

**Progesterone for prevention of recurrent preterm labor after
threatened preterm labor -A randomized controlled trial**



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Submitted by

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The Principal Investigator and Research Team

Executive Summary of the Research

Introduction

Preterm birth is the major cause of neonatal mortality and morbidity. In addition, prematurity is strongly associated with long-term developmental disabilities, accounting for 1 in 5 children with mental retardation, 1 in 3 children with vision impairment, and almost half of children with cerebral palsy. So, prevention of preterm birth is a public health priority.

Methods

A randomized controlled trial was undertaken in BP Koirala Institute of Health Sciences, where 60 patients were randomized into group 1 (n=29, weekly intramuscular Progesterone) and group 2 (n=31, no treatment) after the arrest of preterm labor with tocolysis. Their latency period till delivery and recurrence of preterm labor and neonatal outcomes were compared.

Results

There was significant reduction in recurrence of preterm labor and increase in latency period in progesterone group. However neonatal outcomes were similar.

Conclusion

Progesterone is useful in reducing the recurrence of preterm labor in a patient who had preterm labor.

Key words: Progesterone, preterm labor, tocolysis

Table of Contents

	<u>Page No.</u>
Acknowledgement	2
Executive Summary of the Research	3
Table of Contents	4
 CHAPTER-I INTRODUCTION	 5
Objective of the Study	6
Rationale of the Study	7
Variables to be Studied	7
 CHAPTER-II METHODOLOGY	 8-9
 CHAPTER-III RESULTS	 10
Analysis	12
CHAPTER-IV CONCLUSION	12
References	13-15
 CHAPTER –V ANNEXES	 16
Proforma	16-17
Informed Consent	18

INTRODUCTION

Preterm birth is the major cause of neonatal mortality and morbidity.¹ In addition, prematurity is strongly associated with long-term developmental disabilities, accounting for 1 in 5 children with mental retardation, 1 in 3 children with vision impairment, and almost half of children with cerebral palsy. Importantly, low-birth-weight infants who are spared significant neonatal morbidity are at higher risk for cardiovascular disease (myocardial infarction, stroke, and hypertension) and diabetes as adults.² The incidence of preterm birth in developing countries is higher than in developed countries. So, prevention of preterm birth is a public health priority. Pharmacological therapy with a variety of drugs of different categories has been the primary method of treating acute preterm labour.³ Patients with arrested preterm labor are at increased risk for recurrence, but to this point, continued tocolytic treatment with any agent after arrest of acute preterm labor is of questionable value in extending gestation or improving outcome.^{3,4} The efficacy of maintenance tocolytic therapy after successful arrest of preterm labor remains controversial. This question is not limited to the use of a specific drug as the data are similar for terbutaline, magnesium sulphate, and calcium channel blockers.³

Spontaneous preterm birth, that is preterm birth after labor or rupture of the membranes, represents approximately 75% of all preterm births.⁵ Of all treatments evaluated for the prevention of spontaneous preterm birth to date, progestational agents have demonstrated the greatest promise. The exact mechanism of progesterone in the prevention of preterm birth is not known, although progesterone has been shown to prevent the formation of gap junctions, to have an inhibitory effect on myometrial contractions, and to prevent spontaneous abortion in women in early pregnancy after excision of the corpus luteum.⁶⁻⁸ Progesterone has also been shown to delay parturition in animals.⁹ In the last 40 years, progestins have been administered to pregnant women for several reasons, including threatening miscarriage, recurrent miscarriage, prevention of preterm labor and luteal support during in vitro fertilization treatment.¹⁰⁻¹²

Progesterone is useful in allowing pregnancy to reach its physiologic term because at sufficient levels in the myometrium, it blocks the oxytocin effect of prostaglandin F₂ α and α -adrenergic stimulation and therefore increases the α -adrenergic tocolytic response.¹³ Natural

progesterone is free of any disturbing teratogenic, metabolic, or hemodynamic effects. This is not true for certain artificial progestagens and β -mimetics.¹⁴

In 2003, two widely published double-blind trials, one of daily vaginal progesterone suppositories and the other of weekly intramuscular injections of 17alpha-hydroxyprogesterone, claimed that the treatments effectively reduce the incidence of preterm birth in women at risk of spontaneous preterm labour.^{15,16}

In study published in 2007, vaginal progesterone treatment reduced the rate of preterm birth among women who were at high risk for preterm birth because of a short cervix.¹⁷ Progesterone has long been considered important agents in the maintenance of uterine quiescence and has been used extensively in primary and secondary prevention of preterm labor.^{15,18}

We therefore chose this pharmacological agent as the active drug for our study. This randomized trial was designed to assess the use of natural progesterone therapy in women who presented with symptoms of preterm labor in preventing the recurrence of preterm labor and increase the latency period after successful tocolysis.

Objectives

General

The purpose of this study is to determine whether supplementation of progesterone (Intramuscular) after inhibition of preterm labor increased latency period and decreased recurrent preterm labor.

Specific

1. Find out whether intramuscular progesterone increased the latency period for delivery.
2. To find out whether incidence of low birth weight and perinatal morbidity decreased.

Rationale of the study

The study aims at preventing recurrent preterm labor in the group of patients who already had preterm labor. Preterm delivery is one of the prime reasons for admission of patient in antenatal ward of BPKIHS. Preterm delivery imposes significant burden to healthcare delivery system. In developing counties like Nepal where resources are limited, preterm neonatal care and immediate and long term complications are of considerable importance. Reducing the rate of preterm delivery and improving the fetal weight at delivery will considerably aid in solving the problem. Thus it aims at reducing the health care burden. There are very few studies around the world like this. So this is groundbreaking study on this regard.

Variables to be studied

Primary

- A. Latency (days)
- B. Gestational age at delivery
- C. Recurrence of preterm labor

Secondary Outcomes:

- A. Need to mechanical Ventilator
- B. Neonatal intensive care unit (days)
- C. Sepsis
- D. Respiratory Distress Syndrome
- E. Birth Weight

METHODOLOGY

This randomized controlled trial was performed in the Department of Obstetrics and Gynecology at B.P. Koirala Institute of Health Sciences over the duration of 1.5 years from 2009 January to June 2010. The Institutional Ethical Review Board approved this study. The National Health Research Council (NHRC) approved and supported the study. Women of 28-34 weeks period of gestation who were admitted to the Obstetrics ward with preterm labor were involved in the study after their labor was successfully arrested with tocolytics. Preterm labor was defined as the simultaneous presence of contractions (> six contractions in 30 min) and cervical changes, either shortening and/or softening or dilation, by manual examination.

Recurrence of preterm labor was defined as recurrence of contractions within 48 h after discontinuation of tocolysis and arrest of contractions. Arrested preterm labor was defined as a 12-h contraction-free period after tocolytic therapy had been discontinued.

Inclusion criteria were singleton pregnancy, intact membranes, no cerclage, cervical dilation of < 2 cm, and the dating of pregnancy confirmed through first trimester ultrasound scanning or last menstrual period.

Exclusion criteria included clinical evidence of intra-amniotic infection or pyelonephritis, medical complications contraindicating tocolysis, evidence of fetal growth retardation, and sonographic evidence of congenital anomalies inconsistent with life.

At admission, all patients had a haemogram, urine microscopy and culture sensitivity and a high vaginal swab for culture and sensitivity. All patients were given oral tocolytic, with an initial bolus of 30mg Nifedipine followed by 10mg 8 hourly. All patients received antibiotic prophylaxis consisting of Tablet Azithromycin 500mg once a day for 5 days along with a five day course of oral Metronidazole. They were given single course of Betamethasone, consisting of two 12 mg injections during the first 24 h after admission. After arrested preterm labor was diagnosed, the patient was counseled about the study and offered an institutional review board-approved informed consent document. Patients included in the study were randomized within 24 h of arrest of labor. The random list was prepared with a computer generated number list. Odds (progesterone, Group 1) and pairs (control, Group 2) defined treatment allocation. Patients who were enrolled as cases received Hydroxy progesterone Caproate 250mg intramuscular weekly till 37 completed weeks or earlier if they

delivered. The remaining patients were included as control subjects and received no drugs. They were discharged for observation in the obstetric clinic weekly. They were followed up either at clinic or by telephone if they do not follow at clinic. The primary outcomes measure were the time until delivery (latency period) and recurrence of preterm labor within 48 h after discontinuation of tocolytic treatment and arrest of contraction. Secondary outcome measures were incidence of low birth weight, and perinatal morbidity (respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and proven sepsis) assessed at the admission to neonatal intensive care unit (NICU).

Categorical data were tested for significance with the χ^2 and Fisher exact tests. Continuous data were evaluated for normal distribution and tested for significance with the Student's t-test. Statistical significance was defined as $P < 0.05$. All patients were included in the analysis.

RESULTS AND ANALYSIS

There were total 60 patients at the study duration that fulfilled the inclusion criteria and were randomized to receive either progesterone or no treatment at all. Majority of the patients who were admitted with the diagnosis of preterm labor delivered with the latency period of 2 to 3 days.

Most of the patients admitted were from vicinity of the institute in both groups. Only few of them were (n=8) were illiterate. None of the patient had history of infertility. No patients had history of previous preterm birth. There was no history of polyhydramnios. All the patients had Bishop Score < 3. Both groups were comparable to each other. (Table: 1)

Table: 1 General character of both groups

Variables	Group 1(n=29)	Group 2(n=31)	P value*
Age in years(mean)	23.24±3.47	22.81±3.73	0.642
Period of gestation at admission(weeks)	32.62±1.72	32.90±1.94	0.552
Parity	1.48±0.74	1.29±0.59	0.267

*P value<0.05 was considered significant

There was significant increase in latency period in intervention arm with decrease in incidence of recurrent preterm labor. (Table: 2)

Table: 2 Outcome of patients after intervention

Variables	Group 1(n=29)	Group 2(n=31)	P value*
Period of gestation at delivery(weeks)	36.59±1.94	34.30±1.47	0.004
Recurrent preterm labor	11	20	0.039
Latency period	25.48±14.64	16.42±9.82	0.003

*P value<0.05 was considered significant

There was no difference in neonatal outcome in both groups. The birth weight, incidence of respiratory distress syndrome, need of neonatal intensive care unit admission was similar in both groups. (Table: 3)

Table: 3 Neonatal outcomes

Variables	Group 1(n=29)	Group 2(n=31)	P value*
Birth weight(in kg)	2.903±0.596	2.781±0.444	0.372
Respiratory Distress Syndrome	3	2	0.938
Need of admission in NICU	3	3	1
Presence of sepsis	2	2	1

*P value<0.05 was considered significant

ANALYSIS

The study showed significant reduction in recurrent preterm labor with the use of progesterone (38% vs 64%). However neonatal outcomes were comparable. In 2005, Roberta Mackenzie et al.¹⁹ conducted a metaanalysis evaluating the use of progesterone for women with high risk of preterm birth. Three trials were eligible for inclusion. There was a significant reduction in risk of delivery less than 37 weeks with progestational agents. There was no significant effect on perinatal mortality or serious neonatal morbidity. The finding was similar to our study. In 2006, a meta analysis by Aravinthan Coomarasamy et al.²⁰ evaluated the use of progesterone in prevention of preterm delivery in high risk patients. A total of nine randomized control trials were evaluated comprising of about 500 patients. Meta-analyses showed reductions in delivery rates before 37 weeks as well as in respiratory distress syndrome with progestational agents. Most of the patients had some of one or more risk factors for preterm birth prior to pregnancy. Our study had homogenous comparable population prior to onset of preterm labor. A similar study was carried out by Sedigheh BORNA and Noshin SAHABI²¹ in Tehran in 2004, where progesterone was given to women after threatened preterm labor in one arm where as another arm of patients received no treatment. There was significant increase in mean latency until delivery, decrease in respiratory distress syndrome, and decrease in low birth weight in progesterone arm group. No significant differences were found between recurrent preterm labor, admission to intensive care unit and neonatal sepsis for the progesterone and control groups, respectively. Our study had significantly decreased in incidence of recurrent preterm labor in progesterone arm group.

All the study discussed above except that one by Sedigheh BORNA and Noshin SAHABI, the comparison was difficult because in other study it was to prevent the preterm labor with progesterone with patients already having risk of preterm labor. Our study had progesterone started after the arrest of preterm labor. There was difference in type of progesterone use and the gestational age at which they were recruited. In our study it was bit late (32 weeks).

The limitation of our study was small sample size and was not compared with placebo. Initially sample size of 250 was calculated (125 in each arm). But that could not be achieved due to one of the natural disaster in country that blocked the access of majority of patients coming to the institute from eastern terai. Other studies quoting the use of progesterone have similar sample size.²¹ Nevertheless, results are significant. It was one of the few studies of its kind.

Conclusion

Progesterone are promising agent to reduce the incidence of recurrent preterm birth after arrest of preterm labor. Studies with larger sample size with double blinding as well as earlier recruitment of patient (at 28-32 weeks) would probably give more convincing results.

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ANNEXES

1. Proforma
2. Informed Consent

PROFORMA

Name:

Age:

Address:

Contact No.:

Occupation:

Education:

LMP:

POG:

Patient History

- | | | |
|--|---------------------------|------|
| 1. History of infertility | a)Yes | b)No |
| 2. History of use of Artificial Reproductive Technique | a)Yes | b)No |
| 3. History of preterm birth | a)Yes | b)No |
| 4. Presence of any Uterine Anomalies | a)Yes | b)No |
| 5. History of previous cervical surgery | a)Yes | b)No |
| 6. Presence of polyhydramnios | a)Yes | b)No |
| 7. Parity of the patient | a) Primipara b) Multipara | |
| 8. Modified Bishop Score of ≥ 3 | a)Yes | b)No |

Outcome

A) Primary Outcome

1. Latency (in days)
2. Gestational age at delivery (in weeks)
3. Recurrence of preterm labour a)Yes b)No

B) Secondary Outcome

- | | | |
|--|-------|------|
| 1. Birth weight (in grams) | | |
| 2. Low birth weight | a)Yes | b)No |
| 3. Presence of sepsis | a)Yes | b)No |
| 4. Presence of Respiratory Distress Syndrome | a)Yes | b)No |
| 5. Need of mechanical ventilator | a)Yes | b)No |
| 6. Number of babies requiring NICU admission | | |
| 7. Stay in NICU (in days) | | |

INFORMED CONSENT

I, hereby, have been fully explained about the procedure of the research going to be conducted on me by the researchers. I fully understand that the research is to study the effect of a drug called Progesterone for maintenance of inhibition of preterm labor after it has been arrested initially by other drugs. I have been fully informed that the research consists of two groups divided blindly on random basis as control and test groups in which only the test group will receive the medication. I have also been fully explained about the possible side effects and complications of the drug being tested and hereby give my consent, on my free will to conduct the proposed research on me. I understand that I can withdraw from this research on my own at any time during the research. I've been informed that my participation will remain strictly confidential. I also confirm that I will not blame the researchers or any other involved staffs of the research in case of any complications and side effects arising due to the use of the proposed drug, that have been informed prior to me by the researchers.

Name of the Participant:

Age:

Address:

Signature:

Name of the witness:

Relation to the Participant:

Address:

Signature:

Date: