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The Safety and Effectiveness of Corticosteroids in Twin Pregnancy

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ABSTRACT

Background: Preterm deliveries are disproportionately caused by multiple pregnancies. All things considered, 10.7% of multiple births occur before 32 weeks and 52.2% before 37 weeks. Prematurity represents the largest cause of global perinatal death.

Objective: To evaluate the effectiveness of steroids in twins' pregnancy between 28 and 36 weeks.

Patient and methods: This cross-sectional multi-center research enrolled 150 pregnant women with twin pregnancies at Obstetrics and Gynecology Department, October 6th University Hospital, and Al Galaa Teaching Hospital from June 2022 to February 2023. These patients delivered within 48 hours of receiving antenatal corticosteroids and were followed up for 24 to 72 hours after delivery for the outcome.

Results: There was highly significant variation between those who received steroid than those didn't receive steroid as regard gestational age at birth while there was statistically insignificant difference as regard maternal age, body mass index, gravidity, parity, blood pressure, fetal FL, rate of periventricular leukomalacia (PVL), retinopathy of premature (ROP), birth weight, sex and type of labor. There was statistically significant lower rate of NICU admission, neonatal death, bronchopulmonary dysplasia, respiratory distress syndrome, and intraventricular hemorrhage in those who received steroid than those not received steroid.

Conclusion: Antenatal corticosteroids administration is a crucial antenatal intervention in twin early and late preterm deliveries and must be considered especially in developing countries because of lack of facilities. Further studies are required to recognize the efficacy of steroids therapy in twin pregnancies and postnatal long-term effects and to assess in establishing proper guidelines to this unique risk category.

Keywords: Antenatal corticosteroids, Prematurity of newborn, Twin pregnancy, Multifetal gestations.

INTRODUCTION

Over the past few decades, there has been a considerable rise in the occurrence of twin pregnancies, as a result of increased assisted reproductive approach and older mothers [(1)]. Compared to singleton pregnancies, twin pregnancies are linked to higher rates of unfavorable neonatal outcomes. This is primarily because of preterm delivery, that represents a major concern in the management of such cases and is present in 59% of US pregnancies, with the majority of births taking place in the late-preterm period [(2,3)].

Late preterm has been linked to poor neonatal outcomes, specifically respiratory morbidity, as well as a long-term detrimental impact on cognitive abilities and developmental outcomes as compared to term neonates [(4)].

It is important to investigate methods for enhancing the newborn outcomes of late-preterm twins. Neonatal morbidity and mortality, including respiratory distress syndrome, intraventricular hemorrhages, and necrotizing enterocolitis, are decreased when pregnant female with an elevated risk of preterm delivery are administered antenatal corticosteroids (ACS) before 34 weeks of gestation. This effective therapy has been proved [(5)].

Lung maturation is accelerated when corticosteroids are administered during pregnancy. Fast alveolization is the result of an acceleration of the double capillary loops' typical thinning, which forms the thin gas-exchanging walls of alveoli. Additionally, there is a faster development of type II pneumocytes that produce surfactant. Even though the corticosteroids cause the alveolization to happen quickly [(6)].

Due to rapid lung maturation and its impact on the vascular structure, prenatal corticosteroid therapy may boost the generation of surfactant in the fetal lungs, which may rise the flow of blood in the pulmonary arteries [(7)].

The Society for Maternal-Fetal Medicine (SMFM) and the American College of Obstetricians and Gynecologists (ACOG) revised the guidelines and extended the use of ACS to the late-preterm in cases of potentially preterm birth in singleton pregnancies as a result of this and other supporting evidence. While the likelihood of respiratory morbidity appears to be same in late-preterm twins and singletons [(8-10)].

The aim of this research was to investigate the efficacy of steroids in twins' pregnancy between 28 and 36 weeks.

PATIENTS AND METHODS

This cross-sectional multi-center research included 150 pregnant women with twin pregnancies with 300 live births neonates at Obstetrics and Gynecology Department, October 6th University Hospital, and Al Galaa Teaching Hospital from June 2022 to February 2023. These patients delivered within 48 hours of receiving antenatal corticosteroids and followed for 24 to 72 hours for the outcome.

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Comparison regarding outcomes of mother and neonates were done between the categories. Those outcomes were: ***Primary outcomes*** (Most important measurable outcomes): Need for NICU admission, and ***Secondary outcome*** parameters (other outcomes to be assessed): RDS occurrence, any other complications (safety of usage of corticosteroids in enhancing lung maturity by assessment of complications).

Inclusion criteria: Mothers with a twin pregnancy, between 28 and 36 weeks, accepted to participate and maternal age between 18 – 40 years old.
Exclusion criteria: Singleton pregnancy, pregnancy other than twins, patients refused to participate in the study, severe infection and fetal anomalies.

Method:

The included patients received dexamethasone of 4 doses of 6 mg every 12 hours for total 24 mg, and sometimes 12 mg/12 hours when delivery is eminent. After the beginning of the trial, no critical alterations were done in the methodology. Data of mother, neonates, outcomes and composite morbidity were collected and processed through observational written database, during the inpatient period which was 48 to 72 hours. 7 neonates were transferred soon after delivery for NICU admission outside hospital because of inconvenience.

Sample size estimation:
G*power 3.1.9.2 software and the online sample calculator (https://cliniccalc.com/stats/samplesize.aspx) were used for estimation of sample size.

The 150 pregnant women of our study were divided into groups: Group (1): 80 pregnant women who received corticosteroids (36 of them were early preterm (gestational weeks 28:32 week) and 44 were late pre term (gestational weeks 32:36 week), and **Group (2):** 70 pregnant women who didn't receive corticosteroids (25 of them were early preterm (gestational weeks 28:32 week) and 45 were late preterm (gestational weeks 32:36 week). The 70 pregnant weren't selected to receive corticosteroids as they arrived at the hospital in urgent delivery.

Ethical approval:

The approval was obtained from the Research Ethical Committee of October 6 university (PMC-ME-2209022). This research was established in agreement with Declaration of Helsinki for studies enrolling humans and was registered at Pan African Clinical Trials Registry on 25/10/2022 with the registration number PACTR202210545333862. STROBE checklists were followed. All involved mothers were counselled about the adverse outcomes of prematurity and multiple pregnancy and benefits and assumed side effects of antenatal corticosteroids; they had signed informed consent after agreement for participation.

Statistical methods

Analysis of data was done by IBM SPSS version 25.0. Kolmogorov−Smirnov and Shapiro−Wilk tested the distribution normality of the numerical variables. Normally distributed variables were expressed in mean ± SD, and one-way ANOVA test estimated the group differences. Categorical parameters were presented as frequency and percentages (%), and chi-square (X^2) test detected group differences. P values < 0.05 was considered significant.

RESULTS

There was highly significant variation between those who received steroid (early and late pre-term) than those not received steroid (early and late pre-term) as regard GA at birth while there was statistically insignificant difference as regard maternal age, BMI, gravidity, parity, and blood pressure (Table 1).

Table (1): Comparison of participating subjects characteristics

	Received steroid (N=80)				**Not received steroid (N=70)**				**ANOVA test**	
	Early N=36		**Late** N=44		**Early** N=25		**Late** N=45			
Gestational age (week)	28:32		32:36		28:32		32:36			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	P-value
Maternal age	27.33	3.54	26.95	4.05	26.64	3.02	27.4	3.42	0.31	0.8
Gravidity	2.42	0.87	2.25	0.95	2.34	1.06	3.42	1.61	0.28	0.83
Parity	1.42	0.95	1.2	1.11	1.34	1.06	1.73	1.72	1.3	0.26
GA at birth	30.25	1.54	33.90	1.69	35.44	2.03	37.4	3.01	73.5	<0.001
BMI	27.75	2.05	27.34	1.94	27.42	1.92	28.9	2.1	0.81	0.48
SBP	123.32	6.37	122.72	5.82	121.06	9.67	126.6	9.98	3.04	0.03
DBP	76.30	5.82	77.85	6.12	78.74	6.37	79.83	6.53	2.2	0.08

There was statistically insignificant difference between those who received steroid (early and late pre-term) and those not received steroid (early and late pre-term) as regard fetal FL, AC, and BPD (Table 2).

Table (2): Comparison of fetal ultrasonographic parameters of participating subjects

	Received steroid (N=80)				**Not received steroid (N=70)**				**ANOVA test**	
	Early N=36		**Late** N=44		**Early** N=25		**Late** N=45			
Gestational age (week)	28:32		32:36		28:32		32:36			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	P-value
FL	53.35	5.14	54.64	5.02	55.96	4.95	56.03	5.01	2.29	0.08
AC	238.98	26.38	243.25	23.87	248.39	21.47	249.37	22.03	1.54	0.2
BPD	70.68	6.91	71.35	6.12	72.19	5.03	73.02	5.32	1.18	0.3

There was statistically insignificant difference between those who received steroid (early and late pre-term) than those not received steroid (early and late pre-term) as regard birth weight, sex and type of labor. However, there was highly statistically significant difference between those who received steroid (early and late pre-term) than those not received steroid (early and late pre-term) as regard Apgar score (Tables 3).

Table (3): Comparison of neonatal characteristics of participating subjects.

	Received steroid(N=80)				**Not received steroid(N=70)**				**ANOVA test / Chi square test**	
	Early N=36		**Late** N=44		**Early** N=25		**Late** N=45			
Gestational age (week)	28:32		32:36		28:32		32:36			
Birth weight (g)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	F	P-value
At delivery	1034	(274)	1063	(292)	1085	(301)	1058	(295)	0.1585	0.924
Apgar score	N	%	N	%	N	%	N	%	X^2	P-value
0-3 SCORE	3	8.33	2	4.6	5	20	3	6.7		
4-6	22	61.1	12	27.2	8	32	16	35.5		
7-10	11	30.57	30	68.2	12	48	26	57.8	17.027	0.009
Sex	N	%	N	%	N	%	N	%	X^2	P-value
Male	15	41.6%	21	47.7	8	32	18	40	1.675	0.642
Female	21	58.4%	23	52.3	17	68	27	60		
labor	N	%	N	%	N	%	N	%	X^2	P-value
NVD	9	25%	14	31.8	5	20	12	26.7	1.216	0.749
CS	27	75%	30	68.2	20	80	33	73.3		

There was statistically significant lower rate of NICU admission, neonatal mortality, RDS, BPD, NEC and IVH in those who received steroid (early and late pre-term) than those not received steroid (early and late pre-term). Regarding PVL and ROP, the difference was insignificant among the studied groups (Table 4).

Table (4): Comparison of neonatal outcome of participating subjects

	Received steroid				Not received steroid				Chi square test	
	Early Preterm N=36		Late Preterm N=44		Early preterm N=25		Late Preterm N=45			
Gestational age (week)	28:32		32:36		28:32		32:36			
NICU admission	N	%	N		N	%	N	%	X^2	P-value
Yes	14	38.8%	8	17.7%	4	16%	7	15.5%	8.4	0.04
No	22	61.2%	39	82.3%	21	84%	38	84.5%		
Neonatal mortality	N	%	N		N	%			X^2	P-value
Yes	10	27.7%	9	20%	7	28%	2	4.4%	9.5	0.02
No	26	72.3%	35	80%	18	72%	43	95.6%		
RDS	N	%	N		N	%			X^2	P-value
Yes	10	27.7%	4	9.1%	3	12%	2	4.6%	10.7	0.01
No	26	72.3%	40	90.1%	22	88%	43	95.4%		
IVH	N	%	N		N	%			X^2	P-value
Yes	11	30.5%	4	10%	4	16%	2	4.4%	12.5	0.005
No	25	69.5%	40	90%	21	84%	43	95.6%		
NEC	N	%	N		N	%			X^2	P-value
Yes	12	33.3%	5	11.4%	4	16%	3	6.6%	11.6	0.008
No	24	66.7%	39	88.6%	21	84%	42	93.4%		
BPD	N	%	N		N	%			X^2	P-value
Yes	11	30.5%	6	13.6%	4	16%	3	6.6%	8.7	0.03
No	29	69.5%	38	86.4%	21	84%	42	93.4%		
PVL	N		%		N	%			X^2	P-value
Yes	8	22.2%	5	11.4%	6	24%	3	6.7%	6.07	0.1
No	28	77.8%	39	88.6%	19	76%	42	93.3%		
ROP	N		%		N	%			X^2	P-value
Yes	4	11.1%	4	10%	6	24%	4	8.8%	4.04	0.25
No	32	88.9%	40	90%	19	76%	41	91.2%		

DISCUSSION

A single course of corticosteroid is advised for pregnant mother between gestational age of 24 0/7 and 33 6/7 weeks at risk of premature birth within 7 days, including those with membrane rupture and multiple gestations. The best results from corticosteroid therapy occur two to seven days following the first dosage. Corticosteroids should therefore not be used unless there is a serious clinical risk of an impending preterm birth [(11)].

Interpretation of the current findings and comparison to similar research

This study found that there was statistically significant lower rate of NICU admission, neonatal mortality, RDS, BPD, NEC and IVH in those who received steroid (early and late pre-term) than those not received steroid (early and late pre-term). Despite the lower rate of PVL and ROP in those who received steroid (early and late pre-term) than those not received steroid (early and late pre-term), the difference was significant.

Our study is supported by the observational study of Stanley **Mwita *et al.*** [(12)] in Tanzania's Mwanza region, four hospitals participated in a study. All preterm twins and singletons born between 24 weeks and 6 days of gestation were included in the study population. 210 twin babies and 844 singletons were involved in the study. Fifty-two twins (24.8%) received at least one dose of ACS. Adjusted multivariate processing showed in twin infants, exposure to ACS was linked with a reduced risk of RDS only, adjusted relative risk 0.87 (95% CI 0.78 to 0.98). Also, the study by **Kong *et al.*** [(13)] included 1662 twins at 25 to 34+6 gestational age who were born in China. Their results showed no considerable variation in infant death between the ACS and no-ACS categories ($P = 0.321$). There was a decreased incidence of both moderate and respiratory distress syndrome (RDS) (both $P < 0.05$) in both categories. No remarkable variation was detected in the incidence of prematurity retinopathy, necrotizing enterocolitis, sepsis, bronchopulmonary dysplasia, patent ductus arteriosus, intraventricular hemorrhage, and severe RDS among both groups (all $P > 0.05$). RDS

incidence at 28~34+6 weeks was lower in the ACS mothers than in the no-ACS category (P = 0.036). After controlling for variables, multivariable regression analysis showed a reduced RDS risk (aOR = 0.661, P = 0.002).

And the study **Vaz *et al.*** [14] was a cohort study that was conducted retrospectively from 2006 to 2015 and it included 951 preterm labor (25+0-34+6 weeks). Neonatal outcomes were assessed in relation to the time of therapy associated to delivery and the completion of ACS ("Complete" n = 441; "Rescue" n = 38; "Incomplete" n = 175; "No ACS" n = 98). For respiratory distress syndrome, (OR) for twins was 0.172, for complete or rescue courses, and 0.280 for twins for incomplete courses. Regarding the requirement of mechanical ventilation (MV), twins had an OR of 0.189 for rescue or complete courses, whereas the OR was 0.225 for incomplete courses.

Also, the study of **Riskin-Mashiah *et al.*** [15] included twin infants born between 24 and 31 weeks gestation and free of significant birth defects. Both univariate and multivariate analyses of logistic regression were carried out. Of the 6195 twin infants that were studied, 784 had SGA. Similar to the impact in non-SGA neonates (mortality p < 0.0001; composite outcome p < 0.0001), ACU was correlated with reduced mortality (p < 0.0001) and composite adverse outcome including severe neonatal morbidity or death (p = 0.0015). ACU was linked to an almost 50% lower mortality risk in SGA twin neonates (OR = 0.52) in the multivariable logistic regression analyses. This effect was comparable to that shown in non-SGA twin neonates (OR = 0.56). Additionally, the composite adverse outcome risk was lower in the non-SGA (OR = 0.78) and SGA (OR = 0.78) groups.

On the other hand, our findings did not come in line with **McDougall *et al.*** [16] systematic review, which studied ten trials (4592 mothers; 5018 newborns), 45 cohort research (at least 22,992 females; 30,974 newborns) and two case–control studies (355 mother; 360 babies) and found an optimal administration of ACS to-birth interval, however this interval wasn't identified due to variations in study design.

And the study by **Zhu *et al.*** [17]; a total of 1974 twin pregnancies who were at risk for late preterm labor (34 weeks to 36 weeks and 6 days of gestation) were included in this research of twin pregnancies delivered in a university-affiliated hospital in China. The 1974 mothers with twin pregnancies that made up the study population were divided into two groups: 1671 (84.7%; mean [SD] mother age, 31.2 [4.0] years) and 303 (15.3%; mean [SD] maternal age, 30.8 [4.2] years) who did not receive antenatal corticosteroid medication. The propensity score overlap weighting displayed no considerable variance between both categories regarding the risk of neonatal primary outcome (9.6% vs 2.5%; OR, 1.27 [95%CI, 0.60-2.76]).

Another study found that in spite of the proven effect in singletons it is not proved in twins. It is retrospective cohort study by **Vieira *et al.*** [18] enrolling late preterm births (4,341 female-neonate pairs) from Mount Sinai Health System. An interesting exposure occurred when betamethasone was given as a prenatal corticosteroid during weeks 34 0/7 and 36 6/7 of pregnancy. A total of 4,341 mother-child pairs—1,032 twin and 3,309 singleton—were treated with betamethasone; of these, 745 mothers (40.94%, or 305/745) got the entire course of treatment. A full course of betamethasone was linked to lower odds of respiratory complications (OR = 0.53, p < 0.01) and higher odds of hypoglycemia (OR = 1.86, p < 0.01) in singletons compared to no treatment; however, in twins, the association between respiratory complications and treatment was not significant (OR = 0.42, p = 0.16), but it was linked to higher odds of hypoglycemia (OR = 2.18, p = 2.18).

Another retrospective cohort research by **Ben-David *et al.*** [19] involved 290 females with twin who gave birth to 580 live neonates delivered during LPT period between 2016 and 2018. Women were categorized based on exposure to ACS into two categories. Neonatal composite respiratory morbidity was the main endpoint, and the study's findings showed that, in comparison to the non-exposed group, patients exposed to ACS were older and more frequently had complex pregnancies. In addition, compared to the non-exposed group, women exposed to ACS gave birth earlier (35.6 vs. 36.3 weeks, P < 0.001) and more commonly via cesarean section (76.4% vs. 54.1%, P = 0.002). There was no difference in the rates of composite respiratory morbidity between the groups. However, compared to newborns who had never been exposed to ACS, neonates exposed to ACS had greater rates of hypoglycemia and admission to the neonatal intensive care unit (NICU) (27.8% vs. 11.7%, P = 0.001; 49.3% vs. 27.1%, P < 0.001, respectively). Gestational age at delivery was the only independent risk factor for NICU admission, while the only risk factor for hypoglycemia was exposure to late-preterm ACS, according to multivariable logistic regression [19].

Strengths and limitations

One of the strength points of this work was that it was held in one university and another educational hospital, which gave a representative sample and offering the same management guidelines to decrease the bias. Besides our study is one of few studies concerning the effect of antenatal corticosteroids in twins. However, there are points of weaknesses and limitations for the study, first no long term follow up for studying the influence of antenatal corticosteroids on the exposed neonates, because always mothers are coming from rural areas with loss of communication to the hospitals after delivery. Secondly more patients were needed with more detailed analytic study to accurately prove or deny the claimed effectiveness.

Clinical Implication of the present study

Based on available data, ACS is advised for twin pregnancies with a high risk of premature delivery between 28 and 36 weeks of gestation. The use of ACS for individuals at risk of late preterm delivery is still up for debate. And since there's a chance of an early term delivery, there's no need to offer ACS at this time.

RECOMMENDATIONS FOR FUTURE STUDIES

Future studies should involve advanced statistical modalities such as meta-analysis to determine which ACS administration-to-birth intervals are of benefit, and outcomes of how long and short-term can be optimized for mothers and neonates.

We recommend that further studies with larger scales for confirming our results. And to be performed using large, comparative observational studies or well-designed randomized controlled trials. Data collection using standardized tools and protocols is also needed. Future studies are recommended to involve multicenter, even international studies to validate our findings.
Retrospective studies include the long-term effect of ACS among individuals who were exposed to antenatal corticosteroids.

CONCLUSION

Antenatal corticosteroids administration is a crucial antenatal intervention in twin early and late preterm deliveries and must be considered especially in developing countries because of lack of facilities. Further studies are required to identify the efficacy of steroids therapy in twin pregnancies and postnatal long-term effects and to assess in establishing suitable guidelines to this unique risk group.

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