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Original Article

Comparative Outcome of Threatened Abortion between Patients Receiving Progesterone through Oral and Intramuscular Route

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ABSTRACT

Background: *Threatened abortion is a common condition presenting with varied clinical manifestations. Progestogens have been taken into consideration as a possible healing alternative for the remedy of miscarriage more than 50 years.* ***Objectives:*** *To compare the efficacy and side effects of oral Dydrogesterone and intramuscular progesterone in the management of threatened abortion.* ***Methods:*** *This randomized clinical trial was carried out in the outpatient department (OPD) of Obstetrics & Gynaecology, Dhaka Medical College, Dhaka, from March 2017 to February 2018. A total of 80 threatened abortion patients were enrolled purposively in this study and they were randomly allocated equally into two groups by using a sealed envelope technique. In group I (oral group) oral tablet Dydrogesterone (10mg) and group II (intramuscular group) injection Progesterone (250 mg) was given up to 20 weeks. Serum progesterone level was estimated before starting treatment and after treatment. Detailed information was obtained in a pre-structured data sheet and were analyzed by SPSS-22 for windows.* ***Result:*** *The mean level of progesterone before treatment was 51.08±7.3 ng/ml in group I and 55.16±43.9 ng/ml in group II (p>0.05). The mean level of progesterone after treatment was found 75.0±9.66 ng/ml and 73.81±9.44 ng/ml in group I and group II respectively(p>0.05). The mean gestational age at delivery was found 37.45±1.94 weeks in group I and 37.08±2.14weeks in group II. Live birth observed 38(95.0%) in group I and 37(92.5%) in group II. A half (50.0%) subjects had nausea in group I and 15(37.5%) in group II. The difference was pain at the site of injection and induration formation at the site of injection statistically significant (p>0.05) and others were not significant between two groups.* ***Conclusion:*** *Dydrogesterone and progesterone are safe and simple to use in the management of threatened abortion.*

Keywords: *Threatened abortion; Dydrogestrone; Progesterone injection.*

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INTRODUCTION

Progesterone and estrogen are two key hormones that remain elevated during pregnancy and play significant roles in causing anatomical adjustments within the uterus to create an environment conducive to fetal growth [1]. Progesterone, rightly called the "pregnancy hormone", is crucial in the maintenance of pregnancy as it is involved in modulation of the maternal immune response, suppression of inflammatory response, reduction of uterine contractility, and luteal-phase support [2]. Particularly in early pregnancy, progesterone is responsible for preparing the endometrium for implantation and maintenance of the gestational sac in the uterus [3].

Early spontaneous abortion is a common complication during early pregnancy, and early threatened abortion occurs within the first 12 weeks of pregnancy with the incidence of about 15% [4]. The common factors which contribute to abortion are marked increase of blood glucose, thyroid dysfunction and unhealthy living habits [5]. Pregnancy hormones such as progesterone and estrogen maintain pregnancy and progesterone deficiency is an important reason for early spontaneous abortion [6]. Qing et al [7]. reported that low serum progesterone levels may be the leading cause of threatened abortion, thereby progesterone supplements are the conventional therapeutic choice for threatened abortion. The intramuscular injection of progesterone has been widely used due to its rapid onset and remarkable effect [8]. Authors emphasized the efficacy of progesterone in treatment of patients with early threatened abortion, thus oral administration of progesterone has been increasingly applied to the treatment of early threatened abortion [9].

Dydrogesterone, a progestogen that is highly selective for the progesterone receptor, lacks estrogenic, androgenic, anabolic, and corticoid properties; most studies report no significant side effects including no masculinization of the female fetus or congenital abnormalities [10]. In comparison with micronized progesterone, dydrogesterone was found to cause significantly fewer cases of drowsiness, with no differences in nausea, vomiting, giddiness, bloating, diarrhea, or headache [11].

Intramuscular progestogen is commonly associated with injection-site reactions [12]. Wang et al [13]. concluded that both the intramuscular injection and the oral administration of progesterone are effective for patients with early threatened abortion, without significant adverse effects on perinatal outcomes. As there are very little data regarding the therapeutic aspect of threatened abortion with progesterone in our country, the present study was aimed to evaluate the outcome of threatened abortion between patients receiving progesterone through oral and intramuscular route.

MATERIALS AND METHODS

This randomized clinical trial was done on 80 threatened abortion patients selected purposively in outpatient department (OPD) of Obstetrics & Gynaecology, Dhaka Medical College, Dhaka, from March 2017 to February 2018. Patients were randomly distributed into two groups of 40 patients by using a sealed envelope technique. For random allocation into groups there were two cards–one marked with 'OD' (oral dydrogesterone; group I) and another with 'IP' (intramuscular progesterone; group II). The patients in the group I received as a preliminary dose dydrogesterone 40 mg, orally, accompanied through dydrogesterone 10 mg each 12 hours. The patients in the group II received injected with

progesterone 250 mg, intramuscularly twice weekly. The progesterone levels were measured in patients before treatment and at 2 weeks after treatment.

INCLUSION CRITERIA

1. Menstruation stopped for less than 12 weeks
2. A small amount of vaginal bleeding
3. Ultrasound showed a visible gestational sac within uterus and the size was consistent with the gestational age

EXCLUSION CRITERIA

1. The pregnant women with other known pathologies (Hypothyroidism, Diabetes, Twin pregnancy, etc.)
2. The pregnant women who received any medications during the pregnancy (Thyroxin, steroid, Ovulation induction drugs, Metformin etc.)

ETHICAL CONSENT

Ethical permission was taken from the Ethical Review Committee (ERC) of Bangladesh Medical Research Council (BMRC), Dhaka. The objectives of the study along with its procedure, risk and benefits to be derived from the study was explained to the patients and then informed consent was sought from them.

STATISTICAL ANALYSIS

Statistical analysis was carried out by using the Statistical Package for Social Sciences version 22.0 for Windows. The mean values were calculated by frequencies and percentages. The quantitative observations were indicated by frequencies and percentages. Chi-Square test was used to analyze the categorical variables, and t-test used for continuous variables. P values <0.05 was considered as statistically significant.

RESULT

The mean age was 26.93±4.45 years (range from 18-35 years) in group I and 27.28±4.81 years (ranged from 18-35 years) in group II. In both groups majority were either primi gravida or second gravida. The mean gestational age was found 8.8±0.94 weeks, which ranged from 7-10 weeks in group I and 9.1±1.26 weeks, which ranged from 7-11 weeks in group II. Regarding the clinical features 38(95.0%) had scanty vaginal bleeding in group I, 37(92.5%) in group II. 32(80.0%) subjects had lower abdominal pain in group I and 25(62.5%) in group II and 13(32.2%) subjects had lower back pain in group I and 16(40.0%) in group II. Live birth observed in 38 and 37 cases in group I and group II respectively. The difference was statistically not significant (P>0.05) between two groups.

Table I: Distribution of the study subjects by parity with previous early pregnancy events.

Previous H/O spontaneous abortion, MR/MRM and threatened abortion	Group-I (n=40)		Group-II (n=40)		p value
	n =13	%	n =14	%	
Previous H/O spontaneous abortion					
Para (0)					
No H/O abortion	17	42.5	17	42.5	0.478[a]
H/O abortion	8	20	5	12.5	

Para (One)					
No H/O abortion	9	22.5	5	12.5	0.179[a]
H/O abortion	5	12.5	8	20.0	
Para (Two)					
No H/O abortion	1	2.5	4	10.0	0.624[a]
H/O abortion	0	0	1	2.5	
Previous H/O MR/MRM	n =3		n=5		
Para (0)					
No H/O MR/MRM	23	57.5	17	42.5	0.157[a]
H/O MR/MRM	2	5.0	5	12.5	
Para (One)					
No H/O MR/MRM	13	32.5	13	32.5	0.326[a]
H/O MR/MRM	1	2.5	0	0.0	
Para (Two)					
No H/O MR/MRM	1	2.5	5	12.5	0.102[a]
H/O MR/MRM	-	-	-	-	
Previous H/O threatened abortion	n=12		n=12		
6 weeks	1	2.5	1	2.5	
7 weeks	4	10	4	10	
8 weeks	1	2.5	2	5	
9 weeks	1	2.5	4	10	
10 weeks	3	7.5	1	2.5	
12 weeks	2	5	0	0	
No H/O	28	70	28	70	
Mean±SD	5.00±4.72		9.17±4.78		0.002[b]
Range (min-max)	0-12		6-24		

[a]*p*-value reached from Chi-square test, [b]*p*-value reached from unpaired t-test
Group I: Receive oral progesterone
Group II: Receive intramuscular progesterone

Table II: Distribution of the study subjects by level of progesterone before and after 14 days receiving treatment (ng/ml) (n=80)

Level of progesterone	**Group-I (n=40)**	**Group-II (n=40)**	**p value**
	Mean±SD	**Mean±SD**	
Before treatment received			
Progesterone level (ng/ml)	51.08±7.3	55.16±43.9	0.563[ns]
Range (min-max)	30.7-60.4	29.9-32.38	
After 14 days treatment received			
Progesterone level (ng/ml)	75.0±9.66	73.81±9.44	0.579[ns]
Range (min-max)	34.8-82.1	34.97-80.1	

ns= not significant, p-value reached from unpaired t-test

Table III: Distribution of the study subjects by pregnancy status (n=80)

Pregnancy status	Group-I (n=40)		Group-II (n=40)		p value
	n	%	n	%	
Aborted					0.882ns
Spontaneous complete	2	5	2	5	
Spontaneous incomplete	0	0	1	2.5	
Preterm delivery					
28-31 weeks	1	2.5	1	2.5	
32-36 weeks	4	10	5	12.5	
Continued till term	33	82.5	31	77.5	

ns= not significant, *p*-value reached from Chi-square test

Note: In group I, it was observed that total number of abortion was 2, which become aborted at 12 weeks and 15 weeks respectively and duration of treatment was 3 weeks and 7 weeks, in group II total number of abortion was in 3, which occur in 14 weeks and 12 weeks and duration of treatment was 3 weeks and 2 weeks respectively.

Table IV: Distribution of the study subjects by gestational age at delivery (n=75)

	Group-I (n=38)	Group-II (n=37)	p value
	Mean±SD	Mean±SD	
Gestational age at delivery (weeks)	37.45±1.94	37.08±2.14	0.435ns
Range (min-max)	28-41	28-40	

ns= not significant
p-value reached from unpaired t-test

Table V: Distribution of the study subjects by side effect (n=80)

Side Effect	Group-I (n=40)		Group-II (n=40)		p value
	n	%	n	%	
Nausea	20	50.0	15	37.5	0.259ns
Sleepiness	1	2.5	2	5.0	0.556ns
Headache	7	17.5	1	2.5	0.025ns
Lower abdominal Pain	1	2.5	0	0.0	0.314ns
Heaviness	5	12.5	1	2.5	0.089ns
Constipation	12	30.0	6	15.0	0.108ns
Pedal oedema	10	25.0	14	35.0	0.329ns
Pain at the site of injection					
Yes	0	0.0	40	100.0	0.001s
NA	40	100.0	0	0.0	
Induration formation at the site of injection					
No	0	0.0	33	82.5	0.001s

Yes	0	0.0	7	17.5	
NA	40	100.0	0	0.0	

ns= not significant
p-value reached from Chi-square test

DISCUSSION

Dydrogesterone (oral) and various progesterone given orally, vaginally and intramuscularly are the most commonly used drugs for the treatment of recurrent and threatened miscarriages**.** Insufficient secretion of progesterone in early pregnancy has been linked to aetiology of miscarriage and to prevent spontaneous pregnancy loss.[14] Several studies have been developed to understand the use of progestogens for the treatment of threatened and recurrent miscarriage.

The mean age of the present study was consistent with the study of Kant et al [15]. which showed 50.0% of the patients were in the age group of 35-39 years with mean age being 29.2±3.6 years, which is similar with the present study. On the other hand, in another study Chan et al [16]. found mean age was 31.3±4.3 years and 30.8±4.3 years in group I and group II respectively, which is higher with the present study, which may be due to geographical variations, racial, ethnic differences, and genetic causes.

Sadaf et al [17]. enrolled maximum parity 3 with mean parity of all study was 0.87+0.97 in patients treated with oral Dydrogesterone and Intramuscular Progesterone. Similar findings also observed by Elgergawy et al. in their respective studies [18].

Low maternal serum progesterone in the presence of detectable levels of HCG significantly indicates a risk of miscarriage regardless of gestational age [19]. Yassaee et al [20]. study showed average gestational age was 9 weeks±3 days in group I and 10 weeks±3 days in group II, which are almost similar with the present study.

Threatened abortion, a pregnancy complicated by vaginal bleeding and/or lower abdominal pain, is one of the most common pregnancy complication, which occurs in approx. 20.0% of pregnancies [21]. Norwitz and Park [22]. mentioned in their report that women with ongoing pregnancies, vaginal bleeding may be due to disruption of decidual vessels at the maternal-fetal interface. Threatened miscarriage affects 15-20% of all pregnancies and is a risk factor for adverse pregnancy outcomes including preeclampsia, pre-term delivery, intrauterine growth restriction, preterm premature rupture of membranes and placental abruption [23]. The abdominal pain may present as intermittent cramps, suprapubic pain, pelvic pressure, or lower back pain [24].

In this study it was observed that the mean level of progesterone before and after receiving treatment was almost alike between two group, no statistical significant ($p>0.05$) difference was observed. Greater part of women who have defective ovum or in whom threatened abortion effects in total abortion have serum progesterone levels of less than 20 ng/ml [25]. Progestogen supplementation has been used as treatment for threatened miscarriage to prevent spontaneous pregnancy loss [26]. Li et al. showed the use of oral progestogen reduced risk of miscarriage and increased live birth rate [27]. In another study done by Kalinka et al [28]. study showed there was a significant increase in Progesterone Induced Blocking Factor (PBFI) levels in women treated with dydrogesterone, thereby increasing pregnancy success rates. A double blind study of 54 women

Czajkowski et al [29]. reported a miscarriage rate of 8.3% with dydrogesterone (30 mg/day for 6 weeks) compared with 14.0% with vaginal micronised progesterone (300 mg/day for 6 weeks). Spontaneous abortion occurs in less than 30.0% of the women who experience threatened abortion [30]. In this present study it was observed live birth found 95.0% and 92.5% in progesterone through oral and intramuscular group respectively.

The dydrogesterone tablets are convenient to take with fewer adverse reactions, which helps to improve patient compliance in the long-term treatment of threatened abortion. A review of maternal use of dydrogesterone during pregnancy also found no evidence for an increased risk of congenital malformations [31].

Regarding the side effect, it was observed in this study that 50.0% subjects had nausea in group I and 37.5% in group II. Eight patients in the progesterone group had injection site pain, of whom 6 developed an induration, which was alleviated bylocal hot compress and the patients continued to receive treatment. The routine examinations such as hepatorenal function and blood urine showed no major abnormalities in both groups of patients. The vaginal route of progesterone supplementation possesses several advantages over the intramuscular approach, including fewer side effects, less pain and better compliance besides its lower serum level but increased progesterone level in the uterine endometria [32]. There is no reported evidence of major side-effects associated with the treatment of vaginal progesterone, apart from headache and nausea.[33]

CONCLUSION

Dydrogesterone and injectable progesterone both are almost equally effective to continue the pregnancy. Oral dydrogesterone also convenient to take orally, with good tolerability and compliance and no significant adverse drug reactions. Therefore, dydrogesterone could play a significant role as a therapeutic option in patients with threatened abortion.

RECOMMENDATIONS

Further research want to be carried out to assess the underlying pathophysiology of low progesterone and miscarriage and also take a look at the position of progestogens with inside the control of ladies with threatened miscarriage

LIMITATION

This study has some limitations include small sample size, only one centre study, short duration of study period, blinding could not be done due to one group get oral and other group get I/M injection as well as 25 patients dropped out, due to USG findings of 8 patients were not corresponds with the period of amenorrhea, spontaneous complete abortion was occur in 7 patients who came with moderate vaginal bleeding, 6 of them were distance resident and 4 patients were not interested to include in the study.

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