Oral progestererone for maintenance tocolysis after arrested preterm labor: A meta-analysis*

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ABSTRACT

Background: The consequences of preterm birth not only for the baby but also for the mother has been well documented over the years. Numerous interventions have been tried and tested and yet it is still a significant problem to date. Progesterone has been documented to be an effective prophylactic drug against preterm labor for those considered at high risk for developing the condition. However, little is known about its effectiveness when given in oral form as a maintenance tocolysis for those who already suffered from an acute episode or preterm labor.

Objective: To evaluate the effectiveness of oral progesterone in the prevention of preterm birth after being diagnosed of preterm labor

Design: Meta-analysis

Subjects: The study population consisted of women with singleton gestation who were diagnosed with preterm labor, defined as having contractions associated with corresponding cervical dilatation, which were treated with oral progesterone as a maintenance tocolytic until delivery.

Data Collection: Journals were searched in different journal databases. Reviewers independently assessed the eligibility of the articles included in this study. Methodologic quality was reviewed using the Cochrane handbook for systematic reviews of interventions. Version 5.1.0 (updated March 2011). Data extracted were analysed using the Review Manager 5.3 Software (Revman 2014) and the Comprehensive Meta-Analysis Software (CMA3 2016).

Results: No statistical difference was noted in terms of latency prolongation, gestational age at birth, occurrence of preterm birth, and on neonatal outcomes such as APGAR Score < 7 at birth, neonatal sepsis, respiratory distress syndrome, and neonatal death between those who received progesterone and those who did not. However, babies in the progesterone group had a mean birthweight higher than their placebo counterparts.

Conclusion: The use of oral progesterone as a maintenance tocolysis after arrested preterm labor showed no statistically significant benefit except for higher birthweight in babies upon delivery.

Keywords: progesterone, preterm labor, preterm birth, tocolysis, oral

INTRODUCTION

Many unfavorable neonatal outcomes stem from prematurity of newborns. Premature babies, defined as those born before 37 weeks age of gestation are at increased risk for developing complications.[1] These may involve one or many organ systems and may present with a variety of symptoms including breathing, vision, hearing, neuromuscular, or developmental problems. These may be evident soon after birth or they may develop much later in life. Furthermore, around 65% of non-anomalous fetal and neonatal morbidity and mortality are attributed to prematurity[2]. As such, much research over the years have been focused on finding ways to control preterm labor and ultimately in preventing preterm delivery.

Preterm labor, defined as spontaneous labor occuring before 37 weeks age of gestation[3] is one of the most common cause of hospital admission of pregnant women worldwide. Management of preterm labor commonly include administration of corticosteroids, such as betamethasone and dexamethasone to hasten lung maturity of the unborn baby, as well as giving of tocolytic agents such as isoxsuprine, nifedipine, and terbutaline. Because of the established importance of progesterone in the maintenance of pregnancy particularly in its early stages, many have also investigated the role of progesterone in preventing preterm birth by its administration even during the second or third trimester. Furthermore, in February 3, 2011, the US Food and Drug Administration (FDA) approved for the first time a medication for the prevention of preterm birth in the form of hydroxyprogesterone caproate injections[4].

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Progesterone can be given in different routes such as oral, intravaginal, or injectable forms. Much studies have focused particularly on its efficacy for maintaining pregnancy by the vaginal route[1,4-6] while only a few studies investigated its efficacy if given in oral form[3-7]. Thus, this paper will analyze whether oral progesterone can be given as a form of management of preterm labor.

OBJECTIVES

A. General Objective

To evaluate the effectiveness of oral progesterone in the prevention of preterm birth after being diagnosed of preterm labor

B. Specific Objectives

1. To determine the length of time progesterone can prolong pregnancy after arrested preterm labor
2. To determine the effective dose and frequency of administration of progesterone in the management of preterm labor
3. To compare the birthweight, number of preterm births, and neonatal outcomes in terms of APGAR score at birth, and occurrence of neonatal respiratoy distress syndrome (RDS), sepsis, and death in those receiving progesterone vs placebo

MATERIAL AND METHODS

A. Studies Considered For This Review

1. Types of Studies

Clinical trials and reviews that involved the use of oral progesterone as a tocolytic after being diagnosed of preterm labor were included in this study. Inclusion criteria for these scientific papers to be included are as follows: 1) published in a local or international scientific journal, 2) published from 1990 to present, 3) utilized randomization, 4) have quantitative data which answer the objectives of this meta-analysis. On the other hand, studies which involved animals instead of people as subjects will be excluded, as well as those which are available only as abstracts and not in full text format. Furthermore, studies which are not written in, or translated to English, were not included.

2. Definition of Study Population

The study population consisted of women with singleton gestation who were diagnosed with preterm labor, defined as having contractions associated with corresponding cervical dilatation, which were treated with oral progesterone as a maintenance tocolytic until delivery. Pregnancies with multiple gestations, ruptured membranes during the course of tocolysis, terminated because of maternal or neonatal comorbidities, or those which used vaginal progesterone, were not included in this study.

3. Intervention Done

All the participants in the study received received either nifedipine or ritodrine as tocolytic for the acute phase of the preterm labor. In addition, the participants in the control group all received placebo while the others received oral progesterone in the form of dydrogesterone or micronized progesterone until delivery.

4. Outcome Measures

The primary outcome measured in this study is the duration in weeks of the latency period that the preterm labor was controlled towards term.

Secondary outcomes investigated included number of preterm babies, birthweight of babies delivered, and number of babies with APGAR score less than 7 at birth. Moreover, mean gestational age of babies at birth as well as neonatal outcomes such as neonatal death and presence of respiratory distress syndrome and sepsis will be investigated.

B. Search Strategy for Identification of Studies

Journal articles which involved the use of oral progesterone as a tocolytic agent after a diagnosed episode of preterm labor was done by using search terms such as oral, progesterone, preterm labor, and tocolysis, in recognized scientific search engines such as PubMed, Medline, Cochrane Library, and Herdin. Search results were then screened based on their title and abstracts. Full text of relevant studies were then retrieved for further screening. Cited references of these articles were also browsed to increase the number of possible studies to be included in the meta-analysis.

C. Methods for Review

Based from the search results found from the different scientific search engines, the full text of the articles deemed relevant to this study were reviewed independently by three individuals. Three studies were assessed and found to meet the inclusion criteria previously set and were also found to have good methodological quality based on the criteria stated in the Cochrane Handbook for Systematic Reviews of Interventions[8]. These include adequacy of sequence generation, method of randomization, method of allocation concealment, method of blinding, handling of attrition bias and intention-to-treat analysis, and equality of treatment of groups aside from the main treatment. Trials that were able to meet all the criteria are considered

to be of high quality because they have low risk for bias, while those who were able to meet only a few of the criteria are considered of fair quality, and those which did not meet any of the criteria are said to have high risk for bias and are therefore of poor quality.

D. Data Processing and Analysis

Data from the studies included were extracted and compiled. Analysis of data were carried out using The Review Manager 5.3 Software (Revman 2014) and the Comprehensive Meta-Analysis Software (CMA3 2016). All the data from the three included studies were quantitative and analysis was set to random effects model with 95% confidence interval. The latency period, gestational age, and birthweight were treated as continuous data and the standard difference in means was computed under the Inverse Variance statistical method. On the other hand, the risk ratio (RR) was computed under the Mantel-Haenszel statistical method for the dichotomous data which include occurrence of preterm birth, APGAR score < 7, neonatal death, respiratory distress syndrome, and neonatal sepsis. Assessment of heterogeneity was also done for the outcomes of the three studies. In particular, Q-value, I-squared, and Tau-squared were computed.

RESULTS

A. Search Results and Studies Included

Three randomized control trials were chosen to be included after comprehensive search was conducted. After retrieving the full text, the articles were read and reviewed by two independent reviewers. As seen in Table 1 which summarizes the major characteristics of the studies included, two of the articles used micronized progesterone while one investigated dydrogesterone as the treatment for the subjects in intervention group while those in the control group all received placebo.

Table 1. Characteristics of Included Studies

Variable	Noblot [7]	Choudhary [9]	Areeruk [3]
Study Location	France	India	Thailand
Year of Publication	1991	2014	2016
No. of Patients Progesterone vs Control	40 (19 vs 21)	85 (43 vs 42)	48 (24 vs 24)
Progesterone	Micronized progesterone (Utrogestan)	Micronized progesterone (Utrogestan)	Dydrogesterone (Duphaston)
Daily dose, mg	900-1600	200	20
Control	Placebo	Placebo	Placebo
Primary tocolytic agent	Ritodrine	Nifedipine	Nifedipine
GA at randomization wks	30-32	31-32	31-32 weeks
Definition of PTL	At least 10 contractions persisting after 1 hour of rest accompanied by change in uterine cervix	4 contractions per 20 mins or 8 per 60 mins with progressive change in cervix or cervical dilatation more than 1 cm or at least 80% cervical effacement	Regular uterine contractions accompanied by changes in cervical dilatation
Study primary outcomes	Latency period Effect of progesterone on dose, duration and method of administration of ritodrine	Latency period	Recurrence of contractions after 48 hours of tocolysis

No local studies were identified by the search and there were no excluded clinical trials. All three randomized control trials identified by the search meet the criteria for inclusion in the study.

B. Methodological Quality of Included Trials

Overall, the methodological quality of the selected trials were moderate to high based on the Cochrane Handbook for Systematic Reviews of Intervention (Figure 1). The study conducted by Noblot was noted to have unclear risk for detection bias because it did not state if blinding of outcome assessment was employed or not. However, it has low risk for all the other biases and thus was concluded to be of moderate quality. On the other hand, the study by Choudhary has unclear risk in terms of attrition bias due to a few participants being lost to follow up. Thus, intention-to-treat analysis was utilized. Meanwhile, the study by Areeruk showed low risk of bias for all parameters and thus it may be considered to be of high quality.

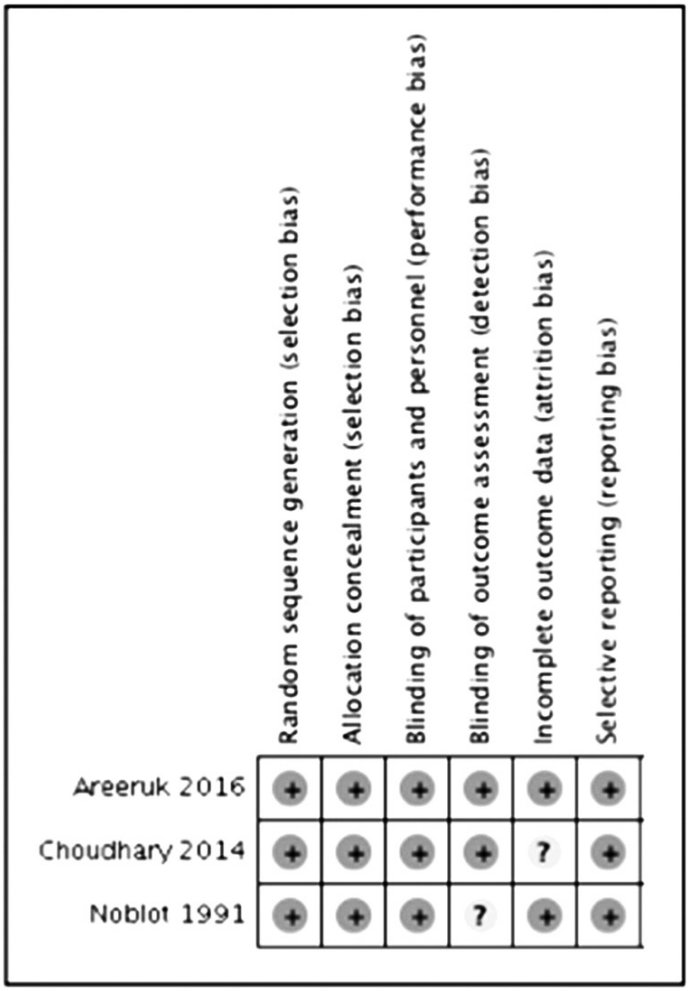

Figure 1. Summary of Methodological Quality of Included Studies

C. Outcome Effects

The summary of the results extracted from the three randomized control trials included in this review and the results of the data and analytical methods performed are presented in Table 2.

a. Primary Outcome: Mean latency period

In the study of Choudhary, the average latency period of those in the progesterone group is 10 days longer than those in the control group. In contrast, the study of Noblot and Areeruk found that those in the control group had an average latency period that is three to five days longer than those in the progesterone group. However analysis of the individual studies did not find significant difference in latency between the intervention and control groups even if there is a difference in their raw means. Furthermore, the synthesis of the studies did not find sufficient statistical evidence of significant difference between and intervention and control. This is evidenced by a 95% confidence interval that contains zero and a p-value of 0.68 based on a random effects assumption.

b. Secondary Outcomes

i. Number of preterm births

The studies by Noblot and Choudhary appear to have homogeneous findings in terms of the magnitude of risk ratios for the occurrence of preterm births. Areeruk had RR=1 due to equality of outomes. However, only Choudhary found significant difference (RR=.564, p=.017) in the occurrence of preterm births between the intervention and control groups. In that study, there is reasonably lower risk (43.6% lower) of preterm birth in the intervention group over the control group. However, the synthesis of all three studies did not find sufficient statistical evidence of significant difference in the occurrence of PTBs between and intervention and control. This is evidenced by a 95% confidence interval that contains RR=1 (equality of effects) and a p-value of 0.095 based on a random effects assumption. Thus, it is not reasonable to infer that the administration of progesterone significantly lowers one's risk of having preterm birth. However, note though that the upper limit of the 95% CI is borderline. Thus, it may be posited that given more evidence, a remarkable RR may be computed in future meta-analyses.

ii. Mean Gestational Age

Only the studies by Choudhary and Areeruk provided information regarding the gestational age of the babies included in their studies. The raw mean gestational age of the babies in the progesterone group is higher by 0.8 week compared to that of those in the control group in the study of Choudhary. Meanwhile, the mean

Table 2. Primary and Secondary Outcomes (Progesterone vs Placebo)

Variable	Noblot (Progesterone vs Placebo)	Choudhary (Progesterone vs Placebo)	Choudhary (Progesterone vs Placebo)	Total	Type of Data	RR / Std Diff in Means (95% CI)
No. of Participants	40 (19 vs 21)	85 (43 vs 42)	48 (24 vs 24)	173 (86 vs 87)	-	-
PTB > 37 wks	16/19 vs 14/21	28/43 vs 16/42	12/24 vs 12/24	56/86 vs 42/87	-	-
PTB < 37 wks	3/19 vs 7/21	15/43 vs 26/42	12/24 vs 12/24	30/86 vs 45/87	Dichotomous	0.691
Mean GA delivery, wk	N/A	36.79 + 2.64 vs 35.90 + 2.00	36.9 + 2.6 vs 36.9 + 2.3	-	Continuous	0.236
Mean latency, d	42 vs 45	33.29 + 22.16 vs 23.07 + 15.42	32.7 + 20.2 vs 38.2 + 24.2	-	Continuous	-0.111
Mean birthweight, g	3077 vs 2832	2440 + 580 vs 2140 + 470	2813 + 614 vs 2817 + 457	-	Continuous	0.389
AS <7 at birth	0/19 vs 0/21	4/43 vs 1/42	2/24 vs 1/24	6/86 vs 2/87	Dichotomous	2.873
Neonatal death	N/A	1/43 vs 1/42	0 vs 0	1/67 vs 1/66	Dichotomous	-
RDS	N/A	6/43 vs 7/42	4/24 vs 2/24	10/67 vs 9/66	Dichotomous	1.071
Sepsis	N/A	2/43 vs 3/42	3/24 vs 1/24	5/67 vs 4/66	Dichotomous	1.175

gestational age of the babies in both the progesterone and the placebo group have almost the same mean gestational age in the study of Areeruk. Both studies did not find significant difference in gestational age between the intervention and control groups and the synthesis of both studies did not find sufficient statistical evidence of significant difference between and intervention and control as evidenced by a 95% confidence interval that contains zero and a p-value of 0.199 based on a random effects assumption.

iii. Mean birthweight

The Noblot and Areeruk studies did not find significant difference in birthweight between the intervention and control groups. However, Choudhary found significant evidence of higher birthweight in the intervention group (300 grams, p=.01). Furthermore, the synthesis of the three studies found sufficient statistical evidence of significant difference between and intervention and control. This is evidenced by a 95% confidence interval of (0.022, .755) and a p-value of 0.0388 based on a random effects assumption.

iv. APGAR score <7 at birth

The studies by Areeruk and Choudhary appear to have homogeneous findings in terms of the direction of risk ratios although both failed to find significance. Meanwhile, the Noblot study was dropped due to equality of outcomes, with no event found on both intervention and control groups. Also, the synthesis of the studies of Choudhary and Areeruk did not find sufficient statistical evidence of significant difference in the proportion of babies with APGAR <7 between the intervention and control as evidenced by a 95% confidence interval that contains RR=1 and a p-value of 0.191 based on a random effects assumption.

v. Neonatal Death

No meta-analysis can be performed since there was no observed difference in the counts per study. As presented in Table 2, one death was reported on each of the groups in the study of Noblot and of Areeruk while no neonatal death was reported in the study of Choudhary.

vi. Respiratory Distress Syndrome (RDS)

The studies by Areeruk and Choudhary appear to have opposite findings in terms of the direction of risk ratios although both failed to find significance. Choudhary found a RR<1 while Areeruk found RR>1. However, both did not have statistically significant findings. Also, the synthesis of both studies did not find sufficient statistical evidence of significant difference in the proportion of babies with RDS between and intervention and control. This is evidenced by a 95% confidence interval that contains RR=1 (equality of effects) and a p-value of 0.875 based on a random effects assumption.

vii. Neonatal Sepsis

The studies by Areeruk and Choudhary appear to have opposite findings regarding neonatal sepsis in terms of the direction of risk ratios although both failed to find significance. Choudhary found a RR<1 while Areeruk found RR>1. However, both did not have statistically significant findings. Furthermore, The synthesis of the two studies did not find sufficient statistical evidence of significant difference in the occurrence of sepsis between and intervention and control. This is evidenced by a 95% confidence interval that contains RR=1 and a p-value of 0.817 based on a random effects assumption.

DISCUSSION

The present study investigated the effects of oral progesterone as a tocolytic after one is diagnosed of having preterm labor. Comprehensive search of existing literature both local and international revealed paucity of data regarding the use of the oral form of progesterone for arrested preterm labor especially when compared to its vaginal form. Furthermore, existing studies which focused on oral progesterone has contrasting results.

The present study showed that the oral form of progesterone is not an effective tocolytic once one is diagnosed of preterm labor in terms of prolonging the latency period and increasing the gestational age of the babies at birth and consequently decreasing the occurrence of preterm birth. Analysis of the three studies showed no statistically significant difference in terms of the number of weeks of latency period and the number of preterm births in those who were given progesterone compared to those who were given placebo. This is consistent with the study of de Tejada, Karolinski, Othenin-Girard et. Al., which also did not show significant prolongation of latency period and decrease in preterm delivery with administration of vaginal progesterone (45 days and 2880 grams in progesterone group vs 52 days and 2955 grams in placebo group respectively)[1]. On the other hand, many other randomized control studies have showed contrasting results and showed the benefits of progesterone use. In 2007, a study conducted by Facchinetti, Paganelli, Comitini, Dante, and Volpe showed that documented cervical shortening in patients who were admitted after an acute episode or preterm labor is attenuated by administration of 17a-hydroxyprogesterone[10]. Longer latency period were also documented with vaginal administration of progesterone in the studies by Saleh Gargari, Habibolahi, Zonobi et. al. (28 $\pm$ 10.5 days in progesterone group vs 9.8 $\pm$ 1.4 days in the control group) and by Borna Sahabi (36.7 $\pm$ 17.9 days in progesterone group vs 24.5 $\pm$ 27.2 days in control group)[2,5]. This phenomenon may be attributed to the ability of progesterone to promoted myometrial muscle relaxation, inihibit formation of gap junctions, and block the action of oxytocin[9,11-15]. Furthermore, progesterone also function as an immunomodulator by increasing Treg cell pool which promotes maternal immune homeostasis[16].

Giving oral progesterone also do not yield statistically improve neonatal outcomes, particularly in terms of APGAR score at birth, and occurrence of neonatal sepsis and respiratory distress syndrome. This is congruent with the findings of de Tejada, Karolinski, Othenin-Girard et. Al. who also included NICU hospitalization in their study.[1] However, the systematic review done by Suhag, Saccone, and Berghella found significant lower neonatal sepsis with administration of vaginal progesterone but not lower incidence of RDS[6].

However, the present study was able to show that babies whose mothers received oral progesterone tend to be heavier compared to their placebo counterparts and the difference is statistically significant.

CONCLUSION

The present study showed that there is no benefit in the administration of oral progesterone for maintenance tocolysis after arrested preterm labor. There were no significant differences in the latency period, occurrence of preterm birth, and neonatal outcomes of those who received progesterone compared to those who were given placebo. However, babies in the progesterone group have significantly higher birthweights compared to their control counter parts.

LIMITATIONS AND RECOMMENDATION

This is the first meta-analysis done involving the use of oral progesterone for maintenance tocolysis after arrested preterm labor. However, as previously stated, only a handful of studies have been conducted on the topic and more are needed to come up with more significant results. The majority of available studies regarding progesterone

concentrated on the oral form's use as a prophylaxis for those considered to be of high in developing preterm labor and on the vaginal form as a maintenance tocolysis after an acute form of preterm labor. Local studies may also be done in order to verify the validity of existing data on the local setting. ■

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