

# Comparative Study Between Vaginal Natural Progesterone and Oral Dydrogesterone in Prevention of Red Degeneration of Uterine Fibroid in Pregnancy

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## ABSTRACT

**Background:** Uterine leiomyomas are highly prevalent benign monoclonal tumors, arising from the smooth muscle of the myometrium; they occur in up to 50-60% of reproductive age women, causing significant morbidity in up to 30% of women. The most serious complication of uterine fibroids; is red degeneration that causes severe pain, and may lead to preterm labour, miscarriage, fetal and maternal morbidity and mortality.

**Objective:** This study was done to study the difference between the effect of vaginal natural progesterone and oral dydrogesterone to prevent red degeneration of uterine fibroid in pregnancy.

**Methodology:** This study was done at El-Shatby Maternity University Hospital. 50 pregnant females were recruited, having large uterine fibroid above 3 cm in size then there were divided into two groups, group (A): twenty five treated by vaginal natural Progesterone, group (B): twenty five treated by oral Dydrogesterone. All patients at 14-15 weeks of gestational age underwent complete history taking, clinical examination and ultrasound examination for mean gestational age and assessment of the type and uterine fibroid.

**Results:** Results showed that there were no statistical significant differences as regards age, obstetric history (gravidity and parity), number, Site, grade and size of the fibroid. There was a significant difference between the two studied groups, regarding the acute abdominal pain, it occurred to only 3 cases (12%) in group (A), versus to 16 cases (64%) in group (B). Regarding occurrence of red degeneration, it occurred only to 3 cases (12%) in group (A), while in group (B) it occurred to 15 cases (60%). Conclusion: Vaginal natural micronized progesterone is more effective than oral dydrogesterone in prevention of red degeneration of uterine fibroid in pregnancy with fewer complications. Vaginal natural progesterone daily dose of 200mg is recommended to all pregnant females with uterine fibroids.

**Key words:** Vaginal Natural Progesterone -Oral Dydrogesterone -Red Degeneration - Pregnancy.

## INTRODUCTION

Fibroids are the most common benign tumor of the females reproductive system.(1) They are smooth muscle cells tumors with abundant extracellular matrix.(2) Despite the fact that their cause is still unknown, yet there is evidence that it's estrogens and progestogens dependent.(3,4)

Most fibroids are asymptomatic. However, localized sever pain can occur if red degeneration occurred. Red degeneration is the most common complication in pregnancy, and is seen most often after the first trimester (5) It occurs in 8% of tumors complicating pregnancy, although the prevalence is about 3% of all uterine leiomyoma.(6).

It causes severe pain; these women should be treated conservatively as any surgical procedure during the pregnancy can result in preterm delivery and fetal loss. Women with fibroids who get pregnant should be allowed

to continue pregnancy and all efforts made to minimize complications with good correction of anemia.(7)

Progesterone is an essential steroid hormone to enhances uterine relaxation and suppresses uterine contraction.(8).

Oral administration shows optimal compliance by patients but has many side effects; such as nausea, headache and sleepiness.

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The vaginal route results in higher concentrations in the uterus but does not reach high and constant blood levels.(9)

Dydrogesterone is a retroprogesterone that has a biological active metabolite of progesterone which lasts longer bioactive in the blood.(10) It also positively affects its selectivity, while oral natural progesterone is less selective.(11) Fibroid pain during pregnancy is usually managed conservatively(5) but definitive treatment being postponed until postpartum.(12).

The aim was to compare between vaginal natural Progesterone and oral Dydrogesterone in prevention of red degeneration of uterine fibroid in pregnancy.

#### Patients:

This study included 50 pregnant females diagnosed having a uterine fibroid more than 3 cm in size, presented to Elshatby maternity university hospitals.

They will be divided into 2 groups:

Group (A): 25 pregnant females treated by vaginal natural Progesterone [200 mg /day from 14- 34 weeks gestation].

Group (B): 25 pregnant females treated by oral Dydrogesterone [20 mg/day from 14-34 weeks gestation].

#### Inclusion criteria:

Pregnant female diagnosed having a uterine fibroid more than 3 cm by ultrasound.

Exclusion criteria:

- 1) A Uterine fibroid less than 3 cm in size.
- 2) Contraindication to Progesterone (as presence of hypersensitivity).
- 3) Patient diagnosed having a uterine fibroid complicated by red degeneration in the current pregnancy.
- 4) Pregnant females with gestational age >34 weeks.

## MATERIALS AND METHODS

All patients was sign a full informed consent.

They will be subjected to the following:

1. History taking.
2. General examination.
3. Transvaginal or abdominal ultrasonography to:
  - a) Assess type and size of the uterine fibroid.
  - b) Exclude any complications of fibroid before the administration of vaginal natural progesterone or oral dydrogesterone.
  - c) Confirm the gestational age and assess fetal wellbeing.
4. Administration of vaginal natural Progesterone for group A [200mg /day from 14- 34 weeks gestation] and oral Dydrogesterone for group B [20 mg per day from 14-34 weeks gestation]
5. to estimate incidence of red degeneration, all patients will undergo every month till delivery:

- a) Physical examination regarding pain as symptom and tenderness as a sign over the site uterine fibroid.
- b) Abdominal ultrasound imaging showing a heterogeneous echogenic pattern or cystic changes of the uterine fibroid.

## RESULTS AND DISCUSSION

The geography of the Himalayan region is very unique and [Table-1](#) shows comparison between the two studied groups according to age, obstetric history and gestational age at start and at end of treatment. There was no significant difference between the two groups regarding age, gravidity, parity and start of treatment ( $p > 0.05$ ). Regarding to the start of treatment, statistically significant differences were noted between the two studied groups ( $p < 0.05$ ).

[Table-2](#) shows comparison between the two studied groups according to fibroid Number. grade and size of the fibroid. There was no significant difference between the two studied groups regarding number of fibroids, grade and size of the fibroid ( $p > 0.05$ ).

[Table-3](#) shows comparison between the two studied groups according to Fibroid Site and occurrence of acute abdominal pain. There was no significant difference between the two groups regarding fibroid site ( $p > 0.05$ ), while regarding occurrence of acute abdominal pain, statistically significant differences were noted between the two studied groups. ( $p < 0.05$ )

[Table-4](#) shows comparison between the two studied groups according to gestational age at delivery, Red degeneration occurrence and labour onset. Regarding gestational age at delivery, statistically significant differences were noted between the two studied groups ( $p < 0.05$ ). There was statistically significant differences were noted between the two studied groups regarding to labour onset ( $p < 0.05$ ).

Presence of myoma during pregnancy is a serious problem and of frequent clinical concern, as fibroid is commonly detected in reproduction age women in up to 50-60%.<sup>(13)</sup> So careful monitoring of the patient is needed during antenatal, perinatal and postnatal period.

The tumor responds differently in individual pregnant women.<sup>(14)</sup> It may causes preterm labour, PROM, uterine dysfunction, obstructed labour, mal presentations, retained placenta, and post-partum hemorrhage.<sup>(15, 16)</sup>

A well-known complication during pregnancy is red degeneration,<sup>(17)</sup>Red degeneration occurs in 8% of tumors during pregnancy,<sup>(18,19)</sup> causing severe pain, localized tenderness with nausea, vomiting, and mild fever.<sup>(21)</sup>

It can be diagnosed by:

**Table-1. Comparison between the two studied groups according to age, obstetric history and gestational age at start and end of treatment**

	Group A (n = 25)	Group B (n = 25)	t	p
Age (years)	27.60 ± 4.37	28.52 ± 4.61	0.724	0.472
Gravidity	2.40 ± 1.0	2.44 ± 1.16	311.00	0.976
Parity	1.0 ± 0.87	0.88 ± 0.83	290.00	0.637
G.A. Start of treatment (weeks)	14.44 ± 0.51	14.40 ± 0.50	0.281	0.780
G.A. End of treatment (weeks)	31.92 ± 4.70	28.28 ± 4.57	2.777*	0.008*

**Table-2. Comparison between the two studied groups according to fibroid Number, grade and size of the fibroid.**

	Group A (n = 25)		Group B (n = 25)		Test of sig.	p
	No.	%	No.	%		
Fibroid					$\chi^2=$ 1.063	$MCp=$ 0.865
1	10	40.0	13	52.0		
2	10	40.0	8	32.0		
3	4	16.0	3	12.0		
4	1	4.0	1	4.0		
Mean ± SD	1.84 ± 0.85		1.68 ± 0.85		U=275.50	0.437
Total fibroid number	46		42			
Grade	5.07 ± 1.34		5.26 ± 1.25		895.50	0.546
Size (cm)	5.13 ± 2.01		4.83 ± 1.26		962.0	0.973

**Table-3. Comparison between the two studied groups according to Fibroid Site and occurrence of acute abdominal pain**

	Group A (n = 46)		Group B (n = 42)		$\chi^2$	p
	No.	%	No.	%		
Site					1.600	0.449
Post wall	27	58.7	19	45.2		
Ant wall	13	28.3	16	38.1		
Fundal	6	13.0	7	16.7		
Acute abdominal pain					14.346*	<0.001*
Positive	3	12.0	16	64.0		
Negative	22	88.0	9	36.0		

**Table-4. Comparison between the two studied groups according to gestational age at delivery and Red degeneration occurrence and laborer onset.**

	Group A (n = 22)		Group B (n = 22)		t	p
Gestational age at delivery	38.36 ± 2.04		36.86 ± 2.05		2.432*	0.019*
Outcome	No.	%	No.	%	$\chi^2$	$MCp$
Red degeneration	3	12.0	15	60.0	13.816*	0.001*
Miscarriage	3	12.0	3	12.0		
Successful	19	76.0	7	28.0		
Labour						
Preterm	1	4.5	8	36.4	6.844*	0.021*
Full term	21	95.5	14	63.6		

- 1- Abdominal ultrasound imaging showing a heterogeneous echogenic pattern or cystic changes of the uterine fibroid.
- 2- Physical examination regarding pain as symptom and tenderness as a sign over the site of uterine fibroid.

Progesterone hormone is indispensable for the maintenance of pregnancy. <sup>(21)</sup> progesterone receptors exhibit higher expression in fibroids compared with the adjacent myometrium.<sup>(22, 23)</sup>

Progesterone supplements are either natural progesterone or synthetic progesterone, Natural progesterone is like vaginal natural micronized progesterone. While, synthetic progesterone is like oral dydrogesterone.

Vaginal natural MP has direct effect on the uterus and absorbed quickly <sup>(24, 25)</sup> without general side effects and better bioavailability.<sup>(26)</sup>

Oral dydrogesterone is similar to natural progesterone, with longer oral bioavailability <sup>(27)</sup> and known for being higher selective progesterone receptor agonist than oral MP, at a dose 10–20 times lower than oral MP.<sup>(28)</sup>

In the current study, the mean age in group A was 27.60±4.37 years while in group B it was 28.52 ± 4.61 years. There was no significant difference between the two groups regarding age. Regarding obstetric history, number, Site, grade and size of the fibroid there was no significant difference between the two groups.

According to the start of treatment, there was no significant difference between the two studied groups as both started at 14-15 weeks of gestation. Only 3 cases (12%), in group (A) suffered from acute abdominal pain, versus to 16 cases (64%) in group (B) complained of it, significant difference was noted between the two studied groups. ( $p < 0.001$ )

Regarding labour onset; in group (A), only one case delivered preterm (4.5%), While In group (B), 8 cases delivered preterm (36.4). There was significant difference between the two studied groups. ( $p = 0.021$ ). In addition to the gestational age at the delivery, the mean in group (A) was 38.36 ± 2.04, while in group (B) was 36.86 ± 2.05. Statistically significant difference was noted between the two studied groups. ( $p = 0.019$ )

Additionally, as expected the tried treatment ended in group B before group A to control complications as acute pain resulted from the aseptic necrobiosis by good hydration, injectable progesterone and analgesics. There was a significant difference between the two groups ( $P = 0.008$ ).

The present study shows that vaginal administration of MP in pregnant women with uterine fibroid results in significantly less occurrence of red degeneration, when compared with oral dydrogesterone ( $P = 0.001$ ). Because

in group (A) it occurred only in 3 cases (12%), while in group (B) it occurred in 15 cases (60%).

In light of the discussion above, the potential clinical benefits of vaginal natural progesterone supplementation appear large, whereas the oral dydrogesterone seems small in comparison.

## CONCLUSION

From this study, the following could be concluded:

- Vaginal natural micronized progesterone is more effective than oral dydrogesterone in prevention of red degeneration of uterine fibroids with fewer complications like acute abdominal pain and preterm labour.
- Vaginal micronized progesterone (200mg once daily) is effective and recommended to all pregnant cases with uterine fibroids.

## RECOMMENDATIONS:

Based on the results of this study, the following could be recommended:

- Conducting this study on a larger sample size of patients in multicenter to ensure these findings and confirm its clinical values.
- Vaginal MP is recommended for all pregnant cases with uterine fibroids.

## Conflicts of Interest

Authors declare that there is no conflict of interests regarding the publication of this paper.

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