Original Article

# Effect of Single Course Versus Repeated Single Course of Antenatal Corticosteroid (Dexamethasone) in Preterm Premature Rupture of Membranes on Neonatal Respiratory Outcome "Randomized Control Trials"

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## ABSTRACT

**Background:** Premature ROM (PROM) refers to rupture of the fetal membranes prior to the onset of labor irrespective of gestational age.

**Aim:** To compare between effects of single course versus repeated single course of antenatal corticosteroids in PPROM on neonatal outcomes.

**Materials and Methods:** The study included 200 pregnant patients with established diagnosis of PPROM admitted to Ain Shams University Maternity Hospital, 100 of them received single course regimen (group I) and the other 100 received single course regimen (group II). Newborns were assessed for gestational age, evidence of RDS and congenital infections.

**Results:** There was no statistical difference between the 2 groups regarding age distribution, Parity, gestational age at the onset of ROM and gestational age at delivery. There was no statistical difference between the 2 groups regarding, mode of delivery, birth weight or neonatal deaths, neonatal sepsis. The only variables which was significantly affected between the 2 groups was the development of RDS which was less in the repeated single course group (Group II) than the single course group (Group I) with high statistical significance suggesting that repeated single course improves lung maturity.

**Conclusion:** Repeated single course of corticosteroid is preferred over single course since it has better effect by decreasing the incidence of RDS and the duration on mechanical ventilation.

**Key Words:** Antenatal corticosteroid, dexamethasone, neonatal respiratory outcome, preterm premature rupture of membranes.

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## INTRODUCTION

Preterm premature rupture of membranes (PPROM) occurs in women with membranes rupture before labor and before 37 weeks of gestation. PPROM is the primary etiology for 25% of preterm births which can result in major perinatal morbidity and mortality. PPROM occurs in 3 percent of pregnancies; approximately 0.5 percent of pregnancies <27 weeks, 1 percent of pregnancies 27 to 34 weeks, and 1 percent of pregnancies 34 to 37[1].

In contemporary obstetric practice, antenatal corticosteroids have become integral to the clinical management of PPROM to reduce the risk of neonatal mortality and morbidity, after a systematic reviews of randomized trials that showed neonatal death, respiratory distress syndrome, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and duration of neonatal respiratory support were significantly reduced by antenatal glucocorticoid treatment, without an increase in either maternal or neonatal infection. Mean risk reduction for these adverse events ranged from 30 to 60 percent[2].

The most common cause of deaths among preterm babies is respiratory distress syndrome (RDS), an acute lung disease related to immaturity of the lungs and, specifically, surfactant deficiency[3]. The incidence and severity of RDS show an inverse relationship with gestational age[4].

Antenatal steroid treatment for women who are at risk of preterm delivery has emerged as the most effective intervention for the prevention of RDS, reducing early neonatal mortality and morbidity[5]. Most glucocorticoid hormones, natural and artificial, are capable of crossing the placenta and trigger the maturational process that leads to the production and release of surfactant into the alveoli of the fetal lung[6].

For women with PPROM, there is controversy about the use of a single course or a repeated single course of antenatal corticosteroids[7]. For women with PPROM before 34 weeks' gestation, one course of antenatal corticosteroids has been recommended by the American College of Obstetricians and Gynecologists (ACOG) and a National Institute of Health consensus panel[8].

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However, surveys from Australia and Canada indicate that, for women at risk of preterm labor and birth, steroid prescribing patterns of obstetricians vary markedly[9].

Although the opportunity to administer a second course of steroids is not an uncommon clinical scenario in the setting of PPROM, it remains uncertain whether rates of neonatal morbidity differ between those receiving a repeat course of antenatal corticosteroids versus a single corticosteroid course. Therefore, analyzing perinatal outcomes of women with PPROM exposed to a single or a repeat course of corticosteroids has potentially important clinical relevance[9,10].

## AIM OF THE WORK

This study aimed to compare between effects of single course versus repeated single course of antenatal corticosteroids in PPROM on neonatal outcomes.

## PATIENTS AND METHODS

### *Type of the study*

Randomized control trial.

### *Place*

Ain Shams University Maternity Hospital.

### *Study period*

From June 2018 till December 2018

### *Sample size justification*

Depending on Chow *et al*.[11] who found that frequency of respiratory distress syndrome was (48%) and (54.5%) in single and repeated courses respectively, and assuming the power =0.80 and α=0.05, and by using PASS 11th release the minimal sample size for an equal size case control study to detect a significant statistical difference between poor and good respondents is 200 women distributed into 2 groups each consisting of 100.

### *Study population*

The study was conducted on two hundred (200) pregnant women with PPROM from June 2018 till December 2018. They were distributed into 2 groups consisting of 100 each. Group A received course of dexamethasone once, while the other group, group B received two courses, one week apart.

### *Allocation, concealment and randomization*

Patients participating in the study were randomized by a computer generated randomization sheet using MedCalc version 13. Two hundred opaque envelopes were numbered serially and in each envelope the corresponding letter which donating the allocated group was put according to randomization table. Then all envelopes were closed and put in one box. When the first patient arrived, the first envelope was opened and the patient was allocated according to the letter inside.

### *Inclusion criteria*

Pregnant women with the following criteria: (Signing the informed consent to participate in the study).

1. Rupture of membranes: Diagnosed by:
    - positive history of gush of clear warm fluid
    - speculum examination: pooling of liquor
    - dressing soaked with liquor
    - Below average MVP < 2cm, AFI<5cm
2. Between 20 to 35 years.
3. Gestational age between 28+0- up to complete 33 weeks.

### *Exclusion criteria*

1. Gestational ages < 28 weeks or > 34 weeks
2. Fetal congenital anomalies.
3. Cervical dilatation of more than 4 cm or effacement more than 80%.
4. Maternal complications as severe preeclampsia, eclampsia, abruptioplacenta, chorioamnionitis, diabetes mellitus, maternal heart disease, SLE, twins, IUGR.
5. Women with a previous preterm labor episode in the current pregnancy or delivered before 48 h after initiating therapy.
6. Documented fetal lung maturity (grade of placenta, turbidity of liquor)
7. Contraindication to corticosteroids.
8. Non-reassuring fetal well being.
9. Non vertex presentation
10. Meconium stained liquor

### *Intervention*

The research consisted of 2 groups each consisting of 100 patients. Patient fulfilling the inclusion criteria was included in the study after taking informed written consent the recruited patients were subjected to the following:

### *(1) History*

### *Personal history*

Name, age, occupation, residence, special habits of medical importance.

### *Obstetric history*

Gravidity, Parity, Mode of previous delivery, Gestational diabetes, Weight gain in current pregnancy, First day of last menstrual period and menstrual regularity.

### *Past history*

History of any medical disorder or surgical history.

### *History of the present pregnancy*

Medical or surgical condition to define high risk pregnancy.

### *(2) Examination*

General examination: for vital signs (blood pressure, pulse and temperature).

Local examination:

i. Abdominal examination: for assessment of uterine tenderness, and contractions.

ii. Vaginal examination (using speculum): for detection of cervical changes, pooling of liquor, prolapsed cord.

### *(3) Investigations*

### *Laboratory testing*

Complete blood picture(follow up TLC)

### *Ultrasonographic scanning*

- Follow up MVP, AFI
- Liquor turbidity
- Placental maturity
- Any structural abnormalities
- Fetal well being according to gestational age

The 1st group received single course of dexamethasone (Decadron), 6mg every 12 hours IM for 48 hours in gestational age of 28 weeks to completed 33 weeks.

The other group received 2 courses of dexamethasone 6mg every 12 hours for 48 hours 1 week apart. (ACOG, 2016)

### *Outcome*

### *1. Primary outcome*

### *RDS (Respiratory Distress Syndrome)*

Symptoms may include (detected by neonatologist attending the delivery up to the next 6 hours)

- Bluish color of the skin and mucus membranes (cyanosis)
- Brief stop in breathing (apnea)
- Decreased urine output
- Working alae nasai
- Rapid shallow breathing
- Shortness of breath and grunting sounds while breathing

### *The following tests are used to detect the condition*

- Blood gas analysis -- shows low oxygen and excess acid in the body fluids.
- Chest x-ray -- shows a "ground glass" appearance of the lungs that is typical of the disease. This often develops 6 to 12 hours after birth.
- Lab tests -- help to rule out infection as a cause of breathing problems by follow up of CBC and CRP[12].

### *1. Secondary outcomes*

- Chorioamnionitis (intra- amniotic infection): detected by 2 of the following criteria:
  1. maternal temp > 38
  2. maternal tachycardia
  3. fetal tachycardia

4. uterine tenderness
5. offensive vaginal discharge
6. TLC>15

### *NEC(necrotizing enterocolitis)*

- IVH (interventricular haemorrhage).
- culture-proven sepsis,
- NICU admission

### *Ethics*

The study protocol was designed in agreement to the declaration of Helsinki for ethical committee of Obstetrics and Gynecology Department, Ain Shams University. The study purpose and procedures are to be explained to all approached and eligible women. Women have to sign an informed written consent before participating in the study. Any participating woman is informed that she has the right to withdraw from the study at any phase without any adverse impact on the medical service she receives.

## STATISTICAL ANALYSIS

Categorical data were compared using the chi-square test or Fisher Exact test and the Student t-test or Mann–Whitney U test for continuous data. The results of these analyses were presented as adjusted least square means (standard error of the mean). Statistical analyses were performed using SPSS 20.0 (IBM Corp., Armonk, NY) and SAS 9.3 (SAS Institute Inc., Cary, NC), with $p < 0.05$ considered as statistically significant.

## RESULTS

Regarding RDS in this study, there was significant difference between the 2 groups in this study. Respiratory distress syndrome was diagnosed clinically and by the need for mechanical ventilation and oxygen for at least 48 hours and the presence of radiological findings. In group I (single course group) 39.4% had neonates with RDS and in group II (repeated single course) 25%. (Tables 1-6).

**Table 1:** Demographic characteristics in the studied groups

| Parameters | Values | Repeated (n=92) | Single (n=94) | *P* |
|---|---|---|---|---|
| Age (years) | Mean±SD | 27.5±3.0 | 27.7±3.0 | ^0.548=NS |
| | Range | 21.0–35.0 | 20.0–35.0 | |
| BMI ($kg/m^2$) | Mean±SD | 29.3±2.0 | 29.0±1.7 | ^0.235=NS |
| | Range | 24.9–29.2 | 25.1–29.2 | |
| Parity n (%) | Primiparous | 32 (34.8) | 36 (38.3) | #0.619=NS |
| | Multiparous | 60 (65.2) | 58 (61.7) | |
| GA at enrollment (weeks) | Mean±SD | 30.7±1.0 | 30.6±1.0 | ^0.336=NS |
| | Range | 28.4–33.7 | 28.1–33.6 | |

^Independent t-test, #Chi square test, NS = no significance

**Table 2:** Delivery findings in the studied groups

| Parameters | Terms | Repeated (n=92) | Single (n=94) | *P* |
|---|---|---|---|---|
| Latency form enrollment to delivery days) | Mean±SD | 15.2±4.5 | 14.3±4.1 | ^0.142=NS |
| | Range | 10.0–28.0 | 7.0–27.0 | |
| GA at elivery (weeks) | Mean±SD | 32.8±1.2 | 32.6±1.1 | ^0.354=NS |
| | Range | 30.5–35.6 | 29.7–35.2 | |
| Mode of elivery (n, ٪) | VD | 59 (64.1%) | 58 (61.7%) | #0.732=NS |
| | CS | 33 (35.9%) | 36 (38.3%) | |
| Birth weight (gm) | Mean±SD | 1944.5±280.5 | 2014.3±274.9 | ^0.088=NS |
| | Range | 1240.0–2510.0 | 1330.0–2610.0 | |

^Independent t-test, #Chi square test, NS = no significance

**Table 3:** RDS in the studied groups

| Findings | Repeated (n=92) | Single (n=94) | #*P* |
|---|---|---|---|
| RDS | 23 (25.0%) | 37 (39.4%) | 0.036* |
| | Value of repeated over single | | |
| Items | Value | 95% CI | |
| Rate reduction | 14.4% | 0.2%–27.8% | |
| Efficacy | 36.5% | 0.5%–60.5% | |
| Relative Rate | 0.64 | 0.41–0.98 | |
| Number needed to prevent | 7.0 | 3.6–>100.0 | |

#Chi square test, *Significant, CI: Confidence interval

**Table 4:** Fetal and neonatal complications in the studied groups

| Findings | Repeated (n=92) | Single (n=94) | *P* | RR (95% CI) |
|---|---|---|---|---|
| Chorioamnionitis | 35 (38.0%) | 29 (30.9%) | #0.302 | 1.23 (0.83–1.84) |
| Sepsis | 20 (21.7%) | 15 (16.0%) | #0.313 | 1.36 (0.744–2.49) |
| NEC | 5 (5.4%) | 7 (7.4%) | #0.577 | 0.73 (0.24–2.24) |
| IVH | 14 (15.2%) | 17 (18.1%) | #0.600 | 0.84 (0.44–1.61) |

#Chi square test, RR: Relative rate, CI: Confidence interval

**Table 5:** NICU and MV in the studied groups

| Parameters | | Repeated (n=92) | Single (n=94) | *P* | RR (95% CI) |
|---|---|---|---|---|---|
| NICU | | 37 (40.2%) | 55 (59.8%) | #0.039* | 0.73 (0.53–0.99) |
| NICU duration (days) | Mean±SD | 3.0±2.4 | 4.5±2.7 | ^0.008* | -- |
| | Range | 0.0–10.0 | 1.0–13.0 | | |
| MV(Mechanical Ventilation) | | 11 (12.0%) | 23 (24.5%) | #0.027* | 0.49 (0.25–0.94) |
| MV duration (days) | Mean±SD | 1.4±0.7 | 2.1±0.8 | ^0.014* | -- |
| | Range | 1.0–3.0 | 1.0–4.0 | | |

#Chi square test,*Significant, RR: Relative rate,^=Non dependant T test,CI: Confidence interval, NICU and MV (Mechanical Ventilation) durations only in required cases,

**Table 6:** Neonatal condition at discharge among the studied groups

| Condition | Repeated (N=92) | Single (N=94) | #P | RR (95% CI) |
|---|---|---|---|---|
| Died | 14 (15.2%) | 23 (24.5%) | 0.114 | 0.62 (0.34–1.13) |
| Lived | 78 (84.8%) | 71 (75.5%) | | |

# Chi square test test, RR: Relative rate, CI: Confidence interval

## DISCUSSION

PROM refers to the spontaneous rupture of the amniotic membranes before the onset of labour at or before term. If rupture occurs prior to 37 weeks gestation it is referred to as preterm PROM (PPROM)[13].

Preterm labour is the main expected consequence of PPROM with a latency between rupture and delivery inversely proportional to gestational age[14].

PPROM is an independent predictor of perinatal complications and pregnancies complicated by PPROM are associated with a higher incidence of severe neonatal morbidity than those with preterm labor with intact membranes[15].

Corticosteroids are frequently used by obstetricians to enhance fetal lung maturity among patients liable to preterm labor[16].

Administration of antenatal corticosteroids to all patients at risk of preterm delivery between 24 and 34 weeks' gestation has been recommended by the National Institutes of Health Consensus Development Panel Conference Statement since[17] when they first found such compelling evidence that antenatal corticosteroid administration benefits premature infants. This has been the recommendation in each year's guideline up to this year.

The benefits of antenatal glucocorticoids for the preterm neonate include reduction in the risk of respiratory distress syndrome, intraventricular hemorrhage, and neonatal mortality[18]. However, the greatest benefit is seen in

infants born within seven days of treatment[19]. The optimal management of women remaining at risk of preterm birth more than seven days after treatment remains unclear[20].

Administration of repeated single course of antenatal corticosteroid remains a common practice but there is insufficient evidence on the benefits and risks of repeated single course to recommend their use outside the context of randomized trials[20].

When steroids are given for acceleration of lung maturity two glucocorticoid regimens have been found effective[21]. Betamethasone 12 mg, as a mixture of 6 mg each of betamethasone phosphate and betamethasone acetate is given intramuscularly (IM) as two doses 24 hours apart. The second option is dexamethasone 6 mg IM administered as four doses every 12 hours[22]. These drugs readily cross the placenta in a biologically active form[16]. Benefits can be seen as early as 24 hours after treatment, and they last about 7 days[23].

The efficacy of steroids in women with premature rupture membrane (PROM) between 32 and 34 weeks' gestation is controversial[24]. Other steroids, such hydrocortisone and prednisone, are not effective in reducing RDS due to placental metabolism of the drugs and poor placental transfer[25].

Regarding RDS in this study, there was significant difference between the 2 groups in this study. Respiratory distress syndrome was diagnosed clinically and by the need for mechanical ventilation and oxygen for at least 48 hours and the presence of radiological findings. In group I (single course group) 39.4% had neonates with RDS and in group II (repeated single course) 25%.

Ghiddini *et al*.[26] and Wijnberger *et al*.[27] with similar studies support this study in that there were statistically significant differences between single and repeat single course of corticosteroids regarding the development of RDS.

Ghiddini *et al*.[26] study which was a cohort study comparing between 2 groups each consisting of 130 patients, a group taking single course of corticosteroid versus the other receiving repeated course at the same gestational age as this study, showed that among single course group 63% developed RDS while among the multiple courses group 40% only which is statisticaly significant difference.

Wijnberger *et al*.[27] study which was a prospective cohort study on 137 patients divided into 2 groups, shows similar results to this study.

***The result of this study was also reinforced by***

Yang *et al*.[28] who found a significant association between RDS and multiple-course corticosteroids, had done a retrospective study on 173 patients, studying the maternal and fetal morbidities and mortalities due to PPROMs and how to minimize these complications.

Abbasi *et al*.[29] found that in the single course group, the incidence of RDS was 45% and in the multiple courses group was 34% and they explained that by the diminution of the maturational effect of corticosteroids after 7 days and they recommend the repeated course of corticosteroids.

However, this study was opposed by; Vermillion and Kooba[30] and Smith *et al*.[31]

In Vermillion and Koobas[30], which was a retrospective study on 119 cases of PPROMS and how they have been dealt with differently to minimize the morbidity and mortality on both the mother and the fetus, they found that the incidence of RDS among the single course group was 7% and among the repeated courses group was 33% and reported that single course of corticosteroids is more beneficial in the reduction of RDS rate than the repeated single course. Vermillion and Kooba,[30] attributed the reduction of RDS incidence among the single course group than the repeated single course group to increase incidence of chorioamnionitis among the repeated single course group in their study and suggested that the development of chorioamnionitis and production of cytokines may play an important role in the development of RDS.

Disagreeing also with the current study is Smith *et al*.[31] who found that 49% of newborns delivered to patients with PPROM who received single course of corticosteroids developed RDS while the incidence was 64% among the repeated courses group, therefore they also recommended the use of single course of corticosteroids. Smith *et al*.[31] study was a retrospective study done on 260 patients with PPROMS.

Another opinion was presented by Guinn *et al*.[32] a cohort study on 1652 patients with PPROMS which was divided into 2 groups evaluating the effect of repeated single course of antenatal corticosteroid versus a single course, demonstrated no difference in composite morbidity (including severe RDS and bronchopulmonary dysplasia, birth weight) between the 2 groups of infants. Banks *et al*.[33] also found that no relationship between the incidence of RDS and the number of courses of steroids.

Regarding the percentage of neonates in need of assisted ventilation in this study, group I (single course

group) 24.5% needed MV while group II (repeat single course group) 12.0%, this shows significant statistical difference between the two groups.

This goes with the results of Abbasi *et al*.[29] who had similar percentage of neonate in need of assisted Ventilation, among the single course group 20% and among the repeated single course group 10% with significant statistical difference.

This was opposed by the results of Vermillion and Kooba[30], who reported a 9% among the single course group and 10% among the repeat single course group, no significant statistical difference.

In this study, there was no significant difference between the latency period in both groups. This was opposed by the results of the study carried out by Vermillion and Kooba,[30] and Lee *et al*.[34].

Vermillion and Kooba,[30] found that latency period among the repeated courses' group was longer and attributed that to inhibition of the release of the mediators responsible for the onset of labor by the potent anti inflammatory effect of corticosteroids. However Lee *et al*.[34] found that repeated courses of steroids was associated with an increased risk of chorioamnionitis and decreased latency period in spite the use of antibiotics. This is due to the immunosuppressant effect of steroids leading to increase liability to infection.

Proven neonatal-sepsis was defined as the presence of a positive blood culture obtained in the first week of life in association with clinical findings suggestive of illness for which the neonate received antibiotics[31].

In this study 15 neonate out of 94 of the single course group (group I) had early onset neonatal sepsis (16%) while in group (II) 20 neonates out of 92 developed early onset neonatal sepsis (21.7%) with no significant statistical difference between the two groups.

Supported by; Abbasi *et al*.[29] reported in their study that the incidence early onset neonatal sepsis was 6.5% among the single course group and among the repeated single course group with no significant statistics difference. Also Lee *et al*.[34] performed a subgroup analysis of randomized trial of repeated single course of antenatal corticosteroids and when comparing those who received repeated single course of antenatal corticosteroids with those who received only single course of therapy, they found no significant difference with regard to neonate sepsis.

This was opposed by increased incidence of neonatal sepsis with repeated single course group as shown by;

Smith *et al*.[31] who reported that the incidence of early onset neonatal sepsis among the single course group was 3.8% while among the repeated courses group was 7.1%, and Vermillion and Kooba,[30] who reported in similar study that 2% of neonates of the single course groups developed early onset neonatal sepsis while in the repeated single course group 15% of the neonates developed early onset neonatal sepsis with high statistical significance.

Regarding birth weight in this study, there was no significant statistical difference between the 2 groups, mean birth weight in the group I 2014g and mean birth weight in group II was 1944g.

These results are similar to those shown by Aghajafari *et al*.[35] and McEvoy *et al*.[36].

In a meta analysis done by Aghajafari *et al*.[35] on the previous similar studies concluded that there was no difference between the 2 groups regarding birth weight. McEvoy *et al*.[36] also who found that there was no significant statistical difference between the two groups regarding birth weight.

However Banks *et al*.[33] reported an association between antenatal corticosteroid treatment and diminished fetal growth, in their study they observed that the birth weight was decreased in neonate born to women who received more than one course of antenatal corticosteroids. French *et al*.[37] also reported a decrease in birth weight and head circumference with increasing courses of antenatal corticosteroid.

The mechanism of growth impairment associated with corticosteroid therapy is thought to be related to reduced biosynthesis of DNA and RNA as well as prolonged inhibition of mitosis and cell synthetic activity. These effects in turn lead to impaired growth particularly in the brain, lung, heart, kidney, adrenal gland, and skeletal muscles.

Regarding intraventricular hemorrhage in this study, no statistically significant difference was found between the 2 groups with the results of 18.1% and 15.2% in group I and II respectively.

This was opposed by Chow, *et al*[11] who showed statistically significant decrease in the incidence of intraventricular hemorrhage in the repeated single course group when compared with the single course group.

Reagarding neonatal deaths in the current study, neonatal deaths among the single course group was 23 cases (24.5 %) and among the repeated single courses group was 14 (15.2%) with no significant statistical difference.

These results agree with that of Abbasi *et al*.[29], they

found that the incidence of neonatal death in the single course group was 2.2% and among the repeated single course group 3.1 with no significant statistical difference between the 2 groups. The low incidence of neonatal death in this study is definitely due to the advanced neonatal ICU care.

In this study preterm PROM was found to be more prevalent among multiparous women (70%).

This is supported by Guinn *et al*.[32] and this is attributed to increase incidence of infection in the cervix and vagina among them, also due to presence of some cervical dilatation which expose the membranes to increased risk of infection.

However Vermillion and Kooba,[30] found no difference between primi-parous and multi-parous as regard preterm PROM.

## CONCLUSION

Administration of single course and repeated single course may have the same benefit and risk factors but they differ in the effect on the incidence of RDS and the duration on mechanical ventilation, repeated single course of corticosteroid decreases the incidence of RDS and the duration on mechanical ventilation compared to the single course. Therefore, repeated single course is preferred over single course.

## CONFLICT OF INTERESTS

There are no conflicts of interest.

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