*n* = 50) Progesterone	31	19	0	
Total (*n* = 100)	71	29	0	0.047

Miscarriages were more common in Pathan and Baloch patients who were more than 35 years old and had more than three miscarriages (Table 2).

The eligibility of 100 individuals was assessed; 50 women were randomly allocated between October 2020 and September 2023 to receive progesterone and Deltacortril, and the remaining 50 were to receive progesterone alone. Both groups were monitored for 24 weeks. Baseline variables including age, mother ethnicity, and parity were comparable. In the progesterone plus Deltacortril group, the live birth rate was 80% (40/50), while in the progesterone group, it was 62% (31/50) (Table 2). The Chi-square test yielded a *p*-value of 0.047, which was significant.

Conclusion

Recurrent miscarriages, which affect about 1% of couples, are defined as the loss of three or more subsequent pregnancies occurring between the period of conception and 24 weeks of pregnancy.[2] Many variables have been looked into as possible causes of RM, including morphological, endocrine, immunological, genetic, and thrombophilia (inherited and acquired) illnesses. Endocrine disorders such as polycystic ovarian syndrome and thyroid problems are included.[23]

Numerous studies have been undertaken to evaluate the use of progesterone in the treatment of miscarriage. This article describes clinical experiments with two patient groups that experienced RM, half of the groups were treated with progesterone alone, while the other half were treated with progesterone plus Deltacortril and observed until 24 weeks of gestation. Our study found that patients who received both progesterone and Deltacortril had healthier ongoing pregnancies than those who just had progesterone therapy. Progesterone has been found to have benefits during pregnancy, and it is known to prevent preterm delivery.[24]

The meta-analysis found that progesterone therapy can reduce the risk of miscarriage.[24,25] Deltacortril, or prednisolone, is also known to be beneficial in pregnancies. It can reduce preconceptual endometrial NK cell levels,[25] which are found to be high in women with RM.[19] Our study concludes that a combination of progesterone and Deltacortril can be beneficial to women with RM. The limitations of our study include a small sample size and a single-center design. More research is needed to study the benefits of progesterone and Deltacortril.

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