ORIGINAL RESEARCH

To determine the effects of corticosteroids to pregnant women and their unborn children in the late preterm phase

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ABSTRACT

Aim: The effects of giving corticosteroids to pregnant women and their unborn children in the late preterm phase. **Material and methods:** Pregnant women who are at risk of having a premature baby are divided into two groups: those who receive prenatal corticosteroids after 34 weeks of pregnancy and those who do not, in line with the current standard of treatment. The former entails giving the patient two 12-milligram shots of betamethasone intramuscularly, 24 hours apart. Singleton pregnancies between $34^{0/7}$ and $36^{6/7}$ weeks were eligible, as were parturient who were close to delivering; fetal death, significant congenital malformations, and chromosomal abnormalities were not. There were 100 test subjects who were exposed and 100 who were not.

Results: ACS usage was greatest in the $34^{0/7}$ to $34^{6/7}$ week group (58% vs. 5%, p <0.001) and lowest in the $36^{0/7}$ to $36^{6/7}$ week category (13% vs. 70%, p <0.001). As a consequence, the study group's mean birth weight was lower (2801.74g vs. 2698.58g; p<0.043). In this research, the incidence of ACS administration as a function of gestational age was higher in patients at 34 weeks than in those at 36 weeks (58% vs. 13%, p <0.001). Preterm labour was the most common reason for delivery (45%), followed by premature preterm rupture of membranes (24%), hypertensive disorders of pregnancy (14%), antepartum haemorrhage (4%), fetal compromise (10%), and elective (1%). Except for higher rates of suspected sepsis (11% vs. 4%, p< 0.02; odds ratio (OR) 3.58, 95% confidence interval (CI) 1.37-7.85) and hypoglycemia (20% vs. 11%, p<0.04; OR 2.18, CI 1.22-4.61) in infants born to mothers exposed to ACS, there was no statistically significant difference in the rate of the primary outcome variable as well as the individual variables studied between the exposed. **Conclusion:** According to the results of this investigation, prenatal corticosteroids did not help prevent newborn morbidity. In fact, there was an increase in the number of neonates diagnosed with hypoglycemia and probable sepsis whose mothers were exposed to steroids. However, if the lack of benefit is verified by further research along with a trend towards increased problems, this treatment should typically be kept to experimental investigations. Antenatal Late Preterm Steroids (ALPS) is a big randomised controlled experiment that is currently recruiting participants and has the potential to settle this debate and standardise care for pregnant women who are at high risk of having their babies prematurely during the LPP.

Keywords: corticosteroids, pregnant women, late preterm

INTRODUCTION

There is a strong correlation between preterm delivery and an increase in infant morbidity and death [1, 2], making it a serious public health problem globally. Almost 75% of all preterm deliveries occur between $34^{0/7}$ and $36^{6/7}$ weeks, making this the fastest rising category of premature neonates [3]. Luckily, the rate of LPP prevalence rise has slowed, and its projected prevalence in 2013 was just 8.0% [4]. The neonatal intensive care unit (NICU) is full with late preterm babies because they are more likely to suffer respiratory and non-respiratory morbidities than their term peers, ages 5-7. It has been challenging to adopt primary and secondary prevention techniques to improve preterm birth worldwide, and this may not be viable in many locations due to a lack of resources. Tertiary prevention, on the other hand, has received a lot of attention since it may affect change in the long run, namely in terms of newborn outcomes [8]. Antenatal corticosteroids (ACS) are given to high-risk pregnant mothers in an attempt to reduce the number of premature births. Standard of care [9] is the

administration of ACS to pregnant women who are at risk of preterm birth and whose gestational age is less than 34 weeks. Members of a workshop held in 2011 by the National Institute of Child Health and Human Development (NICHD) to discuss strategies to reduce preterm birth and neonatal morbidity [10, 12] noted the lack of substantial data to support the administration of ACS in the late preterm period (LPP) and recommended further study. Our study's goal was to determine whether administering ACS to women at high risk of imminent delivery between $34^{0/7}$ and $36^{6/7}$ weeks would have any influence on the rate of short-term newborn morbidities.

MATERIAL AND METHODS

Pregnant women who are at risk of having a premature baby are divided into two groups: those who receive prenatal corticosteroids after 34 weeks of pregnancy and those who do not, in line with the current standard of treatment. The former entails giving the patient two 12-milligram shots of betamethasone intramuscularly, 24 hours apart. The observational study has IRB approval. Singleton pregnancies between $34^{0/7}$ and $36^{6/7}$ weeks were eligible, as were parturients who were close to delivering; foetal death, significant congenital malformations, and chromosomal abnormalities were not. It was up to the discretion of the supervising obstetrician to decide whether or not to use ACS. Ultrasounds performed in the early half of pregnancy verified the last menstrual cycle, which was used to calculate the gestational age. There were 100 test subjects who were exposed and 100 who were not.

Maternal age, parity, gestational age, baby weight, gender, method of birth, presence of labour at presentation, and main indication for delivery were all gathered as demographic factors for this research. Abruptio placentae and placenta previa were two causes of antenatal haemorrhage. Oligohydramnios, abnormal prenatal tests, and severe foetal growth restriction (an estimated foetal weight below the third percentile for gestational age) were all examples of conditions that posed a risk to the developing baby and were considered forms of foetal compromise. Gestational hypertension and preeclampsia were both classified as hypertensive diseases of pregnancy.

These were some of the reasons why patients were admitted to our NICU: neonatologist-determined low birth weight (less than 1,800 g), respiratory morbidity, chronic hypoglycemia, probable sepsis, poor feeding, reduced oxygen saturation, or the need for careful supervision. At the first hour of birth, blood glucose levels below 40 mg/dl were considered hypoglycemic. At the first hour of life, an infant whose core body temperature was below 36.0°C was considered to have hypothermia. The two groups were compared on a number of neonatal outcome characteristics, including NICU admission, RDS, TTN, suspected sepsis, jaundice requiring phototherapy, hypoglycemia, and hypothermia. There was a comparison made between the two groups based on the occurrence of Any Adverse Neonatal Morbidity. In addition, we generated and compared a Neonatal Morbidity Composite that takes into account all seven morbidities.

Statistical analysis

Counts, percentages, and medians were used to summarise the data (SD). Both the Chi-square test for categorical data and the Independent Samples T-test for continuous data were used to determine whether or not there was a statistically significant difference between the two groups. An associated P-value of less than 0.05 was regarded as statistically significant. The statistical analysis was performed using SPSS, the Statistical Program for the Social Sciences, version 25.0. (SPSS Inc., Chicago, IL).

RESULTS

1458 deliveries occurred at our institution throughout the research period. There were 225 instances between $34^{0/7}$ and $36^{6/7}$ weeks. After the exclusion of 25 individuals due to fetal death, 200 were recruited in the research. The study participants were separated into two groups: the study group (n = 100 patients) who got ACS and the control group (n = 100 patients) which did not get the therapy. Table 1 shows the demographic characteristics of the two groups. Three demographic factors showed a statistically significant difference. ACS usage was greatest in the $34^{0/7}$ to $34^{6/7}$ week group (58% vs. 5%, $p < 0.001$) and lowest in the $36^{0/7}$ to $36^{6/7}$ week category (13% vs. 70%, $p < 0.001$). As a consequence, the study group's mean birth weight was lower (2801.74g vs. 2698.58g; $p<0.043$). In this research, the incidence of ACS administration as a function of gestational age was higher in patients at 34 weeks than in those at 36 weeks (58% vs. 13%, $p < 0.001$). Preterm labour was the most common reason for delivery (45%), followed by premature preterm rupture of membranes (24%), hypertensive disorders of pregnancy (14%), antepartum haemorrhage (4%), foetal compromise (10%), and elective (1%).

Except for higher rates of suspected sepsis (11% vs. 4%, $p< 0.02$; odds ratio (OR) 3.58, 95% confidence interval (CI) 1.37-7.85) and hypoglycemia (20% vs. 11%, $p<0.04$; OR 2.18, CI 1.22-4.61) in infants born to mothers exposed to ACS, there was no statistically significant difference in the rate of the primary outcome variable as well as the individual variables studied between the exposed (Table 2).

The impact of ACS on gestational age was also investigated. There was no statistically significant difference in any morbidity, with the exception of a greater risk of sepsis in the ACS group at 35 weeks' gestation (20% vs. 4%, $p<0.04$, OR 3.58, CI 0.87-31.58). The average time between steroid administration and delivery was 13.1 hours. To investigate the impact of ACS exposure length, individuals who got ACS were divided into three

groups: those who were provided less than 8 hours, between 8 and 12 hours, and more than 12 hours after receiving the first dose of ACS. Longer exposures were found to be related with increased morbidity rates. Any Adverse Neonatal Morbidity and Composite Metabolic Morbidity were statistically significant.

Table 1: Basic parameter

	NO ACS	%	ACS	%	P-Value
Maternal age	28.47 ± 4.63		30.01 ± 4.44		0.32
birth weight (g)	2801.74±211.69		2698.58±198.63		0.02
Cesarean delivery	29	29	35	35	0.24
Male gender	53	53	61	61	0.18
Primiparity	55	55	55	55	0.36
Diabetes mellitus	5	5	10	10	0.41
Preterm labor	51	51	45	45	0.24
Preterm premature rupture of membranes	20	20	24	24	0.11
Hypertension	10	10	14	14	0.33
Antenatal hemorrhage	4	4	4	4	0.22
Fetal compromise	7	7	10	10	0.26
Elective	8	8	1	1	0.03
Gestational age ($34^{0/7}$ - $34^{6/7}$)	5	5	58	58	0.001
Gestational age ($35^{0/7}$	25	25	29	29	0.47
Gestational age ($36^{0/7}$	70	70	13	13	0.001

Table 2: Short-term neonatal outcomes following ACS administration

Outcome	No ACS	ACS	*P*-value	OR	95% CI
Any neonatal morbidity	41	47	0.41	1.44	0.769–2.218
NICU admissions	20	28	0.22	1.68	0.855–2.915
Neonatal death	1	0	–	–	–
Mean NICU stay (Days)*	7.99 ± 1.69	9.58 ± 2.01			
Composite respiratory morbidity	15	18	0.51	1.29	0.68–2.74
suspected sepsis	4	11	0.02	3.58	1.37–7.85
RDS	7	8	8	1.33	0.54–3.54
TTN	7	8	0.29	1.47	0.63–3.47
Ventilator	6	7	0.54	1.11	0.49–3.11
Oxygen supply	9	10	0.56	1.27	0.69–2.88
Composite metabolic morbidity	34	38	0.39	1.23	0.78–2.12
Phototherapy	24	28	0.47	1.24	0.77–2.89
Hypothermia	10	11	0.61	1.36	0.39–2.63
	11	20	0.04	2.18	1.22–4.61
Hypoglycemia					

DISCUSSION

It was shown in this trial that giving ACS to pregnant women who were due to give birth soon during the LPP did not reduce the incidence of newborn morbidity. Use of ACS has been linked to better newborn outcomes since at least the late 1960s. Graham Liggins was looking into what triggers labour in a sheep model when he made the fortuitous observation that premature lambs given corticosteroids had better developed lungs than predicted after death [15]. Also, animals who were given steroids throughout pregnancy were able to deliver with less respiratory distress and at a younger gestational age. Betamethasone, a potent glucocorticoid, given to mothers who are expected to give birth prematurely has been shown to improve the respiratory status of preterm neonates [16]. This discovery was made possible by the pioneering work of Liggins and Howie, who conducted the preliminary work that led to the landmark randomised clinical trial. While a consensus conference was conducted by the NICHD in 1994 [17], it was not until then that ACS became widely used to prevent preterm birth. There were no reported dangers to the infants at this conference, and their usage was shown to greatly decrease RDS, IVH, and newborn death. All women at risk of preterm birth between 24 and 34 weeks were advised to get ACS. Last but not least, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists both agreed with this suggestion [18].

Standard obstetric treatment does not include the use of prenatal corticosteroids for women who are at risk of having a premature baby later than 34 weeks. Nonetheless, academics and professional organisations have increasingly focused on late preterm newborns and pregnant women at risk of preterm delivery during the LPP. In addition to making up over 75% of all preterm births, this group also represents the preterm period with the greatest rate of growth, having increased by about 50% between 1981 and 2006 [3]. It is not unexpected that the neonatal intensive care unit is filled with late preterm newborns due to the high risk of developing a variety of neonatal morbidities among these children. Seven morbidities were shown to be considerably higher in late preterm compared to term newborns [10], as determined by a retrospective analysis that reviewed the 18-year experience of a single facility. They included septic shock confirmed by culture, necrotizing enter colitis, idiopathic ventricular hypertrophy (IVH) of grades 1 and 2, and the necessity for phototherapy and mechanical ventilation. Late preterm babies were the focus of another retrospective investigation that examined short-term respiratory morbidities [5].

Infants born at a later stage of prematurity are at a higher risk for respiratory morbidity. There aren't many research looking at the effects of ACS administration after 34 weeks on this outcome, but there are several looking at the effects of ACS administration before 34 weeks on LPP-born neonates. Babies delivered between 34 and 36 weeks were studied by Ventolini et al., who found that those whose mothers had taken prenatal steroids before to 34 weeks had better outcomes than those whose mothers had not [24]. The former group had a considerably lower rate of respiratory distress syndrome (RDS), ventilator requirements, CPAP use, and oxygen use. In this research, newborns who were exposed to steroids were much less likely to need care in a neonatal intensive care unit (NICU) than those who were not. Further studies by Eriksson et al. [25] indicated that late preterm babies who were exposed to ACS before 34 weeks of gestation had lower likelihood of developing respiratory distress. On the other hand, several studies show that giving ACS to neonates delivered in the LPP before 34 weeks does not reduce morbidity [26-29].

The following findings emerged from the small subset of studies that followed participants receiving ACS for more than 34 weeks. A modest randomised controlled study conducted by Shanks et al. [30] was cut short owing to difficulty recruiting women with an immature foetal lung maturity profile on amniocentesis. Participants were assigned at random to either an antenatal steroid therapy group or a sham treatment group. Amniotic fluid was retested 7 days later in both groups, and the treated group had a higher likelihood of having a mature lung maturity profile. On the other hand, a randomised controlled experiment by Porto et al. demonstrated between parturients who received prenatal 2 doses of betamethasone between $34^{0/7}$ and $36^{6/7}$ weeks of gestation and their counterparts who got placebo [31]. In the end, they determined that ACS did not help reduce the prevalence of respiratory illnesses, the number of babies admitted to the NICU, or any other morbidity except jaundice. Most recently, Yinon et al.[32] performed a retrospective cohort analysis of women who had amniocentesis between 34 and 37 weeks of gestation to assess foetal lung development. Individuals with inconclusive tests were split into a study group treated with betamethasone and a control group that did not receive betamethasone medication. If foetal lung immaturity is demonstrated after 34 weeks of pregnancy, antenatal steroid treatment may be an option to enhance newborn prognosis.

In light of the fact that endogenous corticosteroids tend to spike in the late preterm and term period, several writers have voiced worry that using exogenous corticosteroids at these times would have an additional, undesirable impact on neurodevelopment. Researchers P. Stutchfield et al. [33] evaluated the use of ACS for elective caesarean section at term and found that women who had a single course of ACS and had their babies between $37^{0/7}$ and $38^{6/7}$ weeks of gestation had a lower risk of respiratory morbidity. Researchers used parent surveys, standardized test scores, and school evaluations of children's cognitive abilities in a follow-up research [34] including children aged 8 to 15. The results of this research showed no changes in the children's health, conduct, or the likelihood of having asthma later in life. Yet, compared to students who did not get ACS, those who did had a significantly increased chance of being placed in the lowest academic percentile by their schools

(p=0.03). Women at high risk for preterm birth (between 25 and 32 weeks' gestation) were randomised to receive either a single course of ACS or multiple courses, each administered every 14 days until delivery or 32 weeks' gestation was achieved in the MACS-5 study [35]. There was an elevated chance of mortality or survival with a neurodevelopmental deficit in at least one area among children who had received repeated courses of ACS preterm but who went on to deliver at term, as measured by the primary outcome in this study's five-year follow-up. There was likewise no indication of a dosage response connection, however this cohort of children was at a higher risk of neurosensory dysfunction. This information may not be directly applicable to neonates and children who were only given a single course of ACS in the LPP, but it does show that there is reason for concern about the potential for lifelong complications from prenatal exposure to corticosteroids in babies born at a later gestational age. The endogenous corticosteroid rise coinciding with the administration of exogenous corticosteroids lends more credence to these worries.

Women who were at high risk of having a preterm birth during the LPP were not shown to benefit from prenatal corticosteroids in our research. Among our sample, PPROM and preterm labour accounted for 69% of the deliveries. Preterm labour was responsible for 45% of cases, PPROM for 35%, and combined they equal to 80% of all late preterm births [10], which is comparable to the rates described by McIntire et al. Just a tiny percentage of our cohort's births were planned, and those that were were all within a few of days of the due date. Miscalculations of menstrual cycles led to the scheduling of premature births [19].

More patients at 34 weeks of pregnancy got steroids than those at 36 weeks, according to this study's analysis of the association between ACS administration and gestational age. Prenatal steroid usage declines with increasing gestational age, as documented in the group investigated by Joseph et al [11]. Similar to what was shown by Chien et al. [17], ACS usage is maximum between 25 and 31 weeks of gestation and subsequently decreases with lower and higher gestational ages. Consistent with a research by Kamath-Raney et al. [20], we discovered that ACS dramatically elevated the risk of hypoglycemia and sepsis in late preterm newborn babies.

CONCLUSION

According to the results of this investigation, prenatal corticosteroids did not help prevent newborn morbidity. In fact, there was an increase in the number of neonates diagnosed with hypoglycemia and probable sepsis whose mothers were exposed to steroids. However, if the lack of benefit is verified by further research along with a trend towards increased problems, this treatment should typically be kept to experimental investigations. Antenatal Late Preterm Steroids (ALPS) is a big randomised controlled experiment that is currently recruiting participants and has the potential to settle this debate and standardise care for pregnant women who are at high risk of having their babies prematurely during the LPP.

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