

Original Article



The effect of luteal phase prolongation with medroxyprogesterone acetate on endometrial thickness and pregnancy rate in women following recurrent implantation failure

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Abstract

Introduction: Assisted reproductive technology (ART) is increasingly used to help infertile couples to have a child. However, less than one-third of transferred embryos result in successful implantation and live birth. Recurrent implantation failure (RIF) is an outstanding barrier to pregnancy achievement by this advanced technology. This study was conducted to evaluate the hypothesis that luteal phase prolongation would lead to endometrial thickening and decrease the RIF's rate.

Methods: This interventional study was conducted in the infertility clinic of the Alzahra Teaching Hospital and Asadabadi polyclinic, Tabriz, Iran. Sixty women, aged 20–40 years, with a history of RIF following several in vitro fertilization treatment cycles with mid-luteal progesterone levels less than 3 ng/mL, and endometrial thickness less than 8mm were recruited through the purposive sampling method. Participants were treated for six cycles with oral medroxyprogesterone acetate (MPA) tablet 5 mg/12 h initiated from the 16th day of their menstrual cycle for 20 days and evaluated for study outcomes during this course. Endometrial thickness was compared before and after MPA administration in the whole study population. The pregnancy rate was determined. Pregnancy complications and conditions were evaluated during the study.

Results: Endometrial thickness was increased in patients after MPA administration (mean difference [95% CI]: 2.66 [2.43 to 2.89]; $P < 0.001$). Overall, 80% ($n = 48$) of participants achieved biochemical pregnancy during a 6-month treatment. Four pregnancies out of 48, were lost in different stages of pregnancy. One participant experienced gestational diabetes in the 24th week of pregnancy. No embryo-fetal abnormality was present until delivery.

Conclusion: Administration of MPA following RIF induces endometrial development and facilitates embryo implantation by luteal phase prolongation which results in natural pregnancy achievement followed by timed intercourse.

Introduction

Infertility affects about 80 million couples worldwide. Assisted reproductive technology (ART), plays a critical role during in vitro production of human infertility treatments.¹ However, ART procedures consist of several steps. It is so expensive and it has extensive side effects. Therefore it should be used only if necessary.²

ART is increasingly used to help infertile couples to have a child. However, less than one-third of transferred embryos result in successful implantation and live birth. Recurrent implantation failure (RIF) is an outstanding barrier to pregnancy achievement by this advanced technology. The term RIF has been used since 1983 and

is defined as “pregnancy failure following 2–6 consecutive embryo transfer cycles, in which more than 10 good quality embryos were transferred to the uterus”.³⁻⁵ Approximately 10% of women undergoing ART treatments interface to RIF. Over the last decades, RIF has been introduced as a critical clinical impediment of ART.⁶⁻⁸ One of the underlying pathophysiological mechanisms of RIF may be the post-ovulatory production of excessive steroids and the abnormal hormonal milieu and may therefore potentially interfere with the luteal activity of normal ovulatory women^{9,10} due to inessential ovarian stimulation during ART cycles. This hormonal milieu is detrimental to endometrial receptivity for embryo implantation.

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The endometrium is a fundamental portion of ART success; as a matter of fact, endometrial thickness has been proposed as a predictor of implantation.^{11,12} As a result, couples with unexplained infertility and/or RIF are disappointingly stranded in a reproductive vicious cycle.

The measure of endometrial thickness has been proven to be effective in pregnancy outcomes. The thin endometrium is generally defined as <7 mm on the day of ovulation.¹³ A decreased endometrial thickness has been reported to be associated with embryo implantation failure.¹⁴ In ART cycles, the incidence of thin endometrium has been reported to be 1.5%-9.1%. Such differences in incidence could be related to kinds of measurement techniques; such as ultrasound equipment, ART protocols, etc.¹³ In reproductively normal couples, a decreased endometrial thickness indicates an increased risk of infertility and/or pregnancy loss.¹⁴ These pieces of evidence render the urgent need for novel treatments for this problem.

The current interventional study is an investigation of a new treatment for women with RIF. This study aimed to evaluate the effect of luteal phase prolongation with medroxyprogesterone acetate (MPA) on endometrial thickness and pregnancy rate in women with RIF through natural intercourse. To our knowledge, the present method has not been reported in previous studies about ART. It is worth mentioning here that the present technique is not an adaptation or extension, it is a distinct method in its own right.

Methods

Design and setting of the study

We conducted a before and after interventional study at the infertility clinic of the Alzahra teaching hospital and Asadabadi polyclinic, Tabriz, Iran. Participants were enrolled among women aged 20-40 years with RIF following several in vitro fertilization treatment cycles six months before the study, mid-luteal progesterone levels less than 3 ng/mL on the 21st day of the menstrual cycle, and mid-luteal endometrial thickness less than 8 mm in abdominal ultrasonography, had a university education, and consented to participate in a quasi-experimental study on the efficacy of prolongation of luteal phase as a treatment of RIF. Women aged older than 40 years, individuals with abnormal semen analysis of husbands, previous ovarian surgery, oophorectomy, hypogonadotropic hypogonadism, and diminished ovarian reserve were excluded.

Sampling and intervention

Sixty eligible women with thin endometrium and mid-luteal progesterone levels less than 3 ng/ml on the 21st day of the menstrual cycle were recruited through the purposive sampling method. All participants for six cycles received oral MPA (Tablet Medroffem 5 mg; Iran Hormone, Tehran, Iran) with a dosage of 5 mg/12 h

initiated from the 16th day of their menstrual cycle for 20 days and evaluated for study outcomes during this course.

No other induction ovulation agents such as clomiphene citrate, or human menopausal gonadotropin (hMG) were prescribed. The study participants were recommended to have sexual intercourse from the 10th day of the menstrual cycle every other day for 10 times (possible ovulation days).

The data collection tool was a questionnaire that included demographic and obstetric characteristics consisting age, job, education, marriage duration, history of intrauterine fetal death (IUFD), type of ART, ART rate, gravida, para, abortion, and a sheet for recording the baseline and after intervention endometrial thickness (mm) and serum hormonal levels. The validity of these tools was confirmed by eight academic members with related expertise.

Serum β -hCG (human chorionic gonadotropin), progesterone, and estradiol levels were measured before and after intervention with MPA using the enzyme-linked immunosorbent assay (ELISA) method by the same kits and a specific laboratory expert. Ultrasonic assessment (A real-time ultrasonic device, Aloka 3500, Hitachi Aloka, America) of endometrial thickness was carried out before and after the termination of MPA treatment by the same device and radiologist. Clinical pregnancy was evaluated in the second week of pregnancy after a positive β -hCG test by ultrasound. Also, an ultrasound assessment was carried out in the 7th week for verification of a healthy pregnancy by visible heart rate. In cases of pregnancy achievement, standard obstetric care and follow-up were performed until birth.

Thin endometrium was considered as mid-luteal endometrial thickness less than 8mm in abdominal ultrasonography.

Statistical analysis

Statistical analyzes were performed using SPSS 22 software for Windows (Chicago, IL, USA). The normality of data was assessed through Kolmogorov-Smirnov test. Results were expressed as mean \pm SD and percentages. Descriptive analysis was performed and the paired-samples t-test was applied for intra-group comparison. A statistically significant difference was considered at a *P* value < 0.05.

Results

A total of 60 women were included in the study from February 2017 to March 2019 following the assessment of eligibility criteria (Figure 1).

Socio-individual characteristics of the participants are presented in Table 1. In the present study, the average age of participants was 28.6 years (range, 21–37). The mean (SD) infertility duration was 4.1 (1.7) years. Nearly 60% of them had a history of one to three failed ART.

Administration of MPA significantly increased mean endometrial thickness from 5.80 ± 0.91 mm at baseline

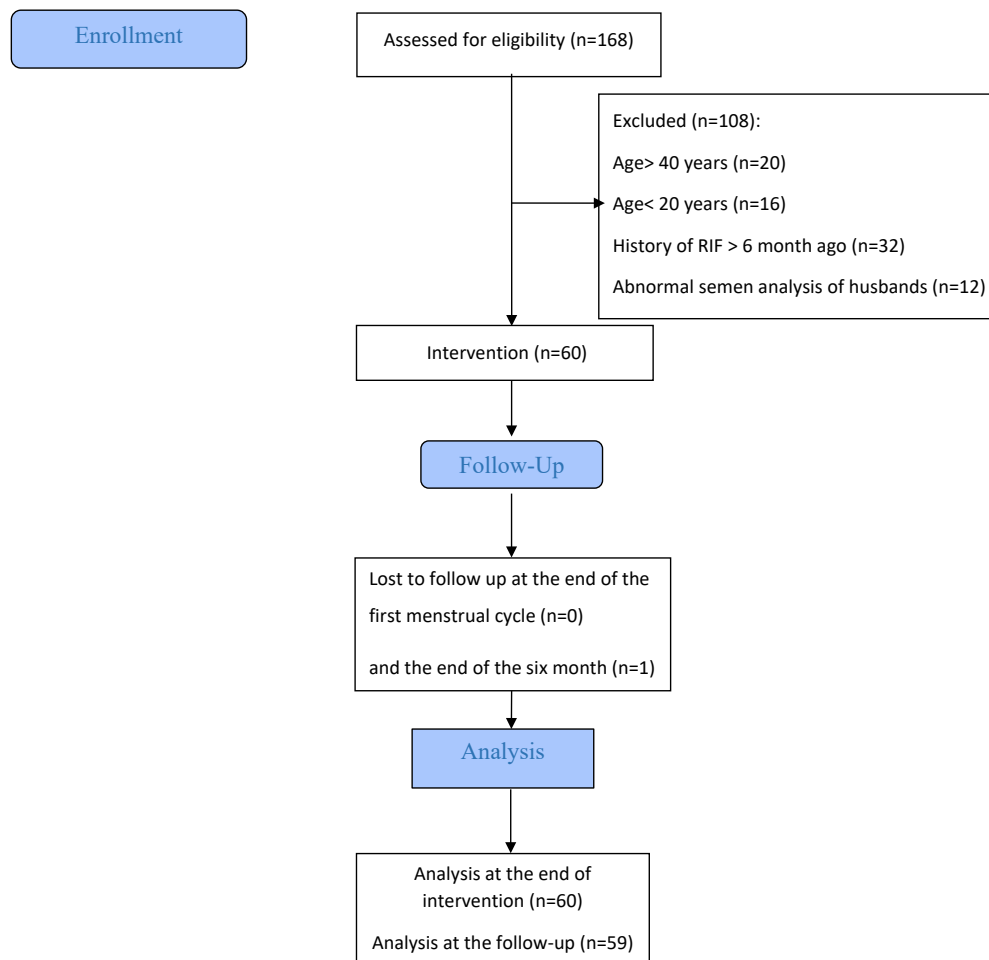


Figure 1. Flowchart of study

to 8.47 ± 1.09 mm (mean difference [95% CI]: 2.66 [2.43 to 2.89] mm; $P < 0.001$) (Table 2). Forty-eight out of the 60 participants (80%) achieved biochemical pregnancies during a 6-month treatment. Clinical pregnancy was confirmed as an observable gestational sac in the uterine at the second week of pregnancy after a positive β -hCG test by ultrasound. Serum progesterone increased significantly after intervention (mean difference [95% CI]: 7.37 [6.88 to 7.87]; $P < 0.001$). Change in estradiol level was not significant (mean difference [95% CI]: 0.21 [-0.29 to 0.71], $P = 0.399$) (Table 3).

Next, an ultrasound assessment was carried out in the 7th week to verify a healthy pregnancy by visible heart rate. One pregnancy was lost due to arrested embryonic development in the 8th week of pregnancy. One pregnancy was lost because of ectopic pregnancy. Another one was lost due to IUFD and the last one, was subjected to amniocentesis because of an abnormal screening test, she carried an embryo with Turner syndrome. Shared decision-making was made and the embryo was maintained; however premature rupture of membrane (PROM) at the 25th week resulted in preterm labor and the fetus do not stay alive. 44 pregnancies resulted in live healthy births. One participant experienced

gestational diabetes in the 24th week of pregnancy. No embryo abnormality was present until delivery. Notably, no participant experienced preeclampsia, or eclampsia during pregnancy and no embryo-fetal abnormalities were reported during pregnancy care. Ultimately 15 out of the remaining pregnancies resulted in live healthy births by natural vaginal delivery (NVD), and 29 by elective cesarean section (CS) (Figure 2).

Discussion

This study, for the first time, demonstrates that an oral mono-drug medication for successful treatment after RIF results in pregnancy achievement by natural intercourse in most of the affected cases. The present protocol does not need any induction ovulation agents. The key to success in this protocol is the correct choice of patients.

Implantation occurs in the luteal phase. Successful implantation depends on progesterone. This agent converts endometrium from a proliferative state to a secretory state and inhibits spontaneous uterine contractions.¹⁵

Progesterone is a steroid hormone that plays an essential role in the reproductive process. It plays a role in

Table 1. Socio-individual characteristics of study women

Variable	n (%)
Age (year)/ mean (SD)	28.6 (4.9)
21-25	25 (41.7%)
26-30	11 (18.3%)
31-37	24 (40.0%)
Job	
Employed	26 (43.3%)
Unemployed	34 (56.7%)
Education	
BSc	36 (60.0%)
MSc	18 (30.0%)
PhD	6 (10.0%)
Marriage duration (year)	5.0 (2.3)
Infertility duration (year)	4.1 (1.7)
IUFD	4 (6.7%)
Type of ART	
IUI	6 (10.0%)
ICSI	54 (90.0%)
Gravida/ mean (SD)	4.4 (1.9)
3	14 (13.3%)
4	22 (36.7%)
5	14 (23.4%)
6-7	10 (16.6%)
Para	
0	56 (93.3%)
1	3 (5%)
2	1 (1.7%)
Abortion/ mean (SD)	4.3 (1.0)
3	14 (23.3%)
4	24 (40.0%)
5	14 (23.3%)
6-7	8 (13.4%)
ART rate/mean (SD)	6.6 (2.5)
1-3	35 (58.4%)
4-6	25 (41.6%)

IUFD, intrauterine fetal death; ART, Assisted reproductive technology; IUI, Intrauterine insemination; ICSI, Intracytoplasmic sperm injection.

Table 2. Results of descriptive statistics and paired sample t-test for endometrial thickness before and after MPA administration

Outcome	Before MPA (n = 60)		After MPA (n = 60)		Mean difference (95% CI)	P*
	Mean	SD	Mean	SD		
Endometrial thickness (mm)	5.80	0.91	8.47	1.09	2.66 (2.43 to 2.89)	<0.001

*Paired-samples t test.

Table 3. Results of serum progesterone and estradiol level in participants

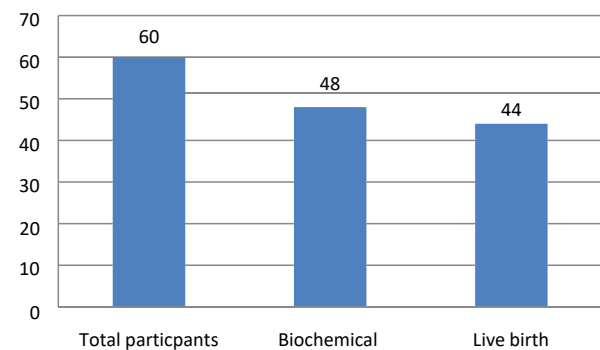
Outcome	Before MPA (n = 60)		After MPA (n = 60)		Mean difference (95% CI)	P*
	Mean	SD	Mean	SD		
Progesterone level (ng/mL)	4.63	0.94	12.01	1.97	7.37 (6.88 to 7.87)	<0.001
Estradiol level (pg/mL)	54.60	7.64	54.81	7.31	0.21 (-0.29 to 0.71)	0.399

*Paired-samples t test.

the menstrual cycle and implantation and is very essential for every stage of human pregnancy. The physiological impacts of progesterone are mainly mediated by interaction with the progesterone receptor.¹⁶ Progesterone causes secretory changes in the mucous membrane of the uterus and is necessary for the successful implantation of the embryo. In early pregnancy, progesterone is secreted by the corpus luteum, whose lifespan is estimated to be 12 ± 2 days. It is essential to maintain the pregnancy until the placenta (syncytiotrophoblast) assumes its function at 7-9 weeks of pregnancy. Therefore, progesterone supplementation can reduce the risk of miscarriage in women with a history of recurrent miscarriages.¹⁷ In addition, progesterone regulates the mother's immune response. It promotes uterine relaxation and suppresses uterine contractions to prevent fetal rejection.¹⁶

MPA, a 17α -hydroxyprogesterone derivative, is a synthetic analog of the natural steroid progesterone. MPA has a more favorable bioavailability and a longer half-life than progesterone.¹⁸

The idea of using MPA as a treatment for RIF emerged from careful attention to the menstrual cycle physiology. Naturally, the endometrial preparation for embryo implantation begins at the proliferative phase and extends throughout the luteal phase. It has been demonstrated that the luteal phase is deficient in some cases of RIF and undergoing several ART cycles. Although several causes for this deficiency have been suggested, however, the

Biochemical and successful pregnancy after intervention**Figure 2.** Frequency of biochemical and successful pregnancy after intervention among total participants

substantial mechanism remains unknown.^{9,10} The use of gonadotropin-releasing hormone (GnRH) agonists in ART cycles, for controlled ovarian stimulation, produces an enhanced inhibition of the hypothalamus-pituitary-gonadal axis resulting from more steroids secreted by multiple corpora lutea. Consequently, luteinizing hormone (LH) levels are lowered due to high levels of steroids.^{19,20} It has been suggested that supraphysiologic serum steroid concentrations might adversely affect LH secretion via feedback mechanisms, which in turn results in premature luteolysis, defective progesterone secretion, and finally luteal phase defect (LPD).⁸ Inadequate secretion of progesterone can cause miscarriage in early pregnancy^{11,12} and possibly, result in unexplained RIF due to endometrial weakness.¹² In ART cycles, progesterone or hCG levels, or both, are insufficient, therefore the luteal phase needs to be supported. Nevertheless, the optimal method for luteal phase supplementation is unclear⁷ and remains a matter of debate.²¹ Thus far, in order to improve pregnancy outcomes in unexplained RIF patients, researchers have applied various methods such as mechanical endometrial injury,² ART, or high-dose vaginal progesterone gel/suppository. However, these methods are invasive or inconvenient and success rates are low.⁷

Despite recent progress in ART, the implantation process has a relatively low success rate.^{6,22} This could be due to the adverse effect of GnRH analogs and the negative effect of the aspiration of granulosa cells during the oocyte retrieval, and the resultant corpus lustrum's inability to produce sufficient progesterone. Finally, it may induce iatrogenic LPD,²³ with decreased endometrial receptivity and implantation rate.^{7,22} Because keeping with the natural processes and strengthening them brings about efficient results on most occasions, the current investigation aimed at assisting implantation by modulating the deficient luteal phase and endometrial thickness. To the best of our knowledge, this treatment has not been reported in previous studies about ART and the treatment proposed in the current investigation is the original innovation of the authors. The cornerstone of the methodology of the current study is precise patient selection in terms of inclusion and exclusion criteria mentioned in the methods. Nevertheless, future trials of this innovative treatment for assisted reproduction of other patients, e.g. for aiding IVF in cases with RIF are, suggested.

The exact etiology of RIF, which is a rather prevalent clinical problem, is unknown and there is no unique treatment protocol. Therefore, many clinicians incorporate empirical approaches for the treatment of this infertility.²⁴

Previous literature is the host of controversies concerning the effect of endometrial thickness on pregnancy achievement after embryo transfer cycles

of IVF. Although some authors stated no significant relationship between endometrial thickness and pregnancy achievement.^{25,26} Many authors demonstrate a close relationship in this regard.²⁷⁻²⁹ Recent studies have even suggested that there is an optimum range of endometrial thickness, needed to obtain a successful pregnancy; which is between 8 and 15 mm.³⁰⁻³² One study indicated no association between EMT and ongoing pregnancy in women undergoing intrauterine insemination (IUI) with gonadotrophin treatment.³³ Another study reported in cases of ovarian stimulation-IUI for unexplained infertility, higher live birth rates are observed with an increment of EMT; however, EMT is not significantly associated with live birth rates when adjusted for the type of ovarian stimulation treatment.³⁴ Nonetheless, in an extensive literature search, we found no report about effective interventions fortifying the physiologic reproductive cycle by endometrial thickening for increasing the rate of natural implantation and pregnancy achievement.

In the present study, significant endometrial thickening was induced by MPA administration followed by successful natural pregnancies in most of the cases. Several studies have shown that MPA has no embryopathy risk and is a safe medication during pregnancy.^{12,31} In this study, pregnancies were followed up until delivery in terms of miscarriage, IUFD, gestational diabetes mellitus (GDM), preeclampsia, eclampsia, preterm labor, CS, NVD, and embryopathy. Except for three pregnancy losses and one case of GDM, no other maternal complications and no embryopathies before and after birth were found. Most pregnant women in the present study gave birth by elective CS. The patient's preference for CS delivery is high in Iran.

Moreover, couples achieving pregnancy after several years of infertility treasure their babies very much and fear complications during delivery, which is why they prefer CS delivery.

In this interventional study, we carefully assessed women who encountered RIF following several in vitro fertilization treatment cycles six months before the study and conducted serum biomarkers (β -hCG, progesterone, and estradiol levels) measurements and ultrasonic assessment before recruitment and evaluated them (60 eligible women) for six cycles. This process lasted more than two years. The most important limitation of the current study was patient selection due to narrow inclusion criteria.

Clinical implication

Using MPA in women with RIF following several in vitro fertilization due to unexplained infertility could be helpful in strengthening the conception results; however, the precise selection of cases is essential for this purpose.

Study Highlights

What is current knowledge?

- Recurrent implantation failure is an outstanding barrier to pregnancy achievement by Assisted reproductive technology.

What is new here?

- Administration of medroxyprogesterone acetate following recurrent implantation failure induces endometrial development and facilitates embryo implantation by luteal phase prolongation.

Conclusion

The results of this study showed that oral prescription of MPA could be a promising approach for unexplained infertility complications due to RIF. This treatment led to pregnancy achievement by natural intercourse and did not induce any serious side effects.

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Authors' Contribution

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Data curation: Azizeh Farshbaf-Khalili.

Formal analysis: Azizeh Farshbaf-Khalili.

Funding acquisition: Behnaz Sadeghzadeh Oskouei.

Investigation: Behnaz Sadeghzadeh Oskouei.

Methodology: Azizeh Farshbaf-Khalili.

Project administration: Behnaz Sadeghzadeh Oskouei.

Resources: Parviz Shahab.

Software: Hossein Babaei.

Supervision: Hossein Babaei.

Validation: Parviz Shahab.

Visualization: Behnaz Sadeghzadeh Oskouei.

Writing—original draft: Azizeh Farshbaf-Khalili, Hossein Babaei.

Writing—review & editing: Behnaz Sadeghzadeh Oskouei, Parviz Shahab.

Competing Interests

The authors have no conflict of interest.

Ethical Approval

The project was approved by the Regional Ethics Committee of Tabriz University of Medical Sciences and the approval number is IR.TBZMED.REC.1395.1062. The procedures were in accordance with the Helsinki Declaration of 1975, as revised in 2008. Written informed consent to participate was obtained.

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