Luteal blood flow as a predictive factor for methotrexate treatment outcome in women with unruptured tubal pregnancy

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Research article

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Abstract

Background Blood flow in the corpus luteum is associated with luteal function. However, the impact of luteal blood flow on the Methotrexate(MTX) treatment in women with unruptured tubal pregnancy has not been reported. The aim of the present study was to observe the impact of luteal blood flow on therapeutic effect of MTX in women with unruptured tubal pregnancy.

Methods A prospective study recruited 129 women with unruptured tubal pregnancy in the First Affiliated Hospital of Xi'an Jiaotong University from September 2016 to June 2018. One hundred and fifteen participants were treated successfully with MTX, and women were divided into 2 groups according to the luteal blood flow, included poor luteal blood flow group and rich luteal blood flow group. The therapeutic effect were compared between the two groups.

Results Women in rich luteal blood flow group had a significantly higher serum β-human chorionic gonadotropin(β-hCG) level 4 days,1 week and 2 weeks after MTX treatment compared with women in poor luteal blood flow group($P < 0.05$).The average diameter of ectopic mass 1 week,2 weeks and 3 weeks after MTX treatment in women with rich luteal blood flow were significantly bigger($P < 0.05$),and the time of serum β-hCG clearance and ectopic mass disappearance were significantly longer compared with women in poor luteal blood flow group($P < 0.05$).

Conclusions Luteal blood flow might be as a predictive factor for MTX treatment outcome in women with unruptured tubal pregnancy, and those with rich luteal blood flow needed longer recovery time.

Background

Ectopic pregnancy(EP) occurs when blastocyst implanted outside the uterine cavity, and EP may result in serious consequences including rupture of the fallopian tube, haemorrhagic shock, decreased future fertility, and even death[1,2]. It is reported that the incidence of EP is 1%–2% of overall pregnancies and is the leading pregnancy-related cause of death in the first trimester of pregnancy[3]. Fallopian tubes are the most common site for the blastocyst to implant[4]. At present, most EP can be diagnosed in the early stage because of the improvement and popularization of transvaginal ultrasound(TVUS)[5]. Once a definitive diagnosis of EP has been made, the patient should be monitored closely and treated with surgical, medical or expectant management. The selection of therapeutic plan depends on serum human chorionic gonadotropin(hCG) level, size of the ectopic mass and fetal cardiac activity(FCA). Methotrexate(MTX) is widely used as first-line treatment for women diagnosed as unruptured EP with low serum hCG concentrations, small size of ectopic mass and a stable hemodynamics. In appropriately selected women, the success rates for single-dose MTX for tubal EP ranged from 65% to 95%, and 3% to 27% of the women required a second dose[6].

The blood flow in corpus luteum can be detected by transvaginal color pulsed Doppler ultrasonography. The luteal blood flow increases gradually after ovulation and corpus luteum becomes one of the most highly vascularized organs in the body[7]. Previous studies have found that insufficiency of corpus

luteum during pregnancy was associated with infertility and spontaneous abortion in the first trimester of pregnancy[8,9]. In addition, blood flow in the corpus luteum is associated with luteal function. Some drugs treatment could improve corpus luteum function by increasing its blood supply[10]. However, to our knowledge, the impact of luteal blood flow on the MTX treatment in women with unruptured tubal pregnancy has not been reported. Our research aims to observe the impact of luteal blood flow on MTX treatment outcome in women with unruptured tubal pregnancy.

Materials And Methods

Study design and participants

A total of 129 women with tubal pregnancy in the First Affiliated Hospital of Xi'an Jiaotong University from September 2016 to June 2018 were recruited in this prospective study. Women at a median age of 32.8 years with age range 21-39 years. The diagnosis of tubal EP was based on serum β-hCG level, absence of intrauterine pregnancy and ectopic mass on the side of the ovary checked through TVUS. All participants were gave written informed consent according to procedures approved by the First Affiliated Hospital, Xi'an Jiaotong University Institutional Review Board.

Inclusion criteria included women who were diagnosed with tubal EP, the β-hCG level lower than 3000 mIU/mL before treatment, without FCA, and the size of ectopic pregnancy <4cm. Exclusion criteria included other locations of EP(ovarian, cervical or cesarean scar), contraindication of MTX treatment including renal and hepatic disease, active pulmonary disease, immunodeficiency and peptic ulcer, etc[11]. Demographic data such as age, body mass index(BMI), number of pregnancies and deliveries, pregnant way, risk factors of EP, duration of pregnancy, clinical symptoms such as abdominal pain and vaginal bleeding were recorded. Serum β-hCG and progesterone concentrations before treatment were detected in our hospital laboratory by chemiluminescence methods. Women were checked by TVUS before treatment, and the findings such as size of ectopic mass, yolk sac, FCA and free fluid in Douglas cavity were recorded.

All ultrasound scans using Voluson E8(GE Medical Systems,USA) ultrasound system with vaginal probe frequency 4-9 MHz. Blood flow was identified in the peripheral area of the corpus luteum, and women were divided into 2 groups according to corpus luteal blood flow patterns, included poor luteal blood flow group and rich luteal blood flow group(Fig.1).

Figure 1.Luteal blood flow checked by TVUS.Arrow marked corpus luteum.(A)Poor blood flow: linear or stellate blood flow around the corpus luteum.(B)Rich blood flow: hemicycle or annular blood flow around the corpus luteum.

Three-dimensional power Doppler ultrasound is generally superior to color Doppler imaging for detecting low-velocity flows and visualizing small vessels. To further detect the index of luteal blood flow, the

ultrasound machine was switched to the 3D mode with power Doppler. The vascularization indices were obtained using the VOCAL(virtual organ computer-aided analysis) imaging program to measure the volume, vascularization index(VI), flow index(FI), and vascularization flow index(VFI) of corpus luteum before treatment.

Outcome measures

All women received intramuscular MTX at a dose of 50 mg/m^2 of body-surface area[12]. The side effects of MTX were questioned and recorded. According to the protocol, the serum β-hCG level was measured on 4 days after MTX treatment, and then weekly serum β-hCG measurements were performed after MTX treatment until it was no longer detectable. In addition, the size of ectopic mass was monitored through TVUS weekly after treatment until it disappeared. If the β-hCG level fails to decline at least 15% between days 4 and 7, then a second dose of MTX was given[6]. Whenever haemodynamic instability and/or clinical signs of tubal rupture(i.e. increasing abdominal pain in combination with a falling haemoglobin level, and signs of intra-abdominal haemorrhage on transvaginal sonography) occurred, surgical intervention was performed.

The primary outcomes was the decline of serum β-hCG to an undetectable level. Secondary outcomes included serum β-hCG clearance time, reduction and clearance time of ectopic mass, side effects of MTX treatment(i.e. nausea, vomiting, diarrhoea, elevation of transaminase).

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, NY, USA).The descriptive statistics for continuous variables were given as mean±standard deviation, and statistical comparison was performed by using the Student's t-test. Differences in dichotomous outcomes between the two groups were given as number and percentage(%),which were compared by chi-square test or Fisher’s exact test when the expected frequencies fell below five. P<0.05 was considered statistically significant.

Results

A total of 129 women were assessed for MTX treatment, and of these, we excluded 3 women accepted surgical intervention, 5 women underwent expectant management, 2 women lost to follow-up, and 4 women declined to participate. Finally, 115 women were included in the study and these women were divided into 2 groups according to the luteal blood flow. Fifty-six women were successfully treated with MTX(poor luteal blood flow group), and 59 women were successfully treated with MTX(rich luteal blood flow group)(Fig.2).

Figure 2. Flow chart of study participation.

Table 1 illustrates the baseline characteristics of women between the two groups. No significant difference was found when comparing the maternal age, BMI, number of pregnancies and deliveries,

pregnant way, risk factors of ectopic pregnancy, duration of pregnancy, clinical symptoms, serum β-hCG level before treatment, ultrasound findings(P>0.05). However, the serum progesterone level before treatment was significantly higher in women with rich luteal blood flow compared with poor luteal blood flow group(P=0.039).

Table 1 Baseline characteristics of women with unruptured tubal EP according to the blood flow of corpus luteum[a].

Characteristics	Poor blood flow group (n=56)	Rich blood flow group (n=59)	*P* value[b]
Maternal age(years)	32.4±7.9	33.1±9.3	0.469
BMI(kg/m^2)	22.5±4.9	23.2±5.0	0.865
Number of pregnancies	2.2±0.8	2.2±0.7	0.889
Number of deliveries	1.0±0.4	0.9±0.5	0.673
Pregnancy by			0.866
Natural conception(%)	87.5	86.4	
ART(%)	12.5	13.6	
Risk factors of EP			
Previous EP(%)	5.4	8.5	0.511
Pregnant with IUD(%)	7.1	5.1	0.645
Duration of pregnancy(days)	46.6±7.1	48.3±8.2	0.414
Clinical symptoms			
Abdominal pain(%)	83.9	81.4	0.716
Vaginal bleeding(%)	91.1	91.5	0.931
Pretreatment β-hCG(mIU/mL)	1767.3±78.9	1898.6±89.4	0.508
Pretreatment progesterone(nmol/L)	28.5±6.1	46.4±7.1	0.039
Ultrasound findings			
Average diameter of ectopic mass(cm)	2.6±1.1	2.5±1.0	0.871
Yolk sac(%)	19.6	23.7	0.928
Free fluid in Douglas cavity(%)	78.6	78.0	0.937

Abbreviations: BMI, body mass index; ART, Assisted reproductive technology; EP, ectopic pregnancy; IUD, intrauterine device.

[a] Values are given as mean ±SD or percentage.

[b]T-test or chi-square test.

No significant difference was found when comparing the volume of corpus luteum(*P*=0.059), however, the VI(*P*=0.016), FI(*P*=0.040) and VFI(*P*=0.027) of corpus luteum were significantly higher in women with rich luteal blood flow compared with women in poor luteal blood flow group(Fig.3).

Figure 3.Corpus luteum measured by 3D power Doppler ultrasound.Arrow marked corpus luteum(*P<0.05).A group:poor luteal blood flow;B group:rich luteal blood flow.(A)Poor luteal blood flow and (B)rich luteal blood flow were presented.(C and D)Volume,VI,FI and VFI of corpus luteum measured by 3D power Doppler ultrasound.

The serum β-hCG level 4 days, 1 week and 2 weeks after MTX treatment in women with rich luteal blood flow were significantly higher compared with women in poor luteal blood flow group(P<0.05). Moreover, the time of serum β-hCG clearance in women with rich luteal blood flow was significantly longer(P=0.028). The average diameter of ectopic mass 1 week, 2 weeks and 3 weeks after MTX treatment in women with rich luteal blood flow were significantly bigger(P<0.05), and the time of ectopic mass disappearance were significantly longer(P=0.046) compared with women in poor luteal blood flow group(Fig.4).

Figure 4.Therapeutic effect of MTX treatment during follow-up.▲:4 days after MTX treatment(*P<0.05).A group:poor luteal blood flow;B group:rich luteal blood flow.(A)The serum β-hCG levels at different time after treatment.(B)The time of serum β-hCG clearance.(C)The average diameter of ectopic mass at different time after treatment.(D)The time of ectopic mass disappearance.

In women with poor luteal blood flow, 55 women(98.2%) accepted one dose MTX treatment, and 1 women(1.8%) underwent second dose MTX treatment because of serum β-hCG level did not decline 15% between days 4 and 7. However, in women with rich luteal blood flow, 52 women(88.1%) accepted one dose MTX treatment, and 7 women(11.9%) underwent second dose MTX treatment. There was significant difference in the application dose of MTX between the two groups(P=0.034). Eight in women with poor luteal blood flow reported side effects versus 11 in rich luteal blood flow group, and laboratory results showed a minor rise in the alanine aminotransferase(ALT) and aspartate transarninase(AST) range from 45-64 U/L. These side effects were mild and returned to normal within 2 weeks after MTX treatment. No significant difference was found when comparing the side effects of MTX between the two groups(P=0.529) (Table 2).

Table 2 Dose and side effects of MTX treatment[a].

Variable	Poor blood flow group (n=56)	Rich blood flow group (n=59)	*P* value[b]
Success rate of MTX treatment			0.034
One dose(%)	98.2	88.1	
Second dose[c](%)	1.8	11.9	
Side effects of MTX	14.3	18.6	0.529
Clinical symptoms			
Nausea(%)	5.4	8.5	
Diarrhoea(%)	3.6	3.4	
Laboratory results			
Rise of ALT(%)	3.6	5.1	
Rise of AST(%)	1.8	1.7	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transarninase.

[a]Values are given as percentage.

[b]Chi-square test.

[c]Second dose was given if serum β-hCG level did not decline 15% between days 4 and 7.

Discussion

Since the first publication by Tanaka et al[13], the use of MTX for the treatment of women with unruptured EP has become common practice[14].The successful treatment of EP depends on several factors, including serum hCG level, route of MTX administration, size of ectopic mass and FCA[15-17]. However, the effect of luteal blood flow during pregnancy on the MTX treatment in women with EP has not been reported. Transvaginal color Doppler ultrasound is a useful and noninvasive technique for detection of blood flow round the corpus luteum[18]. Previous study reported that luteal blood flow was associated with luteal vascularization and luteal function[19-20], which is essential for the support of early pregnancy. Therefore, we speculate that blood supply of corpus luteum may be related to the conservative treatment outcomes of unruptured tubal pregnancy.

The present study observed 115 women with unruptured tubal pregnancy and treated successfully with MTX. Women in the study were divided into 2 groups according to the luteal blood flow. Our data revealed that women with rich luteal blood flow had a significantly higher serum β-hCG level 4 days, 1 week and 2 weeks after MTX treatment compared with women in poor luteal blood flow. Moreover, the average

diameter of ectopic mass 1 week, 2 weeks and 3 weeks after MTX treatment in women with rich luteal blood flow were significantly bigger, and the time of serum β-hCG clearance and ectopic mass disappearance were significantly longer in comparison with women with poor luteal blood flow. These findings illustrated that the luteal blood flow impacted the therapeutic outcomes on women with unruptured tubal pregnancy, those with abundant luteal blood flow needed a second dose MTX treatment and longer recovery time.

Angiogenesis is important for the development of the corpus luteum and maintenance of luteal function[21]. The granulosa cell layer of the follicle is avascular until the time of ovulatory luteinizing hormone(LH) surge, and then vascular endothelial cells of the theca cell layer invade the avascular granulosa cell layer[22]. Thereafter, blood vessels are rapidly formed in the corpus luteum, and the corpus luteum becomes one of the most highly vascularized organs in the body 7 days after ovulation. In order to maintain progesterone production for successful pregnancy, the vascularization and adequate blood flow in the corpus luteum are necessary to provide luteal cells with the large amounts of cholesterol needed for progesterone synthesis and to deliver it to the blood circulation.

According to the early literature, blood vessels were maintained in the corpus luteum until 10 weeks of gestation, and the importance of the corpus luteum as a source of progesterone in the first trimester of pregnancy has been clinically demonstrated by the fact that the removal of the corpus luteum before 7 weeks of gestation causes a decrease in serum progesterone concentration and leads to spontaneous miscarriage[21]. Multiple studies have confirmed that blood supply of corpus luteum was correlated with serum progesterone level, and the blood supply of corpus luteum was decreased in women with luteal phase defect compared with women with normal luteal function[10,18,20]. Progesterone maintains embryonic development during pregnancy through a variety of ways, including increasing the excitatory threshold of uterine smooth muscle, inhibiting uterine contraction, participating in the mediation of maternal-fetal microenvironment, and promoting maternal-fetal tolerance[23-26]. Data in our study demonstrated that the serum progesterone level before treatment, the VI, FI and VFI of corpus luteum were significantly higher in women with rich luteal blood flow compared with women in poor luteal blood flow group. These findings indicated that luteal blood flow was an important factor in regulating progesterone level, and then affected the luteal function and pregnant outcomes. Low blood supply of corpus luteum was associated with luteal function defect, which is consistent with previous reports[20].

This study has some limitations. The corpus luteal function is affected by other factors besides corpus luteal blood flow based on this study design and sample size. In addition, if an ectopic pregnancy was already abortion with falling β-hCG, this may not have had any bearing on intervention with MTX. So the repeatability of the results of this study needs to be confirmed by a large sample.

In conclusion, the present study showed the impact of luteal blood flow during pregnancy on MTX treatment in women with unruptured tubal pregnancy, those with abundant luteal blood flow needed a second dose MTX treatment and longer recovery time. The blood supply of corpus luteum may become an important clinical factor for assessing prognosis for women with EP.

Declarations

Abbreviations

EP: Ectopic pregnancy; TVUS: Transvaginal ultrasound; Hcg: human chorionic gonadotropin; FCA: Fetal cardiac activity; MTX: Methotrexate; VI: Vascularization

index; FI: Flow index; VFI: Vascularization flow index.

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Authors' contributions

LW, XFY conceived the study and wrote the manuscript; JZ,TY collated data; MLP analyzed data. All authors have been involved in revising the manuscript critically, and they have given final approval of the version to be published.

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Ethics approval and consent to participate

This study was approved by the First Affiliated Hospital, Xi'an Jiaotong University Institutional Review Board(No:XJTU1AF2017LSK-2016-218).All participants were gave written informed consent.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

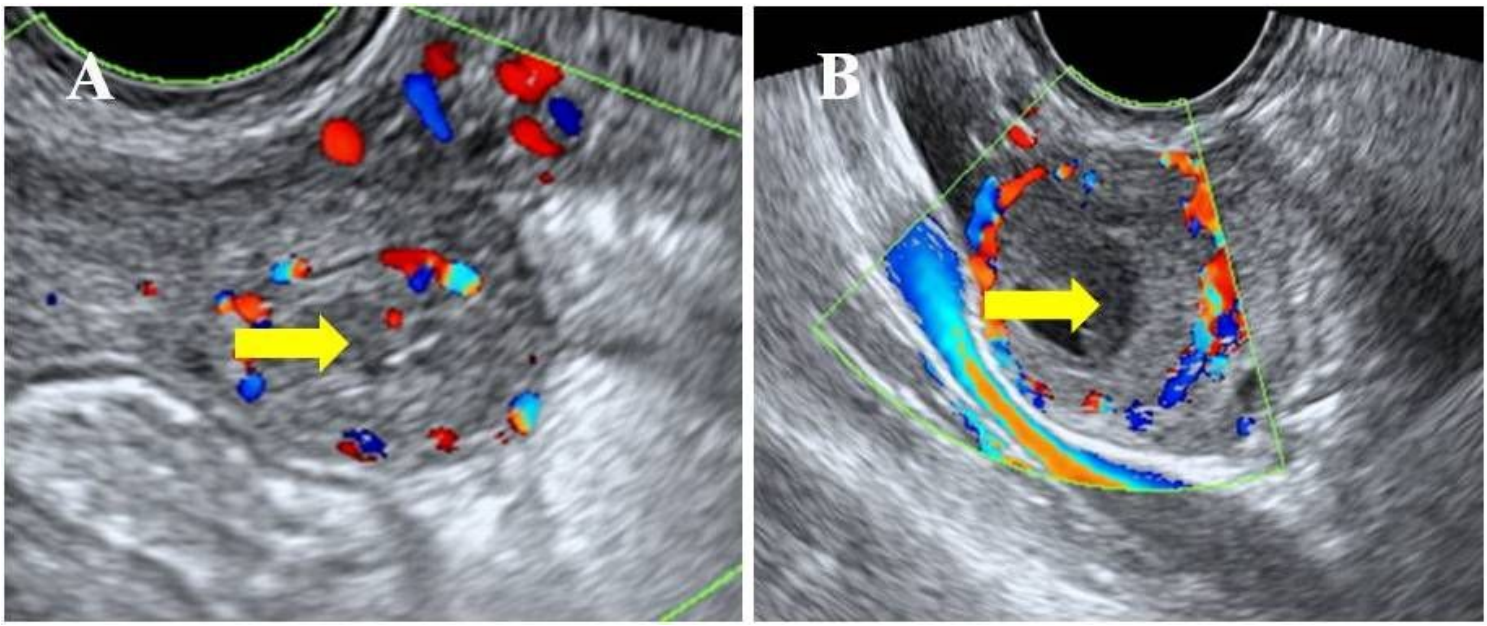

Figure 1

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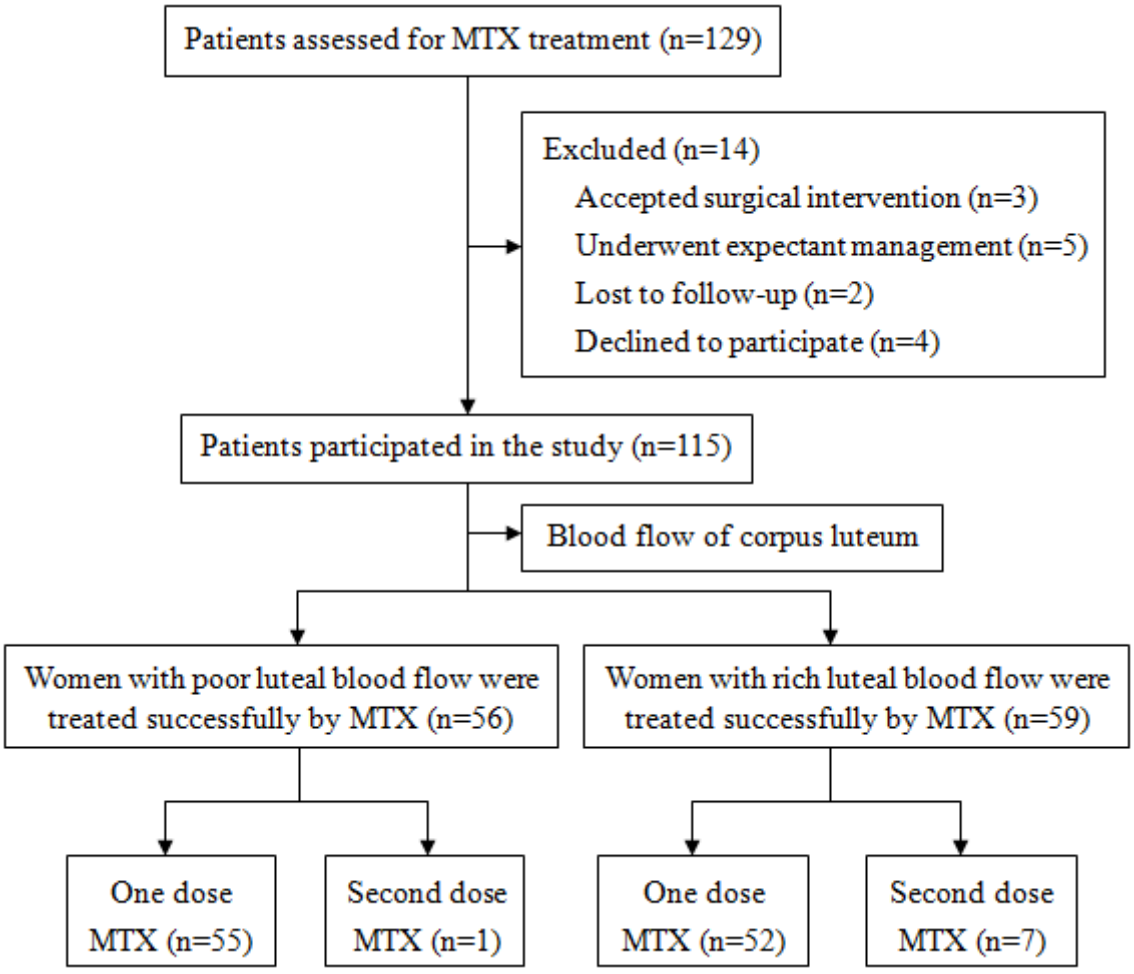

Figure 2

Flow chart of study participation.

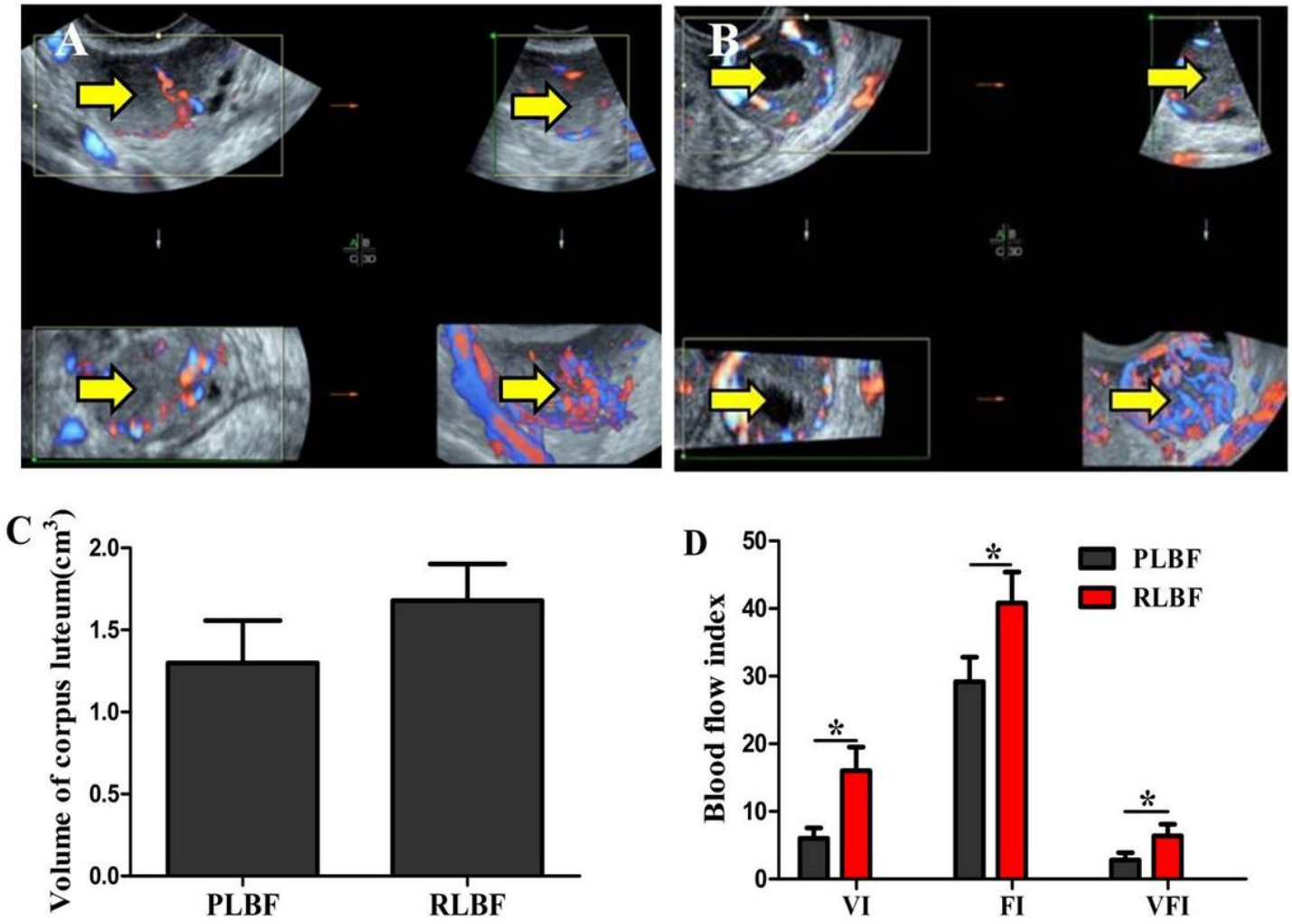

Figure 3

Corpus luteum measured by 3D power Doppler ultrasound.Arrow marked corpus luteum(*P<0.05).A group:poor luteal blood flow;B group:rich luteal blood flow.(A)Poor luteal blood flow and (B)rich luteal blood flow were presented.(C and D)Volume,VI,FI and VFI of corpus luteum measured by 3D power Doppler ultrasound.

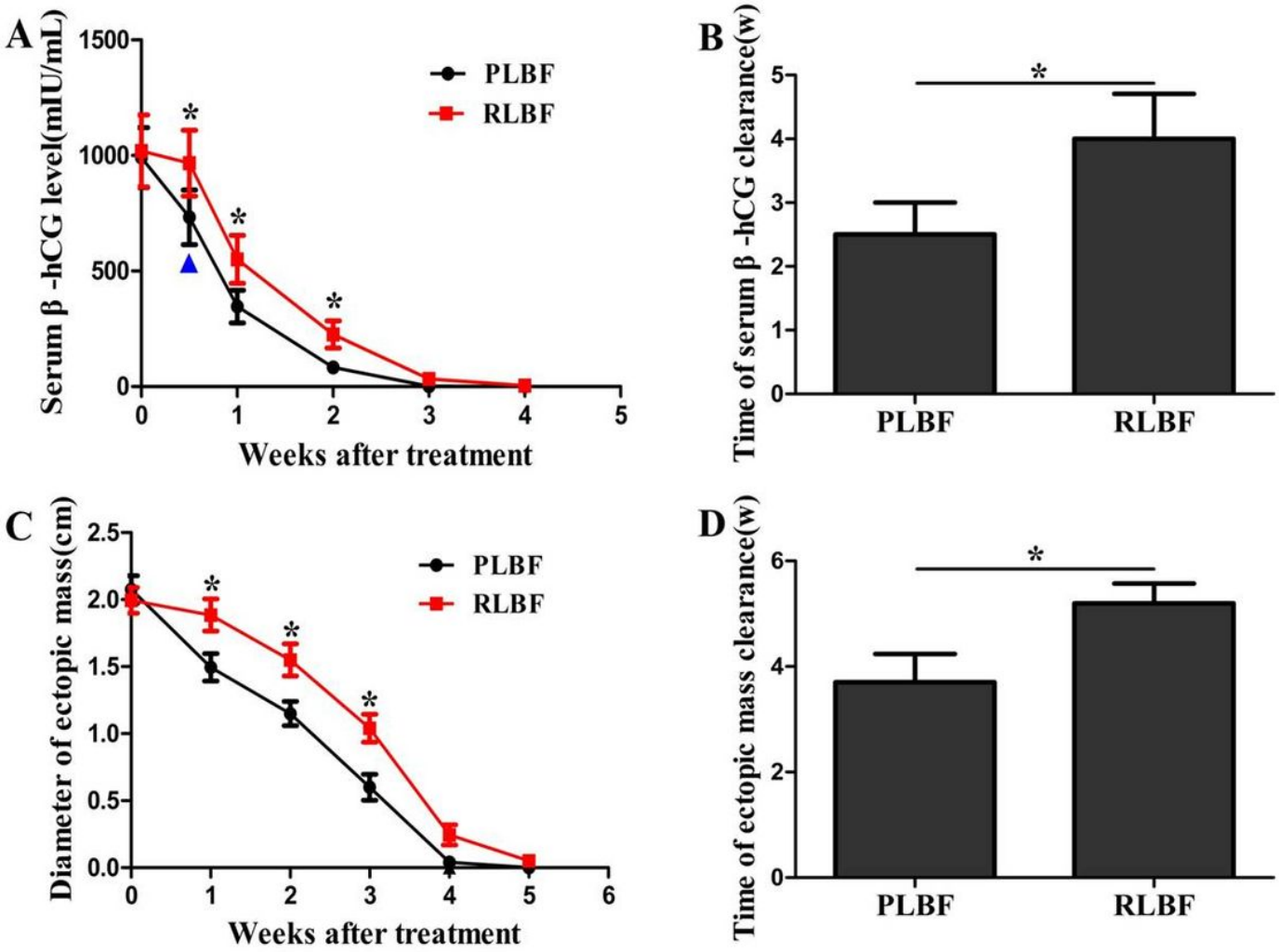

Figure 4

Therapeutic effect of MTX treatment during follow-up.▲:4 days after MTX treatment(*P<0.05).A group:poor luteal blood flow;B group:rich luteal blood flow.(A)The serum β-hCG levels at different time after treatment.(B)The time of serum β-hCG clearance.(C)The average diameter of ectopic mass at different time after treatment.(D)The time of ectopic mass disappearance.