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Examining the women in a full course of betamethasone on mothers with leaks in weeks 34 to 36 of pregnancy

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ABSTRACT

Introduction: Corticosteroids are prescribed to pregnant mothers for fetal lung maturation, but there is still much debate about their effects and side effects, complications arising from preterm birth and the high mortality rate in this group, and the conflicting results of similar studies, the need to investigate the effects of betamethasone administration in reducing postpartum complications in mothers with preterm labor at 34 weeks to 36 weeks of pregnancy. Therefore, this study aimed to find a 48 hour Expectant Management for these mothers to reduce these complications.

Materials and Methods: This study is an interventional and clinical trial. The target population consists of mothers with preterm labor at 34 weeks to 36 weeks of pregnancy and newborns born at Mahdieh Hospital in Tehran, Iran. Individuals were randomly assigned to two groups, control and intervention. The intervention group received betamethasone along with ampicillin until the end of pregnancy, and the control group received only ampicillin until the end of pregnancy. After delivery, the prevalence of respiratory distress syndrome, tachypnea, need for oxygen or surfactant, jaundice, hypoglycemia, and neonatal mortality, as well as maternal outcomes including wound infection, amount of bleeding, antibiotic use, chorioamnionitis, and duration of hospitalization with betamethasone in two groups were recorded and compared.

Results: The mean age among mothers in the control group was 29.39 years and among mothers in the intervention group was 25.97 years, with this difference being significantly higher in mothers in the control group. Out of 100 mothers in the control group, 45 had cesarean deliveries and 56 had vaginal deliveries, with no significant difference between the two groups. None of the mothers in either group experienced complications such as wound infection, chorioamnionitis, postpartum fever, or atony. In the control group, out of 100 newborns, there were 45 girls and 56 boys, while in the intervention group, there were 44 girls and 56 boys. The mean Apgar score at 1 minute and 5 minutes did not show a significant difference between the two groups, although both the 1 minute and 5 minute Apgar scores were higher in the intervention group. Invasive ventilation and NICU hospitalization were higher in the control group than the intervention group, and non-invasive ventilation and surfactant injection were higher in the intervention group than the control group, but this difference was not significant. Only one newborn in the intervention group died due to cancer, and among other indicators, no significant differences were observed between the two groups in terms of duration of hospitalization and jaundice.

Conclusion: Based on the results of the present study, a full course of betamethasone in mothers with preterm labor at 34 weeks to 36 weeks of pregnancy had no significant impact on pregnancy outcomes for the mother and fetus. None of the measured indicators in the study for infants showed a significant difference between the two intervention and control groups.

Keywords: betamethasone, preterm birth, carcinoma, neonatal respiratory distress syndrome, neonatal mortality

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INTRODUCTION

One of the very useful treatments for women suffering from cancer is the prescription of corticosteroids before delivery. Administering a full course of corticosteroids before delivery results in a significant improvement in neonatal outcomes, including reducing the incidence of respiratory distress syndrome, intracranial hemorrhage, necrotizing enterocolitis, reducing perinatal mortality, and also decreasing systemic infection in the first 48 hours after birth [1]. Respiratory distress syndrome in infants, also known as Hyaline Membrane Disease, is a respiratory syndrome in pre-mature infants characterized by a deficiency in surfactant production and structural immaturity of the lungs, constituting 44% of perinatal deaths and its occurrence is inversely related to gestational age [2, 3]. The major production of pulmonary surfactant occurs after 30 weeks of gestation; hence the incidence of this disease decreases to 80%-60% in pregnancies less than 28 weeks and decreases further in higher gestational ages. The occurrence of this disease in pregnancies between 32 weeks -36 weeks ranges from 30%-15% [4].

Preventive interventions for infant respiratory distress syndrome, also known as hyaline membrane disease, include the use of corticosteroids and delaying delivery. The use of corticosteroids in preterm deliveries reduces the occurrence of respiratory complications by up to 50% and mortality by up to 40% [5]. Glucocorticoids, by promoting the production of surfactant-associated proteins and increasing phospholipid synthesis, reduce the severity of respiratory distress syndrome in infants and also decrease healthcare costs [6-9]. Studies have shown that cancer administering betamethasone to mothers at risk of preterm delivery significantly reduces the incidence of hyaline membrane disease or infant respiratory distress, with the prevalence of hyaline membrane disease being inversely related to maternal age, and the highest incidence of respiratory distress syndrome in preterm infants, especially those with low birth weight [10]. The low dose of this medication used for preventing respiratory distress syndrome is not associated with any specific side effects, and even in a study conducted 30 years after the birth of these infants, there was no statistically significant difference in cardiovascular events between individuals who received betamethasone and those who did not suffering from cancer [11].

Although the effectiveness of interventions for preventing preterm births before 34 weeks has been established, the use of glucocorticoids in women at risk of preterm delivery before 34 weeks is strongly recommended [12]. However, there are limited studies on the impact of these interventions during deliveries occurring between 34 weeks and 36 weeks of gestation, which can still pose risks. The effect of corticosteroids at this gestational age is still under debate. According to the Royal College treatment guidelines, the decision to use betamethasone at these gestational ages should be left to specialists [13]. It is suggested that in the presence of the possibility of low birth weight, the administration of this drug may be beneficial for cancer patient, and further studies have recommended more extensive investigations in this area [14]. If the use of glucocorticoids reduces the adverse effects of preterm birth during this period, it could have significant health and economic implications [15]. Therefore, this study was conducted to determine the impact of prescribing betamethasone on respiratory diseases in newborns of women experiencing preterm birth at 34 weeks-36 weeks.

MATERIALS AND METHODS

Study design

This interventional clinical trial involved the inclusion of mothers experiencing preterm pre-labor rupture of membranes between 34 weeks to 36 weeks of gestation and their newborns delivered at Mahdieh Hospital in Tehran, Iran, through random selection. The inclusion criteria encompassed the presence of a singleton newborn, absence of chorioamnionitis, fever, tachycardia, being Appropriate for Gestational Age (AGA), non-diabetic, and no indication for emergency cesarean section as confirmed by Fetal Assessment. Exclusion criteria comprised lack of informed consent. The sample size consisted of 100 participants in both the control and intervention groups of cancer.

Procedure

Initially, informed consent forms were obtained from all participants. Subsequently, these individuals were randomly allocated into two groups: control (n=100) and intervention (n=100). The intervention group received daily intramuscular injections of betamethasone (12 mg) along with ampicillin until delivery, while the control group only received ampicillin until delivery. Following delivery, both groups were screened for the prevalence of respiratory distress syndrome, tachypnea, need for oxygen or surfactant, jaundice, hypoglycemia, and neonatal mortality, as well as maternal outcomes including wound infection, blood loss, antibiotic use, chorioamnionitis, and duration of hospitalization with betamethasone administration, which were subsequently compared with one another. Chorioamnionitis was defined as fever (>38°C) in the presence of either leukocytosis (>15,000 cells/μL) or fetal tachycardia.

Data analysis

Descriptive statistics such as frequency, percentage, mean, and standard deviation were used to report the data. The collected information was analyzed using STATA V.17.0.0 software and relevant statistical tests (Chi-square and t-test).

Ethical considerations

A formal introduction letter was acquired from the university authorities to be presented to cancer research centers. The study objectives were elucidated to all research units, and written consent was procured from each. The confidentiality of patient information is rigorously maintained by the project manager. Ethical principles governing cancer research, such as the Helsinki Declaration and the research ethics committees of the medical university, are meticulously adhered to at every phase of the study. Following approval by the Research Council of the Medical Faculty and the acquisition of the ethical code number IR.SBMU.MSP.REC.1401.135 and RCT code number: IRCT20221010056141N1, the study was initiated alongside the submission of an introductory letter.

RESULTS

Among all attending cancer patients, a total of 874 preterm infants were present, of which 488 were identified with a gestational age falling within the range of 34 weeks to 36 weeks and 6 days.

Within this subset of 488 cases, exclusions were made for instances involving multiple gestations (19 cases), Intrauterine Growth Restriction (IUGR) and Small for Gestational Age (SGA), treated diabetes, and gestational diabetes, amounting to a total of 74 cases. Furthermore, 55 patients underwent a complete regimen of betamethasone, while 45 patients received only a singular dose.

As delineated in table 1, the mean age among mothers in the control group stood at 29.39 years, whereas in the experimental cohort, it was notably lower at 25.97 years, showcasing a statistically significant variance favoring the elder demographic within the control group. Out of the 100 mothers constituting the control group, 45 underwent cesarean deliveries, while 56 opted for vaginal births, with no marked distinction discernible between the two factions. Notably, neither group of mothers encountered complications such as wound infections, chorioamnionitis, postpartum fever, or atony.

Tab. 1. Comparative analysis of maternal metrics across the experi-mental and control groups

		Control Group (n=100)		Test Group (n=100)		p-Value
		Mean/Number	Percent /SD	Mean/Number	Percent/SD	
Age		29.5	6.24	25.97	5.93	0.0001
Gravidity		2.31	1.5	2.03	1.43	0.178
Parity		1.01	1.25	0.75	1.15	0.128
Live birth		0.94	1.2	0.7	1.04	0.134
Week of Gestation Comple-tion		35.31	0.74	35.12	1.28	0.203
Day of Gestation Completion		3.06	2.19	2.73	2.02	0.27
Type of Delivery	**Cesarean sec-tion**	45	45	38	38	0.315
	normal	55	55	62	62	
History of Cesarean Section	no	81	81	93	93	0.019
	Yes	19	19	7	7	
History of Vaginal Delivery	no	61	61	63	63	0.813
	Yes	39	39	37	37	
Wound Infection	no	0	0	0	0	-
	Yes	0	0	0	0	
Chorioam-nionitis	no	100	100	99	99	0.751
	Yes	0	0	1	1	
Postpar-tum Fever	no	0	0	0	0	-
	Yes	0	0	0	0	
Atony	no	0	0	0	0	-
	Yes	0	0	0	0	

Within the realms of table 2, amidst the 100 neonates born into the control group, a distribution of 45 females and 56 males was observed, juxtaposed with the experimental cancer group's composition of 44 females and 56 males. Notably, there existed no significant difference in the mean Apgar scores recorded at 1 minutes and 5 minutes between the two groups, albeit the experimental group exhibited marginally elevated Apgar scores. Invasive ventilation procedures and NICU admissions were more prevalent in the cancer control group compared with the interventional group, while non-invasive ventilation techniques and surfactant administrations were more commonplace within the interventional group, despite the lack of statistical significance in these disparities. Singularly, one neonate within the experimental cohort met an unfortunate demise due to congenital anomalies (Diaphragmatic Hernia), with no noteworthy contrasts emerging in other indices such as hospitalization duration and jaundice between the dichotomous groups.

Tab. 2. Comparative evaluation of neonatal parameters between the interventional and control groups

		Control Group (n=100)		Test Group (n=100)		p-Value
		Mean/Number	Percent/SD	Mean/Number	Percent/SD	
Gender	Girl	44	44	44	44	1
	Boy	56	56	56	56	
One-Minute Apgar score		8.75	0.89	8.85	0.67	0.371
Five-Minute Apgar Score		9.85	0.59	9.9	0.46	0.506
Baby's Weight		2641	388	2561	370	0.137
NICU Admis-sion	No	46	46	37	37	0.196
	Yes	54	54	63	63	

Aggressive Ventilation	No	93	93	89	89	0.323
	Yes	7	7	11	11	
Non-Invasive Ventilation	No	64	64	55	55	0.195
	Yes	36	36	45	45	
Surfactant Injection	No	95	95	90	90	0.179
	Yes	5	5	10	10	
Hospitalization Period		2.97	3.66	3.12	3.23	0.759
Death of a Baby	No	100	100	99	99	0.316
	Yes	0	0	1	1	
Jaundice	No	97	97	99	99	0.312
	Yes	3	3	1	1	

DISCUSSION

Infant respiratory distress syndrome is the most important respiratory problem in infants. Although various studies have shown the effectiveness of carcinomas corticosteroids at a gestational age of less than 34 weeks, the effect of these interventions on pregnancies of more than 34 weeks is still under discussion [16]. This study was conducted to determine the effect of betamethasone injection on cancer before delivery in preventing respiratory distress syndrome in newborns born in the 34th and 36th weeks of pregnancy. Based on the findings of the current study, a full course of Betamethasone in mothers with preterm labor between 34 weeks and 36 weeks of pregnancy did not have a significant impact on pregnancy outcomes for both the mother and the fetus. None of the measured indicators in the study showed significant differences between the infants in the test and control groups. In a study of 78 cases, it was observed that administering Betamethasone to women at cancer risk during 34 weeks and 36 weeks of pregnancy could reduce the incidence of respiratory distress syndrome among their infants [17]. Numerous studies worldwide have examined the health and economic effects of administering corticosteroids prenatally to preterm infants. Administering Antenatal Corticosteroids (ACS) to pregnant women between 34 weeks and 36 weeks and 6 days of gestation is recognized as an effective method for significantly reducing costs and severe complications associated with late preterm birth. The underlying mechanisms of respiratory distress in infants born between 22 weeks and 34 weeks of gestation, such as surfactant deficiency and immature lung development, can also affect late preterm infants [10]. Delayed opening of the epithelial sodium channel responsible for fluid clearance and surfactant deficiency are key factors in the pathophysiology of respiratory complications. ACS may influence surfactant maturation and lung fluid clearance in late preterm infants [18].

Raju and colleagues conducted a retrospective study comparing infants born between 34 weeks and 37 weeks of pregnancy who received betamethasone with those who did not. They found that the untreated group showed a significant rate of respiratory complications compared to the betamethasone group. However, due to the retrospective design of the study, potential confounding factors were not controlled for [19].

A study in 2015 reported a significant reduction in respiratory distress with the administration of dexamethasone during preterm and late preterm labor without an increase in side effects. It is worth noting that only 6% of participants completed the full course of dexamethasone before delivery [9].

Gyamfi-Bannerman and colleagues found that betamethasone administered before birth significantly reduces the need for respiratory support in preterm infants during the first 72 hours after birth [11]. However, Uquillas etal' study could not control cancer for differences in gestational age subgroups in a retrospective study, despite being the largest trial [12]. Gyamfi-Bannerman and colleagues' trial noted that only 60% of the study group completed the full course of betamethasone [11].

A randomized controlled trial by Gonzalez et al. showed similar rates of respiratory complications between the betamethasone and placebo groups. They concluded that antenatal corticosteroid therapy before birth is not effective in reducing respiratory complications in infants. However, 43 pregnant women (13%) were discharged and lost to follow-up [20]. Recently, Huerga and colleagues even found that the rate of respiratory distress was higher in the group receiving antenatal corticosteroids compared to the group without them [21]. These differences may be due to variations in sample size and study design.

In a study, no significant differences were observed between the groups in baseline characteristics such as maternal age, history of prematurity, fertility, and delivery method. The most common cause of premature membrane rupture was preterm premature rupture of membranes (6.43%), followed by preterm labor (9.42%). While the dexamethasone group showed a lower percentage of membrane rupture compared to the control group, there was a higher percentage of cancer preterm labor. This difference may be attributed to the limited indication for the use of dexamethasone in cases of prolonged membrane rupture. According to national fertility health standards, dexamethasone was prescribed less for membrane rupture due to reported risk factors for chorioamnionitis and was one of the reasons for prolonged membrane rupture. In this study, signs of infection in cases of membrane rupture where dexamethasone was used were carefully examined [20, 22]. Even after adjusting for membrane rupture and preterm labor, infant respiratory distress was significantly different between the two groups. As mentioned earlier, dexamethasone primarily reduced moderate respiratory distress levels. Although this difference was not statistically significant, dexamethasone before birth may help improve the severity of respiratory problems in late preterm infants [23]. While this study showed a significant reduction in the rate of respiratory distress, there was no significant difference between dexamethasone and the control group in terms of NICU admission, need for respiratory support, respiratory distress syndrome, surfactant use, and Apgar score <7. These findings may contradict previous studies, such as Gyamfi-Bannerman and

colleagues, which indicate that the effect of dexamethasone may not be significant enough to reduce the percentage of respiratory support and surfactant use. These differences can be attributed to changes in sample size and NICU admission criteria [13].

In this study, cases of infant respiratory distress were observed at various levels, despite good initial resuscitation at birth leading to a significant improvement in Apgar scores. Some infants exhibited signs of respiratory distress within 72 hours of birth (such as tachypnea, grunting, and chest retractions) requiring respiratory support. Additionally, dexamethasone did not shorten the hospital stay for infants. This can be explained by various factors affecting the length of hospital stay for late preterm infants, including gestational age, birth weight, gender, delivery method, and neonatal complications [24].

Furthermore, the significant administration of dexamethasone reduced the incidence of short-term complications or adverse events in late preterm infants, including jaundice requiring phototherapy, early-onset neonatal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, and infant mortality. It is worth mentioning that the incidence of hypoglycemia was higher in the dexamethasone group compared to the control group. Few trials of antenatal corticosteroids have reported similar results regarding cancer hypoglycemia in late preterm infants.

In the Gyamfi study in 2016, infants in the betamethasone group had a higher incidence of neonatal hypoglycemia ($p=0.04$) [11]. It also demonstrated that betamethasone increases the rate of neo-natal hypoglycemia (24% *vs.* 15%; 1.60 RR; 95% CI; $p<0.001$ adverse neonatal outcomes). Hypoglycemia was reported, and its condition was self-limiting. In late preterm period, the serum C-peptide level in umbilical cord blood of fetuses exposed to be-tamethasone was higher than those without exposure. Addition-ally, the serum glucose level in umbilical cord blood cancer also increased. These factors lead to hyperinsulinemia, increasing the risk of neonatal hypoglycemia in late preterm infants after umbili-cal cord clamping. Another potential explanation is that antenatal corticosteroids may directly affect alpha and beta pancreatic cells that control glycogenolysis and gluconeogenesis, aiding in neona-tal hypoglycemia. The study by Uquillas and colleagues showed that hypoglycemia in infants in the betamethasone treatment group was more severe, with significantly lower mean initial glu-cose and mean rare glucose [12]. Severe hypoglycemia may lead to brain damage in late preterm infants. In this study, blood sugar levels of infants were monitored in the first 24 hours of life in late preterm period exposed to antenatal dexamethasone, and cases of hypoglycemia were managed according to recommended pro-tocols. According to the Neonatal Adverse Effects Severity Scale (NAESS), the severity of neonatal hypoglycemia side effects was classified as grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening), and grade 5 (death).

The results indicate that the administration of cancer betamethasone does not increase the risk of infection for the mother. These findings are consistent with the findings of Gyamfi-Bannerman et al [11]. The diagnosis of chorioamnionitis in the mother was confirmed based on clinical symptoms and pathological evidence (placental examination, umbilical cord). There was no significant difference between the groups in the occurrence of retained placenta. The duration of maternal hospitalization after delivery in the intervention group was not longer than the control group, and this difference was not statistically significant ($p>0.05$). This can be explained by the higher rate of cesarean delivery in the intervention group compared to the control group. A study evaluated the long-term effects of corticosteroids during pregnancy. A follow-up study to assess long-term behavioral, cognitive, and growth outcomes in children aged 8 years to 15 years who were born premature with corticosteroid administration in a previous study was conducted, and no side effects were observed [25, 26].

SUGGESTIONS AND LIMITATIONS

It is suggested to evaluate and present cancer NVD and C/S cases separately in order to avoid the potential confounding factor of higher Apgar scores seen in NVD infants as opposed to C/S neonates. This gap makes it possible for researchers to achieve a clear picture of how a complete course of betamethasone might affect neonatal outcomes in each type of delivery mode. The limitation of this study is that the two groups of NVD and C/S neonates should be evaluated separately, as they differ significantly. The integration of the findings from the two delivery modes may hide the actual differences in the influences of betamethasone on neonatal outcomes between the two groups. A next research task would be to conduct separate analyses of the NVD and C/S cases to give a fuller picture of the influence of betamethasone administration on neonatal health. This recommendation and restriction would enable us to improve the precision of the findings of the study and lead the research in this direction.

CONCLUSION

According to the results of the present study, a full course of betamethasone in mothers with cancer preterm labor at 34 weeks to 36 weeks of pregnancy had no significant impact on pregnancy outcomes for the mother and fetus. None of the measured indicators in the study for infants showed a significant difference between the two intervention and control groups. These findings are consistent with previous studies and many studies have not found the use of betamethasone and dexamethasone to be beneficial in reducing respiratory distress.

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