# Association Between Antenatal Corticosteroid Administration and Neonatal Glycemic Status

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## Abstract

**Background and Aim**: Antenatal corticosteroids are recommended to improve neonatal outcomes; however, their usage is associated with the development of neonatal hypoglycemia. We aimed to assess the association between the administration of antenatal corticosteroids and the increased risk of developing neonatal hypoglycemia within the first 48 hours of life.

**Materials and Methods:** This was a prospective cohort study conducted on 80 preterm neonates delivered between 31 and 36 weeks of gestation. The neonates were divided 2 groups: (1) case group, which included preterm neonates whose mothers received antenatal corticosteroids, and (2) control group, which included preterm neonates whose mothers did not receive antenatal corticosteroids. The study compared the outcomes of 2 antenatal corticosteroid regimens: (1) 2 doses of 12 mg of betamethasone given intramuscularly in a 24-hour interval, and (2) 4 doses of 6 mg of dexamethasone given intramuscularly in 12-hour intervals.

**Results:** The incidence of neonatal hypoglycemia within 48 hours of life was not statistically significantly different between those neonates whose mothers received antenatal corticosteroids and those neonates whose mothers did not receive. Our study results show that the occurrence of hypoglycemia was more in the first 4 hours of life in neonates whose mothers received betamethasone, and the occurrence of hypoglycemia was more from 4 to 48 hours in neonates whose mothers received dexamethasone.

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**Conclusion:** Our study results conclude that administration of antenatal corticosteroids does not increase the risk of the neonates developing hypoglycemia within the first 48 hours of life in preterm neonates.

**Key Words:** Antenatal corticosteroids, preterm birth, neonatal hypoglycemia, betamethasone, dexamethasone, maternal hyperglycemia

# Introduction

Prematurity is the most common cause of deaths during the neonatal period. It accounts for approximately 70% of neonatal deaths, 36% of infant deaths, and a high percentage of long-term neurologic impairment in childhood.[1]

The neonates born before 37 weeks of gestation are considered preterm neonates. They are further subdivided into late preterm neonates (born between 34 and < 37 weeks of gestation), moderate preterm neonates (born between 32 and < 34 weeks of gestation), very preterm neonates (born between 28 and < 32 weeks of gestation), and extremely preterm neonates (born in < 28 weeks of gestation).[2,3]

Preterm neonates are predisposed to developing short-term (at birth or soon after birth) and long-term (later phases of life) health issues. Short-term health issues include respiratory distress syndrome, patent ductus arteriosus, intraventricular hemorrhage, heat instability, necrotizing enterocolitis, anemia, neonatal jaundice, and a high risk of sepsis.[4] In addition, preterm neonates are at a high risk of having altered glucose homeostasis, especially low levels of blood glucose. This occurs more in preterm neonates than in term neonates and within the first few hours after birth due to low glycogen and fat stores with limited capacity to generate glucose via the gluconeogenesis pathway.[5,6] Some long-term health issues that may occur in the later phases include cerebral palsy, retinopathy of prematurity, hearing loss, and behavioral or psychologic problems.[7]

Antenatal corticosteroids improve neonatal outcomes in preterm neonates, as they reduce neonatal deaths by about 30% and serious neonatal morbidities by 35% to 55%.[8]

Corticosteroids boost biosynthesis of phospholipids, increase protein production, activate lipogenesis-stimulating enzymes, and increase surfactants in fetal lungs. They also accelerate the development of organs by stimulating cell multiplication, protein synthesis, and enzyme activity. They support lung maturation and improve oxygenation, ventilation, and circulatory stability, which in turn prevent serious neonatal complications.[8]

Antenatal corticosteroid regimen primarily consists of either betamethasone (dosage: 2 doses of 12 mg given intramuscularly in 24-hour interval) or dexamethasone (dosage: 4 doses of 6 mg given intramuscularly in 12-hour interval).[9,10] The regimen is considered complete if all doses of antenatal corticosteroids are given before 48 hours of delivery. On the other hand, the course is considered incomplete in case antenatal corticosteroids are given in < 24 hours before delivery.[10]

The administration of antenatal corticosteroids may result in maternal hyperglycemia, followed by fetal pancreatic B-cell hyperplasia and/or hyperinsulinemia, resulting in neonatal hypoglycemia subsequently. Corticosteroid-induced hyperglycemia in mothers is because of direct stimulation of hepatic gluconeogenesis.[11]

Neonatal hypoglycemia is defined as a plasma glucose level of < 25 mg/dL, with actionable levels ranging from 25 to 40 mg/dL in the first 4 hours of life. From 4 to 48 hours of life, < 35 mg/dL is considered as the lower range, with actionable values ranging from 35 to 45 mg/dL.[12]

Neonatal hypoglycemia in the first day of life results in hypotonia, lethargy, apathy, poor feeding, jitteriness, seizures, hypothermia, cyanosis, and apnea. It can also

cause other life-threatening conditions of the central nervous system (CNS) and cardiopulmonary disturbances.[7] The study conducted by Kim et al[13] mentioned that the risk of hypoglycemia is significantly high in neonates born between 32 and 34 weeks of gestation and whose mothers have received antenatal corticosteroids. The detection and treatment of neonatal hypoglycemia is easy. Early detection and treatment can avoid permanent and potentially fatal complications such as brain damage, seizures, and developmental delays.

# Aim

To study the association between antenatal corticosteroid administration and occurrence of hypoglycemia within the first 48 hours in preterm neonates

# Materials and Methods

## Study design

This was a prospective cohort study conducted in Suez Canal University Hospital (Ismailia, Egypt), from April to September 2018. The study included 80 preterm neonates born at < 37 weeks of gestation. They were divided to 2 groups: (1) case group and (2) control group. Ethical approval was obtained from the ethics committee of Suez Canal University Hospital. Informed consent was obtained from all the parents of the neonates enrolled, after explaining the aim, benefits, and procedures of the study.

## Inclusion criteria

The neonates included in the case group were preterm neonates whose mothers received antenatal corticosteroids, while the control group included preterm neonates whose mothers did not receive antenatal corticosteroids.

## Exclusion criteria

- All neonates with coarse facial features and apparent congenital anomalies that may be associated with hypoglycemia (eg, congenital hypopituitarism, Turner's syndrome, Down's syndrome, congenital adrenal hyperplasia, Beckwith–Wiedemann syndrome, inborn errors of metabolism, and glycogen storage disease)
- Neonates of mothers who had hypoglycemia or hyperglycemia[14]
- Preterm neonates who received IV fluids (glucose infusion) that interrupt the occurrence of hypoglycemia
- Preterm neonates who needed NICU admission, which in turn can affect the euglycemic state because of conditions such as sepsis and asphyxia

## Sample size

The sample size for the study was decided based on the following method:

$$N = \frac{(Z_{\alpha/2} + Z_{\beta})^2}{(P_1 + P_2)^2} (P_1q_2 + P_2q_2), \text{ in which}$$

$N$ = sample size, $Z_{\alpha/2}$ = 1.96 (the critical value that divides the central 95% of the Z distribution from the percentage in the tail), $Z_{\beta}$ = 0.84 (the critical value that separates the lower 20% of the Z distribution from the upper 80%); $P_1$ is the prevalence in the study group, and $P_2$ is the prevalence in the control group.[15] In addition, q = 1 - P. Therefore, based on this formula, the sample size arrived at was 40 in each group, with a total sample size of 80 neonates.

## Study procedure

A detailed medical history of the parents was obtained by interviewing one or both of them. Details such as name, date of birth, maternal age, gestational age at delivery, gender of the neonate, maternal illnesses, medications taken during pregnancy, mode of delivery, history of preterm births and abortions, and history of receiving antenatal corticosteroids (types and doses) were recorded.

After the delivery, complete physical (general and local) examinations—including vital signs (ie, temperature, pulse rate, and blood glucose level for every 4 h for the first 48 h), gestational age, and systemic examination (ie, chest, cardiac, abdominal, and neurologic examination)—were performed for neonates. Capillary blood samples were collected using a blood glucose monitoring device after heating the heels of the neonates. Blood glucose levels were tested using electrochemical

test strips.[16] Complete blood count with differential and C-reactive protein were also tested to exclude septicemia.

The first blood glucose test in neonates was done an hour after feeding. The neonates were fed every 3 hours for 24 hours, and the blood glucose levels were checked before each feeding and values were recorded in data collection sheets.

In our study, the following definition and classification of hypoglycemia was adapted[12]:

1. Within the first 4 hours after birth:
   Hypoglycemia: blood glucose level ≤ 40 mg/dL
   Severe hypoglycemia: blood glucose level ≤ 25 mg/dL
2. In the postnatal 4 to 24 hours:
   Hypoglycemia: blood glucose ≤ 45 mg/dL
   Severe hypoglycemia: blood glucose ≤ 35 mg/dL
3. In the postnatal 24 to 48 hours:
   Hypoglycemia: blood glucose ≤ 45 mg/dL
   Severe hypoglycemia: blood glucose ≤ 35 mg/dL

## Statistical analyses

The data were analyzed using SPSS version 16 (SPSS Inc, Chicago, IL, USA).

Quantitative data were expressed as mean and standard deviation, while qualitative data were expressed as number and percentage.

Student's *t* test was used to analyze the significance of difference for quantitative variables, and $\chi^2$ test was used to analyze the significance of difference for qualitative variables.

A *P* value of < .05 was considered statistically significant.

# Results

Eighty neonates born between 31 and 36 weeks of gestation and met the inclusion criteria were enrolled in the study. The neonates were divided into case group and control group, of which 57.5% in the case group and 37.5% in the control group were female neonates.

Of these 80 neonates, 60% in the case group and 65% in the control group were categorized as late preterm neonates (born between 34 and 36 weeks); 37.5% in the case group and 32.5% in the control group were categorized as moderate preterm neonates (born between 32 and 33 weeks); and 2.5% in the case group and 2.5% in the control group were categorized as very preterm neonates (born between 28 and 31 weeks). Further, of these 80 neonates, 77.5% in the case group and 75% in the control group were delivered by mothers in the age group of 20 to 30 years (*P* = .793), and 22.5% in the case group and 20% in the control group were delivered by mothers in the age group of 30 to 40 years (*P* = .785). The remaining 5% in the control group were delivered by mothers aged < 20 years, whereas there was none in the case group.

Apart from antenatal corticosteroids, other medications received by the mothers were iron, folic acid, calcium, vitamins, recommended schedule of vaccination, enoxaparin sodium (Clexane), antihypertensives (the most common one being Aldomet), and antibiotics. There was no statistically significant difference between the groups regarding occurrence of illnesses during pregnancy. It was found that 57.5% of the mothers whose neonates were in the case group and 62.5% of the mothers whose neonates were in the control group had no illness during pregnancy (*P* = .648). Further, 25% of the mothers whose neonates were in the case group and 22.5% of the mothers whose neonates were in the control group had preeclampsia during pregnancy (*P* = .793); and 12.5% of the mothers of neonates in the case group and, 10% of the mothers of neonates in the control group had urinary tract infection during pregnancy (*P* = 1.0).

As mothers would have received different corticosteroid doses and delivered at various times after the administration, we collected the information pertaining to the effect of corticosteroid administration and the number of doses received—92% had received a complete course, and 75% had received antenatal dexamethasone, and the remaining 25% had received betamethasone.

Table 1 shows that there was no statistically significant difference between the 2 groups with regard to blood glucose levels in the first 48 hours of life.

In the first 4 hours of birth, hypoglycemia occurred in 17.5% of the neonates in the control group and 7.5% of the neonates in the case group (odds ratio [OR]: 0.3822; 95% confidence interval [CI]: 0.0913–1.600; *P* = .188). In the next postnatal 4 to 24 hours, hypoglycemia occurred in 17.5% of the neonates in the case group and 15% of the neonates in the control group (OR: 1.2020; 95% CI: 0.3653–3.9551; *P* = .762). From 24 to 48 hours of life, hypoglycemia occurred in 10% of the neonates in the case group and 5% of the neonates in the control group (OR: 2.111; 95% CI: 0.364–12.241; *P* = .675).

In our study, no neonates had severe hypoglycemia (< 25 mg/dL). We observed that administration of any antenatal corticosteroid (complete or incomplete course) is not associated with an increased risk of neonatal hypoglycemia in the first 48 hours of life, compared with those mothers who did not receive.

Table 2 shows that there was no statistically significant difference in blood glucose levels in neonates of mothers who received different types of antenatal corticosteroids.

In the first 4 hours of life, only 3 neonates had hypoglycemia with a 10% risk associated with betamethasone.

In neonates whose mothers received betamethasone, 24.3% had normal glucose level and 10% had hypoglycemia (OR: 0.6429; 95% CI: 0.052–7.952). In neonates

**Table 1.** Comparison of Blood Glucose Levels in Neonates Between the Case and the Control Groups

| Blood Glucose Level | Case Group (*n* = 40) | | Control Group (*n* = 40) | | OR | *P* Value | 95% CI |
|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | | | |
| The First Postnatal 4 Hours | | | | | | | |
| Normal (> 40 mg/dL) | 37 | 92.5 | 33 | 82.5 | 1 | — | — |
| Hypoglycemia (25–40 mg/dL) | 3 | 7.5 | 7 | 17.5 | 0.3822 | .188 | 0.0913–1.600 |
| From Postnatal 4–24 Hours | | | | | | | |
| Normal (> 45 mg/dL) | 33 | 82.5 | 34 | 85.0 | 1 | — | — |
| Hypoglycemia (35–45 mg/dL) | 7 | 17.5 | 6 | 15.0 | 1.2020 | .762 | 0.3653–3.9551 |
| From Postnatal 24 to 48 Hours | | | | | | | |
| Normal (> 45 mg/dL) | 36 | 90.0 | 38 | 95.0 | 1 | — | — |
| Hypoglycemia (35–45 mg/dL) | 4 | 10.0 | 2 | 5.0 | 2.111 | .405 | 0.364–12.241 |
| There was no statistically significant difference in values if the *P* value was > .05. | | | | | | | |

**Table 2.** Comparison of Blood Glucose Levels Based on the Type of Antenatal Corticosteroid Administered

| Antenatal Corticosteroid | Blood Glucose Level | | | | OR | *P* Value | 95% CI |
|---|---|---|---|---|---|---|---|
| | Normal | | Hypoglycemia | | | | |
| | *n* | % | *n* | % | | | |
| The First Postnatal 4 Hours | *n* = 37 | | *n* = 3 | | | | |
| Dexamethasone | 28 | 75.7 | 2 | 6.6 | 1.556 | .731 | 0.126–19.242 |
| Betamethasone | 9 | 24.3 | 1 | 10 | 0.6429 | .731 | 0.052–7.952 |
| Postnatal 4–24 Hours | *n* = 33 | | *n* = 7 | | | | |
| Dexamethasone | 24 | 72.7 | 6 | 20 | 0.444 | .480 | 0.0468–4.223 |
| Betamethasone | 9 | 27.3 | 1 | 10 | 2.250 | .480 | 0.237–21.377 |
| Postnatal 24–48 Hours | *n* = 36 | | *n* = 4 | | | | |
| Dexamethasone | 26 | 72.2 | 4 | 13.3 | 0.280 | — | 0.0139–5.677 |
| Betamethasone | 10 | 27.8 | 0 | 0.0 | 3.660 | — | 0.176–72.197 |

whose mothers received dexamethasone, (75.7% had normal glucose level and 6.6% had hypoglycemia (OR: 1.556; 95% CI: 0.126–19.242) ($P$ = 0.731).

In the postnatal 4 to 24 hours, 7 neonates had hypoglycemia with a 20% risk associated with dexamethasone.

In neonates whose mothers received dexamethasone, 72.7% had normal glucose level and 20% had hypoglycemia (OR: 0.444; 95% CI: 0.0468–4.223). In neonates whose mothers received betamethasone, 27.3% had normal glucose level and 10% had hypoglycemia (OR: 2.250; 95% CI: 0.237–21.377) ($P$ = 0.480).

Lastly, in postnatal 24 to 48 hours, only 4 neonates had hypoglycemia with a 13.3% risk associated with dexamethasone.

In neonates whose mothers received dexamethasone, 72.2% had normal glucose level and 13.3% had hypoglycemia (OR: 0.280; 95% CI: 0.0139–5.677). In neonates whose mothers received betamethasone, 27.8% had normal glucose level, and no one had hypoglycemia (OR: 3.660; 95% CI: 0.176–72.197).

Finally, we found that the occurrence of hypoglycemia was more in the first 4 hours of life in neonates whose mothers received betamethasone, and the occurrence of hypoglycemia was more from 4 to 48 hours in neonates whose mothers received dexamethasone.

# Discussion

The study conducted by Redlich et al[17] mentioned that giving antenatal corticosteroids to mothers increases the risk of neonatal hypoglycemia, especially in preterm neonates. This was a surprising finding that gave way to significant debate among neonatologists because of the relationship between neonatal hypoglycemia and adverse neurologic outcomes.

We studied 80 preterm neonates, who met the inclusion criteria, to assess the relation between antenatal corticosteroid administration and the risk of developing neonatal hypoglycemia within the first 48 hours and also to detect the effect of dose and type of antenatal corticosteroid administration on blood glucose levels in neonates.

In our study, we found that there is no association between maternal corticosteroid administration and neonatal hypoglycemia. However, the pioneering antenatal corticosteroid trial conducted by Liggins et al[18] states that there is no association between antenatal corticosteroid administration and neonatal hypoglycemia. Further, the study conducted by Porto et al[19] in late preterm neonates mentioned that there is no association between antenatal corticosteroid administration and occurrence of hypoglycemia.

Kuper et al[20] reviewed 653 neonates who were born between 23 and 34 weeks of gestation, in whom the incidence of hypoglycemia within the first 48 hours of life was not significantly different between those who received any antenatal corticosteroids and those who did not (23% vs 16.1%, adjusted OR [aOR]: 1.3; 95% CI: 0.5–3.6).

On the contrary, Pettit et al[11] found a statistically significant higher rate of hypoglycemia in neonates who were exposed to antenatal corticosteroids compared with those who were not exposed (5.7% vs 4.2%; $P$ > .05). The study was conducted on 6675 neonates who were born between 32 and 37 weeks of gestation (aOR: 1.60; 95% CI: 1.24–2.07).

The study conducted by Gyamfi-Bannerman et al[17] found a statistically significant higher rate of hypoglycemia in neonates who were born between 34 and 36 weeks of gestation and were exposed to antenatal corticosteroids compared with those who were not exposed to antenatal corticosteroids (24% vs 15%; relative risk: 1.60; 95% CI: 1.37–1.87; $P$ < .001).

In a meta-analysis of randomized controlled trials conducted by Saccone et al,[22] neonates who were born between 34 and 36 weeks of gestation and exposed to antenatal corticosteroids had an increased occurrence of hypoglycemia compared with those who were not exposed.

Kim et al[13] found that the risk of hypoglycemia was significantly higher in neonates whose mothers received antenatal corticosteroids (OR: 5.832; 95% CI: 1.096–31.031; $P$ = .039). This study analyzed 82 neonates born between 29 and 32 weeks of gestation.

However, we did not find an association between antenatal corticosteroid administration and neonatal hypoglycemia. Also, neither Pettit et al[11] nor Gyamfi-Bannerman et al[21] had any time limit set on the development of neonatal hypoglycemia. We do not consider the fact that neonatal hypoglycemic episodes caused by antenatal corticosteroids can last from days to weeks after delivery as exposure to maternal hyperglycemia ceases with the clamping of the umbilical cord. Thus, measurement of random blood glucose level in neonates during the first 48 hours after delivery is more appropriate if we consider an association between antenatal corticosteroids and neonatal hypoglycemia.

Antenatal corticosteroids (ie, dexamethasone and betamethasone) are recommended for improving fetal lung development.[22,23] It is found that using corticosteroids in short-term course in critical pregnancies is beneficial.[24-27] The 18th list of the WHO, which included antenatal corticosteroids for the first time, lists only dexamethasone for fetal indications,[28] as it is considered as the most appropriate medication based on availability and cost.[29]

In some instances, betamethasone is preferred because of its longer half-life (ie, its decreased clearance and larger volume of distribution).[30]

In our study, 75% of neonates were exposed to dexamethasone antenatally and the remaining were exposed to betamethasone, and of these, 92% had received a complete course.

In our study, we found that 10% of the neonates with hypoglycemia in the first 4 hour of life were exposed to betamethasone ($P$ = .731, not statistically significant). On the other hand, 20% of the neonates with hypoglycemia in the postnatal 4 to 24 hours were exposed to dexamethasone ($P$ = .480, not statistically significant), and also 13.3% of the neonates with hypoglycemia in the postnatal 24 to 48 hours of life were exposed to dexamethasone.

Finally, we found that the occurrence of hypoglycemia was more in the first 4 hour of life in neonates whose mothers received betamethasone, and the occurrence of hypoglycemia was more from 4 to 48 hours in neonates whose mothers received dexamethasone.

Likewise, receiving a complete or an incomplete course of antenatal corticosteroids did not increase the risk of developing neonatal hypoglycemia. Most of the studies reviewed mention that the usage of betamethasone as an antenatal corticosteroid is better than dexamethasone. Porto et al[15] reviewed using betamethasone in mothers who gave birth to late preterm neonates, with no association between antenatal corticosteroid administration and hypoglycemia. On the other hand, Gyamfi-Bannerman et al[21] found that the risk of hypoglycemia was more common in neonates whose mothers received betamethasone than in the placebo group. However, no adverse events related to hypoglycemia were reported, which suggests the self-limiting condition.

Pettit et al[11] observed that neonates exposed to antenatal betamethasone were at 1.6 times higher risk of developing hypoglycemia (aOR: 1.60; 95% CI: 1.24–2.07). In contrast to the potential limitations of our study, including those inherited retrospective studies, Pettit et al[11] did not identify the association and could not confirm causation, as groups were not randomized based on exposure to a particular corticosteroid. However, they controlled confounding variables that could directly affect the rates of neonatal glycemic outcomes, particularly hypoglycemia. We hope that this fact strengthens the validity of our findings.

In addition, while we were able to explore the association between antenatal corticosteroid administration and the outcomes of neonatal hypoglycemia, the intervening factor of maternal hyperglycemia could not be explored, as we did not routinely assess maternal blood glucose values during administration.

On the other hand, our study has several strengths. We evaluated 2 separate scenarios (ie, type of corticosteroid and dose of corticosteroid) to determine whether there is an association between antenatal corticosteroids and neonatal hypoglycemia. In addition, we placed a time limit (within 48 h of birth) on the development of neonatal hypoglycemia that could be caused by antenatal corticosteroids, as exposure to maternal hyperglycemia ends at the time of cord clamping.

Finally, our study results indicate that receiving antenatal corticosteroids did not increase the risk of developing neonatal hypoglycemia within the first 48 hours of life in preterm neonates.

# Conclusions

We found that neonatal hypoglycemia is a frequent occurrence in preterm neonates, regardless of receiving an antenatal corticosteroid. Therefore, all preterm neonates should be frequently monitored for the development of neonatal hypoglycemia. Monitoring strategies should not differ based on the antenatal corticosteroid administered.

Further, larger studies should verify our findings and continue to focus on ways to screen and monitor neonatal hypoglycemia accurately.

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