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Effect of Maternal Body Mass Index on the Efficacy of Antenatal Betamethasone Administration in Neonatal Outcomes

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ABSTRACT

Background: Maternal obesity affects the health of infants and pregnancy outcomes. Few studies, to the best of our knowledge, have assessed the relationship between maternal body mass index (BMI) at antenatal corticosteroid therapy (ACS) and the frequency of preterm adverse outcomes results of which were discrepant. The present study aimed to investigate the prevalence of several neonatal morbidities based on maternal BMI among pregnant women who received a single course of ACS.

Methods: The present retrospective study was conducted on pregnant women referred to Mahdieh Hospital in Tehran, Iran between 2021 and 2022. Medical records of pregnant women were included who received a single course of betamethasone with the risk of preterm birth. The mothers were divided into three groups in terms of weight after checking the inclusion criteria. Clinical characteristics and neonatal outcomes were collected and analyzed using soft statistics.

Results: A total of 610 medical records (30.49%: normal weight, 57.54%: overweight, and 11.98%: obese) were included. Also, the cesarean section rate in overweight and obese cases was significantly higher than that of the normal BMI group ($P<0.05$). No significant relationship was observed between maternal BMI and neonatal mortality or morbidity ($P> 0.05$).

Conclusion: BMI was more associated with increased cesarean section rate in overweight and obese groups. However, no significant relationship was observed between maternal BMI and neonatal outcomes. This result suggests that BMI fails to affect the efficacy of betamethasone.

Keywords: Betamethasone, Body mass index, Perinatal, Premature birth, Neonatal

Introduction

Preterm birth as a critical challenge results in perinatal mortality and morbidity and its frequency has increased from 9.98% to 10.09% during the recent decade (1). Premature rupture of membranes, hypertensive disorders of pregnancy, complications of pregnancy, placental abruption, cervical insufficiency, and intrauterine growth restriction are some of the significant risks associated with preterm birth (2-4).

The administration of antenatal corticosteroids

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has been recommended to prevent or reduce the adverse outcomes related to preterm birth since 1972. Guidelines of the American College of Obstetricians and Gynecologists recommend intramuscular injections of 2 doses of 12 mg betamethasone or 4 doses of 6 mg dexamethasone at intervals of 24 and 12 h, respectively during 24-34 weeks of gestation for pregnant women at risk of preterm birth (5). Until now, the doses of antenatal corticosteroid (ACS) therapy have been fixed and prescribed regardless of maternal BMI (6). Furthermore, maternal obesity appears to affect drug absorption, distribution, metabolism, and efficacy by altering several body compositions such as blood flow, protein binding, adipose tissue, hormones, and enzyme function (7).

Recently, very few studies, to the best of our knowledge, have assessed the correlation between maternal BMI at ACS administration and adverse outcomes in preterm (8, 9). Bicocca et al. (2019) indicated that maternal BMI was not a significant factor in modifying the effects of betamethasone on neonatal respiratory morbidity (10). Hashima et al. (2009) also delineated that maternal BMI could not influence the efficacy of ACS on adverse outcomes in preterm (11). The administration of ACS should preferably be performed based on maternal BMI to prevent overdosing in lean mothers or underdosing in obese ones (12,13). Further studies are required due to the discrepancy in results. Therefore, the present study aimed to demonstrate adverse neonatal outcomes based on maternal body mass index among pregnant women who received a single course of antenatal corticosteroid therapy.

Methods

The present retrospective cross-sectional study was conducted at Mahdieh Hospital (a tertiary center) affiliated with Shahid Beheshti University of Medical Sciences, Tehran, Iran in 2022. Pregnant women with the risk of preterm birth were included in the study.

Nonprobability sampling is used in this study (available samples). All subjects had received a single course of 2 doses of 12 Mg betamethasone intramuscular injection at intervals of 24 h 2-7 days after the first dose of corticosteroid injection. A total of 610 eligible cases were selected according to the inclusion and exclusion criteria between July 1, 2021 to July 1, 2022 (Figure 1).

Inclusion criteria were 1) single pregnancy, 2) 24-34 weeks gestation, 3) injection of betamethasone and 4) delivery 2 to 7 days after corticosteroid therapy.

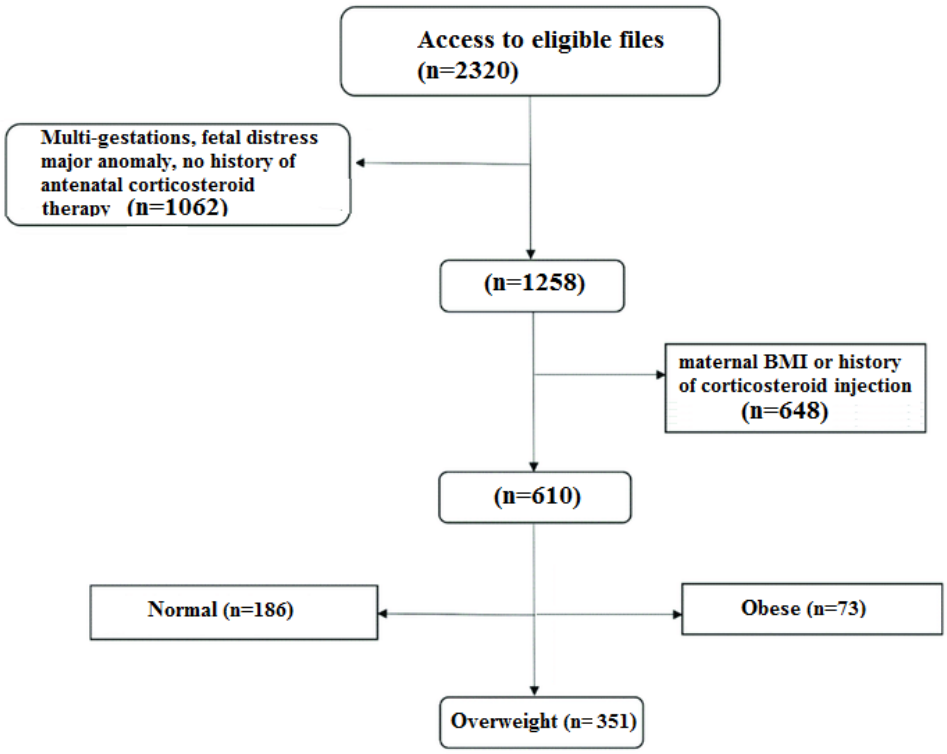

Figure1. Selection criteria for the formation of the final study population

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Exclusion criteria included: 1) multiple gestations, 2) fetal distress, 3) major anomaly, 4) no history of antenatal corticosteroid therapy, 5) systemic steroid treatment, 6) cervical dilatation> 4 cm, 7) initiation of active labor, 8) lack of data on maternal BMI or 9) history of corticosteroid injection.

All demographic and obstetrical characteristics including race, age, levels of education, occupation, pre-pregnancy BMI, numbers of gravidity, parity, abortion, type of delivery, gestational ages at corticosteroid injection, and delivery were extracted from medical records. Neonatal characteristics, clinical data, and perinatal outcomes such as birth weight, height, head circumference, 1- and 5-min Apgar scores, history of neonatal death, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), the requirement of mechanical ventilation, and length of stay in NICU were also collected and recorded in a checklist.

All medical records were categorized into three groups normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (BMI ≥30 Kg/m^2) based on maternal pre-pregnancy BMI (10). BMI was calculated as weight (kg) divided by height (m2). Gestational age was determined based on the last menstrual period. Furthermore, all neonatal outcomes were divided into five groups based on gestational age (24-26, 26-28, 28-30, 30-32, and 32-34 weeks) to eliminate a significant confounding factor. Finally, all data were statistically analyzed to determine any correlations between maternal BMI and neonatal morbidities in mothers who received antenatal corticosteroids. The follow-up of patients from betamethasone injection to the birth of the baby was evaluated based on the checklist of the researcher.

Data Analysis

All data were statistically analyzed using SPSS software (version 22). Quantitative and qualitative data were shown by mean±standard deviation and number (%), respectively. Paired t-test, one-way ANOVA, and Pearson correlation tests were used to analyze the correlations between variables. The odd ratio was calculated using univariate and multivariate logistic regression. A P-value less than 0.05 was considered statistically significant.

Ethical Considerations

The present study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences, Tehran, Iran according to the Helsinki declaration (IR.SBMU.MSP.REC.1400.744). Written consent was received from participants and all data were considered confidential.

Results

A total of 610 participants were included in the study based on medical records. Of them, 186 (30.49%), 351 (57.54%), and 73 (11.98%) subjects were normal-weight, overweight, and obese, respectively (Figure 1). The average age of the participants was 30.24 ± 4.86. Also, 77 subjects were Afghan. Premature rupture of membranes (305) and preeclampsia (219) were the most frequent causes of preterm birth (P=0.055) (Table 1).

According to the demographic and obstetrical characteristics of the mothers, the mean age of the obese group was significantly higher compared to their normal and overweight counterparts (P=0.001). The cesarean section rate in overweight and obese cases was also significantly higher than that in the group with normal BMI (P<0.001). The numbers of gravidity and abortion in the obese group were also higher than that in the group with normal BMI, however, these differences were not statistically significant between the groups (P=0.324 and P=0.485). No significant difference was observed in the interval between delivery and antenatal corticosteroid administration in the group with normal BMI compared to the overweight and obese groups (P=0.116).

The three groups were also similar to each other in terms of fetal gender (P=0.450) and anthropometric measures (P>0.05). The mean birth weight in the obese group was higher compared to that in the normal or overweight groups, however, the differences were not statistically significant (P=0.450).

Also, no significant relationship was observed between neonatal head circumference in the investigated groups (P=0.631). The results related to the associations between maternal BMI and neonatal outcomes among pregnant women with a history of administration of a single course ACS demonstrated no significant differences between the three groups regarding 1- (P=0.407) and 5- (P=0.562) min Apgar scores, surfactant requirement (P=0.326), length of hospitalization (P=0.488), gestational age at ACS administration (P=0.570), or delivery (P=0.549).

Table 1. The comparison of maternal and neonatal characteristics in participants with different BMI

Variable	BMI			*P*-value
	Normal n=186	Overweight n=351	Obesen=73	
Type of delivery				
NVD	122 (65.6)	127 (36.2)	20 (27.4)	*P*<0.001
Cesarean	64 (34.4)	224 (63.8)	53 (72.6)	
The interval between ACS and delivery (days)	4.42±2.00	4.11±1.95	3.95±1.85	0.116
Gravidity	1.97±1.08	2.09±1.10	2.18±1.21	0.324
Parity	0.66±0.82	0.85±0.95	0.84±1.04	0.075
Number of live birth	0.61±0.74	0.78±0.83	0.74±0.93	0.073
History of IUFD	0.04±0.23	0.05±0.25	0.07±0.30	0.750
Number of abortions	0.31±0.68	0.26±0.60	0.34±0.77	0.485
Cause of preterm delivery				
IUGR	5 (50)	4 (40)	1 (10)	0.055
Chronic hypertension	1 (100)	0	0	
Preterm rupture of membrane	83 (27.2)	191 (62.6)	31 (10.2)	
Preeclampsia	45 (28.3)	94 (59.1)	20 (12.6)	
Preterm labor pain	52 (38.5)	62 (45.9)	21 (15.6)	
Gender				
Male	102 (54.8)	190 (54.1)	34 (46.6)	0.450
Female	84 (45.2)	161 (45.9)	39 (53.4)	
Birth weight (g)	1541.92±501.07	1542.85±520.00	1563.70±511.53	0.450
Birth height (cm)	40.97±5.08	41.04±5.07	40.74±5.01	0.900
Birth head circumference (cm)	28.81±3.22	28.76±3.30	28.39±3.11	0.631
1-min Apgar score	8.05±1.45	8.01±1.49	7.78±1.55	0.407
5-min Apgar score	9.27±1.25	9.28±1.25	9.11±1.24	0.562
Surfactant requirement				
Yes	105 (56.5)	219(62.4) 132(37.6)	47(64.4)	0.326
No	81(43.5)		26(35.6)	
Duration of hospitalization	22.96±26.26	25.53±27.52	25.66±23.11	0.544
Gestational age at ACS administration (weeks)	30.29±2.83	30.14±2.91	30.51±2.67	0.570
Gestational age at delivery (weeks)	30.83±2.91	30.69±2.96	31.09±2.71	0.549

According to Table 2, regression analysis reveals that the risk of aging in mothers with higher BMI is more than twice (95% confidence interval: 0.23-5.31). Also, the increased risk of cesarean delivery was 5.5 times higher in mothers with higher BMI (95% confidence interval: 0.29-9.03). BMI was not effective on other variables.

Further analyses after adjustment of gestational age demonstrated no significant difference in risks of neonatal mortality and morbidities among siblings of pregnant women with different BMI (Table 3). The results demonstrated that all preterm neonates with gestational 24-30 weeks had RDS symptoms and maternal BMI failed to affect respiratory morbidity.

Also, RDS was frequently observed in the neonates of overweight and obese mothers whose gestational age was over 30 weeks compared to neonates of mothers with normal

Table 2. Multiple logistic regression analysis displaying the adjusted odds ratios for the variables of interest with their corresponding 95% CI

Variable	*P*-value	Adjusted odds ratio	95% CI
Age (year)	0.04	2.29	0.23–5.31
Type of delivery	0.007	5.56	0.29–9.03
The interval between ACS and delivery (days)	0.14	1.32	0.62–1.78
Gravidity	0.37	1.05	0.66–1.70
Parity	0.07	0.72	0.22–2.08
Number of live birth	0.09	1.48	0.58–3.47
History of IUFD	0.61	0.96	1.31–4.52
Number of abortions	0.49	1.13	0.60–9.47
Cause of preterm delivery	0.05	2.08	0.13–1.44
Gender	0.41	1.22	0.27–4.95
Birth weight (g)	0.45	1.13	0.16–3.46
Birth height (cm)	0.90	0.94	0.23–3.61
Birth head circumference (cm)	0.63	1.09	0.51–2.31
Apgar score	0.24	1.46	0.59–3.61
Duration of hospitalization	0.51	1.28	0.56–2.75
Gestational age at ACS administration (weeks)	0.29	1.67	1.05–6.12
Gestational age at delivery (weeks)	0.57	1.35	0.43–1.43

weight (P=0.514 and P=0.321). The frequency of IVH was higher among neonates of overweight and obese mothers compared to neonates of mothers with normal weight (P>0.05). Furthermore, neonates of obese mothers (with gestational age 30-34 weeks) were more likely to be admitted to NICU compared to neonates of the other counterpart groups, however, these differences were not also statistically significant (P=0.139 and P=0.149). NEC was more frequent

Table 3. The frequency of neonatal mortality and morbidity based on gestational age in women with different BMI receiving a single course of antenatal corticosteroid

Neonatal morbidity	Gestational age at delivery (Weeks)	Normal weight n=186 (n%)	Overweight n=351 (n%)	Obese n=73 (n%)	*P*-value
RDS	24-26	6(100)	14(100)	2(100)	-
	26-28	37(100)	72(100)	12(100)	-
	28-30	18(100)	39(100)	10(100)	-
	30-32	27(90)	55(94.8)	12(100)	0.51
	32-34	48(50.5)	94(56.0)	24(64.9)	0.32
IVH	24-26	4(66.7)	11(78.6)	2(100)	0.61
	26-28	3(8.1%)	8(11.1)	2(16.7)	0.67
	28-30	2(11.1)	2 (5.1)	3(30.0)	0.07
	30-32	5(16.7)	12(20.7)	2 (16.7)	0.93
	32-34	2(2.1)	13(7.7)	2(5.4)	0.16
NEC	24-26	0	1(7.1)	1(50.0)	0.24
	26-28	8(21.6)	13(18.1)	1(8.3)	0.60
	28-30	2(11.1)	1(2.6)	0	0.23
	30-32	1(3.3)	3(5.2)	0	0.84
	32-34	0	2(1.2)	0	0.64
Sepsis	24-26	0	1(7.1)	1(50.0)	0.23
	26-28	2(5.4)	2(2.8)	2(16.7)	0.09
	28-30	2(11.1)	1(2.6)	0	0.23
	30-32	2(6.7)	3(5.2)	1(8.3)	0.84
	32-34	0	3(1.8)	0	0.70
Requirement of mechanical ventilation	24-26	6(100)	14(100.0)	2(100.0)	-
	26-28	37(100)	71(98.6)	11(91.7)	0.28
	28-30	13(72.2)	22(56.4)	6(60.0)	0.56
	30-32	17(56.7)	30(51.7)	5(41.7)	0.67
	32-34	15(15.8)	30(17.9)	10(27.0)	0.30
BPD	24-26	1(16.7)	3(21.4)	1(50.0)	0.565
	26-28	7(18.9)	16(22.2)	1(8.3)	0.619
	28-30	2(11.1)	2(5.1)	0	0.611
	30-32	1(3.3)	3(5.2)	0	1.00
	32-34	0	0	1(2.7)	0.123
NICU admission	24-26	6(100)	14(100)	2(100)	-
	26-28	37(100.0)	72(100)	12(100)	-
	28-30	18(100)	39(100)	10(100)	-
	30-32	27(90.0)	57(98.3) 79(47.0)	12(100)	0.14
	32-34	44 (46.3)		22(59.5)	0.34
Surfactant requirement	24-26	6(100)	14(100)	2(100)	-
	26-28	36(97.3)	72(100)	12(100)	0.40
	28-30	16(88.9)	35(89.7)	8(80.0)	0.67
	30-32	20(66.7)	46(79.3)	10(83.3)	0.39
	32-34	27(28.4)	52(31.0)	15(40.5)	0.39
ROP	24-26	1(16.7)	6(42.9)	0	0.39
	26-28	5(13.5)	4(5.6)	1(8.3)	0.31
	28-30	3(16.7)	4(10.3)	1(10.0)	0.86
	30-32	2(6.7)	7(12.1)	4(33.3)	0.07
	32-34	1(1.1)	1(0.6)	0	-
Fetal death	24-26	1(16.7)	1(7.1)	0	0.60
	26-28	4(10.8)	3(4.2)	0	0.31
	28-30	0	1(2.6)	1(10)	0.34
	30-32	1(3.3)	3(5.2)	0	0.99
	32-34	2(2.1)	3(1.8)	1(2.7)	0.85

RDS: respiratory distress syndrome; IVH: intraventricular hemorrhage; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity

among neonates of mothers with normal weight and gestational age of more than 26 weeks compared to neonates of mothers with high BMI; however, the difference was not significant (P>0.05). The requirement for mechanical ventilation was more frequent in 26-32 week old neonates of mothers with normal weight compared to those of the overweight and obese groups (P>0.05). Although surfactant requirement was higher among 30-34 weeks old neonates of obese and overweight mothers compared to neonates of mothers with normal weight, the differences were not also notable (P=0.391 and P=0.398).

No significant differences were also observed between 24-34 weeks old neonates in the three groups regarding the frequencies of neonatal ROP, sepsis, or BPD (P>0.05). The frequency of fetal death through 24-34 weeks of gestation was also similar between the three groups. All detailed data are shown in Table 3.

The risk factors of neonatal mortality, morbidity, and related points are also presented in Table 4, according to the odds ratio (OR) value of the multivariate logistic analysis. No significant relationship was observed between maternal BMI and neonatal risk factors.

Table 4. Risk factors of neonatal morbidity under multivariate logistic regression

Neonatal morbidity	Multivariate logistic regression		
	P-value	OR	95% CI
RDS	0.06	1.94	1.20–4.28
IVH	0.06	1.64	1.11–5.24
NEC	0.08	1.37	2.02–6.28
Sepsis	0.16	0.94	0.99–5.09
Requirement of mechanical ventilation	0.32	1.05	0.09–3.49
BPD	0.07	0.76	0.01–0.27
NICU admission	0.54	1.04	1.00–2.71
Surfactant requirement	0.12	1.24	1.59–5.24
ROP	0.08	3.27	2.09–4.82
Fetal death	0.43	1.14	0.52–3.64

Discussion

The present study aimed to investigate the impact of maternal BMI on the efficacy of betamethasone on neonatal mortality and morbidity. The primary outcome was to determine whether a standard dose of the ACS regimen is adequate to improve perinatal outcomes in women with high BMI.

According to the result, pregnant women with higher BMI were older than their counterparts with normal BMI. Bicocca et al. indicated a significant positive correlation between maternal age and prepregnancy BMI among four groups of pregnant women with different BMI (BMI<18.5: 25.3±5.4 years, BMI= 18.5-24.9: 27.7±6.1 years, BMI=25-29.9: 28.4±6.1 years, and BMI ≥30: 29.3±6.0 years) which results are consistent with those of the present study (10). A significant correlation (P<0.001) was also reported by Faden et al. between the increase in maternal age and high BMI (>25Kg/m2) (14).

The results demonstrated a higher rate of cesarean section among overweight and obese cases compared to those with normal BMI. Such a result was not unexpected due to prenatal morbidity associated with obesity such as macrosomia and soft tissue barriers in the birth canal (11, 12). Other studies presented a significant relationship (P<0.001) between increased pregnancy or prepregnancy BMI and the risk of cesarean section delivery, which is in line with the findings of the present study (17-19).

Based on the results of the present study, high prepregnancy BMI was not a significant factor in the alteration of betamethasone efficacy and adverse neonatal outcome. Also, the risk of neonatal mortality or morbidities such as RDS, IVH, NEC, ROP, sepsis, or BPD was not statistically different among siblings of pregnant women with different BMI and history of ACS administration after adjusting for gestational age (as a notable confounding factor). These findings may be associated with several reasons. First, various morbidities with diverse incidence and small sample sizes, particularly in the obese group (n=73) may be involved in the interpretation of such results. Therefore, further studies with larger sample sizes and more cases in each BMI category based on the incidences of neonatal morbidities should be considered to generalize the results. Secondly, phases of the pharmacokinetics of betamethasone can be assumed to occur in the body regardless of maternal BMI. Della Torre et al. reported that the range of distribution and clearance of betamethasone was not significantly different among 77 pregnant women with BMI between 17 to 52 Kg/m2. Also, they concluded that maternal lean body weight may be a significant factor affecting the pharmacokinetics of betamethasone and its exposure in the body instead of BMI (13). Third, the present study failed to evaluate the serum concentration of betamethasone in the mother or umbilical cord as fetuses of all mothers were supposed to receive an equal dose of medication in different BMI groups. Gyamfi et al. reported no significant difference between cord blood betamethasone levels in siblings of obese and non-obese mothers by measuring serum

betamethasone in 43 samples (11).

Similar previous studies confirmed the efficacy of betamethasone in reducing neonatal morbidities regardless of maternal BMI which is consistent with the present study. Gyamfi et al. found no significant correlations between maternal serum and cord blood betamethasone concentrations, maternal obesity, and plurality. By such a finding, the authors emphasized the efficacy of an acceptable betamethasone regimen in preventing RDS regardless of fetal plurality or maternal obesity (11). Bicocca et al. also demonstrated that maternal BMI at delivery was not a significant factor influencing betamethasone efficacy or treatment response in neonatal RDS (10). Hashima et al. conducted a similar study to demonstrate neonatal morbidities among 183 pregnant women with prepregnancy BMI below and above 25 Kg/m2 receiving a single course of betamethasone. According to their results, the rate of neonatal morbidity (IVH, BPD, NEC, ROP …) was not significantly different among cases with different BMIs. Moreover, they indicated that the numbers of stillbirths were not significantly different between groups with different BMI (1 vs. 2; P>0.99) (12). Also, Salim et al. showed a variation in betamethasone levels among 5 women with different BMI values which is in contrast to the results of the present study (26.4-33.1 Kg/m2). The authors concluded that the acceptable antenatal betamethasone regimen may not provide a sufficient dose to improve perinatal outcomes among pregnant women with different weights (20).

The present study delineated that the dosage of antenatal betamethasone was not a variable based on maternal BMI by large sample size, including several morbidities, and adjusting for several confounding variables. The risks of neonatal mortality or morbidities were similar among siblings of pregnant women with different BMI and history of a single course of ACS administration. Also, the present study has several limitations. The sample size in the obese group was smaller than the other groups. The present retrospective study had notable missing data. Furthermore, the data related to maternal BMI at ACS administration or delivery were not included. Finally, the included groups were not adjusted for maternal age or type of delivery and these factors may affect the results. Further studies with larger sample sizes and more variables regarding maternal BMI, and adjusting confounding variables will provide more informative data to generalize the results.

Conclusion

The results of the present study demonstrated that pregnant women with higher BMI are older and at higher risk for cesarean section compared to their counterparts with normal BMI. However, no significant relationship was observed between maternal BMI and neonatal outcomes. Maternal BMI failed to affect the effectiveness of prenatal betamethasone administration; however, further studies with larger sample sizes are required to confirm the results of the present study.

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Conflicts of interest

The authors declare that there is no conflict of interest regarding the authorship or publication of the present study.

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Authors' contributions

Dr. M.M, Dr. M.A., and Dr. S.SG. designed and coordinated the study, and participated in most of the experiments. Dr. Z.N, Dr. N.R., Dr. M.Sh., and Dr. P.P. performed all experiments and analyzed the data. Dr. M.M, Dr. T.A., Dr. N.A, and Dr. M.A. participated in the research and preparation of the manuscript. All authors have read and approved the content of the manuscript.

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