IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Original Article

Association between Corticosteroid Administration in Pregnant Women with COVID-19 and Neonatal Outcomes

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ABSTRACT

Background: The evidence for the effect of corticosteroid administration on neonates in pregnant women who tested positive for COVID-19 is rare. This study aims to evaluate the effect of the administration of corticosteroids on pregnant women with COVID-19 on neonatal metabolic outcomes of hypoglycemia and hyperbilirubinemia.

Methods: The present retrospective cohort study was conducted on pregnant women with COVID-19 referred to Mousavi Hospital in Zanjan, Iran in 2020. We compared post-delivery complications in women who had received corticosteroids with a control group. The data were extracted from the medical records of the patients by a resident of the gynecology. The chi-square test was used to compare the rate of hyperbilirubinemia and hypoglycemia between groups.

Results: Of a total of 71 investigated patients, only 32 received non-steroidal anti-inflammatory drugs (NSAIDs),. The mean age of the patients was 29.77±6.87 years and there was not a significant difference between the two groups in terms of age, BMI, education, blood sugar, bilirubin, neonate weight, and 1 and 5-minute Apgar score (P>0.05). In the corticosteroid-receiving group, a significantly higher rate of hypoglycemia (37.5% vs. 7.69%, P=0.002) and hyperbilirubinemia (25% vs. 5.13%, P=0.02) was reported.

Conclusion: The results suggested that the administration of corticosteroids as a treatment modality for pregnant women with COVID-19 is associated with an increased rate of neonatal hypoglycemia and hyperbilirubinemia. Therefore, glycemic control is necessary for neonates born from pregnant women with COVID-19 exposed to corticosteroids during the pregnancy.

Keywords: Blood sugar, Bilirubin, COVID-19, Corticosteroids, Pregnant women

Introduction

Pregnancy is a specific physiological condition during which the suppression of the immune system can lead to vulnerability to viral infections. COVID-19 infection can give way to serious consequences for pregnant women, especially those with comorbidities such as hyperglycemia and high blood pressure (1). In some parts of the world, up to 15% of pregnant women tested positive for COVID-19 (2).

Corticosteroid is commonly administered in the field of obstetrics. In most cases, one or two doses of corticosteroids are administered intramuscularly at 24-hour intervals from 23 to 34 weeks of gestation, to fuel the development of fetal lung, especially when preeclampsia or premature rupture of the membranes may lead to premature delivery (3). The effects of corticosteroid administration on improving preterm delivery outcomes in pregnant women have been demonstrated (4, 5). The

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Please cite this paper as:
Gholami H, Tofighi Sh, Molaei B, Dabiri Oskoei A, Hatami R, Garrosi L, Abdi R, Shafaghat Ardabili A. Association between Corticosteroid Administration in Pregnant Women with COVID-19 and Neonatal Outcomes. Iranian Journal of Neonatology. 2022 Oct: 13(4). DOI: 10.22038/ijn.2022.63490.2215

professional community continues to support the administration of prenatal corticosteroids if they help fetal lung maturation in women with COVID-19. However, they conclude that there is insufficient evidence to recommend the use of corticosteroids after 34 weeks of pregnancy (6).

Although corticosteroids are commonly used as treatments for the inflammatory phase of COVID-19 (7), they stimulate the motility of energy storage molecules and the production of glucose molecules. This triggers the production of glucose molecules from other molecules, the breakdown of fat in fat cells, proteins in the muscle, and glycogen in muscle cells to release glucose, and contribute to the production of glycogen by glucose in the liver (8). Maternal hyperglycemia following corticosteroid administration can lead to fetal hyperinsulinemia and subsequently neonatal hypoglycemia (9). Moreover, corticosteroids may act as a competitive inhibitor and decrease the hepatic uptake of unconjugated bilirubin, leading to hyperbilirubinemia (10).

Given the paucity of evidence in this regard, this study was conducted to evaluate the effect of administrating corticosteroids as a treatment modality in pregnant women with COVID-19 on neonatal outcomes, especially the neonatal metabolic outcomes of hypoglycemia and hyperbilirubinemia.

Methods

The present retrospective cohort study was conducted on COVID-19-positive pregnant women referred to Mousavi Hospital in Zanjan, Iran, in 2020. All eligible pregnant women with COVID-19 were selected using the census method. Accordingly, a total number of 71 subjects were included in the study of whom 32 received NSAIDs and the rest (n=39 patients) did not receive any corticosteroid.

The Ethics Committee of Zanjan University of Medical Sciences approved the study (Research ethics code: IR.ZUMS.REC.1400.303). In this study, only pregnant women who tested positive on real-time reverse-transcription polymerase chain reaction (RT-PCR) using upper respiratory nasopharyngeal swabs and exhibited moderate to severe symptoms were included in the study. Women with pre-term delivery, abortion or fetal death were excluded from the study. Moreover, patients for whom delivery and neonatal data were not available were also excluded from the study.

A comparison was made between post-delivery complications in women receiving corticosteroid (8 *mg/day* dexamethasone, I.V. form, from 1-10 days) with a control group. In the present study, blood sugar less than 40 mg/dl was considered as hypoglycemia, bilirubin above 11 µmol/L was treated as hyperbilirubinemia and the neonate weight less than 2500 g was deemed as low birth weight.

The required data including age, BMI, education level, birth weight, gestational week, 1 and 5 min Apgar score, neonatal blood sugar and bilirubin was taken from the medical records of patients by a resident of the gynecology. Blood sugar was measured 4 hours post-delivery and bilirubin level was measured 24-h post-delivery.

The biochemical and clinical characteristics of the patients were described using mean, standard deviation, median and range. The rate of hyperbilirubinemia and hypoglycemia was compared between groups using thefisher exact test. the effects of administering corticosteroids to pregnant women with COVID-19 on pregnancy-related complications were assessed using the logistic regression model. The correlation of dexamethasone dose and bilirubin with the blood sugar level was assessed by the Pearson correlation method. Data analysis was conducted using Stata 14 (StataCorp, College Station, TX, USA). A significance level of less than 0.05 was considered.

Results

The mean age of patients was 29.77±6.87 years. There was not a significant difference between the two groups in terms of age, BMI and education (P>0.05). Table 1 compares the biochemical and clinical characteristics of the patients. The two groups were homogenous in terms of blood sugar, bilirubin, birth weight, and 1-5 min Apgar score.

Table 2 compares complications associated with COVID-19 infection in two groups of pregnant women. The rate of hypoglycemia was significantly higher in the corticosteroid-receiving group (37.50% vs. 7.69%, P=0.002) than in the hyperbilirubinemia group (25.00% vs. 5.13%, P=0.02). However, there was not a significant difference between the two groups in terms of low birth weight and neonatal death (P>0.05).

The effects of corticosteroid administration in COVID-19-positive pregnant women on pregnancy complications are outlined in Table 3. Patients receiving corticosteroids during pregnancy to

Table 1. Biochemical and clinical characteristics of the patients

Variable	Corticosteroid group (n=32)	Control group (n=39)	P-Value*
Blood sugar	Median (IQR): 52.0 (58.00) Mean (SD): 89.28(94.65) Range: 25, 439	Median (IQR): 92.00 (44.00) Mean (SD): 106.36 (56.24) Range: 26, 254	0.34
Bilirubin	Median (IQR): 4.00 (4.75) Mean (SD): 5.19 (3.41) Range: 1.5, 28	Median (IQR): 5.30 (2.6) Mean (SD): 5.28 (2.24) Range: 1.50, 13	0.89
Neonate weight (gr)	Median (IQR): 3125.00 (675.0) Mean (SD): 3050.50 (568.7) Range: 1360, 4000	Median (IQR): 3200.00 (450) Mean (SD): 3193.60 (412.9) Range: 2200, 4300	0.22
1 min Apgar score	Median (IQR): 9.00 (0.5) Mean (SD): 8.56 (1.13) Range: 3, 9	Median (IQR): 9.00 (0) Mean (SD): 8.87 (0.41) Range: 7, 9	0.36
5 min Apgar score	Median (IQR): 10.00 (0) Mean (SD): 9.72 (0.92) Range: 5, 10	Median (IQR): 10.00 (0) Mean (SD): 9.87 (0.41) Range: 8, 10	0.12

IQR: Intra quintile range, SD: Standard deviation, * *Mann–Whitney U test*

Table 2. Comparison of complications following COVID-19 infection in the two groups of pregnant women

Complication	Corticosteroid group (n=32)	Control group (n=39)	P-value*
Hypoglycemia	12 (37.50)	3 (7.69)	0.002
Hyperbilirubinemia	8 (25.00)	2 (5.13)	0.02
Low birth weight	4 (12.50)	2 (5.13)	0.27
Neonate death	1 (3.13)	1 (2.56)	0.89

*Fisher exact test

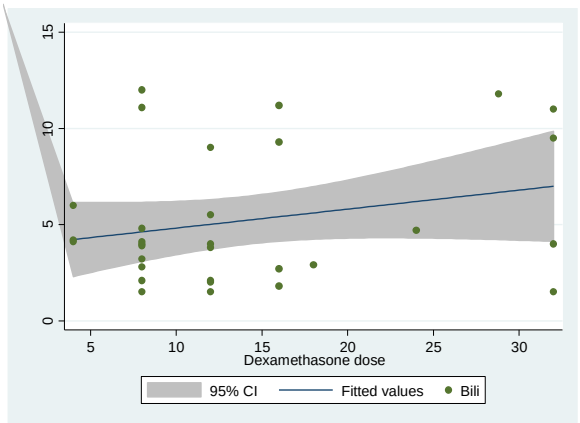
Table 3. Effects of Corticosteroid administration in COVID-19-positive pregnant women on pregnancy complications

Complication	Odds Ratio	95% CI	P-Value*
Hypoglycemia	7.20	1.81, 28.57	0.005
Hyperbilirubinemia	6.16	1.21, 31.55	0.03
Low birth weight	2.64	0.45, 15.47	0.28
Neonate death	1.22	0.07, 20.40	0.89

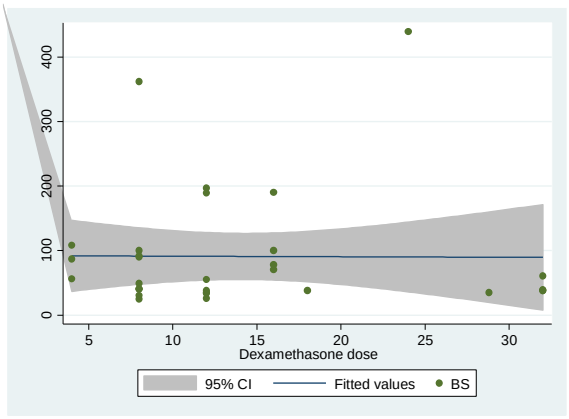
*Logistic regression test

treat COVID-19 were 7.2 and 6.16 times more likely to develop hypoglycemia (OR=7.20, 95% CI: 1.81, 28.57) and hyperbilirubinemia (OR=6.16, 95% CI: 1.21, 31.55**).**

There was a non-significant positive correlation between Dexamethasone dose and bilirubin (r=0.25, P=0.17). Moreover, A similar correlation was observed between Dexamethasone dose and blood sugar (r= - 0.008, P=0.97) (Figure 1).



a. Bilirubin rate



b. Blood sugar rate

Figure 1. Correlation between the dose of Dexamethasone and the rate of bilirubin and blood sugar

Discussion

In the present study, we investigated the effect of corticosteroid administration as a treatment modality for COVID-19-positive pregnant women on their neonatal outcomes. We found that the administration of Corticosteroids was significantly associated with a higher rate of neonatal hypoglycemia and hyperbilirubinemia.

Although Corticosteroids is a treatment option for the inflammatory phase of COVID-19, the short and long-term effects of antenatal corticosteroids on neonates should be taken into consideration.

Some studies on the effect of corticosteroid administration during pregnancy on hypoglycemia and hyperbilirubinemia in preterm infants did not report any significant relationship (11-13). Madendag et al. found a significant reduction in neonatal hyperbilirubinemia in term-born babies exposed to corticosteroids before 34 weeks of pregnancy (14). However, contrary to the results of these studies and consistent with the findings of our research, Pettit et al. reported that the rate of hypoglycemia as well as hyperbilirubinemia was significantly higher in corticosteroid-exposed patients (10). The discrepancy in the results of these studies may be due to different sample sizes and weeks of pregnancy at the time of corticosteroid administration.

Unlike the positive effects of corticosteroid administration on inflammatory mitigation in the inflammatory phase of COVID-19 infection, its effects on neonatal blood sugar and bilirubin level in pregnant women should be further studied (15). As reported in a study, monitoring glucose after the administration of antenatal corticosteroid in non-diabetic patients led to increased maternal blood glucose on days 1 and 2 and reversion to the normal range on day 3 (16). Zigron et al. reported neonatal hypoglycemia in one-fifth of neonates exposed to corticosteroids, which was independently associated with delivery 24 to 48 h after corticosteroid administration (17). Maternal hyperglycemia leads to fetal hyper-insulinemia and subsequently neonatal hypoglycemia (9)., Aydin et al. presented secondary fetal adrenal suppression as another mechanism for neonatal hypoglycemia (18).

Pettit et al. found that neonatal hypoglycemia following the administration of antenatal corticosteroid during pregnancy is not associated with the interval between corticosteroid administration and delivery (19). Therefore, glycemic control is necessary for neonates exposed to corticosteroids during pregnancy (20).

The present study had a number of limitations. First, since corticosteroids were not administered during different weeks of pregnancy, we could not evaluate the relationship between corticosteroid administration and neonatal hypoglycemia and hyperbilirubin in different weeks of pregnancy. Second, due to the small sample size, it was not possible to assess the relationship between prescription corticosteroid dose and pregnancy outcome.

Conclusion

We found that corticosteroid administration, as a treatment modality in pregnant women with COVID-19, is associated with the increased rate of neonatal hypoglycemia and hyperbilirubinemia. Therefore, glycemic control is vital for neonates born from COVID-19-positive pregnant women exposed to corticosteroids during pregnancy.

Acknowledgments

This study was financially supported by Zanjan University of Medical Sciences (Research ethics code: IR.ZUMS.REC.1400.303). We would like to acknowledge the kind support of participants for their precious contribution to this study as well as the staff of Mousavi Hospital.

Conflicts of interest

The authors do not have any conflict of interest.

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