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Dydrogesterone has no effect on uterine fibroids when used to prevent miscarriage in pregnant women with uterine fibroids

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ABSTRACT

Objectives: To analyse the effect of dydrogesterone use during pregnancy on uterine fibroids, pregnancy complications, and pregnancy outcome.

Material and methods: In all, 372 pregnant women with uterine fibroids who were treated at the Affiliated Provincial Hospital of Shandong University were included in this study. Thirty-three of these women received dydrogesterone and constituted the treatment group, and the 27 women who were found to have uterine fibroids during the first trimester but did not receive intervention to prevent miscarriage composed the control group. The changes in uterine fibroids before and after pregnancy and the pregnancy complications were recorded; immunohistochemistry was used to detect the expression of progesterone receptor (PR) and proliferation- and apoptosis-related proteins in the uterine fibroid tissue.

Results: No significant difference was observed in the change in uterine fibroid volume during pregnancy between the treatment group and the control group ($p > 0.05$). The percentage of uterine fibroids with red degeneration was lower in the treatment group than in the control group, but the difference was not statistically significant. No significant difference was observed in newborn weight, height, Apgar score, threatened miscarriage, or premature birth, among other characteristics, between the two groups ($p > 0.05$). Immunohistochemistry showed no significant difference in the expression of PR, cyclinD1, insulin-like growth factor (IGF1), or B-cell lymphoma 2 (Bcl2) between the two groups.

Conclusions: The use of dydrogesterone during pregnancy has no significant effect on uterine fibroids, pregnancy progression, or pregnancy outcomes in pregnant patients with uterine fibroids.

Key words: pregnancy, uterine fibroids, dydrogesterone, miscarriage

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INTRODUCTION

Most cases of uterine fibroids occur in women of child-bearing age with strong ovarian function; thus, uterine fibroids are closely related to pregnancy. The incidence of pregnancy with uterine fibroids has continued to increase year after year and has attracted a great deal of attention [1, 2]. Studies have reported that up to 10.7% of pregnant women have uterine fibroids [3]. However, the relationship between uterine fibroids and adverse pregnancy outcomes is unknown. The effect of uterine fibroids on pregnancy depends on the size and location of the fibroids. Proper treatment of uterine fibroids that cause infertility might, to some extent, affect the outcomes of the next pregnancy.

Uterine fibroids are hormone-dependent. Due to the significant fluctuations in hormone levels during pregnancy, the size and nature of uterine fibroids, of which there are different types and locations, may change. For pregnant women, the growing uterus may cause torsion of pedunculated subserosal fibroids, and uterine fibroids at the uterine isthmus or the posterior lip of the uterine cervix may block the birth canal. Moreover, uterine fibroids may affect uterine contractions and prevent natural placental separation after delivery,

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which may cause postpartum haemorrhage. Our previous study demonstrated that resection of uterine fibroids during caesarean section does not affect the incidence of pregnancy complications such as postpartum haemorrhage [4]. However, pregnant women with uterine fibroids are at a higher risk for perioperative complications, and numerous studies have demonstrated that uterine fibroids are related to pregnancy complications, such as miscarriage, premature birth, premature placental separation, malpresentation, and low newborn weight. The incidence of these complications varies but, nevertheless, has continued to rise year by year [5].

Dydrogesterone (Duphaston) is commonly used to prevent miscarriage in pregnant women with threatened miscarriage before gestational week 20. Clinical studies have shown that Duphaston exhibits effects similar to those of adrenal hormones, oestrogen, and androgens. Studies have demonstrated that the progesterone receptor (PR) is highly expressed in uterine fibroid tissue, whereas progesterone agents cause an elevation in the mitochondrial membrane potential, and ultimately, abnormal cell proliferation [6]. In addition, studies have shown that PR directly activates and acts on relevant signalling pathways to cause cell proliferation in uterine fibroids [7]. Currently, researchers believe that uterine fibroids rely on the synergistic effect of ovarian steroid hormones, oestrogen, and progesterone for their development and progression and that progesterone may play a more critical role than oestrogen. To date, no in-depth studies have been conducted to investigate the specific effect of Duphaston on uterine fibroids.

To investigate the effect of Dydrogesterone on uterine fibroids during pregnancy, pregnancy complications, and pregnancy outcomes in pregnant women with uterine fibroids, we analysed fibroid growth, pregnancy outcomes, and pregnancy complications in pregnant women with uterine fibroids with or without Duphaston treatment to prevent miscarriage. The purpose was to obtain clinical guidance for the use of Duphaston (to prevent miscarriage) in pregnant women with uterine fibroids.

MATERIAL AND METHODS

This study was approved by the local research Ethics Committee of Shandong Provincial Hospital in Jinan, China.

General information

In all, 372 pregnant women with uterine fibroids treated at Affiliated Provincial Hospital of Shandong University between November 2013 and June 2015 were included in this study; of these women, 82 required intervention during pregnancy to prevent miscarriage for various reasons, including the following: red degeneration of uterine fibroids per an abdominal B ultrasound scan during pregnancy (n = 12; usually presenting with severe sudden lower abdominal pain, which may be accompanied by fever and vomiting), hypothyroidism (n = 2), subclinical hypothyroidism during pregnancy examination (n = 2), threatened miscarriage due to incompliance with the dose adjustment of levothyroxine tablets during pregnancy, threatened miscarriage due to antiphospholipid antibody syndrome (n = 1), severe gestational vomiting (n = 1), gestational diabetes (n = 8), gestational hypertension (n = 10), premature rupture of membranes (n = 9), placental abnormalities (n = 2), and unexplained vaginal bleeding and lower abdominal pain (n = 43) (Tab. 1).

Table 1. Analysis of the pathogeny of pregnant women with uterine fibroids

Pathogeny	N	Percentage (%)
Red degeneration of uterine fibroids (diagnosed by abdominal B ultrasound scan)	12	14.63
Hypothyroidism	2	2.44
Antiphospholipid antibody syndrome	1	1.22
Severe gestational vomiting	1	1.22
Gestational diabetes	7	8.54
Gestational hypertension	5	6.10
Premature rupture of membranes	9	10.89
Placental abnormalities	2	2.44
Unexplained vaginal bleeding and lower abdominal pain	43	52.44
Total	82	100

Among the 372 pregnant women with uterine fibroids, 82 received intervention to prevent miscarriage. Among them, 33 women with indications during the first trimester received oral Duphaston 20 mg/day for 2 months or longer and did not receive other drugs (the treatment group), and 27 were found to have uterine fibroids during the first trimester but did not receive intervention to prevent miscarriage (the control group). Patients in both groups underwent a caesarean section. General clinical information was compared between the two groups, including the gestational age of the current pregnancy, the number of miscarriages, gestational age, body mass index (BMI), and fibroid size during the first trimester. A B ultrasound scan was performed to measure the maximum diameter (cm) of the fibroid during the first trimester. BMI = weight (kg)/height^2 (m^2). Maternal weight and height were measured at the time of admission for labour.

Immunohistochemical staining

For all patients, uterine fibroids were resected during caesarean section. Fibroids were paraffin-embedded and prepared as 5-μm-thick sections for immunohistochemical

staining to determine the PR, cyclinD1, insulin-like growth factor 1 (IGF1), and B-cell lymphoma 2 (Bcl2) expression in the two groups. Next, the sections were deparaffinized and rehydrated, and 0.5% Triton X-100 was used to rupture the membranes. Then, warm 0.01 M citrate buffer (pH 6.0) was used for antigen retrieval for 15 minutes, and the sections were immersed in 3% hydrogen peroxide (diluted in methanol) for 20 minutes to inactivate endogenous catalase. Next, 10% normal goat serum was used to block the sections, and then the primary antibody (1:100) was added for an overnight incubation at 4°C. IgG (same dilution) was used as the primary antibody for the negative control. After PBS washes (3 times × 5 minutes), the sections were incubated with a biotinylated goat anti-rabbit or goat anti-mouse secondary antibody (Wuhan Boster Biological Technology, Ltd.) at a dilution of 1:200 at room temperature for 40 minutes. After DAB staining and haematoxylin counterstaining, the sections were observed and photographed under an Olympus microscope. Five fields (× 400) were randomly selected to analyse the staining density of the cytoplasm and the nucleus. The final immunohistochemical staining score (0–12) = density value × percentage score.

Statistical analysis

A WPS table was used to establish the database, and SPSS20.0 (Statistical Product and Service Solutions 20.0) statistical software was used for the data analysis. Numerical data are expressed as the mean ± standard deviation (SD) ($\bar{x} \pm s$); an independent sample t-test was performed for between-group comparisons, and a chi-squared test was performed to compare the incidence between the two groups.

For the immunohistochemistry results, brown particles indicated positive staining, and the semi-quantitative analysis that was performed incorporated the staining intensity and the scope of distribution. The staining intensity was rated as follows: 0: no staining, 1: light staining, 2: moderate staining, and 3: strong staining. The scope of distribution was rated as follows: 0: positive percentage of 0%, 1: 1% to 25%, 2: 25% to 50%, 3: 51% to 80%, and 4: 81% to 100%. The product of these two scores indicated the protein expression level. A two-tailed Student's t-test was performed to analyse the difference in immunohistochemical staining between the two groups. The data are expressed as the mean ± SD. $P < 0.05$ was considered statistically significant.

RESULTS

General information of the patients

The general clinical information, including the gestational age of the current pregnancy, the number of miscarriages, gestational age, BMI, and fibroid size during the first trimester, was compared between the treatment group (n = 32) and the control group (n = 27). No significant differences were observed (all p > 0.05) (Tab. 2).

Table 2. General clinical information of the patients treated with Dydrogesterone and those who were not

General information	Treatment subjects (n = 33, $\bar{x} \pm s$)	Control subjects (n = 27, $\bar{x} \pm s$)	p
Gestational age	32.40 ± 4.11	32.74 ± 4.74	> 0.05
Number of miscarriages	1.00 ± 1.27	0.78 ± 0.84	> 0.05
Gestational week	37.82 ± 2.68	38.47 ± 1.47	> 0.05
BMI [kg/m^2]	29.08 ± 3.24	28.62 ± 2.72	> 0.05
Fibroid size during the first trimester [cm]	3.44 ± 2.70	3.37 ± 2.65	> 0.05

Changes in uterine fibroids after caesarean section

Fibroid size was indicated as the maximum diameter (cm), and ΔΦ (diameter variation) was used to indicate the change in fibroid size before and after caesarean section, wherein ΔΦ = fibroid diameter at the time of caesarean section — fibroid diameter during the first trimester. For the treatment group, the mean fibroid diameter was 3.44 ± 2.70 cm during the first trimester and 7.11 ± 2.38 cm at the time of caesarean section (ΔΦ1 = 3.66 cm). For the control group, these values were 3.37 ± 2.65 cm and 7.57 ± 1.35 cm during the first trimester and at caesarean section, respectively (ΔΦ2 = 4.20 cm) (Tab. 3). In both groups, the uterine fibroids were significantly larger at the time of caesarean section than during the first trimester (both p < 0.01), but no significant difference was observed in the change in the uterine fibroid volume between the two groups (p > 0.01) (Tab. 3).

Effect of Duphaston on the red degeneration of uterine fibroids

Routine pathological examination showed that the section of degenerated fibroids was red and soft and that the swirl structure had disappeared. Microscopic observation

Table 3. Changes in uterine fibroids during pregnancy

Fibroid size	Treatment subjects (n = 33, $\bar{x} \pm s$)	Control subjects (n = 27, $\bar{x} \pm s$)
Fibroid diameter during the first trimester [cm]	3.44 ± 2.70	3.37 ± 2.65
At the time of caesarean section [cm]	7.11 ± 2.38$^{\#}$	7.57 ± 1.35$^{\#}$
Size change [cm]	3.66 ± 1.44	4.20 ± 2.14

Note: $^{\#}p < 0.01$

showed tissue oedema, small vein thrombosis in the tumour, vascular dilatation and congestion, extensive bleeding and haemolysis, a low number of muscle cells, and nuclei dissolution and disappearance. Pathological diagnosis revealed that in the treatment group (intervention was given to prevent miscarriage) (n = 33), 20 patients (60.61%) had red degeneration of uterine fibroids, 7 (21.21%) had no red degeneration, and the remaining patients had other types of degeneration; in the control group (n = 27), 21 patients (77.78%) had red degeneration of uterine fibroids, 3 (11.11%) had no red degeneration, and the remaining patients had other types of degeneration. The incidence of red degeneration of uterine fibroids was lower in the treatment group than in the control group, but the difference was not statistically significant (p > 0.05) (Fig. 1).

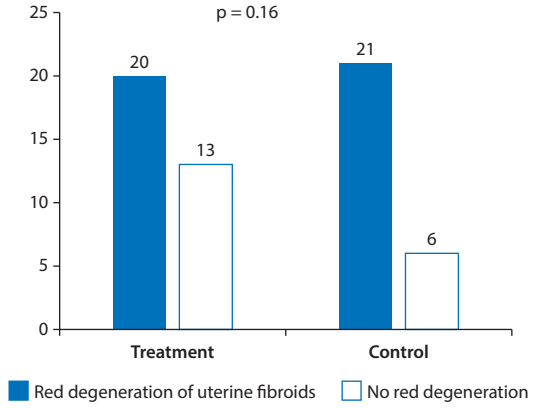

Figure 1. Red degeneration of uterine fibroids in pregnancy.
Note: In the treatment group (dydrogesterone was given to prevent miscarriage), 20 patients (60.61%) had red degeneration of uterine fibroids, and 13 had no red degeneration; in the control group, 21 patients had red degeneration of uterine fibroids, and 7 had no red degeneration. The incidence of red degeneration of uterine fibroids was lower in the treatment group than in the control group, but the difference was not statistically significant (p = 0.16)

Pregnancy complications and pregnancy outcomes

The percentage of premature rupture of membranes and abnormal foetal position was higher in the treatment group than in the control group; the percentage of foetal distress, placenta previa, postpartum haemorrhage, and large foetus was lower in the treatment group than in the control group. The newborn weight, height, and delivery time (in hospital) were larger or longer in the treatment group than in the control group, and the intraoperative blood loss and operative time were lower or shorter, respectively, in the treatment group than in the control group. However, the differences were not statistically significant (all p > 0.05) (Tab. 4a, 4b). No premature birth or foetal abnormalities were observed in the two groups.

Expression of PR and proliferation- and apoptosis-related proteins in uterine fibroid tissue obtained from pregnant women during caesarean section

We first performed immunohistochemical staining to evaluate the PR expression in uterine fibroid cells. Figu-

Table 4a. Pregnancy complications

Complications	Treatment subjects (total 33)		Control subjects (total 27)		p
	n	%	n	%	
Premature rupture of membranes	3	9.09	2	7.41	> 0.05
Abnormal foetal position	2	6.06	1	3.70	> 0.05
Foetal distress	1	3.03	1	3.70	> 0.05
Placenta previa	1	3.03	1	3.70	> 0.05
Postpartum haemorrhage	1	3.03	1	3.70	> 0.05
Large foetus	1	3.03	2	7.41	> 0.05

Table 4b. Pregnancy outcomes

Outcomes	Treatment subjects (n = 33)	Control subjects (n = 27)	p
Blood loss [mL]	271.52 ± 124.98	324.07 ± 105.95	0.09
Operative time [min]	121.66 ± 37.62	127.59 ± 30.17	0.51
Time in hospital (days)	6.48 ± 3.21	5.48 ± 1.09	0.13
Apgar score (score)	10.00 ± 0.00	10.00 ± 0.00	–
Newborn height [cm]	48.24 ± 1.90	48.04 ± 3.06	0.22
Newborn weight [g]	3480.76 ± 461.38	3309.37 ± 531.74	0.08

Table 5. Comparison of PR expression in uterine fibroid tissue

Tissue	n	PR				p
		+	++	+++	PR expression detected (%)	
Study subjects	32	3	10	15	87.5	0.488
Control subjects	27	5	7	9	77.8	

Note: PR expression was found in 87.5% of patients in the treatment group, but the difference between the two groups was not statistically significant ($p > 0.05$)

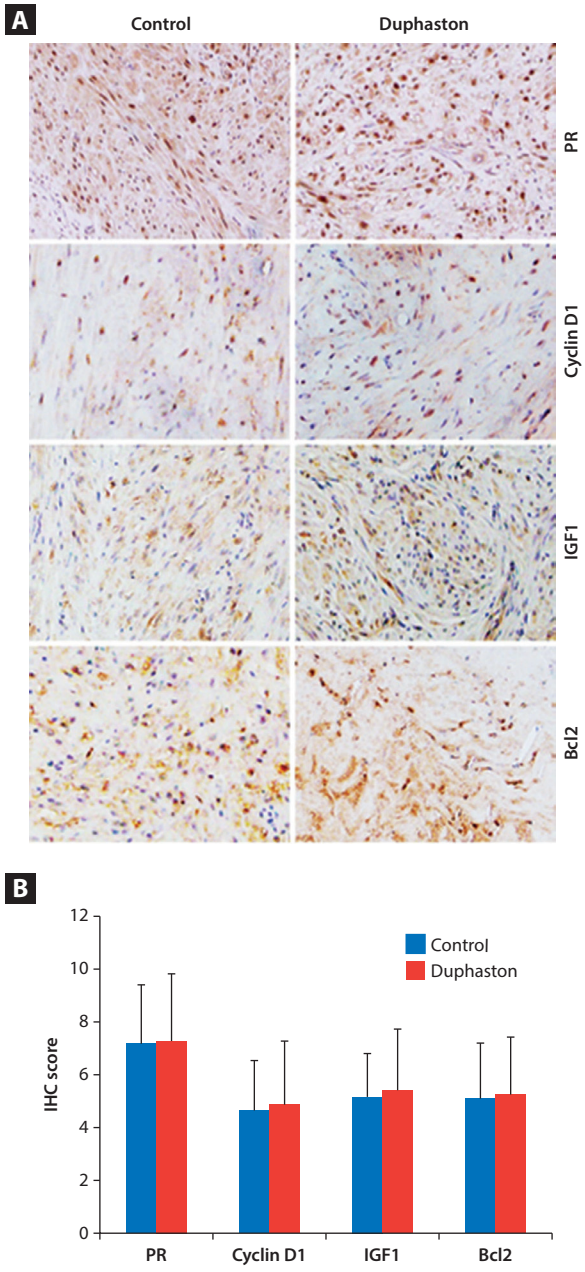

Figure 2. Expression of PR and proliferation- and apoptosis-related proteins in the control group and the treatment (Duphaston) group
Note: In this study, we performed immunohistochemical staining to evaluate the expression of PR, cyclinD1, IGF1, and Bcl2 in the control and treatment groups. The results showed no significant difference in protein expression between the two groups

re 2 shows no significant difference in PR expression in the nucleus between the treatment group and the control group, which indicates that Duphaston had no effect on PR expression in the nucleus. PR expression was found in 87.5% of patients in the treatment group, which was higher than the percentage in the control group (77.8%), but the difference was not statistically significant ($p > 0.05$) (Tab. 5).

We examined the expression of the proliferation-related genes cyclinD1 and IGF1. Duphaston had no significant effect on cyclinD1 or IGF1 expression, which was consistent with our clinical experience (no significant increase in fibroid size was observed after Duphaston treatment).

We determined the Bcl2 expression in the treatment (Duphaston) group and the control group but observed no significant difference between the two groups (Fig. 2).

DISCUSSION

Progesterone and uterine fibroids

Numerous clinical studies and experiments have shown that uterine fibroids are hormone-dependent. Recent studies have shown that progesterone promotes uterine fibroid proliferation and inhibits apoptosis, thereby promoting fibroid growth [8]. Oestrogen and progesterone promote fibroid growth in different ways. During pregnancy, the level of maternal oestrogen and progesterone increases significantly, which provides the appropriate conditions for fibroid growth. Currently, it is unclear whether the use of agents such as progesterone during pregnancy to prevent miscarriage may promote fibroid growth or increase the occurrence of red degeneration in uterine fibroids.

Effect of progesterone on uterine fibroids during pregnancy

In the past three decades, researchers have debated the effect of pregnancy on uterine fibroid volume. Numerous researchers have conducted relevant research but have reached different conclusions [9].

De ViVo et al. [10] revealed that the volume of uterine fibroids significantly increased during pregnancy. Rosati et al. [11] showed that the uterine fibroid volume increased during the first trimester, did not continue to increase during the second and third trimesters, and decreased after

birth. Some studies have indicated that during pregnancy, uterine fibroids grew at a rate of 0.667 mm per week during the first and second trimesters [12]. Benaglia et al. [13] also showed that the uterine fibroid volume increased rapidly and significantly during the first trimester.

Most studies showed that uterine fibroids grew during pregnancy; however, some studies reported that during pregnancy, the uterine fibroid volume decreased or remained unchanged. Ozturk et al. [14] reported no significant change in the volume of uterine fibroids during pregnancy. Neiger et al. [15] conducted a longitudinal study of 137 pregnant women with uterine fibroids and found that very few patients showed an increase in uterine fibroid volume (per ultrasound). Phelan et al. [16] suggested that the level of circulating progesterone was significantly higher during pregnancy, but most pregnant women with uterine fibroids did not show an increase or even a decrease in uterine fibroid volume during pregnancy.

In this study, we compared the general clinical information between the treatment group and the control group. We observed no significant difference between the two groups. This study showed that uterine fibroids were significantly larger at the time of caesarean section (end of third trimester) than during the first trimester in both groups; however, the change in the uterine fibroid volume before and after caesarean section did not significantly differ between the two groups. Therefore, although the volume of uterine fibroids increased significantly during pregnancy, the use of progesterone (to prevent miscarriage) did not significantly increase the uterine fibroid volume in pregnant women.

Progesterone promotes the proliferation of uterine fibroid cells [7]. Our results showed that Duphaston had no significant effect on the expression of cyclinD1 or IGF1. This was consistent with our clinical experience, which showed no significant increase in fibroid size after Duphaston treatment. Moreover, we determined the expression of Bcl2 in the treatment group (Duphaston) and the control group, and no significant difference was observed between the two groups. This finding contradicted previous reports, which showed that progesterone inhibited apoptosis [8]. This contradiction may be related to the small sample size in this study.

Red degeneration of uterine fibroids during pregnancy

During pregnancy, uterine fibroids may undergo red degeneration due to the unstable state of the coagulation and fibrinolysis system. Studies in pregnant women with degenerated uterine fibroids showed that high-dose natural progesterone affected the blood vessels, increased the blood flow in fibroids, and relieved the acute abdominal syndrome caused by fibroid degeneration, with an intraoperative finding of shrinkage or disappearance of the original degenerated fibroids [17]. The present study showed red degeneration in 60.61% of uterine fibroids in the treatment group (progesterone to prevent miscarriage), which was lower than in the control group, but the difference was not statistically significant. In addition, PR expression was found in 87.5% of patients in the treatment group, which was higher than the percentage of patients in the control group (77.8%), but the difference was not statistically significant. This finding may be related to the small sample size in this study; nevertheless, the present study demonstrated that Duphaston treatment did not increase the occurrence of red degeneration of uterine fibroids during pregnancy.

Effect of progesterone on pregnancy complications and pregnancy outcomes

Progesterone is an important steroid hormone that functions to maintain pregnancy during the first trimester. Studies have shown that progesterone prevents premature birth and helps to prevent miscarriage in pregnant women with a short cervix. However, the mechanism by which progesterone prevents premature birth or prolongs gestation is unknown. The conventional belief is that progesterone prevents miscarriage via the inhibition of preterm contractions of uterine muscle fibres or via the inhibition of the expression of factors involved in uterine contractions in the myometrium, such as prostaglandin, oxytocin receptor, and gap protein [18]. Increasingly, researchers believe that progesterone exerts both immunomodulatory and anti-inflammatory effects [19].

Some researchers believe that progesterone may cause the placenta to adhere too tightly, making it difficult to separate during labour, thus contributing to postpartum haemorrhage. Some meta-analyses found no significant difference in maternal or foetal adverse reactions between the progesterone (to prevent miscarriage) group and the control group [20, 21]. The present study demonstrated that the use of dydrogesterone during the first trimester to prevent miscarriages had no adverse effects on pregnancy complications and pregnancy outcomes.

In summary, this was the first study to investigate the effect of dydrogesterone on uterine fibroids during pregnancy, pregnancy complications, and pregnancy outcomes. We conducted several analyses of clinical and laboratory specimens and demonstrated that dydrogesterone (to prevent miscarriage) had no significant effect on the change in uterine fibroids during pregnancy, pregnancy progression, or pregnancy outcomes in pregnant women with uterine fibroids. These results thus provide a theoretical basis for dydrogesterone treatment (to prevent miscarriage) with far-reaching clinical significance.

Acknowledgements

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