Original Article

Role of Micronized Progesterone Versus Dydrogestron in Patients with Threatened Abortion

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Abstract

Objective: To compare the efficacy of Micronized Progesterone versus Dydrogestron in patients with Threatened Abortion.
Methodology: This Randomized Controlled Trial study was conducted in outpatient department of Obstetrics and Gynaecology, Sheikh Zayed Women CMC Hospital Larkana, from January 2021 to September 2021. A total of 140 patients with age ranging from 20 to 45 years, presented with signs of threatened abortion before 20 weeks of gestation, having single intrauterine pregnancy based on ultrasound findings, presenting with vaginal bleeding were enrolled for the study. Demographic information including patient number, name, age, gestational age, body mass index, history of previous miscarriages, duration of bleeding, extent of bleeding at presentation and after treatment and side effects (nausea, vomiting, giddiness, bloating, diarrhea and headache). The miscarriage rate until 24 weeks of gestation was noted. All this information was recorded on a predesigned performa.
Results: The mean age of Micronized Progesterone group (28.65 ± 5.2) was similar to Dydrogestron group (29.35 ± 4.85). There was no significant (P-value > 0.05) difference between both groups on the basis of gestational age (7.52 ± 3.2 vs. 7.25 ± 3.4), body mass index (23.4 ± 3.6 vs. 22.9 ± 3.2) and previous miscarriage rate (68.57% vs. 61.43%). Post treatment extent of bleeding was almost comparable in both groups. The rate of drowsiness (61.43% vs. 31.43%) and giddiness (22.86% vs. 8.57%) was significantly (P-value < 0.05) higher in Micronized Progesterone group as compared to Dydrogestron group. The side effects of nausea and abdominal bloating were similar in both treatment groups.
Conclusions: Micronised Progesterone and Dydrogesterone treatments showed similar efficacy in the treatment of threatened miscarriage. Although the rate of side effects was significantly higher in women treated with Micronised Progesterone.
Key words: Vaginal bleeding, Micronised Progesterone, Dydrogesterone, Threatened Abortion

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Introduction

Miscarriage, defined as the spontaneous loss of a pregnancy before 24 weeks gestation, is common, with about 25% of women experiencing one at some point in their life and 15% to 20% of pregnancies ending in miscarriage. Miscarriage is a frequent pregnancy problem that can have serious physical and psychological consequences.[1] Vaginal bleeding with or without abdominal pain is a sign of threatened miscarriage. While the cervix is closed and the foetus remains viable inside the uterine cavity. Unfortunately, half of the threatened abortion pregnancies ended in miscarriage, which had a significant psychological impact on women and their families. Physiological studies have revealed that progesterone is involved in a variety of actions, ranging from preimplantation to the entire pregnancy, including endometrium transfer and decidualization, regulation of extravillous trophoblast invasion, control of uterine contractions, protection of the

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semi-allogenic foetus from the mother's immune system, and so on[2,3]

Three or more consecutive pregnancy losses within 20 weeks of gestation are considered recurrent spontaneous miscarriage. In about half of these patients, the aetiology of the illness is unknown.[4]

In pregnant women who are facing a miscarriage risk, progesterone medication, particularly oral dydrogesterone, can successfully prevent miscarriage. By boosting uterine quiescence, progesterone helps to keep a pregnancy progressing. The syncytiotrophoblast produces and releases human chorionic gonadotropin (hCG) during early pregnancy, which increases progesterone synthesis in the corpus luteum by inhibiting this tissue's regression. Progesterone is directly released by the syncytiotrophoblast after seven to nine weeks of pregnancy. Abortions in the first trimester may be predicted by low hCG or progesterone levels in the blood. Progesterone levels were lower in individuals who experienced a second miscarriage during early pregnancy in women who had been threatened with abortion than in those whose pregnancies progressed to foetal viability. Furthermore, progesterone receptor antagonists may cause miscarriage or labour during pregnancy by increasing myometrial contractility and excitability.[5,6]

Progesterone is an essential pregnancy hormone that contributes in the continuation of the pregnancy. Women with early pregnancy bleeding have been treated with a number of progesterone-like medications. They're also used to prevent miscarriage in women who have had miscarriages previously. The efficiency, safety, and side effects of available progestogens for avoiding miscarriage in these various categories of women are unknown.[7,8]

Early pregnancy supplementation with various progestogens has been explored to maintain a pregnancy in women who are experiencing early pregnancy bleeding (threatened miscarriage) and to prevent miscarriages in asymptomatic women who have had three or more previous miscarriages (recurrent miscarriage).[9] In a study by Siew JYS et al, it was noted that there was no statistically significant difference between micronized progesterone group and dydrogesterone group with respect to miscarriage rate (10.2% vs. 15.2%, p-value=0.581), rate of complete resolution of bleeding (89.7% vs 96.6%; p=0.272) and different side effects (nausea, vomiting, giddiness, bloating, diarrhea and headache) except drowsiness which was found significantly higher in micronized progesterone group as compared to dydrogesterone group.[10]

The use of both micronized progesterone and dydrogesterone is common with significantly improved outcomes as compared with placebo trials but the data on direct comparison of micronized progesterone with dydrogesterone is not available in our population. So, this present study has been planned to compare both of these treatments based on clinical outcome and safety profile in our population.

Methodology

This randomized controlled trial study was conducted in outpatient department of Obstetrics and Gynaecology, Sheikh Zayed Women CMC Hospital Larkana, from January 2021 to September 2021. The patients presenting with threatened miscarriage were enrolled for the study. The study was started after taking necessary ethical approval from hospital ethical committee. All the patients were briefly described about the purpose of the study and informed written consent was taken.

A total of 140 patients with recurrent miscarriage were included in the study and were divided into two equal groups of 70 patients each. The sample size was calculated by using WHO sample size calculator taking level of significance 10%, Power of test = 80%, Anticipated population proportion (rate of no change in bleeding in Micronized progesterone group) 5%, and (rate of no change in bleeding in dydrogestrone group) 13.6% were used.[10] The patients with age ranging from 20 to 45 years, presented with signs of threatened abortion before 20 weeks of gestation, having single intrauterine pregnancy based on ultrasound findings, presenting with vaginal bleeding were enrolled for the study. Patients who had an unavoidable miscarriage, had used progestogen in the previous pregnancy, had a history of recurrent miscarriages, or were pregnant using assisted reproductive technology were excluded from the trial.

Using computer-generated random numbers, all of the patients were divided into two equal groups. The patients in Micronized Progesterone group received oral micronized progesterone 200 mg twice a day for two weeks and the patietns in Dydrogestron group received dydrogestrone 10mg twice a day for two weeks. This is the standard treatment dose for threatened abortion by the manufacturer.

Demographic information including patient number, name, age, gestational age, body mass index, history of previous miscarriages, duration of bleeding, extent of bleeding at presentation and after treatment and side effects (nausea, vomiting, giddiness, bloating, diarrhea and headache). The miscarriage rate till 24 weeks of gestation was noted. All this information was recorded on a predesigned performa.

The collected data was entered and analyzed with SPSS v. 25. Descriptive statistics were used to calculate mean and standard deviation for quantitative data along with independent sample t-test and frequency with percentages for qualitative data along with chi-square test. A p-values of ≤ 0.05 was taken as significant.

Results

In this randomized controlled trial study a total of 140 patients were included, consisting on 70 patients in each group. Micronized Progesterone group, received Micronized Progesterone and Group B, received Dydrogesterone. The mean age of Micronized Progesterone group (28.65 ± 5.2) was similar to Dydrogestron group (29.35 ± 4.85) having no significant (P-value > 0.05) difference between both groups. There was no statistically significant (P-value > 0.05) difference between both groups based on gestational age (7.52 ± 3.2 vs. 7.25 ± 3.4) and body mass index (23.4 ± 3.6 vs. 22.9 ± 3.2). Similarly, no significant (P-value > 0.05) difference was observed between both groups on the basis of previous miscarriage. Majority of the patients in both groups (68.57% vs. 61.43%, P-value > 0.05) had no history of miscarriage. The mean duration of bleeding was recorded almost similar (P-value > 0.05) between both groups with mean value of 2.6 ± 1.6 days in Micronized Progesterone group and 2.9 ± 1.5 days in Dydrogestron group. Majority of the patients (87.14%) in Micronized Progesterone group and (81.43%) in Dydrogestron group, presented with spotting at the time of presentation but there was no statistically significant (P-value > 0.05) difference between both groups as elaborated in table I.

The distribution of extent of bleeding shows that overall response of both drugs was similar with both treatment modalities and the post treatment extent of bleeding was almost comparable in both groups without any statistical significant (P-value > 0.05) difference as elaborated in table II.

Table II: Comparison of Extent of bleeding after treatment between both patients

Characteristics	Micronised Progesterone group		Dydrogesterone group		P-value
	N	%	N	%	
Increased	8	11.43	3	4.29	0.314
Similar	5	7.14	8	11.43	
Reduced	17	24.29	14	20.00	
Resolved Completely	40	57.14	45	64.29	

The comparison of side effects showed that the rate of drowsiness was significantly (P-value < 0.05) higher in Micronized Progesterone group, (61.43% vs. 31.43%) as compared to Dydrogestron group. The rate of giddiness was also noted significantly (P-value < 0.05) higher in Micronized Progesterone group (22.86%) as compared to Dydrogestron group (8.57%). The side effects of nausea and abdominal bloating were similar in both treatment groups having no statistically significant (P-value > 0.05) difference between both groups as elaborated in table III.

Table I: Distribution of Demographic Characteristics of the patients

Characteristics	Micronised Progesterone group		Dydrogesterone group		P-value
	N	%	N	%	
Age of the patients					
Mean ± SD	**28.65 ± 5.2**		**29.35 ± 4.85**		0.412
Gestational Age					
Mean ± SD	**7.52 ± 3.2**		**7.25 ± 3.4**		0.629
Body Mass Index					
Mean ± SD	**23.4 ± 3.6**		**22.9 ± 3.2**		0.387
History of previous miscarriage					
None	48	68.57%	43	61.43%	0.675
One	13	18.57%	16	22.86%	
Two	9	12.86%	11	15.71%	
Duration of bleeding					
Mean±SD	2.6 ± 1.6		2.9 ± 1.5		0.240
Extent of bleeding at presentation (days)					
Spotting	61	87.14%	57	81.43%	0.353
Wet pad	9	12.86%	13	18.57%	

Table III: Comparison of Treatment Side effects between both groups.

Characteristics	Micronised Progesterone group		Dydrogesterone group		P-value
	N	%	N	%	
Drowsiness					
Yes	43	61.43%	22	31.43%	0.000
No	27	38.57%	48	68.57%	
Giddiness					
Yes	16	22.86%	6	8.57%	0.020
No	54	77.14%	64	91.43%	
Nausea					
Yes	18	25.71%	24	34.29%	0.268
No	52	74.29%	46	65.71%	
Abdominal bloating					
Yes	11	15.71%	13	18.57%	0.654
No	59	84.29%	57	81.43%	

Discussion

When the cervix is closed and there is a living embryo or foetus inside the womb, common signs of threatened miscarriage include vaginal bleeding with or without abdominal pain. Progesterone stimulates the uterus in preparing for the fertilized egg's implantation and controls uterine contractions until the infant is delivered. Progestogens are drugs that counteract the effects of progesterone. Many studies back up the findings that progesterone is effective in preventing miscarriage in women who are at risk. The use of progesterone, significantly enhances the chance of success full delivery (91% vs. 73%) as compared to control group.[11]

By promoting uterine quiescence, progesterone helps to keep a pregnancy continue. The syncytiotrophoblast secretes human chorionic gonadotropin (hCG) during early pregnancy, which increases progesterone synthesis in the corpus luteum by inhibiting this tissue's regression. Progesterone is directly released by the syncytiotrophoblast after seven to nine weeks of pregnancy. Low levels of hCG or progesterone in the blood can indicate abortions in the first trimester.[12]

Progesterone treatment was found to be beneficial in avoiding miscarriages in pregnant women who were at risk of abortion in a meta-analysis. Although there was no difference in treatment efficacy of miscarriage between oral and vaginal progestational agents in pregnant women with threatened abortion, oral dydrogesterone prevented miscarriage in pregnant women more effectively than the control-treated groups.[13]

According to the results of this present study, it was noted that the mean age of Micronized Progesterone group (28.65 ± 5.2) was similar to Dydrogestron group (29.35 ± 4.85). There was no statistically significant (P-value > 0.05) difference between both groups on the basis of gestational age (7.52 ± 3.2 vs. 7.25 ± 3.4), body mass index (23.4 ± 3.6 vs. 22.9 ± 3.2) and rate of none previous miscarriage (68.57% vs. 61.43%, P-value > 0.05). These results were similar to previous studies in the literature like a study by Griesinger G, et al.[14]

Progesterone is necessary for pregnancy maintenance, and various studies have shown that it can help avoid spontaneous miscarriage. Progesterone also causes secretory alterations in uterine endothelium cells, making them more receptive to the fertilised embryo's implantation. As a result, it's regularly administered to women who have had many abortions. Oral, vaginal, and intramuscular progesterone administration are all options. The oral method is the most convenient to give and has the best patient compliance, but it is also the most likely to cause adverse effects such nausea, vomiting, and headache. The use of progesterone intravaginally has been linked to a lower risk of these adverse effects.[15]

The results of this present study revealed that oral dydrogestrone has better efficacy in terms of bleeding completely resolved (57.14% vs. 64.29%) as compared to micronized vaginal progesterone group. But the overall distribution of extent of bleeding shows that response of both drugs was similar with both treatment modalities and the post treatment extent of bleeding was almost comparable in both groups without any statistical significant (P-value > 0.05) difference. The rate of efficacy in previous studies is variable some studies showed better results with dydrogestrone [16] and some studies showed no difference in efficacy of both treatment modalities.[17]

The findings of this present study showed that the rate of drowsiness (61.43% vs. 31.43%) and rate of

giddiness (22.86% vs. 8.57%) was found to be significantly (P-value < 0.05) higher in Micronised Progesterone group as compared to Dydrogesterone group. The side effects of nausea and abdominal bloating were similar in both treatment groups having no statistically significant (P-value > 0.05) difference between both groups. These findings are quite comparable to those seen in the literature, which reveal that Micronised Progesterone participants had much more sleepiness than Dydrogesterone individuals. This was unsurprising, given that Micronised Progesterone has been found to have sedative and hypnotic characteristics, as well as anaesthetic qualities. Progesterone metabolites mediate this impact, and individuals' susceptibility to these metabolites varies, resulting in varied responses.[10] Due to the induction of larger amounts of these sedating metabolites, micronised progesterone, like a natural progesterone, may cause increased sleepiness and giddiness. The fact that the complaint was self-reported, non-specific, and the sense of sleepiness and dizziness might be extremely subjective[18, 19] must be taken into account.

Conclusion

In the management of threatening miscarriage or bleeding, both Micronised Progesterone and Dydrogesterone therapies were found to be equally effective. Although the rate of side effects like drowsiness and giddiness was significantly higher in women treated with Micronised Progesterone as compared to women treated with Dydrogesterone. So Dydrogesterone can be used as a better alternate to Micronised Progesterone with fewer side effects.

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