Original research article

Comparison between Dydrogesterone and micronized Progesterone on threatened abortion- A Prospective Observational Study

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Abstract

Background: Threatened abortion is defined as *"pregnancy-related bloody vaginal discharge or frank bleeding without cervical dilatation during the first half of pregnancy.* Progesterone also called 'pregnancy hormone' is prescribed among pregnant women with threatened abortion as it plays a critical role in the maintenance of pregnancy. **AIM:** This study aimed at comparing the clinical effectiveness of dydrogesterone and micronized Progesterone in continuing pregnancy among pregnant women diagnosed with threatened abortion. **Material and Methods**: This was a single Centre, hospital-based, prospective observational study conducted at LN Medical College, Bhopal, for a duration of 24 months. The present study enrolled a total of 143 pregnant women: 97 women with threatened abortion were given 40 mg Dydrogesterone stat followed by 20-30mg daily, continued for one week after stopping bleeding and 46 women were given micronized Progesterone 400 mg per day vaginally, continued until the end of vaginal bleeding. **Results:** Bleeding stopped in significantly higher proportions of patients of the dydrogesterone group (80.4%) as compared to 65.2% cases of micronized progesterone group (p= 0.032). The mean duration of bleeding after giving the drug in the dydrogesterone group was 3.58 (±1.44) days in comparison to micronized progesterone group it was 4.48(±1.60) days. Continuation of pregnancy 15 days after the initiation of bleeding was found in 80.4% of cases in the dydrogesterone group as compared to micronized progesterone group (67.4%) (p= 0.072). Dizziness and Bloating were noted in 10.33% and 7.2% cases respectively in the dydrogesterone group. Whereas dizziness, headache and breast heaviness were noted in 10.9%, 2.2% and 2.2% cases respectively in micronized progesterone group. The observed difference in side effects between the two groups was statistically insignificant (p>0.05). **Conclusion:** Both dydrogesterone group and micronized progesterone are effective in threatened abortion. Dydrogesterone has lesser side effects when compared to natural micronized progesterone.

Introduction

Abortion, also called miscarriage, is defined as the extraction or expulsion of an embryo or fetus (weighing less than 500 grams) from the mother when it is not capable of independent survival i.e., before 20 weeks of gestation(1). Miscarriage or abortion may be of the following types- missed, threatened, inevitable, incomplete, complete, and septic abortion(1). Missed abortion refers to the expulsion of tissue or products of conception peri-vaginally along with vaginal bleeding. However, threatened abortion refers to vaginal bleeding in presence of via able fetus and closed cervical os(2).

According to World Health Organization, threatened abortion is defined as *"pregnancy-related bloody vaginal discharge or frank bleeding without cervical dilatation during the first half of pregnancy"*(3). Literature suggests that approximately one-fourth of women present with some degree of vaginal bleeding during the first and second trimesters of pregnancy(4). Half may progress to pregnancy loss. The exact etiology of threatened abortion is unknown but it has been associated with certain risk factors such as advanced maternal age, previous history of miscarriage, maternal thrombophilia, maternal obesity or underweight, antiphospholipid antibody syndrome, and maternal hypertension(2,5). Other maternal risk factors associated with high risk of miscarriage include cigarette smoking, malnutrition and trauma. The causes are unexplained in approximately 50% of the cases presenting with threatened abortion(5,6).

Progesterone is prescribed in women with threatened abortion as this "pregnancy hormone" plays an important role in the maintenance of pregnancy(7,8). During early pregnancy, this hormone prepares the endometrium for implantation and acts as an immunomodulator i.e. modulates maternal immune response and suppresses anti-inflammatory response(7,8). Also, progesterone reduces uterine contractility, provides luteal phase support and improves uteroplacental circulation(7,8). The immune tolerance of the mother for the developing fetus is one of the major factors determining fetal survival.

Synthetic progesterone may be given by various routes such as oral, vaginal, rectal or parenteral. Since oral progesterone undergoes substantial first-pass metabolism, its bioavailability is less, approximately 10%(9). Two progesterone-containing drugs namely natural (micronized) progesterone and dydrogesterone has been approved by FDA for use in threatened abortion(10–12). Both these drugs are related closely to endogenous progesterone with respect to their pharmacological properties and molecular structure. In micronized progesterone, the average diameter of progesterone particles is reduced by the process of micronization. Dydrogesterone, on the other hand, is 6-dihydro-retro progesterone, which has a high affinity for progesterone receptors and no affinity for estrogenic, androgenic, mineralocorticoid as well as glucocorticoid receptors(13). The oral bioavailability of Dydrogesterone is documented to be higher as compared to micronized progesterone. Also, Dydrogesterone is reported to have less adverse effects as compared to other progesterone preparations(14). The primary aim of the current study was to compare the clinical effectiveness of dydrogesterone and micronized Progesterone in pregnant patients diagnosed with threatened abortion and also to evaluate and compare the fetal outcome.

MATERIALS AND METHODS

Study Settings: Antenatal clinic, LN Medical College and J.K. Hospital Bhopal
Study Duration: 24 months, i.e. from 1st July 2020 to 30th July 2022.
Study design- Prospective observational study.
Study area- Antenatal clinic, LN Medical College and J.K. Hospital Bhopal.
Sample size- All pregnant women with symptoms of threatened abortion coming to Antenatal clinic during the study period were enrolled using convenient sampling.
Study population- pregnant women with symptoms of threatened abortion. **INCLUSION CRITERIA:** (i) All pregnant women with ≤ 20 weeks pregnancy with symptoms of threatened abortion; (ii) All pregnant patients giving consent. **EXCLUSION CRITERIA:** (i) multiple gestation; (ii) preexisting medical or surgical conditions; (iii) absence of a normal gestational sac in 5th week, the absence of fetus at the 6th weeks of gestation, and absence of heart activity in 7th weeks of pregnancy; (iv) women with congenital uterine anomalies and (v) History of trauma.

Informed Consent: Written consent was obtained from all the study participants after explaining them nature and purpose of study. They were ensured that confidentiality will be maintained and options to withdraw from the study was always kept open.

Data Collection: All the females were subjected to thorough history taking. Sociodemographic history was obtained in detail including name, age, socioeconomic status, occupation, residence, contact details using proforma. Presenting complaints, obstetric history, past history, menstrual history, history of threatened abortion, booking status, immunization etc. was obtained and documented. All the females were then subjected to detailed general, systemic and obstetric examination. All patients will be hospitalized and following investigations were done: Blood group and RH typing, Complete blood picture, Urine routine microscopy, Urine culture sensitivity, Thyroid profile, Fasting blood glucose, Serology, HIV, HBsAg, VDRL, HCV, and USG Obstetrics.

Study Groups: All the females were allocated in either of the two groups based upon the clinical acumen of consultants. The recommended standard drug dose was followed.

- Group I (Dydrogesterone group) received 40 mg Dydrogesterone stat followed by 20-30mg daily, continued for one week after stopping bleeding.
- Group II (Progesterone group) was given micronized Progesterone 400 mg per day vaginally and was continued until the end of vaginal bleeding.

Then after completing the course of the drug, patients were called for follow up after 15 days in the ANC OPD for assessment and repeat ultrasonography was advised to look for the Continuation of pregnancy 15 days after the initiation of bleeding of the pregnancy. Data Analysis: Data was compiled using MS Excel and analyzed using IBM SPSS software version 20. Categorical variables were expressed as frequency and proportion whereas continuous/ numerical variables were represented as mean and standard deviation. Two groups were compared with respect to baseline variables and pregnancy outcomes using Chi square test. P value of less than 0.05 was considered statistically significant.

Results:

A total of 143 women was enrolled- 97 pregnant women were given Dydrogesterone and the remaining 46 women were given micronized progesterone. Most of the participants in both groups were between 21-30 years of age. The mean age of patients of the Dydrogesterone group was 26.16±3.83 years whereas the mean age of patients of micronized progesterone group was 27.67±3.84 years (p= 0.073).

In present study, 56.7% of the pregnant women who received dydrogesterone were primigravida and 47.4% women were primiparous. History of abortion was present in 49.5% cases, and of them, history of two or more abortions were noted in 10.3% cases. History of 1 and 2 live children was present in 48.5% and 9.3% cases respectively whereas history of death of child after birth was reported in 1 case. Majority of pregnant women in micronized progesterone group were primigravida (67.4%) and 54.3% women were nulliparous. History of abortion was present in 23.9% cases and history of 1 and 2 live children was present in 19.6% and 26.1% cases respectively. History of death of child after birth was reported in 17.4% cases

Table 1: Descriptive characteristics of the participants

	Dydrogesterone (n=97)	Micronized progesterone (n=46)	P-value

	Frequency	Percentage	Frequency	Percentage	
Age					
≤20	9	9.3	3	6.5	
21-30	69	71.1	32	69.6	
>30	19	19.6	11	23.9	
Mean	26.16±3.83		27.67±3.84		0.073
Gravida					
1	55	56.7	31	67.4	0.371
2	25	25.77	7	15.21	
3	10	10.3	3	6.52	
≥4	7	7.2	5	10.9	
Parity					
0	41	42.3	25	54.3	0.078
1	46	47.4	3	6.5	
2	10	10.3	13	28.3	
≥3	0	0	5	10.9	
Livebirth					
0	41	42.3	25	54.3	0.093
1	47	48.5	9	19.6	
2	9	9.3	12	26.1	
Abortion					
0	49	50.5	35	76.1	0.083
1	38	39.2	11	23.9	
2	3	3.1	0	0	
≥3	7	7.2	0	0	
Died					
0	96	99.0	38	82.6	0.075
1	1	1.0	3	6.5	
2	0	0	5	10.9	
History of Threatened Abortion					
No	82	84.5	41	89.1	0.068
Yes	15	15.5	5	10.9	

Table 2: Details of the Index Pregnancy

Period of gestation	**Dydrogesterone (n=97)**		**Micronized progesterone (n=46)**		**P-value**
	Frequency	**Percentage**	**Frequency**	**Percentage**	
5 to 8 weeks	41	42.3	27	58.7	-

8-12 weeks	36	37.1	10	21.7	
>12 weeks	20	20.6	9	19.6	
Mean	9.6 (1.2)		9.2(1.3)		0.0720
Duration of Bleeding (Days)					
Mean (SD)	3.58 (1.44)		4.48 (1.60)		0.001
Stoppage of Bleeding					
No	19	19.6	16	34.8	0.048
Yes	78	80.4	30	65.2	
Continuation of pregnancy 15 days after the initiation of bleeding					
Yes	78	80.4	31	67.4	0.088
No	19	19.6	15	32.6	
Duration of Hospital Stay					
Mean (SD)	5.52 (1.9)		5.17 (1.6)		0.2818

Majority of pregnant women who received dydrogesterone presented in 5 to 8 weeks of gestation with threatened abortion (42.3%), followed by 37.1% and 20.6% pregnant women belonging to 8 to 12 weeks and more than 12 weeks of gestation respectively. Majority of pregnant women with threatened abortion who received micronized progesterone presented in 5 to 8 weeks of gestation (58.7%), followed by 21.7% and 19.6% pregnant women belonging to 8 to 12 weeks and more than 12 weeks of gestation respectively. The difference in the mean gestational age among the participants in the two groups was statistically not significant (p=0.0720). Mean duration of bleeding in dydrogesterone group was 3.58±1.44 days, whereas that in micronized progesterone group was 4.48±1.60. Bleeding duration was significantly prolonged in micronized progesterone group (p =0.001).

In present study, bleeding stopped in significantly higher proportions of patients of dydrogesterone group (80.4%) as compared to 65.2% cases of micronized progesterone group (p =0.048). Continuation of pregnancy 15 days after the initiation of bleeding was found in 80.4% cases in dydrogesterone group as compared to micronized progesterone group (67.4%), however, the observed difference was statistically insignificant (p= 0.088). Though mean duration of hospital stay was higher in dydrogesterone group as compared to micronized progesterone group, we observed no significant difference in duration of hospital stay between the groups (p=0.38).

Table 3: Comparison of side effects between two groups

	Dydrogesterone (n=97)		Micronized progesterone (n=46)		P-value
	Frequency	Percentage	Frequency	Percentage	
Bloating	7	7.2	0	0	0.062
Dizziness	10	10.33	5	10.9	0.919
Breast heaviness	0	0	1	2.2	0.145

Headache	0	0	1	2.2	0.145
Bloating and headache	0	0	1	2.2	0.145
Dizziness and breast heaviness	0	0	1	2.2	0.145
None	84	86.6	37	80.4	0.340

In our study, Dizziness and Bloating were noted in 10.33% and 7.2% cases respectively in dydrogesterone group. Whereas dizziness, headache and breast heaviness were noted in 10.9%, 2.2% and 2.2% cases respectively in micronized progesterone group. The observed difference in side effects between two groups was statistically insignificant ($p>0.05$).

Discussion:

Threatened abortion refers to vaginal bleeding during early pregnancy, often accompanied by cramping or mild abdominal pain, but with the cervix closed and the pregnancy still viable(2). The experience of threatened abortion can be distressing for women and may have an impact on their mental health. The outcome of threatened abortion varies depending on the underlying cause and the severity of the symptoms(5,8). In some cases, the bleeding and cramping may resolve on their own, and the pregnancy may continue without further complications. However, in other cases, threatened abortion may progress to a miscarriage(5,7,8).

The risk of miscarriage varies depending on the gestational age at which the bleeding occurs. According to some studies, the risk of miscarriage is around 10-20% in women who experience bleeding during the first trimester of pregnancy. However, other factors, such as the presence of a fetal heartbeat and the size of the gestational sac, may also influence the risk of miscarriage. Treatment may include rest, avoidance of strenuous activity, and medications to reduce the risk of infection or to manage pain or bleeding(15). It is also important for healthcare providers to provide emotional support and counseling to women who experience threatened abortion, as the experience can be distressing and may have an impact on mental health(15). With appropriate care and management, many women who experience threatened abortion can go on to have successful pregnancies.

Research has shown that women who experience threatened abortion may have higher levels of anxiety, depression, and post-traumatic stress disorder (PTSD) symptoms compared to women who do not experience vaginal bleeding during pregnancy(5). This may be due to the uncertainty and fear associated with threatened abortion, as well as concerns about the potential loss of the pregnancy. It is important for healthcare providers to provide support and reassurance to women experiencing threatened abortion, as well as to monitor their mental health and offer appropriate interventions if necessary(16,17). This may include counseling, therapy, or medication if indicated. It is also important to note that the impact of threatened abortion on mental health may be influenced by a range of factors, including the woman's individual coping mechanisms, social support, and overall mental health status prior to the pregnancy. In the present study we analyzed the clinical effectiveness of dydrogesterone and micronized progesterone among pregnant women diagnosed with threatened abortion.

In the present study, vaginal bleeding stopped in 80.4% of cases following dydrogesterone and the mean duration of bleeding was 3.58±1.44 days, whereas bleeding stopped in 65.2%

of cases following micronized progesterone, with a mean duration of 4.48±1.60 days. The bleeding stopped significantly earlier and in higher proportions of patients belonging to the dydrogesterone group as compared to micronized progesterone group in our study ($p<0.05$).

The findings of the present study were concordant with the findings of **Verma S et al (2020)**, in which the bleeding stopped following dydrogesterone in significantly higher proportions of cases (93.7%) as compared to 79.4% cases in micronized progesterone group ($p<0.05$)(18). Our study findings were supported by the findings of **Lou C et al (2021),** in which mean hemostasis time in dydrogesterone group was higher (3.79±1.06 days) as compared to micronized progesterone group (3.87±1.21 days), but the difference was not statistically significant ($p>0.05$)(19). **Siew JY et al (2018)** in another study found no significant difference in the rate of bleeding control between patients managed on micronized progesterone and dydrogesterone ($p>0.05$)(20). **Siew S et al (2015)** in their study reported no significant difference in two treatment arms in the extent of bleeding with similar, less or complete resolution of bleeding by 4 to 10 days after taking treatment ($p>0.05$)(21). **Qing G et al (2015)** included 172 cases of threatened abortion, who presented with bleeding and the mean duration of treatment, probably reflecting the control of bleeding to be 7.2 ± 3.5 days in dydrogesterone group and 8.0 ± 3.2 days in Progesterone group(22).

The mean duration of bleeding in a study of **Srivastava M et al (2018) was** 2.61±1.50 days in dydrogesterone group and 2.70 ±1.6 days in progesterone group, and the difference was statistically insignificant ($p>0.05$)(23).

We assessed the outcome in both groups in terms of continuation of pregnancy 15 days after initiation of bleeding. The outcome favorable in higher proportions of cases following dydrogesterone (80.4%) as compared to micronized progesterone group (67.4%), but the difference was statistically insignificant ($p>0.05$). Our study findings were supported by the findings of **Shaikh R et al (2022)**, in which the authors documented the efficacy of Micronized Progesterone and Dydrogesterone treatments for threatened abortion to be similar in terms of stoppage of bleeding, however, the rate of side effects were significantly higher in women managed with Micronized Progesterone(24). **Lou C et al (2021)** in their study reported the success rate of dydrogesterone for preventing miscarriage to be 87.22% and that of progesterone group was 86.13%, with no significant difference between the groups ($p>0.05$)(19).

Limitations:

The maximum duration of follow up was one month, thus, we could not assess the outcome of the pregnancy in terms of maternal and fetal outcomes. In addition, we could not ascertain the development of any morbidities during the antenatal period among the participants.

Conclusion:

Both dydrogesterone group and micronized progesterone are effective in threatened abortion. Dydrogesterone has lesser side effects when compared to natural micronized progesterone

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