Original Research Paper

Volume - 11 | Issue - 12 | December - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Obstetrics & Gynaecology

MATERNAL AND PERINATAL OUTCOMES WITH ANTENATAL CORTICOSTEROID ADMINISTRATION IN PRETERM DELIVERIES AT GOVERNMENT DISTRICT HOSPITAL, NANDYAL- AN OBSERVATIONAL STUDY

Dr. P. Swathi — DGO DNB OBG, Department of Obstetrics and Gynaecology, Government District Hospital, Nandyal, Andhra Pradesh.

Dr. K. Radhikajyothi* — MS OBG, Guide, Civil Surgeon, Senior consultant, DNB Coordinator, Department of Obstetrics and Gynaecology, Government District Hospital, Nandyal, Andhra Pradesh. *Corresponding Author

ABSTRACT

BACKGROUND: Preterm birth remains a major health issue worldwide. Preterm delivery affects over 7–12% of births in India and is responsible for up to 75% of neonatal deaths. Despite advances in medical technology, the prevalence of preterm birth is increasing**.** Discovery of antenatal corticosteroid for fetal maturation and its adoption into clinical practice highlights several fascinating and universal truths about science and medicine. The challenge in human studies is to demonstrate antenatal corticosteroid administration in pregnancy contributes to developmental programming and how this is manifested in later life. The World Health Organization recommends the use of one course of antenatal steroids for all pregnant women between 26 and 35 weeks of gestation who are at risk of preterm delivery within 7 days. Both, the American College of Obstetricians and Gynaecologists and the Royal College of Obstetricians and Gynaecologists recommend their use between 24 and 34 weeks of gestation (1). The use of antenatal steroids after 34 or 35 weeks of gestation is not recommended unless there is evidence of fetal pulmonary immaturity. Despite this, antenatal steroids are widely used globally across all gestational periods. In a diverse country like India, diversity in clinical practice is a reality. Hence, the present research study intends to study the maternal and perinatal outcomes with antenatal corticosteroid administration in preterm deliveries at Government district hospital, Nandyal in South India.

AIMS AND OBJECTIVES

- To determine the incidence of RDS at District hospital, Nandyal among neonates delivered between 28-37 weeks due to PTL, PPROM or severe PET whose mothers received ACS and in those whose mothers did not receive ACS.
- To determine the severity of RDS at District hospital, Nandyal among neonates delivered between 28-37 weeks due to PTL, PPROM or severe PET whose mothers received ACS and in those whose mothers did not receive ACS.
- To compare the neonatal mortality among neonates delivered between 28-37 weeks due to PTL, PPROM or severe PET whose mothers received ACS with those whose mothers did not receive ACS.
- To determine the effectiveness of antenatal corticosteroid administration in preventing early neonatal respiratory distress syndrome in early preterm labour versus late preterm labour.
- To determine the effectiveness of ACS administration in preventing neonatal complications with respect to the mode of delivery.

METHODOLOGY: Study was conducted at Government District Hospital, Nandyal from 01/01/2019 to 30/10/2019. A structured questionnaire was prepared under guidance of thesis guide. All pregnant women with gestational age between 28 completed weeks to 37 completed weeks, presenting in OPD either in labour or getting admitted due to any other maternal medical complication, are initially assessed thoroughly to estimate the gestational age by history, LMP, early USG, and clinical examination. They are given a course of ACS if they were not expecting delivery within next 1 hour, after explaining the benefits and risks of ACS as per recommendations of International Federation of Gynecology and Obstetrics. Those who did not receive ACS or those who delivered within 24hrs of administration of 1st dose of ACS were considered as subjects in NACS group. Those who received ACS were considered as subjects in ACS group. After delivery, the neonate is followed up in NICU until discharged or until 7 days whichever is shorter. Mother is followed up for any clinical signs of infection, until she is discharged. Data is analyzed scientifically.

RESULTS: In Antenatal corticosteroids group (ACS), there were 36 subjects within 20 years, 43 subjects between 20-25 years, 29 subjects between 25-30 years, 25 subjects between 30-35 years. In No Antenatal corticosteroids group (NACS), there were 32 subjects within 20 years, 49 subjects between 20-25 years, 25 subjects between 25-30 years, 10 subjects between 30-35 years. Study observed that Antenatal corticosteroids group had lower incidence of Respiratory distress syndrome compared to No Antenatal corticosteroids group (12.07% versus 23.28%). Antenatal corticosteroids group had lower incidence of severe Respiratory distress syndrome compared to No Antenatal corticosteroids group (21.3 % versus 33.33%) among those who had Respiratory Distress Syndrome. Antenatal corticosteroids group had fewer admissions to NICU than No Antenatal corticosteroids group (20.69% versus 33.62%). Antenatal corticosteroids group had lower mortality than No Antenatal corticosteroids group (12.07 % versus 22.41%). Antenatal corticosteroids group had 35 % less chances of Respiratory distress syndrome compared to No Antenatal corticosteroids group. In No Antenatal corticosteroids group, subjects who underwent vaginal delivery had 10% less risk compared to those who underwent LSCS for their neonates to have Respiratory distress syndrome. In Antenatal corticosteroids group, subjects who underwent vaginal delivery had 14.29 % less risk compared to those who underwent LSCS for their neonates to have Respiratory distress syndrome. Antenatal corticosteroids group had maternal infection rate comparable to No Antenatal Corticosteroids group**.**

CONCLUSION: Use of antenatal corticosteroids was found to be beneficial in pregnant women with Gestational age of 28 completed weeks to less than 37 completed weeks at Government District hospital, Nandyal. Antenatal corticosteroids did not have statistically significant adverse effects (i.e. increased rate of infection) in mothers.

KEYWORDS : Antenatal corticosteroids (ACS), Non-Antenatal Corticosteroids group (NACS), Respiratory distress syndrome (RDS), Pre term delivery, Neonatal mortality.

INTRODUCTION

In India, 27 million babies are born every year. Out of these, 3.5 million babies born are preterm. Preterm delivery is the cause of at least 75% of neonatal deaths, not attributable to congenital malformations (5). It is estimated that more than 60% of the world's preterm births occur in African and South Asian countries (2).

Preterm delivery can be spontaneous in onset or induced due to various indications for the benefit of the mother and baby. Rate of preterm birth and its complications also depends on the socio-economic development of the countries because there is enhanced basic care and awareness in high-income countries compared to low-income countries. Hence the survival rates of preterm babies also significantly vary in different places depending on the socio- economic status. More than three-quarters of preterm or premature babies can be saved with often inexpensive care such as antenatal corticosteroid injections, essential care during child birth, and postnatal kangaroo mother care and basic care for infections and breathing difficulties.

Prematurity can be a lethal condition, particularly for those newborns born at earlier gestational ages (<34weeks). Complications of preterm birth are the leading cause of death in children under 5 years of age globally, accounting for 1.06 million deaths (uncertainty range 0.935 to 1.179 million) of the 5.9 million deaths annually (3).

Preterm infants experience higher rates of respiratory distress syndrome, bronchopulmonary dysplasia, necrotising enterocolitis, kernicterus, hypoglycaemia, periventricular leucomalacia, seizures, intraventricular haemorrhage, cerebral palsy, infections, feeding difficulties, hypoxic ischaemic encephalopathy, retinopathy of prematurity, as well as visual and hearing loss and hence a significant negative psychosocial and financial impacts on families of preterm new-borns. While the risks of mortality and morbidity affecting preterm newborns are considerably more frequent at lower gestational ages, late preterm infants (sometimes called 'near-term') still experience significantly higher risks compared with babies born at term.

Studies have shown that antenatal corticosteroids given to mothers at risk of preterm birth between 24 and 34 weeks reduce the incidence and severity of respiratory distress syndrome, intraventricular haemorhage, necrotizing enterocolitis and neonatal deaths (4).

The World Health Organization recommends the use of one course of antenatal steroids for all pregnant women between 26 and 35 weeks of gestation who are at risk of preterm delivery within 7 days. Both, the American College of Obstetricians and Gynaecologists (ACOG) and the Royal College of Obstetricians and Gynaecologists (RCOG) recommend their use between 24 and 34 weeks of gestation(5). The use of antenatal steroids after 34 or 35 weeks of gestation is not recommended unless there is evidence of fetal pulmonary immaturity. Despite this, antenatal steroids are widely used globally across all gestational periods.

In a diverse country like India, diversity in clinical practice is a reality. Hence, the present research study intends to study the maternal and perinatal outcomes with antenatal corticosteroid administration in preterm deliveries at Government district hospital, Nandyal in South India.

Aims And Objectives

Broad objective:

To determine the effectiveness of antenatal corticosteroids in reduction of neonatal morbidity and mortality in infants delivered between 28-37 weeks due to PTL, PPROM or severe Preeclampsia or any other cause at District hospital, Nandyal over a period of 10 months from 01/01/2019 to 30/10/2019.

Specific objectives:

- To determine the incidence of RDS at District hospital, Nandyal among neonates delivered between 28-37 weeks due to PTL, PPROM or severe PET whose mothers received ACS and in those whose mothers did not receive ACS.
- To determine the severity of RDS at District hospital, Nandyal among neonates delivered between 28-37 weeks due to PTL, PPROM or severe PET whose mothers received ACS and in those whose mothers did not receive ACS.
- To compare the neonatal mortality among neonates delivered between 28-37 weeks due to PTL, PPROM or severe PET whose mothers received ACS with those whose mothers did not receive ACS.
- To determine the effectiveness of antenatal corticosteroid administration in preventing early neonatal respiratory distress syndrome in early preterm labour versus late preterm labour.
- To determine the effect on infection rate in mother with ACS.
- To determine the effectiveness of ACS administration in preventing neonatal complications with respect to the mode of delivery.

Materials And Methods

(i) Study area: Obstetric Inpatient department and ward, Department of Obstetrics and Gynaecology, Government District Hospital, Nandyal, Andhra Pradesh

(ii) Study population: All pregnant women attending Government District Hospital, Nandyal, delivering at gestational age of 28 completed weeks to 37 completed weeks.

(iii) Inclusion Criteria

1. Pregnant women at Gestational age of 28 completed weeks to less than 37 completed weeks.
2. Pregnant women planned for induction and delivering at Gestational age of 28 completed weeks to less than 37 completed weeks
3. Pregnant women delivering in the Government District Hospital, Nandyal, within 1week of antenatal corticosteroid administration.

(iv) Exclusion Criteria:

1. Pregnant women getting discharged to go home antenatally after corticosteroid administration.
2. Pregnant women being referred to higher centre for any reason
3. Pregnant women who had past medical conditions e.g. diabetes mellitus, thyrotoxicosis, cardiac disease, tuberculosis
4. Pregnant women who had the following obstetric complications: IUFD, congenital fetal malformations and chorioamnionitis diagnosed on or before admission.
5. Pregnant women with contraindications to steroid use.

(v) Sample size

With reference to Hospital register, estimated prevalence of pre-term delivery was 9 %. Total population based on number of pre-term deliveries last year in the hospital was 360. For confidence level of 95% with margin of error of around 5 %, sample size taken for the study was calculated using following formula (6):

Formula: $n = (z^2 \times p\,(1-p))/e^2$ **where:**

- Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI)
- P is expected true proportion (of total admissions)
- e is desired precision (half desired CI width).

After substituting the values, sample size of 192 was obtained.

(vi) Study design: Prospective observational study

(vii)Study duration: 10 months from 01/01/2019 to 30/10/2019

(viii)Method of measurement of outcome of interest

Outcome Variable:

- Incidence of respiratory distress syndrome
- Severity of respiratory distress syndrome
- Prevalence of Neonatal admission to NICU
- Neonatal mortality
- Infection rate in mother

(ix) Methodology:

A structured questionnaire was prepared under guidance of thesis guide. All pregnant women with gestational age between 28 completed weeks to 37 completed weeks, presenting in OPD either in labour or getting admitted due to any other maternal medical complication, are initially assessed thoroughly to estimate the gestational age by history, LMP, early USG, and clinical examination. Patients are assessed whether they are in Labour and which stage of labour and any other medical complication that can complicate pregnancy. They are given a course of ACS if they were not expecting delivery within next 1 hour, after explaining the benefits and risks of ACS as per recommendations of International Federation of Gynaecology and Obstetrics. Those who did not receive ACS or those who delivered within 24hrs of administration of 1st dose of ACS were considered as subjects in NACS group. Those who received ACS were considered as subjects in ACS group. Information was entered into the structured questionnaire. In-patient numbers were obtained from admission and discharge registers in labour ward, maternity ward labour and delivery records (vaginal or induced vaginal or through caesarean), treatment sheets, infant notes, admission and discharge records and operating theatre notes was extracted and information entered in a structured questionnaire. The neonate is followed up in NICU until discharged or until 7 days whichever is shorter. Patients who do not deliver within 1week of ACS or get referred to higher centres due to maternal medical complications or who get discharged due to subsidence of labour pains, are excluded from the study.

(x) Statistical Analysis

The collected data was entered and analyzed using Microsoft office excel 2018 and MINITAB version 17. Frequencies of all variables were taken as check frequencies. Mean and standard deviation (SD) was calculated for continuous variables. Chi square test was used to analyse frequencies. Odds Ratio and Relative risk was calculated using MEDICAL software. Test was considered statistically significant when the p value was less than 0.05.

Observation And Results

- **Age Profile:**

In Antenatal corticosteroids group (ACS), there were 34 subjects

within 20 years, 43 subjects between 20-25 years, 29 subjects between 25-30 years, 8 subjects between 30-35 years. In No Antenatal corticosteroids group (NACS), there were 24 subjects within 20 years, 28 subjects between 20-25 years, 19 subjects between 25-30 years, 7 subjects between 30-35 years.

Both the groups were compared with Chi square test of independence. P value of 0.959 was derived which suggested no statistically significant difference between the groups (P > 0.05).

- **Incidence of Respiratory distress syndrome:**

In Antenatal corticosteroids group (ACS- Neonates), 14 (12.61%) neonates had developed Respiratory distress syndrome where as in No Antenatal corticosteroids group (ACS - Neonates) 18 (24.00%) neonates had developed Respiratory distress syndrome.
Both the groups were compared with Chi square test of independence. P value of 0.044 was derived which suggested statistically significant difference between the groups (P < 0.05).

- **Severity of Respiratory distress syndrome**

In Antenatal corticosteroids group -Neonates (ACS -N), 11(78.57%) neonates had Mild Respiratory distress syndrome and 3 (21.43%) had Severe Respiratory distress syndrome. In No Antenatal corticosteroids group -Neonates (NACS -N), 6 (33.33%) neonates had Mild Respiratory distress syndrome and 12 (66.67%) had Severe Respiratory distress syndrome.

Both the groups were compared with Chi square test of independence. P value of 0.011 was derived which suggested statistically significant difference between the groups (P < 0.05).

- **Prevalence of neonatal admissions**

In Antenatal corticosteroids group - Neonates (ACS -N), 24 (21.62%) neonates were admitted to NICU. In No Antenatal corticosteroids group - Neonates (NACS -N), 26 (34.67 %) neonates were admitted to NICU.

Both the groups were compared with Chi square test of independence. P value of 0.049 was derived which suggested statistically significant difference between the groups (P < 0.05).

- **Respiratory distress syndromes in Early versus Late preterm delivery**

Among Early pre term (28-34 weeks) newborns, 52 were given Antenatal corticosteroids group -Neonates (ACS - N) and 42 did not receive ACS [No Antenatal corticosteroids group-Neonates (NACS - N)] . Among ACS-N group, 8 (15.38%) newborns developed Respiratory distress syndrome. Whereas among 42 NACS-N group, 11 (26.2) newborns developed Respiratory distress syndrome. P value of 0.034 was derived which suggested statistically significant difference between the groups (P< 0.05).

Among late pre term (34+0 to 36+6 weeks) newborns, 59 recieved Antenatal corticosteroids group -Neonates (ACS - N) and 33 did not receive ACS (NACS-N). In ACS-N group, 6 (10.17%) newborns developed Respiratory distress syndrome whereas among No Antenatal corticosteroids group -Neonates (NACS - N), 7(21.21%) newborns developed Respiratory distress syndrome. P value of 0.048 was derived which suggested statistically significant difference between the groups (P< 0.05).

- **Neonatal mortality**

In Antenatal corticosteroids group-Neonates (ACS-N), 12 (10.81%) neonates expired. In No Antenatal corticosteroids group-Neonates (NACS-N), 19 (25.33 %) neonates expired.

Both the groups were compared with Chi square test of independence. P value of 0.022 was derived which suggested statistically significant difference between the groups (P < 0.05).

- **Effectiveness of antenatal corticosteroid administration in preventing early neonatal respiratory distress syndrome**

Study groups	Relative risk (96% CI)
No Antenatal corticosteroids group (NACS)	1 (reference)
Antenatal corticosteroids group (ACS)	0.65 (0.6-0.7)

No Antenatal corticosteroids group (NACS), was considered as reference value of 1.when compared with Antenatal corticosteroids group (ACS), relative risk was 0.65.

- **Effectiveness of antenatal corticosteroid administration in preventing neonatal complications with respect to the mode of delivery.**

Study groups	Relative risk (96% CI)
No Antenatal corticosteroids group (NACS) – LSCS	1
No Antenatal corticosteroids group (NACS) – Vaginal delivery	0.9
Antenatal corticosteroids group (ACS) – LSCS	0.7
Antenatal corticosteroids group (ACS) – Vaginal delivery	0.6

LSCS in No Antenatal corticosteroids group (NACS), was considered as reference value of 1.when compared with No Antenatal corticosteroids group (NACS)-Vaginal delivery, relative risk was 0.9 in terms of neonatal complications. Antenatal corticosteroids group (ACS)-LSCS had relative risk of 0.7 and Antenatal corticosteroids group (ACS)-Vaginal delivery had relative risk of 0.6.

- **Infection rate in mother**

In Antenatal corticosteroids group (ACS), 12 (10.53 %) subjects had clinical features of infection. In No Antenatal corticosteroids group (NACS), 8 (10.67 %) subjects had clinical features of infection.

Both the groups were compared with Chi square test of independence. P value of 0.315 was derived which suggested no statistically significant difference between the groups (P > 0.05).

- **Mode of delivery and Respiratory distress syndrome**

In Antenatal corticosteroids group (ACS), 77 underwent LSCS, of which 10 neonates developed Respiratory distress syndrome. Further, 37 underwent vaginal delivery, of which 4 neonates developed Respiratory distress syndrome. Both the groups were compared with Chi square test of independence. P value of 0.643 was derived which suggested no statistically significant difference between the groups (P > 0.05).

In No Antenatal corticosteroids group (NACS), 48 underwent LSCS, of which 11 neonates developed Respiratory distress syndrome. Further, 27 underwent vaginal delivery, of which 7 neonates developed Respiratory distress syndrome. Both the groups were compared with Chi square test of independence. P value of 0.542 was derived which suggested no statistically significant difference between the groups (P > 0.05).

DISCUSSION

Management of Pre-term labour

Corticosteroids

The American College of Obstetricians and Gynecologists (ACOG) recommends either betamethasone or dexamethasone to promote fetal lung maturity. Intramuscular administration of betamethasone 12 mg every 24 hours for two doses or dexamethasone 6 mg every 12 hours for four doses is indicated for women at risk for preterm birth between 26 and 34 weeks' gestation. Repeat doses of corticosteroids are not beneficial for improving outcomes following preterm birth (20).

Role of corticosteroids

Antenatal administration of corticosteroids accelerate development of type 1 and type 2 pneumocytes, leading to structural and biochemical changes that improve both lung mechanics (maximal lung volume, compliance) and gas exchange. Induction of type 2 pneumocytes increases surfactant production by inducing production of surfactant proteins and enzymes necessary for phospholipid synthesis.

Other effects of antenatal corticosteroids include induction of pulmonary beta-receptors, which play a role in surfactant release and absorption of alveolar fluid when stimulated . Induction of fetal lung antioxidant enzymes and upregulation of gene expression for the epithelial Na+ channel, which is important for absorption of lung fluid after birth. For these changes to occur, however, the lungs need to have reached a stage of development that is biologically responsive to corticosteroids.

The biologic rationale for repeating antenatal corticosteroid therapy is

based upon the observation that biochemical stimulation of surfactant production appears to be reversible in cell culture models (eg, surfactant protein mRNA levels decline to control levels after cortisol is removed). However, other beneficial effects, such as cytostructural maturation, persist (in rhesus monkeys) after steroid exposure is withdrawn (21).

Timing before delivery: As per various studies, maximum efficacy appears to occur when delivery occurs two to seven days after administration of the first dose of antenatal corticosteroids. Efficacy is incomplete <24 hours from administration and appears to decline after 7 days. Studies have recommended that antenatal corticosteroid therapy should be administered when indicated unless imminent delivery is anticipated. Therapy should not be withheld if delivery is anticipated prior to completion of the second dose of the first course of medication. Liberal approach to treatment because the minimal interval between drug administration and delivery required to achieve neonatal benefits has not been clearly defined and the hour of delivery cannot be predicted accurately. In study by Hashima et al, only one-quarter of women delivered within the optimal window after steroid administration (22).

Choice of drug and dosage:
In meta-analyses of randomized trials comparing use of different corticosteroids in women at risk of preterm birth, no statistical differences in accelerating fetal lung maturation were observed between dexamethasone and betamethasone. In a randomized trial directly comparing dexamethasone with betamethasone, the incidence of survival without neurosensory disability at age 2 years was also similar for both drugs.

A course of therapy consists of:
- Betamethasone two doses of 12 mg given intramuscularly 24 hours apart **or**
- Dexamethasone four doses of 6 mg given intramuscularly 12 hours apart. A nonsulfite- containing preparation should be used as the sulfite preservative (NNF60211) commonly used in dexamethasone preparations may be directly neurotoxic in newborns (27).

These steroids are preferred over other steroids because they are less extensively metabolized by the placental enzyme 11 beta-hydroxysteroid dehydrogenase type 2.

Repeated courses of therapy: The American College of Obstetricians and Gynaecologists (ACOG) opine that "a single repeat course of antenatal corticosteroids should be considered in women who are less than 34+0 weeks of gestation who have an imminent risk of preterm delivery within the next 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously. Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario". ACOG does not limit rescue steroids to women whose initial course of antenatal corticosteroids was administered at ≤28 weeks of gestation (23).

American College of Obstetricians and Gynaecologists: Recommendations:
- A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation, and may be considered for pregnant women starting at 23 0/7 weeks of gestation, who are at risk of preterm delivery within 7 days .
- It also may be considered for pregnant women starting at 23 0/7 weeks of gestation who are at risk of preterm delivery within 7 days, based on a family's decision regarding resuscitation, irrespective of membrane rupture status and regardless of fetal number
- Administration of corticosteroids for pregnant women during the periviable period who are at risk of preterm delivery within 7 days is linked to a family's decision regarding resuscitation and should be considered in that context.
- A single course of betamethasone is recommended for pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids.
- Regularly scheduled repeat courses or serial courses (more than two) are not currently recommended.
- A single repeat course of antenatal corticosteroids should be considered in women who are less than 34 0/7 weeks of gestation who are at risk of preterm delivery within 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously. Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario.
- Whether to administer a repeat or rescue course of corticosteroids with preterm prelabor rupture of membranes (PROM) is controversial, and there is insufficient evidence to make a recommendation for or against.
- Continued surveillance of long-term outcomes after in utero corticosteroid exposure should be supported.
- Quality improvement strategies to optimize appropriate and timely antenatal corticosteroid administration are effective and should be encouraged (24).

FIGO (International Federation of Gynaecology and Obstetrics) Recommendations:
1. Clinicians should offer a single course of prenatal corticosteroids to all women between 24 and 34 weeks of gestation who are at risk of preterm birth within 7 days.
2. Administration of corticosteroids for pregnant women at less than 24 weeks of gestation with a risk of preterm birth within 7 days is linked to a family's decision regarding resuscitation. Due consideration should be given to local limits of fetal viability when determining the lowest limit of gestational age at which steroids should be administered.
3. A single course of betamethasone is recommended for pregnant women between 34 and 36.6 weeks of gestation with a risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids. Although there is a paucity of data on longer‒ term follow‒ up.
4. A single course of corticosteroids can be considered for women undergoing planned cesarean delivery at 37–38.6 week's gestation. However, there should be a clear medical reason; an elective delivery should not be performed before 39 week's gestation.
5. The most extensively studied regimens of corticosteroids treatment for the prevention of RDS are: two doses of betamethasone 12 mg given intramuscularly 24 hours apart, or four doses of dexamethasone 6 mg given intramuscularly 12 hours apart.
6. Antenatal corticosteroids are most effective in reducing RDS in pregnancies that deliver 24 hours after and up to 7 days after administration of the second dose of antenatal corticosteroids.
7. Weekly repeat courses of antenatal corticosteroids are not recommended.
8. A single repeat course of antenatal corticosteroids should be considered in women at less than 34 weeks of gestation who have an imminent risk of preterm delivery within the next 7 days, and whose prior course of antenatal corticosteroids was administered more than 7–14 days previously.
9. One course of antenatal corticosteroids should be administered to all patients who are between 24 and 34 weeks of gestation and at risk of delivery within 7 days, irrespective of whether a single or multiple birth is anticipated.
10. Antenatal corticosteroid therapy is recommended for women with pre‒ gestational and gestational diabetes who are at risk of imminent preterm birth. Women who are receiving fetal steroids should have additional insulin according to an agreed protocol and be closely monitored.
11. There is insufficient evidence to conclude on the benefits or harms of antenatal corticosteroids therapy in women whose infants are growth restriction.
12. Antenatal corticosteroids should not be administered if there is no substantiated clinical suspicion of preterm delivery in the next 2–7 days.
13. In women with symptoms of preterm labor, cervical length and fibronectin/PAMG1 measurements should be considered to prevent unnecessary hospitalization and use of tocolytic drugs and/or antenatal steroid (25).

The research titled "Study on maternal and perinatal outcomes with antenatal corticosteroid administration in preterm delivery "was conducted at Government district hospital, Nandyal, from 01/01/2019 to 30/10/2019 on 192 subjects.

In Antenatal corticosteroids group - Neonates, there were 112 singleton deliveries, 2 twin deliveries. Among these, 111 were live born and 5 were still born. In No-Antenatal corticosteroids group, there were 77 singleton deliveries, 1 twin delivery. Among these, 75 were live born and 4 were still born.

In Antenatal corticosteroids group (ACS), there were 34 subjects

within 20 years, 43 subjects between 20-25 years, 29 subjects between 25-30 years, 8 subjects between 30-35 years. In No Antenatal corticosteroids group (NACS), there were 24 subjects within 20 years, 28 subjects between 20-25 years, 19 subjects between 25-30 years, 7 subjects between 30-35 years. P value was >0.05 and hence both study groups were comparable in terms of age.

Incidence of Respiratory distress

In the present study Antenatal corticosteroids group (ACS), 14 (12.61%) neonates had developed Respiratory distress syndrome whereas in No Antenatal corticosteroids group (NACS), 18 (24.00%) neonates had developed Respiratory distress syndrome. P value was <0.05 and hence the difference in incidence of RDS was statistically significant.

In a study by Liggins et al, in the unplanned deliveries, in infants of mothers who had received betamethasone for at least 24 hours before delivery, the respiratory distress syndrome occurred less often in treated babies (9.0%) than in controls (25.8%, p= 0.003), but the difference was confined to babies of under 32 weeks of gestation who had been treated for at least 24 hours before delivery (7).

In a study by Maria et al, in Antenatal corticosteroids group (ACS), 13.27 % neonates had developed Respiratory distress syndrome whereas in No Antenatal corticosteroids group 18.63% had Respiratory distress syndrome (8). In a study by Cynithia et al, respiratory distress syndrome occurred in 165 of 1427 infants (11.6%) in the betamethasone group and 202 of 1400 (14.4%) in the placebo group (relative risk in the betamethasone group, 0.80; 95% confidence interval [CI], 0.66 to 0.97; P=0.02). Severe respiratory complications, transient tachypnea of the newborn, surfactant use, and bronchopulmonary dysplasia also occurred significantly less frequently in the betamethasone group (9). In a study by Szu yu Liu et al, subset population of very low birth weight infants less than 25 weeks' of gestation, antenatal corticosteroids has statistical significance in decreasing surfactant use during the complete 17-year study period (odds ratio [OR] 0.55–0.64, P < 0.05). However, the protective effect was not evident in the late period (GA > 23wks: P = 0.051; GA 24wks: P= 0.079) when more antenatal corticosteroids were given to the periviable birth. For VLBW infants with gestational age 26–33 weeks, administering two doses of antenatal corticosteroids has significantly protective effect and is associated with 40–57% reduction for surfactant use at different gestational ages (OR 0.43–0.60, all P < 0.05). For VLBW infants with gestational age 34 weeks and more, there was no significant beneficial effect in reducing surfactant use even when two doses of antenatal corticosteroids were completed (OR 0.32, P = 0.127) (10). In a study by Viteri et al on cohort of preterm twins, they observed that antenatal corticosteroid administration was not associated with a reduced incidence of RDS (41 % in Antenatal corticosteroids group compared to 45 % in Non Antenatal corticosteroids group).Among preterm singletons, antenatal corticosteroid administration is a well-established strategy for the reduction in the rate of respiratory distress syndrome (RDS), intraventricular hemorrhage, necrotizing enterocolitis, and death. However, the benefits of current antenatal corticosteroid regimens in twin gestations remain unclear (11). Hence, as evident from the comparison with other studies, present study is in concurrent with their observation. Most of the studies had incidence of respiratory distress syndrome between 9 – 14 % among Antenatal corticosteroids group and 14–26 % among No Antenatal corticosteroids group. All these studies had in common similar profiles of the case group (12). However, when same study has been carried on by Viteri et al on premature twins, same findings as in singleton pregnancy could not be reproduced. In another study conducted by Maitre et al on multiple pregnancy, there was no difference between case and control group (11). In the Cochrane systematic review of 26 trials, the rate of respiratory distress syndrome (RDS) was reduced by 35% in the corticosteroids group (RR 0.65, 95% CI 0.58–0.73; 25 studies, 4590 infants). Moderate and severe RDS was also reduced (RR 0.55, 95% CI 0.43– 0.71; 6 studies, 1686 infants). The mean duration of mechanical ventilation was reduced in the corticosteroids group (MD -1.42 days, 95% CI -2.28 to -0.56; 3 studies, 518 infants). Mean duration of oxygen supplementation was reported in one trial and results favoured the corticosteroids group (MD -2.86 days, 95% CI -5.51 to -0.21; 73 infants) (13). Numerous reports summarize large amount of data documenting the effect of these drugs on the stimulation of type II pneumocytes and release of surfactant, and the efficacy and necessity of their use, which surpasses the possible adverse effects. A meta-analysis of data collected by Crowley, from 15 projects published over a period of 22 years (1972–1994), revealed a 50% drop in the RDS rates (OR 0.35; 95% CI: 026–0.46), as well as lower rates of intraventricular hemorrhage — IVH (OR 0.38; 95% CI: 0.23–0.94) and necrotizing enterocolitis — NEC (OR 0.32; 95% CI: 0.16–0.64) (14).

Severity of Respiratory distress syndrome

In the present study, Antenatal corticosteroids group-Neonates (ACS-N), 11(78.57%) neonates had Mild Respiratory distress syndrome and 3 (21.43%) had Severe Respiratory distress syndrome. In No Antenatal corticosteroids group-Neonates (NACS-N), 12 (66.67%) neonates had Mild Respiratory distress syndrome and 6 (33.33%) had severe Respiratory distress syndrome. P value of 0.011 was derived which suggested statistically significant difference between the groups (P < 0.05).

In study by Liggins et al, among Antenatal corticosteroids group, 16.5 % had severe Respiratory distress syndrome whereas among No Antenatal corticosteroids group, 28.5 % had severe Respiratory distress syndrome (7). In study by Maria et al, among Antenatal corticosteroids group, 19 % had severe Respiratory distress syndrome whereas among No Antenatal corticosteroids group, 32.6 % had severe Respiratory distress syndrome (8). As the studies indicate, severity of RDS decreases with use of ACS. Mechanism of lung maturity in response to ACS seems to make more difference and less requirement of surfactant post natally.

Prevalence of neonatal admissions

In present study, among Antenatal corticosteroids group-Neonates (ACS-N), 24 (21.62%) neonates were admitted to NICU. In No Antenatal corticosteroids group-Neonates (NACS-N), 26 (34.67%) neonates were admitted to NICU.

In study by Liggins et al, 21.60% of Antenatal corticosteroids group had admission in NICU whereas 31.20 % had NICU admission in No Antenatal corticosteroids group (7). Maria et al observed that Antenatal corticosteroids group had 16.80 % of NICU admissions and No Antenatal corticosteroids group had 26.50 % had NICU admission (8).

Cynithia et al reported that 22.30% required NICU admission in Antenatal corticosteroids group and 33.75% required NICU admission in No Antenatal corticosteroids group)(9).

In a study by Viteri et al on cohort of preterm twins, they observed that antenatal corticosteroids was associated with increased rates of neonatal intensive care unit admissions (58% in Antenatal corticosteroids group compared to 59 % in Non Antenatal corticosteroids group).

As shown in the various studies, NICU admissions were higher in Antenatal corticosteroids group than No Antenatal corticosteroids group. However, in study by Viteri et al, there was no significant difference between NICU admissions rates as case group was that of pre term twins.

Neonatal mortality

In comparison of Neonatal mortality, most of studies reported mortality between 8 - 15 % in Antenatal corticosteroids group whereas, 20 – 26 % mortality rate in No Antenatal corticosteroids group. It is evident from the comparison that mortality rates are double in No - Antenatal corticosteroids group than that in Antenatal corticosteroids group. The difference in mortality rates can be explained from the fact that Respiratory distress syndrome, Intra ventricular haemorrhage, Entereocolitis were significantly less in Antenatal corticosteroids group in all these mentioned studies.

In the Cochrane systematic review of 26 trials, compared with placebo, corticosteroid therapy was associated with significantly fewer fetal and neonatal deaths (RR 0.77, 95% CI 0.67–0.89). This was largely due to a 32% reduction in neonatal deaths (RR 0.68, 98% CI 0.58–0.80; 21 studies, 4408 infants, corresponding to 9.5% in the treatment group versus 14% for controls). In the same study, corticosteroid therapy was associated with a reduction in the occurrence of cerebroventricular haemorrhage (RR 0.54, 95% CI 0.43–0.69; 13 studies, 2872 infants), infant systemic infection in the first 48 hours of life (RR 0.57, 95% CI 0.38–0.86; 6 studies, 1359 infants) and necrotizing enterocolitis (RR 0.46, 95% CI 0.29–0.74; 8 studies, 1675

infants) when compared with placebo. No significant difference between the groups was observed for small-for-gestational-age (SGA) infants (RR 1.05, 95% CI 0.78–1.42; 4 studies, 698 infants), mean infant birth weight (MD -6.93 g, 95% CI -39.41 to 25.55; 13 studies, 2961 infants), admission to a neonatal intensive care unit (NICU) (RR 0.88, 95% CI 0.73–1.06) (15)

In a study by Porto et al, ACS exposure decreased respiratory distress syndrome and severe intraventricular hemorrhage in infants born between 24 and 29 weeks of gestation. Analysis revealed that ACS exposure was associated with a significant decrease in mortality of preterm infants born at 22 or 23 weeks of gestation (adjusted hazard ratio, 0.72; 95% CI, 0.53 to 0.97; P = .03). This effect was also observed at 24 to 25 and 26 to 27 weeks of gestation population but not more (16).

In Cochrane review, Corticosteroid therapy was associated with a trend towards a reduction in the number of children treated for cerebral palsy in childhood (RR 0.60, 95% CI 0.34–1.03; 5 studies, 904 children), as well as a reduction in developmental delay (RR 0.49, 95% CI 0.24– 1.00; 2 studies, 518 children). Differences between groups for visual and hearing impairment, neurodevelopmental delay, intellectual impairment and behavioral or learning difficulties were not statistically significant in children or adults, although the relative risks were all in favour of a reduction (15).

However, in meta-analysis by Black RE et al, fetal deaths were comparable in both groups (RR 0.98, 95% CI 0.73–1.30). There were no significant differences in terms of childhood deaths (RR 0.68, 95% CI 0.36–1.27) or deaths occurring during adulthood (RR 1.00, 95% CI 0.56–1.81; 1 study, 988 adults) (16).

Effect on infection rate in mother

In Antenatal corticosteroids group (ACS), 12 (10.53 %) subjects had clinical features of infection. In No Antenatal corticosteroids group (NACS), 8 (10.67%) subjects had clinical features of infection.

In a study by Cynithia et al, there were no significant between-group differences in the incidence of chorioamnionitis or neonatal sepsis. Neonatal hypoglycemia was more common in the betamethasone group than in the placebo group (24.0% vs. 15.0%; relative risk, 1.60; 95% CI, 1.37 to 1.87; P<0.001).

In Cochrane review, Compared with placebo, corticosteroid therapy was not associated with increased risk of maternal infection (RR 0.98, 95% CI 0.06–15.50). Romain et al 2 % reported maternal admission to intensive care in Antenatal corticosteroids group and 2.2 % admission in No Antenatal corticosteroids group ; there was no significant difference between the groups (RR 0.74, 95% CI 0.26–2.05; 319 women) (15).

In a study by Wang et al ,corticosteroid therapy was not associated with increased risk of maternal infection; the rates of chorioamnionitis were similar in both groups (RR 0.90, 95% CI 0.69–1.17), as were the rates of puerperal sepsis (RR 1.35, 95% CI 0.93–1.95), and postnatal fever (RR 0.92, 95% CI 0.64–1.33) (17).

Effectiveness of antenatal corticosteroid administration in preventing early neonatal respiratory distress syndrome

In present study, No Antenatal corticosteroids group (NACS), was considered as reference value of 1.when compared with Antenatal corticosteroids group (ACS), relative risk was 0.65.

In a study by Liggins et al, in the unplanned deliveries, in infants of mothers who had received betamethasone for at least 24 hours before delivery, relative risk of Antenatal corticosteroids group was 0.72. (7). In a study by Maria et al, in Antenatal corticosteroids group Respiratory distress syndrome, relative risk was 0.56 (8). Study by Cynithia et al observed that relative risk of 0.60 (9).

Antenatal corticosteroids in early pre term deliveries. In present study, In Antenatal corticosteroids group -Neonates (ACS - N), among Early pre term (28-34 weeks) newborns, 8 (15.38%) newborns developed Respiratory distress syndrome whereas among No Antenatal corticosteroids group -Neonates (NACS - N), among Early pre term (28-34 weeks) newborns, 11 (26.2%) newborns developed Respiratory distress syndrome. P value of 0.034 was derived which suggested statistically significant difference between the groups (P< 0.05).

In Cochrane review, RDS was reduced in all gestational ages with the exception of less than 26 weeks gestation. Neonatal death was significantly reduced in corticosteroid-treated infants entering a trial from 26 to 29 6/7 weeks (RR 0.67, 95%CI 0.45–0.99) but not from less than 26 weeks (RR 1.87, 95% CI 0.61–5.87) (15).

However, present study did not include subgroup analysis below 26 weeks. But overall early pre term cohort reported significant benefit. It is also possible that antenatal corticosteroids can only improve lung function once adequate numbers of primitive alveoli and lamellar bodies have started to appear, which typically occurs in the saccular phase of lung development beginning at approximately 25 weeks gestation, though some in vitro studies would suggest a maturational effect can occur earlier in gestation.

Antenatal corticosteroids in late pre term deliveries

In Antenatal corticosteroids group -Neonates (ACS - N), among late pre term (34+0 to 36+6 weeks) newborns, 6 (10.17%) newborns developed Respiratory distress syndrome whereas among No Antenatal corticosteroids group -Neonates (NACS - N), among late pre term (34+0 to 36+6 weeks) newborns, 7(21.21%) newborns developed Respiratory distress syndrome. P value of 0.048 was derived which suggested statistically significant difference between the groups (P< 0.05).

Cochrane review reported decrease in the rate of RDS in the subgroup of infants receiving treatment between 33 and 34 6/7 weeks (RR 0.53, 95% CI 0.31–0.91) (15).

It has been hypothesized that corticosteroids may be effective at later gestational ages not because of an increase in surfactant production from type II alveolar cells or acceleration in lung structural development reducing the incidence of classic RDS, but by increasing expression of epithelial sodium channels (ENaC) which allow the alveoli to convert from active fluid secretion to sodium and fluid absorption with subsequent reduction of fetal lung fluid.

Effectiveness of ACS administration in preventing neonatal complications with respect to the mode of delivery.

In present study, No Antenatal corticosteroids group (NACS) – LSCS group, reference value was considered as 1.In comparison, subjects in No Antenatal corticosteroids group (NACS) who underwent vaginal delivery, relative risk was 0.9.In Antenatal corticosteroids group (ACS) who underwent LSCS, relative risk was 0.6, whereas, in Antenatal corticosteroids group (ACS) who underwent vaginal delivery was 0.7.

Cesarean delivery is a risk factor for the development of neonatal respiratory complications, mostly RDS and transient tachypnea of the newborn, in infants both at term and preterm. Infants born at term by cesarean delivery are more likely to develop respiratory morbidity than infants born vaginally, and this risk increases further for the subgroup of children born after scheduled cesarean section—that is, before onset of labor with potentially severe implications.

The risk decreases with advancing gestational age, and infants born at 37^{0}-37^{6} weeks' gestation are at 1.7 times more risk for respiratory complications than those born at 38^{0}-38^{6} weeks' gestation who in turn are at 2.4 times more risk than the infants born at 39^{0}-39^{6} weeks' gestation. This trend is particularly pronounced for RDS. Respiratory morbidity in term planned cesarean delivery seems to have a different pathophysiology from that in preterm birth, with lack of the physiological catecholamine surge and fluid retention in the lungs being the most likely causes (18).

Recent evidence indicates that, apart from the mechanical concept of vaginal squeeze, molecular mechanisms (lung epithelial sodium channels) promote alveolar fluid drainage, and these channels may be underactive in fetuses not exposed to the process of labor. Glucocorticoids appear to increase the number and function of sodium channels as well as the responsiveness to catecholamine and thyroid hormones, providing a rationale for their exogenous use in planned cesarean deliveries (19).

CONCLUSION

ACS group had lower incidence of Respiratory distress syndrome compared to NACS group. ACS group had lower incidence of severe Respiratory distress syndrome compared to NACS group among those who had Respiratory distress syndrome.

ACS group had fewer admissions to NICU than NACS group. ACS group had lower mortality than NACS group. ACS group had 35 % less chances of Respiratory distress syndrome compared to NACS group.

Antenatal corticosteroids were found to be beneficial in both early preterm and late preterm deliveries. In NACS group, subjects who underwent vaginal delivery had 10% less risk compared to those who underwent LSCS for their neonates to have Respiratory distress syndrome. In ACS group, subjects who underwent vaginal delivery had 14.29 % less risk compared to those who underwent LSCS for their neonates to have Respiratory distress syndrome.

ACS group had comparable maternal infection rate with NACS group. Use of antenatal corticosteroids was found to be beneficial in pregnant women with Gestational age of 28 completed weeks to less than 37 completed weeks.

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