

## Research Article

# Comparative study between progesterone and ritodrine for maintenance tocolysis in management of preterm labour

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### Abstract

**Objective:** The aim of this study is to compare the efficacy and safety of Ritodrine and Progesterone for maintenance tocolysis after arrested preterm labour for prolongation of pregnancy and prevention of recurrence of preterm labour.

**Type of the study:** Comparative study.

**Setting:** Department of Obstetrics and Gynecology, Faculty of Medicine, Minia University, Minia, Egypt.

**Patients and methods:** 60 patients attended and admitted from the outpatient clinic of the Obstetric department in Minia University Hospitals with preterm labor symptoms between 28 and 37 weeks gestation which were divided into two groups and assigned for the following drugs:

**Group A:** 30 patients received oral ritodrine (yutopar) Pharco pharmaceuticals.

**Group B:** 30 patients received progesterone vaginal suppository (prontogest 400 IBSA).

**Results:** The present study, showed that there is overall difference between progesterone, and ritodrine, in their efficacy as maintenance tocolysis for prevention of recurrence of preterm labor. As we discuss in our study progesterone has the upper hand on ritodrine in maintenance tocolysis.

**Conclusion:** We would only comment that progesterone looks like a promising drug in this regard and further large studies are required to establish this fact.

### Introduction

Despite advances in perinatal medicine, the incidence of preterm birth continues to increase. The primary goal of tocolytic therapy is to reduce neonatal morbidity and mortality. While studies have demonstrated a prolongation of pregnancy, no tocolytic drug has been shown to improve neonatal outcomes [1].

Resources used to care for low birth weight newborns is one measure of the financial burden of preterm birth. In the United States, more than one third of the dollars expended for infant health care during the first year of life is spent on the 7% of neonates born who weigh less than 2500 gm with also the additional expenditures for developmental handicaps during the remainder of childhood [2].

The early detection of pregnant women at high risk for preterm labor could be the best way to prevent preterm labor [3]. Thereby, bed rest, cervical cerclage, bacterial vaginosis treatment, and prophylactic use of tocolytic drugs could be one of the managements in this high-risk population. The most commonly used tocolytic agents are beta-adrenergic agonists. Meta-analysis has shown that beta-adrenergic agonists, especially ritodrine are associated with a postponement of delivery 24, 48 hours and 7 days. However, such a delay has not been associated with a significant reduction in either perinatal mortality or morbidity. There is a need for an effective tocolytic drug that has a fewer side effects than those in use.

Progesterone is useful in allowing pregnancy to reach its physiologic term. In animal studies medroxyprogesterone treatment prevented labor and possessed anti-inflammatory activity *in vivo*.

Moreover, progesterone antagonists given at term increase the rate of spontaneous labor.

Progesterone at sufficient levels in the myometrium blocks the oxytocin effect of prostaglandin F<sub>2α</sub> and α-adrenergic stimulation and therefore increases the α-adrenergic tocolytic response [4]. Natural progesterone is free of any disturbing teratogenic, metabolic, or hemodynamic effects. This is not true for certain synthetic gestagens and β mimetics [5].

### Aim of the work

The aim of this comparative study is to compare the efficacy and safety of Ritodrine and Progesterone for maintenance tocolysis after arrested preterm labour for prolongation of pregnancy and prevention of recurrence of preterm labour.

### Patients and methods

This comparative study was held in the period from May 2014 till December 2014 on 90 patients attended and admitted from the

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outpatient clinic of the Obstetric department in Minia University Hospitals with preterm labor symptoms between 28 and 37 weeks gestation which were divided into three groups and assigned for the following drugs:

Group A: 30 patients received oral ritodrine (yutopar) Pharco pharmaceuticals.

Group B: 30 patients received progesterone vaginal suppository (prontogest 400) IBSA.

Regimens of administration of tocolytics: All regimens of administration started after stoppage of acute attack of preterm labour whatever the method of management.

Group A: 30 women received Oral Ritodrine 10 mg tablet was given every 12 hours till 37 weeks of pregnancy or till deliver whichever occurs early.

Group BS: 30 women received progesterone pessaries containing 400 mg of natural progesterone per pessary. It was used by the patient as one pessary per vaginum at bed time until 37 weeks or till delivery whichever occurs early. Medication will have started at 28 weeks and stopped at the end of 37 weeks.

#### **Inclusion criteria:**

1. Painful, regular uterine contractions associated with boats of diarrhea or associated with menstrual like cramps.
2. Singleton pregnancy.
3. Intact membranes.
4. Cervical dilation of 3cm or less.
5. The dating of pregnancy confirmed through first trimester ultrasound scanning or last menstrual period.

#### **Exclusion criteria:**

- Acute attack of preterm labour
- Cervical dilatation > 3 cm.
- Hypotension (less than 80 mmHg systolic or 50 mmHg diastolic).
- Major fetal congenital anomalies.
- Unreassuring traces of fetal cardiotocography.
- Antepartum hemorrhage or history of recurrent vaginal bleeding.
- Rupture of membranes.
- Multiple pregnancy.
- Polyhydraminos.
- Chorioamnionitis.
- Unexplained pyrexia.
- Medical disorders i.e. diabetes, cardiac disease.
- Sensitivity or contraindication to nifedipine or  $\beta$ -agonist.
- Other tocolytic therapy during this pregnancy.

#### **All patients are subjected to:**

1. Informed written consent.
2. History taking.

3. General examination: With special attention to blood pressure, pulse and temperature.
4. Abdominal examination: To palpate the uterine contractions and monitoring of the fetal heart rate.
5. Sonographic assessment: To estimate the gestational age, amount of liquor and to exclude placenta previa, placental abruption and major fetal congenital anomalies. Several ultrasound parameters were used to estimate gestational age including biparietal diameter (BPD), head circumference (HC), and femur length (FL). The ultrasound machine used was Toshiba SSA- 340A.
6. Pelvic examination: To assess the state of membranes and exclude their rupture through examination with a sterile Cusco speculum, to exclude vaginal bleeding and assess the state of the cervix.
7. Urine analysis to detect urinary tract infection.
8. Haemoglobin level for correlation between anaemia, urinary tract infection and preterm labour.
9. Electronic monitoring of uterine contractions and fetal heart rate until the uterine contractions disappeared.
10. The women were initially hydrated with 500 mL of Ringer's lactate over a 30-min period. All patients received antibiotic prophylaxis consisting of 3rd generation cephalosporin intravenous (1-g dose every 12 hours) for 48 h. All patients with gestational age less than 36 weeks received corticosteroids in the form of 6mg Dexamethasone to be repeated/ 12 hours for 4 doses.
11. Administration of tocolytic agent in the form of vaginal progesterone, oral ritodrine or oral nifedipine. If the women were stable and undelivered after 48 h of maintenance tocolysis, they were discharged and followed-up in the antenatal care clinic.

All patients discharged with the following instructions: Avoid intercourse, heavy work and carrying heavy things, Return back to the hospital if develop symptoms of preterm labour.

At every visit, fetal growth was assessed clinically and patients were evaluated for side-effects. Maintenance tocolysis was given until 37 weeks or until the onset of spontaneous labour, whichever was earlier. Tocolytic failure was defined as the persistence of symptomatic uterine contractions despite maximal attainable doses of therapy, rupture of previously intact membranes, or occurrence of severe side effects necessitating discontinuation of therapy.

Follow up of the patient weekly in the obstetric outpatient clinic until delivery to detect the date and mode of delivery and the fetal outcome. Repeated episodes of preterm labor that might occur were treated with the same lines of treatment as the first episode. Gestational age at delivery, mode of delivery, birth weight, apgar scores at 1 and 5 minutes and still birth or neonatal death were recorded. The primary outcomes measure was the time until delivery (latency period) and recurrent attacks of preterm labour during period of maintenance tocolysis. Secondary outcome measures were incidence of low birthweight and perinatal morbidity (respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, proven sepsis) assessed at the admission to neonatal intensive care unit (NICU).

Data were statistically described in terms of range, mean  $\pm$  standard deviation ( $\pm$  SD), frequencies (number of cases and percentages when appropriate). Comparisons of quantitative variables between the study groups was done using one-way analysis variance (ANOVA) test with

postoc multiple 2-group comparisons. Within group comparisons between pre-and post-treatment values were done using paired t test. For comparing categorical data, Chi square ( $\chi^2$ ) test was performed. Exact test was used instead when the expected frequent is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2003 (Microsoft Corporation, USA) and SPSS (Statistical Package for the Social Science; SPPS Inc., Chicago, II, USA) version 15 for Microsoft windows.

## Results

Outcome data were available for 60 women (30 women in the ritodrine group & 30 women in the progesterone group). The results of this study are summarized in the Tables 1-6.

## Discussion

Prematurity is the leading cause of neonatal death and future disabilities. Improvement in neonatal care have led to higher rates of survival among very preterm infants, but a major effect on the associated mortality and morbidity will be achieved only by better identification of women at higher risk for preterm labor and by development of an effective intervention to prevent this complication. Prevention of preterm birth is a public health priority and is a major challenge for the obstetrician. Primary prevention is desirable but not always possible, as the pathophysiology is multifactorial and poorly understood [6].

**Table 1.** Patient demographic criteria at admission.

	Group I (Ritodrine) N=30	Group II (Progesterone) N=30	P value
<b>Maternal age:</b>			
<b>Range:</b>	(18-30)	(20-33)	0.232
<b>Mean ± SD</b>	25.6 ± 3.99	26.7 ± 3.64	
<b>Parity:</b>			
<b>PG.</b>	5 (16.7%)	3 (10%)	0.131
<b>MG.</b>	25 (83.3%)	27 (90%)	
<b>Previous PTL or abortion:</b>			
<b>No.</b>	12 (40%)	15 (50%)	0.669
<b>Yes.</b>	18 (60%)	15 (50%)	
<b>BMI</b>			
<b>Range:</b>	(18-25)	(18-25)	0.474
<b>Mean ± SD</b>	23.6 ± 1.76	24.1 ± 1.48	

**Table 2.** Comparison between the study groups as regard investigations prior to starting tocolytic drug.

	Group I (Ritodrine) N=30	Group II (Progesterone) N=30	P value
<b>Hb:</b>			
<b>Range:</b>	(8.2-11.4)	(8-11.8)	0.920
<b>Mean ± SD</b>	10.79 ± 0.87	10.71 ± 1.01	
<b>U.A:</b>			
<b>No.</b>	26 (86.7%)	24 (80%)	0.787
<b>Yes.</b>	4 (13.3%)	6 (20%)	

**Table 3.** Comparison between study groups as regard frequency of recurrence of attack of preterm labour.

	Group I (Ritodrine) N=30	Group II (Progesterone) N=30	P value
<b>Frequency of recurrence:</b>			
<b>Range:</b>	(1-4)	(1-3)	0.008*
<b>Mean ± SD</b>	2.5 ± 1.13	1.93 ± 0.73	

P value: 0.008; \* (significant)

**Table 4.** Comparison between the study groups according to mean gestational age at delivery.

	Group I (Ritodrine) N=30	Group II (Progesterone) N=30	P value
<b>Gestational age at delivery:</b>			
<b>Range:</b>	(28-38)	(28-38)	0.015*
<b>Mean ± SD</b>	33.43 ± 3.61	35.8 ± 2.57	
<b>Gestational age at delivery:</b>			
<b>28-32 w</b>	9 (30%)	3 (10%)	0.024*
<b>32-35 w</b>	6 (20%)	0 (0%)	
<b>35-37 w</b>	8 (26.7%)	9 (30%)	
<b>≥ 37w</b>	7 (23.3%)	18 (60%)	

**Table 5.** Comparison between the study groups as regard prolongation of gestation to 37 weeks duration of tocolysis.

	Group I (Ritodrine) N=30	Group II (Progesterone) N=30	P value
<b>Gestational age at delivery:</b>			
<b>&lt; 37w</b>	23 (76.7%)	12 (40%)	0.015*
<b>≥ 37w</b>	7 (23.3%)	18 (60%)	
<b>Tocolysis duration:</b>			
<b>Range:</b>	(0.57-2)	(0.71-8)	< 0.001*
<b>Mean ± SD</b>	1.36 ± 0.58	4.42 ± 2.78	
<b>Outcome:</b>			
<b>Take home baby</b>	9 (30%)	18 (60%)	0.067
<b>Incubation</b>	12 (40%)	10 (33.3%)	
<b>END</b>	9 (30%)	2 (6.7%)	

**Table 6.** Comparison between the study groups according to maternal side effects and complications.

	Group I (Ritodrine) N=30	Group II (Progesterone) N=30	P value
<b>Hypotension:</b>			
<b>No.</b>	24 (80%)	29 (96.7%)	0.118
<b>Yes.</b>	6 (20%)	1 (3.3%)	
<b>Palpitation:</b>			
<b>No.</b>	23 (76.6%)	29 (96.7%)	0.031*
<b>Yes.</b>	7 (23.4%)	1 (3.3%)	
<b>Tachycardia:</b>			
<b>No.</b>	23 (76.6%)	29 (96.7%)	0.031*
<b>Yes.</b>	7 (23.4%)	1 (3.3%)	
<b>Nausea &amp; vomiting:</b>			
<b>No.</b>	29 (96.7%)	29 (96.7%)	1
<b>Yes.</b>	1 (3.3%)	1 (3.3%)	
<b>Flushing and redness:</b>			
<b>No.</b>	27 (90%)	30 (100%)	0.074
<b>Yes.</b>	3 (10%)	0 (0%)	
<b>Constipation:</b>			
<b>No.</b>	29 (96.7%)	30 (100%)	0.160
<b>Yes.</b>	1 (3.3%)	0 (0%)	
<b>Atonic pphge:</b>			
<b>No.</b>	29 (96.7%)	28 (93.3%)	0.809
<b>Yes.</b>	1 (3.3%)	2 (6.7%)	

The early detection of pregnant women at high risk for preterm delivery could be the best way to prevent preterm birth. In the present study, 60 eligible pregnant women with a gestational age between 28 weeks and 37 weeks were included, out of which for maintenance tocolysis, 30 received ritodrine, 30 women received progesterone and 10 women were lost to follow-up.

When comparing patient characteristics in the two study groups there was no statistically significant difference between study groups as regards the age, parity, gestational age at admission and number of previous preterm labor.

Also, there is no statistically significant difference in Hb level and presence of asymptomatic bacteruria in between patients included in the study groups with special noting that anemic patients in this study were associated with urinary tract infection.

A series of studies were done and showed that ritodrine and progesterone were effective in the management of preterm labor. Most of the studies were comparing only two drugs with each other; however, in the present study we compared the three drugs in their efficacy, maternal side effects and complications. Those studies and their results will be discussed and compared with the results of the present study. As regard recurrence of attacks of preterm labour there was statistically significant difference between the three study groups with higher percentage of recurrence in ritodrine group (80%) if compared with and progesterone group (40%).

This agreed with Freak-Poli, *et al.* [7] study in which 200mg daily vaginal progesterone was used in pregnant women with short cervix from 24 to 34 weeks of gestations and reported that incidence of delivery before 34 weeks of gestation was 19.2% in progesterone group compared with 34.4% in placebo group and the difference was statistically significant.

However, these results are not in agreement with the results reported by O'Brien *et al.* [8] in which 659 pregnant women with history of spontaneous preterm labor assigned randomly to one daily treatment with 90 mg progesterone vaginal gel or placebo from 23 weeks of gestation till 37 weeks. They reported that progesterone did not decrease the frequency of preterm birth rates (<32 weeks of gestation). As regard frequency of recurrence of attacks of preterm labour there was statistically significant difference between the three study groups with higher mean of recurrence in ritodrine group ( $2.5 \pm 1.13$ ) if compared to both and progesterone group ( $1.93 \pm 0.73$ ).

These findings are supported by the results reported by Freak - Poli *et al.* [7] where uterine contractions were more frequently found among placebo group than in the progesterone group (54.3% Vs 23.6%) respectively. As regard the mean gestational age at delivery there was statistically significant difference between the three study groups with higher mean in progesterone group ( $35.8 \pm 2.57$ ) if compared to ritodrine group ( $33.43 \pm 3.61$ ) but there is no significant difference compared to ritodrine group ( $33.43 \pm 3.61$ ), P value: 0.015\* (significant). As regard prolongation of gestation to 37 weeks or more there was statistically significant difference between the study groups with more prolongation of gestational age in progesterone group 18 cases (60%) if compared to ritodrine group 7 cases (23.3%)

On the other hand, study was done by Papatsonis *et al.* [9], to compare the efficacy with ritodrine in the management of preterm labor on one hundred eighty-five singleton pregnancies with preterm labor. The principal outcome assessed was delay of delivery. Ritodrine was discontinued in 12 patients because of severe maternal side effects, and their results were excluded from further analysis. More women in the ritodrine group delivered within 24 hours (22 versus 11, p-value = .006), within 48 hours (29 versus 21, p-value = .03), within 1 week (45 versus 36, p-value = .009).

As regards prolongation of gestation from time of admission to time of delivery (duration of tocolysis) in weeks there was statistically

significant difference between the two study groups with higher mean in tocolytic duration in weeks in progesterone group (4.42) if compared to ritodrine group (1.36) but there is no significant difference between progesterone group (4.42) if also there is no significant difference between compared to ritodrine group. P value: 0.001\* (significant).

This comes in accordance with the randomized, multi-centric trial done by Van De Water *et al.* [10], on ninety-three patients, who compared the tocolytic effectiveness of nifedipine and ritodrine and included a long-term follow-up of the newborns after 2 years of age. Patients with imminent preterm labor were randomized and received ritodrine. Side-effects, tocolytic effectiveness and neonatal outcome were studied. Development of the children was studied after the age of 2 years by a parental questionnaire. Birth was postponed for an average of 4.3 weeks (30.1 days) in the ritodrine group

As regard, neonatal outcome there was no statistically significant difference between the two study groups but there was statistically significant difference between progesterone group if compared to ritodrine group (significant p value 0.025\*) as 60% of babies discharged together with the mother to the home, 33.3% of babies were incubated and 6.7% of babies develop early neonatal death. However, in ritodrine group 30% of babies were taken to the home, 40% were incubated and 30% of babies develop early neonatal death.

Papatsonis *et al.* [9], supported his previous work ritodrine for treatment of preterm labor with respect to neonatal outcome. There were no significant differences in umbilical artery pH values and Apgar scores between groups. progesterone was associated with lower admission rates to the NICU (49% versus 66%) compared with ritodrine, and lower incidences of RDS (21% versus 37%), intracranial bleeding (18% versus 31%), and neonatal jaundice (52% versus 67%).

As regard maternal side effects there was statistically significant difference between the three study groups as regards maternal side effects as tachycardia and palpitation which were more common in patients receiving ritodrine than in other patient groups (p-value: 0.031\*), while flushing and redness were more common in ritodrine group (16.6%) than progesterone groups (10%) (0%) but without significant difference between the two groups also there was higher incidence of hypotension in ritodrine group.

However, no women in our study discontinued medication due to adverse effects or medication intolerance. As regard, maternal postpartum complications atonic postpartum hemorrhage is the main complication of tocolysis but there was no statistically significant difference between the two study groups on incidence of postpartum haemorrhage [11-12].

## Conclusion and recommendations

The present study, showed that there is overall difference between progesterone, and ritodrine, in their efficacy as maintenance tocolysis for prevention of recurrence of preterm labor. As we discuss in our study progesterone has the upper hand on ritodrine in maintenance tocolysis. Also, it showed that the maternal side effects were fewer with progesterone than ritodrine. Also, vaginal progesterone reduces the rate of preterm labor, prolongs gestational age at delivery, reduces the frequency of uterine contractions, improves the symptoms of preterm labor and improves neonatal outcome.

Although the sample size we studied was reasonable, it might be difficult to give clear recommendations upon our results only, and it is proposed that further larger multi-centric study would be done on

this topic to confirm or negate our results. We would only comment that progesterone looks like a promising drug in this regard and further large studies are required to establish this fact.

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