Effect of Progesterone on Latent Phase Prolongation in Patients With Preterm Premature Rupture of Membranes

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Abstract- Preterm premature rupture of membranes (PPROM) is a condition leading to an increased risk of maternal and neonatal morbidity and mortality in pregnant women. To prevent this complication, some studies have proposed using prophylactic progesterone. However, due to lack of sufficient relevant data, there is still need for further studies in this regard. This study was performed to determine the effect of rectal progesterone on the latent phase and maternal and neonatal outcome variables in females with PPROM. During the present randomized clinical trial study (IRCT201512077676N4), a total of 120 patients with PPROM at pregnancy ages between 26 and 32 weeks were randomly assigned to 2 equal intervention and control groups. In the intervention group, progesterone suppositories (400 mg per night) were administered until delivery or completion of the 34th gestational week and was compared with placebo effect in control group. The latent phase and maternal and neonatal outcome variables were compared between the two groups. The mean age of patients was 29.56±5.66 (19-42) and 29.88±5.57 (17-40) years in the intervention and control group, respectively. The two groups were almost identical in the confounding factors. The median latent phase was 8.5 days in the intervention group vs. 5 days in the control group in the 28^{th}-30^{th} weeks of gestation, which was significantly higher in the intervention group (P=0.001). Among maternal and neonatal outcome variables, only the mean birth-weight was significantly higher in the intervention group than that in the controls (1609.92±417.28 gr vs. 1452.03±342.35 gr, P=0.03). Administration of progesterone suppository in patients with PPROM at gestational ages of 28 to 30 weeks is effective in elongating the latent phase and increasing birth-weight with no significant complications.

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Keywords: Preterm premature rupture of membranes; PPROM; Progesterone; Latent phase

Introduction

Preterm delivery is defined as the delivery before the end of the 37^{th} week of gestation and is possibly the single most important health related issue in pregnancy. One of the main etiologies for premature birth is Preterm premature rupture of membranes (PPROM) which occurs in 3% of all pregnancies (1,2). Preterm delivery is one of the most important risk factors for future morbidity and mortality among the neonates comprising up to 85% of prenatal morbidity and mortality (3). An increased latent phase in the context of PPROM is also linked to complications, which can be harmful to the mother and the child, the most common being infections (4-6). Morbidities can arise from PPROM involving the vital organs and systems of the body, including the lungs, the gastrointestinal system, the heart and the central nervous system are drastically higher in preterm newborns (7-9). Morbidity is also higher in the birth giving mother, complications such as chorioamnionitis and sepsis being the most fearsome (10). The economic burden was as much as 26.2 billion dollars in the united states alone (11). Also premature birth causes dramatic decrease in quality of life of the parents notably the mother (12). It is thus

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obvious that preventing premature birth can have vast beneficence in many aspects. Identification of the patients in risk of preterm delivery has enhanced in recent years because of new techniques such as transvaginal cervical length measurements and fibronectin testing (13-16), but therapeutic measures have not been satisfactory in delaying birth. Regarding PPROM, many therapeutic measures have been introduced including the use of antibiotics, corticosteroids (17), tocolytics (18), cervical cerclage (19) and most notably progesterone (20,21). Alike the general trend in premature birth, previous methods regarding PPROM have also largely been unsuccessful, but progesterone has shown great promise, as a safe medication, not having any major clinical complications during pregnancy and afterwards (22). Progesterone is a sex hormone having many well understood roles in the normal pregnancies, one being the anti-inflammatory effect which counters acts against the inflammatory cytokine produced routinely during birth, which precipitates preterm delivery. Thus progesterone theoretically could have a positive effect in preventing premature birth (23). But there is contradicting evidence whether progesterone suppositories should be used in clinical contexts (20,24), and there are debates about the proper route of administration and on the most efficient dosage (3).

The present study aims to investigate the effect of progesterone on patients with PPROM and the possible change in the premature delivery rates and other pregnancy outcomes and complications regarding its use.

Materials and Methods

During the present double blind randomized controlled trial, which was conducted in Educational-Medical centers of Tabriz University of Medical Sciences (Tabriz, Iran) between February 2014 to April 2016, 120 patients with PPROM were included in the study.

Ethical considerations

This study was registered at Iranian Registry of Clinical Trials (http://www.irct.ir) with the registration number of IRCT201512077676N4 and the study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences which was in compliance with Helsinki Declaration. All patients signed informed written consent before inclusion in the study. Before every stage of the research project, patients were clearly informed of the procedures and had the ability to leave the study at will. No harm resulting from the procedures was reported in the literature.

Study design and population

Inclusion criteria consisted of singleton pregnancy, PPROM (based on the agreed definition of the rapture of membranes prior to the 37th week of gestation) (25,26) between the 26-32 weeks of gestation and desire of the mother to participate in the study. Exclusion criteria were proven fetal anomalies in previous tests, including genetic testing and structural abnormalities discovered with sonography or trisomy screening tests (double marker or Quad Screen Test) between the 18-20 and 28-32 weeks of gestation, multiple gestation, pregnancies being complicated with preeclampsia, chronic Hypertension, overt diabetes, gestational diabetes, abruption, cord prolapse and chorioamnionitis and a gestational age of more than 32 weeks in the initial presentation. This exclusion criterion was implemented because of the fact that treatment would fail to be effective in such a short time. Patients presenting more than 36 hours after the rapture of the membranes and patients with Active PPROM were also excluded.

Randomizing, blinding and masking

Randomizing was done in the initial presentation by the block randomization method using Randlist software (version 1.2) into two equal groups, so factors such as educational status, occupation (whether the patient was a housewife or not), residence (urban or rural), and socioeconomic levels (determined by income), previous parities, previous miscarriages, number of alive children, previous preterm deliveries and gestational age were parallel to each other. Allocation concealment was achieved by use of a placebo, which appeared identical to the active drug in every aspect and was made of Castor Oil which is proven to be safe and does not contain any therapeutic effect (27). Participants, clinicians, pharmacists, and all counterparts involved in performing the intervention, assessing results, or analyzing data remained masked to treatment allocation until the end of the study (Pharmacists were only aware of the composition of the medication given to the patients and were not aware of the allocation).

Study protocol

PPROM was proven by vaginal examination and observing the leakage of amniotic fluid by a single team of physicians and the placental alpha microglobuline-1 (PAMG-1) test using AmniSure ROM Test (28). Sonography was performed, and the Amniotic fluid index was measured by the same single group of radiologists, then gestational age was documented according to the first-trimester sonography. In the intervention group, 400

mg progesterone suppositories (CYCLOGEST 400 mg-L.D. COLLINS and CO) were used once a day at night. Suppositories were continued up to delivery or to 34 completed weeks. In the control group placebo suppositories (Castor Oil), exactly in the same shape and color of the progesterone suppositories were used. All patients with PPROM were admitted to the high-risk ward and received antibiotics and betamethasone during the course of the study. Tocolytics were not used. Evaluation for chorioamnionitis and Fetal Non-Stress Test (NST) was performed daily and biophysical profile (BPP) bi-weekly. Finally, the outcome of pregnancy was examined in the following criteria: duration of latent phase (the first step of labor before the cervix dilates), from admission to delivery, route of delivery, wound infection, APGAR score (Appearance, Pulse, Grimace, Activity, and Respiration), fetal weight at delivery, admission to NICU (neonatal intensive care unit), neonatal sepsis, the occurrence of chorioamnionitis, and puerperal metritis.

Statistical analysis

Statistical analysis was performed by Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, USA). Quantitative data were presented as the mean±standard deviation (SD), while qualitative data were demonstrated as frequency and percent (%). for statistical analysis, after determining the distribution of continuous variables by Kolmogorov-Smirnov test, Independent sample t-test was applied to compare two group's results. Also, collected data were studied using descriptive statistical methods, the mean difference test for independent groups, Chi Square2 test or Fisher's exact test. *P* less than 0.05 was statistically considered significant in all steps. Power of the study was 80%.

Results

Patients were identical in age, education, socioeconomic status. There were no significant differences in any of the fields. Data are summarized in Table 1. Number of previous parities, number of previous miscarriages, number of live births, history of previous preterm delivery, gestational age and the time the rapture of membranes happened is depicted in Table 2. There wasn't any significant difference between any of the aforementioned.

The outcome of pregnancy was evaluated in both groups as the average amniotic fluid index, the average time from PPROM to the initial contractions, route of delivery (vaginal or cesarean), wound infection, APGAR score in the first and fifth minutes after birth, neonate blood PH, average birth weight, neonatal sepsis,respiratory distress syndrome (RDS) and days of admission in NICU. There were no significant differences between the two groups in any of the criteria except in the time from PPROM to the initial contractions when the rapture happened in the 28^{th}-30^{th} week of gestation, in which the time period was 8.5 days in the intervention group and 5 days in the control group ($P<0.001$), and the average birth weight which was 1609.92±417.28 gr in the intervention group and 1452.03+-342.35 gr in the control group ($P=0.03$). Results are summarized in Table 3. Also, there was no case of chorioamnionitis, puerperal infection, neonatal seizure, and necrotizing enterocolitis in two groups.

Table 1. Socioeconomic state of the patients being included in the study and the comparison between the intervention and control group

Groups / **Social determinants**		**Intervention**	**Control**	***P***
Education	**Did not graduate high school**	28 (46.7)	25 (41.6)	0.93
	High school degree	17 (28.3)	16 (26.7)	
	College degree	15 (25)	19 (3.7)	
Occupation	**House keeper**	35 (58.3)	36 (60)	0.85
	Occupied	25 (41.7)	24 (40)	
Residence	**Urban**	48 (80)	45 (75)	0.51
	Rural	12 (20)	15 (25)	
Income($)	**≤300**	19 (31.7)	20 (33.3)	0.51
	300 < <1000 $	36 (60)	38 (63.3)	
	1000 $≥	5 (8.3)	2 (3.3)	

*Data are shown as frequency (percentage)

Table 2. Criteria matched in the control and intervention groups

Groups / Criteria	Intervention	Control	*P*
Age of mother (Year)	29.56 ± 5.66 (19-42)	29.88 ± 5.57 (17-40)	0.76
Number of Previous parities	2.18 ± 1.11 (1-5)	2.03 ± 1.23 (1-6)	0.49
number of previous miscarriages	0.43 ± 0.08 (0-2)	0.48 ± 0.12	0.74
number of live births	0.73 ± 0.09 (0-2)	0.58 ± 0.1 (0-2)	0.28
Gestational age in delivery (Day)	203.03 ± 13.29 (182-226)	202.40 ± 12.11 (182-224)	0.79
Mean gestational age of premature rapture of membranes (Day)	203.05 ± 13.22 (182-226)	203.32 ± 15.48 (182-227)	0.92

* data was shown as mean ± standard deviation (range)

Table 3. Outcome of pregnancy in the intervention and control group

Groups / Outcome		Intervention	Control	*P*
amniotic fluid index (centimeters)		5.25±1.65	4.81±1.97	0.18
PPROM to initial contractions (days)	**26th-28th week**	9.5	5.5	0.08
	28th-30th week	8.5	5	0.001
	30th-32th week	6	6.5	0.55
Vaginal delivery		34 (56.7)	25 (41.7)	0.1
wound infection		1 (1.7)	4 (1.6)	0.36
APGAR score	**First minute**	8.02±1.26	7.78±1.26	0.31
	Fifth minute	9.43±0.72	9.40±0.94	0.83
neonate blood PH		7.33±0.16	7.33±0.13	0.94
average birth weight		1609.92±417.28 gr	1452.03±342.35 gr	0/03
neonatal sepsis		0 (0)	1(1.75)	0.5
respiratory distress syndrome (RDS)		53 (88.3)	48 (80)	0.21
Admission to NICU		10.53±1.10	14.23±1.89	0.09

*Data was shown as mean ± standard deviation and Frequency (percentage)

Discussion

In the present study, the effect of progesterone on delaying delivery after PPROM was evaluated. This intervention significantly delayed this period from a mean of 5 days to 8 in the intervention group being in the 28th-30th week of gestation. Also, a significant increase in the birth weight of the neonates was observed.

Norman *et al*., conducted a multi-center randomized clinical trial to investigate the effect of progesterone on the prophylaxis of preterm delivery in PPROM and found that there was no significant increase in the time period between PPROM and delivery in the intervention group. They also concluded that progesterone did not increase morbidity or mortality in the mother or the child (29). The results of this study were not in compliance to the present study, thought the difference could be because of the fact that lower doses of progesterone were used by them (200 compared to 400 mg). Another possible explanation would be the beneficence of progesterone administration in special ethnic groups or in mothers with specific risk factors, a fact that is also cited in the aforementioned study.

Meis *et al*., selected 459 patients with a previous history of preterm delivery and injected intramuscular progesterone 250 mg/weekly in one group and placebo in the other group. Preterm delivery was significantly lower in patients receiving progesterone. Neonatal complications such as intraventricular hemorrhage and necrotizing enterocolitis were also lower in this group. There wasn't any side effect reported for progesterone (30). The results followed the present study, although neonatal complications such as sepsis, respiratory distress syndrome weren't significantly reduced in the present

study.

Defonseca *et al*., conducted a study with 142 cases of PPROM which compared the use of progesterone (100 mg suppository/day) with placebo. The rate of preterm delivery was significantly reduced when they used progesterone (31). The results were in concordance to the present study using a smaller dose and the same route of administration. Further studies could be needed to determine a safe minimal and efficient dose for this route of administration.

Mirzaei *et al*., also conducted a study to evaluate the effect of progesterone on the prolongation of pregnancy in patients with PPROM. 171 patients with PPROM were selected, in group 1 (57 patients), they used 17OHP 250 mg/weekly, in group 2 (57 patients), they used 400 mg progesterone suppository/day, and in group 3 (102 patients), they didn't use any medication.The average of latent phase from rupture of membranes to delivery was 15/5 days in the first group, 15/2 days in progesterone receivers, and 11/5 days in patients with no medications. The difference was statistically significant (32). The results of the present study also proved the same fact. However, prolongation of latent phase was lower in our study. None of the patients of the present study reached 34 weeks; this could be because of the lower gestational age among our patients meaning they encountered PPROM in lower gestational age.

Maher *et al*., conducted a randomized clinical trial to compare the effectiveness of intra-muscular with vaginal suppositories and found that even in lower doses, the vaginal method was significantly superior, thus making it more beneficial for clinical use. Also, the adverse effects were almost twice as high in the intramuscular group compared to the vaginal group (14.1 % vs. 7.5%) (33).

Briery *et al*., performed another randomized controlled clinical study in which patients were injected with 250 mg of progesterone in the intervention group and placebo in the control group. They found that this procedure was not beneficial for neither the mother or the neonate in terms of morbidity and mode of delivery (vaginal vs. cesarean section) (24). The results of the present study contradicted these results. The difference could be because of the different way of delivery and higher dosage in the previous study.

Aside from the controversy of progesterone administration in PPROM patients, there remains the adherence to the evidence based guidelines. Crane *et al*., found that only half of the patients who were possible candidates for progesterone therapy ever received the treatment, and the main reason for this low status was that clinicians did not offer the option in the first place rather than not recognizing its prophylactic effect (34).

The limitation of the present study was that it did not include enough patients to be able to generalize the results to wide scopes of patients, as there may be differences between patients in different geographical areas, which the present study is not able to determine. Also in the present study, the positive effect of progesterone was only seen between the 28th and thirty first week of pregnancy, and no beneficence was shown in any other time period. This could be the subject of future studies, further examining the effect of progesterone, and conducting the procedure of the present study, in larger number of patients, from multiple centers in multiple areas. Understanding of methods of diagnosing and preventing PROM and PPROM are developing at an astonishing rate, so it seems comprehensive studies, comparing these methods, would be of great merit.

Results of the present study showed that progesterone suppositories reduced the latent phase of pregnancy and increased the mean age of birth significantly, without any significant change in other complications. Thus progesterone can be prescribed for women with PPROM specially between the 28th-30th week of gestation.

References

1. Mercer BM. Preterm premature rupture of the membranes. Obstet Gynecol 2003;101:178-93.
2. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162-72.
3. Norwitz ER, Caughey AB. Progesterone supplementation and the prevention of preterm birth. Rev Obstet Gynecol 2011;4:60.
4. Sweet RL, Gibbs RS. Chlamydial infections. In: Sweet RL, Gibbs RS, Sweet R, Gibbs R, eds. Infectious diseases of the female genital tract. Philadelphia, PA: Lippincott Williams & Wilkins, 2002:57.
5. Greulich B, Tarrant B. The latent phase of labor: diagnosis and management. J Midwifery Women Health 2007;52:190-8.
6. Xia H, Li X, Li X, Liang H, Xu H. The clinical management and outcome of term premature rupture of membrane in East China: Results from a retrospective multicenter study. Int J Clin Exp Med 2015;8:6212-7
7. Ibrahimou B, Anozie C, de la Cruz C, Salihu H. Previous Preterm Birth and Current Maternal Complications as a Risk Factor of Subsequent Stillbirth. Adv Epidemiol 2015;2015:819146.

8. Spittle AJ, Treyvaud K, Doyle LW, Roberts G, Lee KJ, Inder TE, et al. Early emergence of behavior and social-emotional problems in very preterm infants. J Am Acad Child Psychiatry 2009;48:909-18.
9. Jones M. Effect of preterm birth on airway function and lung growth. Paediatr Respir Rev 2009;10:9-11.
10. Linehan LA, Walsh J, Morris A, Kenny L, O'Donoghue K, Dempsey E, et al. Neonatal and maternal outcomes following midtrimester preterm premature rupture of the membranes: a retrospective cohort study. BMC Pregnancy Childbirth 2016;16:25.
11. Hodek J-M, von der Schulenburg J-M, Mittendorf T. Measuring economic consequences of preterm birth-Methodological recommendations for the evaluation of personal burden on children and their caregivers. Health Econ Rev 2011;1:6.
12. Wang P, Liou S-R, Cheng C-Y. Prediction of maternal quality of life on preterm birth and low birthweight: a longitudinal study. BMC pregnancy and childbirth. 2013;13:124.
13. Khooshideh M, Radi V, Hosseini R, Hosseini L. The accuracy of placental alpha-microglobuline-1 test in diagnosis of premature rupture of the membranes. Iran J Reprod Med 2015;13:355-60.
14. Behrman RE, Butler AS. Preterm birth: causes, consequences, and prevention. National Academies Press, 2007.
15. Gezer C, Ekin A, Golbasi C, Kocahakimoglu C, Bozkurt U, Dogan A, et al. Use of urea and creatinine levels in vaginal fluid for the diagnosis of preterm premature rupture of membranes and delivery interval after membrane rupture. J Matern Fetal Neonatal Med 2016;30:772-8.
16. Lee SM, Park KH, Jung EY, Jang JA, Yoo H-N. Frequency and clinical significance of short cervix in patients with preterm premature rupture of membranes. PloS One 2017;12:e0174657.
17. Brookfield KF, El-Sayed YY, Chao L, Berger V, Naqvi M, Butwick AJ. Antenatal corticosteroids for preterm premature rupture of membranes: single or repeat course? Am J Perinatol 2015;32:537-44.
18. Mackeen AD, Seibel-Seamon J, Muhammad J, Baxter JK, Berghella V. Tocolytics for preterm premature rupture of membranes. Cochrane Database Syst Rev 2011;10:CD007062.
19. To MS, Alfirevic Z, Heath VC, Cicero S, Cacho AM, Williamson PR, et al. Cervical cerclage for prevention of preterm delivery in woman with short cervix: randomised controlled trial. Lancet 2004;363:1849-53.
20. Lim AC, Bloemenkamp KW, Boer K, Duvekot JJ, Erwich JJH, Hasaart TH, et al. Progesterone for the prevention of preterm birth in women with multiple pregnancies: the AMPHIA trial. BMC Pregnancy Childbirth 2007;7:7.
21. How HY, Sibai BM. Progesterone for the prevention of preterm birth: indications, when to initiate, efficacy and safety. Ther Clin Risk Manag 2009;5:55-64.
22. Kumar P, Magon N. Hormones in pregnancy. Niger Med J 2012;53:179.
23. Luo G, Abrahams VM, Tadesse S, Funai EF, Hodgson EJ, Gao J, et al. Progesterone inhibits basal and TNF-α-induced apoptosis in fetal membranes: a novel mechanism to explain progesterone-mediated prevention of preterm birth. Reprod Sci 2010;17:532-9.
24. Briery CM, Veillon EW, Klauser CK, Martin RW, Magann EF, Chauhan SP, et al. Women with preterm premature rupture of the membranes do not benefit from weekly progesterone. Am J Obstet Gynecol 2011;204:54. e1-.e5.
25. Caughey AB, Robinson JN, Norwitz ER. Contemporary diagnosis and management of preterm premature rupture of membranes. Rev Obstet Gynecol 2008;1:11-22.
26. Shahnazi M, Khalili AF, Azimi S. Effect of Zinc Supplement on Prevention of PPROM and Improvement of some Pregnancy Outcomes in Pregnant Women with a History of PPROM: A Randomized Double-Blind Controlled Trial. Iran Red Crescent Med J 2017;19:e41931.
27. Kelly AJ, Kavanagh J, Thomas J. Castor oil, bath and/or enema for cervical priming and induction of labour. Cochrane Database Syst Rev 2013;:CD003099.
28. Abdelazim IA, Makhlouf HH. Placental alpha microglobulin-1 (AmniSure® test) for detection of premature rupture of fetal membranes. Arch Gynecol Obstet 2012;285:985-9.
29. Norman JE, Marlow N, Messow C-M, Shennan A, Bennett PR, Thornton S, et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. Lancet 2016;387:2106-16.
30. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348:2379-85.
31. da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003;188:419-24.
32. Mirzaei F, Moradi P. Effects of Progesterone on Latency Period in Patients with Preterm Premature Rupture of Membranes during 24-34 Weeks of Pregnancy. J Kerman Univ Med Sci 2015;22:240-8.
33. Maher MA, Abdelaziz A, Ellaithy M, Bazeed MF.

Prevention of preterm birth: a randomized trial of vaginal compared with intramuscular progesterone. Acta Obstet Gynecol Scand 2013;92:215-22.

34. Crane SS, Naples R, Grand CK, Friebert S, McNinch NL, Kantak A, et al. Assessment of adherence to guidelines for using progesterone to prevent recurrent preterm birth. J Matern Fetal Med 2016;29:1861-5.