International Journal of Clinical Trials
Tahir F et al. Int J Clin Trials. 2015 Nov;2(4):97-101
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259

DOI: http://dx.doi.org/10.18203/2349-3259.ijct20151239

Research Article

The effect of rectal progesterone on latency period as well as maternal and prenatal outcome between 24 to 33 weeks

Fadwah Tahir[1], Mohammed Badawi[2]*, Abdulelah Nuqali[3], Yasir Katib[1], Irfanallah Muhammad Siddiqui[4], Fawaz Edris[1], Entsar Madani[5], Muaid Morad[6], Omar Taibah[7], Yahya Al-Ghamdi[8]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Umm Al Qura University, P. O. Box: 6707, Makkah-21955, Saudi Arabia
[2]Department of Medical Education, Faculty of Medicine, Umm Al Qura University, P. O. Box: 6707, Makkah-21955, Saudi Arabia
[3]Department of Internal Medicine, Faculty of Medicine, Umm Al Qura University, P. O. Box: 6707, Makkah-21955, Saudi Arabia
[4]Department of Community Medicine, Faculty of Medicine, Umm Al Qura University, P. O. Box: 6707, Makkah-21955, Saudi Arabia
[5]Department of Obstetrics and Gynecology, Faculty of Medicine, King Abdulaziz University, P. O. Box: 80215, Jeddah-21589, Saudi Arabia
[6]Department of Internal Medicine, Faculty of Medicine, Albaha University, P.O. Box: 1988, Albaha-65431, Saudi Arabia
[7]Department of Pediatrics, Faculty of Medicine, Umm Al Qura University, P. O. Box: 6707, Makkah-21955, Saudi Arabia
[8]Department of Pathology, Faculty of Medicine, Umm Al Qura University, P. O. Box: 6707, Makkah-21955, Saudi Arabia

Received: 16 October 2015
Accepted: 29 October 2015

***Correspondence:**
Dr. Mohammed Badawi,
E-mail: badawi270@gmail.com

ABSTRACT

Preterm Premature Rupture Of Membranes (PPROM) is directly linked to prematurity associated with severe neonatal morbidity and mortality. Randomized clinical trials have shown that weekly injections of 17-alpha-hydroxyprogesterone (17P) or daily vaginal progesterone application decreases the number of preterm deliveries, particularly for women with a history of preterm delivery or those with a shortened cervix. However, no studies have yet been conducted to prove or disprove the effect of rectal progesterone on latency period. To address this issue, we will conduct a multicenter randomized triple-blind controlled trial of 216 participants (108 in each group) from January 1, 2016 to August 31, 2016. Inclusion criteria, exclusion criteria, data collection procedure, data analysis, and assessment of safety procedures are explained in the study protocol. The primary objective will be to determine the effect of rectal progesterone on the latency period in PPROM. The secondary objective will be to study the effect of rectal progesterone on maternal outcomes of hospitalization, intensive care unit admission, chorioamnionitis, post-partum hemorrhage, post-partum pyrexia, endometritis, and maternal death. In addition, we will evaluate prenatal birth weight, Apgar score, neonatal morbidity, duration of neonatal intensive care unit stay, intrauterine fetal death, and neonatal death associated with PPROM.

Keywords: Preterm premature rupture of membranes, Pregnancy prolongation, Progesterone

INTRODUCTION

Preterm Premature Rupture Of Membranes (PPROM) is directly linked to prematurity and is associated with severe neonatal morbidity and mortality.[1] Nearly 3% of all pregnancies are complicated by PPROM, and three quarters of identified cases are delivered within seven days.[2,3] In the United States, nearly one-third of preterm deliveries and 18% to 20% of prenatal deaths are associated with PPROM. Current management of women with PPROM is hospitalization, fetal testing, and treatment with antibiotics and steroids. Delivery usually occurs at 35 weeks of gestation or sooner if fetal-maternal indications are present.[3]

Randomized clinical trials have shown that weekly injections of 17-alpha-hydroxyprogesterone (17P) or daily vaginal progesterone application decreases the number of preterm deliveries, particularly for women with a history of preterm delivery or those with a shortened cervix.[4,5] Indeed, support by the American College of Obstetricians and Gynecologists and March of Dimes as well as other healthcare organizations has made progesterone treatment the standard of care in many areas of the United States.

Given preterm delivery is clearly associated with PPROM, there is a strong need to study if either vaginal or rectal progesterone is effective in delaying preterm delivery. Infection stimulates the production of pro-inflammatory cytokines that are commonly associated with preterm birth and PPROM. *In vivo* studies have suggested that 17P can modulate infection-related cytokine production.[6] Additionally, animal studies of 17P have been successful in reducing inflammation and cytokine production in hypertension models.[7,8] In high-risk patients with a prior spontaneous preterm birth or short cervix, progesterone works at the cellular level to prolong pregnancy.[4-6] Progesterone inhibits the expression of cellular protein genes in the myometrium and inhibits inflammatory factors very important to maintaining a healthy pregnancy and preventing coordinated contractions.[9] Peltier et al. have also shown that pro-inflammatory cytokine production in cases of preterm birth is blunted by progesterone administration.[7] Progesterone, an endogenous steroid hormone produced by the ovaries, has been widely used for a variety of medical conditions, and has proven to be safe.[5,6]

With respect to this study, certain precautions will be instituted to ensure patient safety. For example, progesterone has been reported to cause a mild allergic reaction and in rare cases a serious allergic reaction known as anaphylactic shock. All patients will be informed about this side effect during the first meeting, before consent is obtained. If a patient develops any allergic reaction, a SARUS (Suspected Unexpected Serious Adverse Reaction) form will be submitted to the SFDA (Saudi Food and Drug Authority).

A recent clinical trial concerned with the effect of 17P showed no significant effect of the drug on the prevention of preterm delivery among PPROM patients.[10]

One limitation of this study was that the researchers experienced a higher-than-expected preterm delivery rate among placebo patients and the patients were not stratified in groups according to gestational age. Furthermore, no studies have yet been conducted to prove or disprove the effect of vaginal or rectal progesterone on *latency period* (defined as the period from the onset of PPROM until onset of labor). However, several studies have noted the concentration of progesterone in endometrial cells may become 10 to 20 times higher after vaginal administration than after intramuscular administration.[11,12] Thus, in this study vaginal route will be replaced with a rectal route based on the work of Aghsa and colleagues,[13] who showed similar efficacy between vaginal and rectal routes for progesterone administration.

We believe that by conducting this trial we can determine the effect of rectal progesterone on the latency period among patients with PPROM. Our primary objective is to determine the effect of rectal progesterone on the latency period in PPROM. Our secondary objective is to study the effect of rectal progesterone on maternal outcomes of hospitalization, intensive care unit admission, chorioamnionitis, post-partum hemorrhage, post-partum pyrexia, endometritis, and maternal death. In addition, we will evaluate prenatal birth weight, Apgar score, neonatal morbidity, duration of neonatal intensive care unit stay, intrauterine fetal death, and neonatal death associated with PPROM. We will evaluate maternal demographics, gestational age at birth, route of delivery, and indications for delivery. Selected infant outcomes include birth weight, 5-minute Apgar score, total days spent in neonatal intensive care unit, and the occurrence of significant neonatal morbidity such as respiratory distress syndrome (i.e., signs of tachypnea, with respiratory rate more than 60 breaths per minute, retractions, grunting, nasal flaring, and cyanosis in room air, or need for treatment with supplemental oxygen, nasal continuous positive airway pressure, endotracheal intubation, or exogenous surfactant),[14] intraventricular hemorrhage (for grades III or IV only),[15] necrotizing enterocolitis (if the neonate has one or more of the following clinical signs: bilious, gastric aspirate or emesis, abdominal distention, or occult or gross blood in stool without evidence of a rectal fissure; and one or more of the following radiographic findings: pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum),[16] bronchopulmonary dysplasia (oxygen dependency at 36 weeks postmenstrual age),[17] sepsis and seizures, and death during the neonatal period.

METHODS

This multicenter randomized triple-blind controlled trial will be conducted from January 1, 2016 to August 31,

2016. To determine sample size, we used $\alpha<0.05$ and a power of 80%. A 10% difference between the two study groups was considered to be a clinically significant effect size. Hypothesis testing for the two populations with one-sided test will be used and a calculated sample size of 90 was determined for each group in order to validate the results and statistical assessment.[18] Refusal to give consent and patient dropouts are an inherent part of any clinical trial. This issue is even more widespread in the developing world, so 36 (20%) more patients were factored into the calculated sample size to arrive at a total of 216 patients (108 in each group).

Inclusion criteria

Patients between 18 to 45 years old with a single living fetus between 24 to 33 weeks of gestational age will be enrolled at least one week between the onset of management and the termination of gestation, which is the minimal significant latency period.[19] The patient will have to have a confirmed diagnosis of PPROM (suspected amniorrhexis confirmed by sonography, visualization of fluid coming from the cervix, and positive ferning and AmniSure).[20] Informed consent will be obtained and signed. Women with oligohydramnios will also be included in the study, provided fetal heart rate tracings are reassuring during observation.

Exclusion criteria

Exclusion criteria will focus on fetal and maternal factors that could affect outcomes, including fetal chromosomal abnormality, fetal anomaly, non-reassuring surveillance (e.g., fetal persistent tachycardia, late deceleration or severe variable deceleration, or abnormal biophysical profile <4), intrauterine growth restriction (IUGR) (defined as birth weight less than the 10^{th} percentile based on the Alexander growth standard),[21] maternal fever, ante-partum hemorrhage (defined as bleeding from the birth canal after the 24^{th} week of pregnancy),[22] chorioamnionitis (based on criteria such as maternal fever, uterine tenderness, malodorous amniotic fluid, maternal or fetal tachycardia, and maternal leukocytosis),[23] diabetes mellitus type 1, preeclampsia (hypertension and significant proteinuria detected for the first time after 20 weeks gestation), hypertension (defined as systolic blood pressure 140 mmHg or diastolic blood pressure 90 mmHg),[20] proteinuria (defined as 300 mg/d or 30 mg/mmol in a single specimen or 1^+ on dipstick),[24] cervical discharge, and severe medical/ obstetric diseases such as sickle cell disease with severe crisis. Also, patients will be required to have no history of allergy to progesterone or placebo or any other medical condition that might adversely interact with progesterone or any medical condition treated with systemic steroid medications.

Data collection

Informed consent will be obtained from patients meeting the inclusion criteria. Patients who do not want to participate in the study will receive the current standard management. Furthermore, patients have the right to withdraw at any time and receive the standard treatment and follow-up assessments. Participants who withdraw will not be replaced and will be counted as dropping out of the study. Participants who withdraw from the trial will complete a Research End form. Criteria for premature discontinuation from the study for an individual participant are: (1) loss to follow up, (2) non-compliance with study medication, (3) request for withdrawal, (4) request by the primary care provider if s/he thinks the study is no longer in the best interest of the participant, or (5) a completion of defined study endpoint. Patients who accept the invitation to participate in the study will be randomized to receive either rectal progesterone or a placebo suppository on a daily basis. Data will be collected from three different forms: a participation form, follow-up form, and discharge form. All forms are designed specifically for the study and were developed through a series of focus group discussions. Once the forms are completed, data entry and analysis will be conducted by an independent statistician.

Women in each group will be placed on bed rest and monitored in a labor and delivery suite for 24 hours to rule out early infection, prolapsed umbilical cord, Non-Reassuring Fetal heart Tracing (NRFT), placental abruption, or instantaneous preterm labor. Randomization will occur after this observation period. The selected patients will be randomized by adopting a blocking technique (i.e., randomized block design), which will ensure that both treatment groups are similar in size.[25] The patients will be divided into groups of 10. A staff member who is not part of the research team will prepare the marked papers. Half of the papers of each block of 10 will be marked as “treatment group 1” (TR1) and the rest will be marked as “treatment group 2” (TR2). Each eligible participant will be invited to blindly pick one of the 10 available. Once a sheet was picked up, after noting the treatment group allocation, it will be placed back in the drawer so that every patient would have an equal chance of being assigned to either of the two treatment groups. The procedure will be repeated for a second block of 10 until all patients meeting the inclusion criteria are registered.

Sheets will be pulled from a drawer by the patient at the time of informed consent, so the allocation is concealed. Each paper is inscribed with either rectal progesterone or placebo suppository. Doses of rectal progesterone or placebo will be prepared by an independent company and shipped to the pharmacy, where the envelopes will be stored per protocol. When a patient is randomized, an order will be written by the treating physician and faxed to the pharmacy indicating the patient is participating in a progesterone-PPROM trial. The pharmacy will be

supplied with an envelope labeled TR1 or TR2 as written by the consultant. Both the rectal progestin (400 mg) and placebo (starch) will be supplied in opaque, coded envelopes. The code numbers will be recorded on each patient's treatment chart, and on a daily basis, a similar order will be faxed to the pharmacy so medication from the same numbered envelopes is taken for the duration of the pregnancy. Daily rectal progesterone or placebo suppository will continue until 35 weeks or delivery, whichever comes first. Patients, their families, research personnel, counterpersons, and physicians/nurses will be blinded to group assignment. The code is not deciphered until all participants complete the research study and their data are entered, unless the data safety/monitoring committee determines it necessary to break the code in order to assess an unwanted event.

All women will be given a seven-day course of antibiotic prophylaxis, including one dose of oral azithromycin (1 g) upon admission plus intravenous ampicillin (2 g every 6 h) for 48 hours, followed by oral amoxicillin (500 mg every 8 h or 875 mg every 12 h) for the remaining five days,[26,27] and all patients will receive a full course of steroids for fetal lung maturation. After completing their stay in the labor and delivery area, patients will be transferred to the high-risk floor. All patients will undergo vaginal swab testing, routine fetal testing (daily non-stress testing and twice-weekly biophysical profiles), and frequent maternal assessments for infection (temperature, maternal-fetal tachycardia, fundal tenderness, white blood cell count, and C-reactive protein). Treatment will begin at different gestational points, thus all patients will stop therapy after completing 35 weeks of gestation based on regular menstrual cycle data and/or early ultrasound findings. There will be no additional visits or costs associated with the study. Moreover, the study is not supported by any pharmaceutical company.

Data analysis

All data will be input in SPSS software, version 21 (IBM Corp., Armonk, NY, USA). The main outcome variable, the prolongation of gestation, will be analyzed using Student's *t*-test for the independent sample; for the secondary objectives, chi-square, or *t*-test will be used depending on the type of variable.

Safety assessment

To ensure patient and data safety, an assigned group of physicians familiar with the study, yet not participating or employed at any of the enrolled centers, will be formed. This group, the Safety Monitoring Board (SMB), will hold a series of meetings among its members as needed to perform various functions. An important objective of the SMB is to review two designated reports regarding Adverse Events (AE) and Serious Adverse Events (SAE). These reports will be designed based on standardized forms. SAE reports will be reviewed within 24 hours, while AE reports will be reviewed within 10 days. The SMB will study each report to determine whether the study medications or procedures are the reason for the adverse event. Based on the findings, the SMB will decide if the code has to be broken in order to further evaluate the event. The principle investigator of each hospital will be required to submit SAEs by email within 24 hours to the SMB. Anaphylactic shock or other life-threatening reactions caused by the study medication will be considered SAEs. Expected complications associated with PPROM, including neonatal morbidities caused by preterm delivery and/or perinatal infection, will not be considered AEs. Known maternal morbidities associated with PPROM will also be excluded (e.g., abruptio placentae, prolonged hospitalization, intraamniotic infection). Likewise, PPROM-associated neonatal complications such as neonatal sepsis, positive newborn blood culture, necrotizing enterocolitis, respiratory distress syndrome, intracerebral hemorrhage, or death at 28 weeks or less will be excluded.

The second objective of the SMB is to conduct a planned provisional analysis. Once 50% of the sample size is recruited, an analysis will be performed to ensure patient safety and the efficacy of the results. Outcomes of the provisional analysis will be compared between the treatment groups to assess any statistical significance; this comparison will include AE and SAE frequency. Continuation of the trial will depend on results of the analysis. The trial will be discontinued in the following instances: (1) a significant difference (alpha = 0.0031) found between the groups; (2) based on the conditional probability analysis, there is an extremely low possibility that continuation of the trial will reveal a significant difference; or (3) a significantly high number of neonatal morbidities, AE, or SAE in the rectal progesterone group. If the trial were discontinued, new participant enrollment and randomizations would stop promptly.

A final data analysis will be completed after data receipt of all randomized participants. In the event that the study continues, details of the provisional analysis would not be available to the investigators. However, a summary report would be issued by the SMB stating that the continuation of the study was justified.[28]

Funding: The study was funded by The Institute of Scientific Research and Revival of Islamic Culture, Umm Al-Qura University
Conflict of interest: None declared
Ethical approval: The study was reviewed and approved by the ethical committee of the Faculty of Medicine at Umm Al-Qura University (reference number 14/BME/0030, dated February 17, 2014) and by the Saudi Food and Drug Authority (SFDA) (Application # 15012902). The trial was registered on July 21, 2014, at www.controlled-trials.com (ISRCTN65694106)

REFERENCES

1. American College of Obstetricians and Gynecologists. Clinical management of preterm premature rupture of the membranes. Obstet Gynecol. 1998;1:848-57.
2. Mercer BM. Preterm premature rupture of the membranes. Obstet Gynecol. 2003;101:178-93.
3. Lieman JM, Brumfield CG, Carlo W, Ramsey PS. Preterm premature rupture of membranes: is there an optimal gestational age for delivery? Obstet Gynecol. 2005;105:12-7.
4. 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.
5. Da Fonseca EB, Bittar RE, Carvalho MH, Sugaib 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.
6. DeFranco EA, O'Brien JM, Adair CD, Lewis DF, Hall DR, Fusey S, et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized, double-blind, placebo-controlled trial. Obstet Gynecol. 2007;30:697-705.
7. Peltier MR, Tee SC, Smulian JC. Effect of progesterone on proinflammatory cytokine production by monocytes stimulated with pathogens associated with preterm birth. Am J Reprod Immunol. 2008;60:346-53.
8. Veillon EW, Keiser SD, Parrish MR, Bennett W, Cockrell K, Ray LF, et al. 17-Hydroxyprogesterone blunts the hypertensive response associated with reductions in uterine perfusion pressure in pregnant rats. Am J Obstet Gynecol. 2009;201:324.
9. Elovitz MA, Mrinalini C. Can medroxyprogesterone acetate alter Toll-like receptor expression in a mouse model of intrauterine inflammation? Am J Obstet Gynecol. 2005;193:1149-55.
10. Sfakianaki AK, Norwitz ER. Mechanisms of progesterone action in inhibiting prematurity. J Matern Fetal Neonatal Med. 2006;19:763-72.
11. 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.
12. Cicinelli E, de Ziegler D, Bulletti C, Matteo MG, Schonauer LM, Galantino P. Direct transport of progesterone from vagina to uterus. Obstet Gynecol. 2000;95(3):403-6.
13. Einer-Jensen N, Hunter R. Counter-current transfer in reproductive biology. Reproduction. 2005;129(1):9-18.
14. Aghsa MM, Rahmanpour H, Bagheri M, Davari-Tanha F, Nasr R. A randomized comparison of the efficacy, side effects and patient convenience between vaginal and rectal administration of Cyclogest® when used for luteal phase support in ICSI treatment. Arch Gynecol Obstet. 2012;286(4):1049-54.
15. Yee W, Amin H, Wood S. Elective Cesarean delivery, neonatal intensive care unit admission, and neonatal respiratory distress. Obstet Gynecol. 2008;111(4):823-8.
16. Volpe JJ. Neurology of the newborn. In: Volpe JJ, eds. A Book. 3rd ed. Philadelphia, PA: WB Saunders; 1995.
17. Guthrie SO, Gordon PV, Thomas V, Thorp JA, Peabody J, Clark RH. Necrotizing enterocolitis among neonates in the United States. J Perinatol. 2003;23:278-85.
18. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163:1723-9.
19. Lwanga SK, Lemeshow S. Sample size determination in health studies: a practical manual. Geneva: World Health Organization; 1991: 38-39.
20. Kenyon SL, Taylor DJ, Tarnow-Mordi W. Broad-spectrum antibiotics for preterm, prelabor rupture of fetal membranes: the ORACLE I randomised trial. Lancet. 2001;357(9261):979-88.
21. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstet Gynecol. 1996;87:163-8.
22. American College of Obstetricians and Gynecologists. Premature rupture of membranes. Obstet Gynecol. 2007;109:1007-19.
23. Sweet RL, Gibbs RS. Chorioamnionitis. In: Sweet RL, Gibbs RS, eds. Infectious Diseases of the Female Genital Tract. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 1995: 554.
24. Duley L, Meher S, Abalos E. Management of pre-eclampsia. BMJ. 2006;332(7539):463-8.
25. NICE. Hypertension in pregnancy - the management of hypertensive disorders during pregnancy. NICE clinical guideline 107, 2011. Available at: guidance.nice.org.uk/cg107. Accessed 1 January 2011.
26. Crawford P. Effectiveness of cinnamon for lowering hemoglobin A1C in patients with type 2 diabetes: a randomized, controlled trial. J Am Board Fam Med. 2009;22(5):507-12.
27. Mercer BM, Miodovnik M, Thurnau GR, Goldenberg RL, Das AF, Ramsey RD, et al. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of membranes: a randomized controlled trial. JAMA. 1997;278:989-95.
28. Combs CA, Garite T, Maurel K, Mallory K, Edwards R, Lu G, et al. 17-Hydroxyprogesterone caproate to prolong pregnancy after preterm rupture of the membranes: early termination of a double-blind, randomized clinical trial. BMC Res Notes 2011;4(1):568.

Cite this article as: Tahir F, Badawi M, Nuqali A, Katib Y, Siddiqui IM, Edris F, et al. The effect of rectal progesterone on latency period as well as maternal and prenatal outcome between 24 to 33 weeks. Int J Clin Trials 2015;2(4):97-101.