The effects of antenatal corticosteroid and sex on morbidity and mortality in preterm infants: a cohort study

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Abstract

Objective: To study the linked result of a complete course of antenatal corticosteroids (ANS) on mortality and short-term morbidity rates among preterm infants in our population.

Study design: This single-center retrospective study included the infants born before 32 weeks' gestation and admitted to neonatal intensive care unit (NICU) between January 1, 2018 and December 31, 2020. The following data of gestational age, birth weight, sex, the etiology of labor, type of delivery, need for intubation in delivery room, APGAR scores (1^{st} and 5^{th} min), the rates of respiratuvary distress syndrome (RDS), surfactant administration, patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and bronchopulmonary dysplasia (BPD) were collected from medical records.

Results: The study included 210 infants with a median gestational age of 28.6 weeks (24-31.6), a birth weight of 1065 g (445-2165) and with an ANS use rate of 80%. The mortality rate was lower (p=0.001) with a longer hospital stay (p=0.029), but the rate of BPD was higher (p=0.014) in male infants who received ANS than who did not. According to sex distribution, there was a significant decrease in mortality rate in male infants compared with female ones in ANS received group (11% vs. 23%, p=0.038) with a higher BPD rate (p=0.005).

Conclusion: ANS is related with less mortality in male infants born before 32 weeks' gestation. Further research is currently needed to evaluate advantage of antenatal steroids in different populations.

Introduction

Preterm birth is a leading cause of neonatal morbidity and mortality with associated long-term consequences. Male and female preterm infants still have different outcomes in neonatal period. Male infants have been shown to have a decreased rate of survival, increased rate of respiratory morbidity and poorer long-term neurologic outcome [1–3].

Antenatal corticosteroid (ANS) therapy is recommended since 1994 to promote fetal maturation in all pregnant with a risk of premature labour before 34 weeks of gestation. ANS is known to reduce the neonatal mortality, respiratory morbidity, and intraventricular haemorrhage (IVH) [4–6]. In studies that evaluating the effect of ANS on mortality and preterm associated morbidities according to sex, one found positive effects of ANS in male preterm infants on acute respiratory morbidity and mortality, whereas the other showed a greater beneficial effect of ANS in female infants in reducing death before discharge [7, 8].

The aim of this study is to evaluate the effect of ANS on premature related morbidities and mortality depending on sex in our cohort including preterm infants born before 32 weeks' gestation.

Materials And Methods

This single-center retrospective cohort study included infants born before 32 weeks' gestation and admitted to neonatal intensive care unit (NICU) between January 1, 2018 and December 31, 2020. The study was approved by local ethic committee. Our Research Ethical Committee approved the study (Approval no. 21/2017). The informed consent was obtained.

The complete ANS course was defined as the administration of two doses of corticosteroids to the mother (Betamethasone, Celestone®, 24 mg) between 24 h and seven days before delivery. The following data of gestational age (GA), birth weight (BW), sex, the aetiology of labour, type of delivery, need for intubation in delivery room, Apgar scores (1st and 5th min), the rates of respiratory distress syndrome (RDS), surfactant administration, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intraventricular haemorrhage (IVH), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD) were collected from medical records. The infants who received ANS or who did not were compared depending on sex distribution. The main outcome variable was survival, considering it at hospital discharge.

All statistical analyses were performed using SPSS for Windows version 11.5 software (SPSS Inc., Chicago, IL, US). Descriptive statistics were expressed as means ± standard deviations and median (minimum-maximum) for quantitative variables and the number (percent) for qualitative variables. Compatibility of data with normal distribution was examined graphically and using the Kolmogorov-Smirnov test. When to look whether there was a statistically significant difference between the categories of a qualitative variable with two categories in terms of a quantitative variable, Student's t-test was used if the normal distribution assumption was met; if not, Mann-Whitney U test was used. The chi-square test and Fisher-exact test were used to examine the relationship between two categorical variables. A p-value of 0.05 was considered statistically significant.

Results

The study included 210 patients with a mean GA of 28.7 ± 2.1 weeks, and a mean BW of 1165 ± 376 g. Of these, 80% (n = 168) received a complete course of ANS and 20% (n = 42) did not receive any ANS. There was no difference between the groups in terms of prenatal characteristics except for having pathological Doppler finding before birth which is higher in No ANS group (p = 0.046) (Table 1).

Table 1
Prenatal, natal and postnatal characteristics according to ANS administration

	ANS (n = 168)	No ANS (n = 42)	p
Gestational age (w)*	28.7 ± 2.1	28.6 ± 2.3	0.803
Birth weight (g)*	1171 ± 352	1141 ± 462	0.069
Gender (male)‡	90 (54)	23 (55)	0.890
Type of delivery (CS)‡	132 (79)	32 (76)	0.739
Antenatal $MgSO_4$‡	52 (31)	9 (21)	0.224
Multiple pregnancy‡	60 (36)	14 (33)	0.773
Maternal disease‡	26 (16)	6 (14)	0.505
Suspected cause of preterm birth‡	114 (68)	22 (52)	0.090
Infection/inflammation	49 (29)	18 (43)	0.129
Vascular	5 (3)	2 (5)	0.629
Other			
Pathologic Doppler finding‡	19 (11)	10 (24)	0.046
Apgar score 1st min†	6 (5–7)	5 (4-6.25)	0.104
Apgar score 5th min†	8 (7–9)	8 (7–8)	0.468
RDS	73 (44)	21 (50)	0.445
Surfactant	72 (43)	21 (50)	0.405
PDA (treated) ‡	41 (24)	5 (12)	0.080
IVH (Gr ≥ 3) ‡	14 (8)	0	0.053
NEC (any stage)‡	36 (21)	4 (10)	0.079
BPD (moderate/severe)‡	32 (19)	1 (2)	0.008
ROP (treatment required)‡	3 (2)	1 (2)	0.480

*mean ± SD; †median (IQR); ‡number (%).

ANS: antenatal corticosteroid; BPD: Bronchopulmonary dysplasia; CS: caesarean section; IVH: Intraventricular haemorrhage; NEC: Necrotizing enterocolitis; PDA: Patent ductus arteriosus; RDS: Respiratory distress syndrome; ROP: Retinopathy of prematurity.

	ANS (n = 168)	No ANS (n = 42)	p
Mortality‡	28 (17)	13 (31)	0.037
Duration of hospitalization (d)*	39 ± 26.1	27.7 ± 23	0.007

*mean ± SD; †median (IQR); ‡number (%).

ANS: antenatal corticosteroid; BPD: Bronchopulmonary dysplasia; CS: caesarean section; IVH: Intraventricular haemorrhage; NEC: Necrotizing enterocolitis; PDA: Patent ductus arteriosus; RDS: Respiratory distress syndrome; ROP: Retinopathy of prematurity.

The overall mortality rate was 19% (n = 41) in the study group which was similar according to sex (male 17%, female 23%, p = 0.285), but the incidence of moderate/severe BPD was higher in male infants compared to females (43% vs. 24%, p = 0.025).

Analysis of the male infants in this study, the mortality rate was lower of whom received ANS (11% vs. 39%, p = 0.001) with a longer hospital stay (p = 0.029), whereas the incidence of moderate/severe BPD was higher in ANS received ones. In female's infants, both the rates of mortality and BPD were similar with respect to ANS receive (p = 0.850, and 0.742) (Table 2).

Table 2
Demographic findings and neonatal outcomes according to ACS administration depending on sex distribution

	ACS (n = 168)		p[1]	No ACS (n = 42)		p[2]	p[3]
Gestational age (w)*	Male (n = 90)	28.5 ± 2.3	0.158	Male (n = 23)	28.2 ± 2.2	0.118	0.465
	Female (n = 78)	29 ± 1.8		Female (n = 19)	29.3 ± 2.3		0.641
Birth weight (g)*	Male (n = 90)	1197 ± 374	0.304	Male (n = 23)	1041 ± 445	0.127	0.133
	Female (n = 78)	1141 ± 326		Female (n = 19)	1262 ± 465		0.190
Apgar 1st min†	Male (n = 90)	6 (5–7)	0.941	Male (n = 23)	5 (4–6)	0.140	0.042
	Female (n = 78)	6 (5–7)		Female (n = 19)	5 (4–7)		0.864
Apgar 5th min†	Male (n = 90)	8 (7–9)	0.586	Male (n = 23)	7 (7–8)	0.426	0.424
	Female (n = 78)	8 (7–9)		Female (n = 19)	8 (7–9)		0.892
RDS‡	Male (n = 90)	37 (41)	0.511	Male (n = 23)	14 (61)	0.121	0.089
	Female (n = 78)	36 (46)		Female (n = 19)	7 (37)		0.464
Surfactant‡	Male (n = 90)	36 (40)	0.421	Male (n = 23)	14 (61)	0.121	0.072
	Female (n = 78)	36 (46)		Female (n = 19)	7 (37)		0.464
PDA (treated) ‡	Male (n = 90)	17 (19)	0.074	Male (n = 23)	2 (9)	0.644	0.243
	Female (n = 78)	24 (31)		Female (n = 19)	3 (16)		0.191

*mean ± SD; †median (IQR); ‡number (%).

p[1]: Comparision of male and female infants received ACS; p[2]: Comparision of male and female infants did not receive ACS; p[3]: Comparision of infants received and did not received ACS.

ACS: antenatal corticosteroid; BPD: Bronchopulmonary dysplasia; IVH: Intraventricular haemorrhage; NEC: Necrotizing enterocolitis; PDA: Patent ductus arteriosus; RDS: Respiratory distress syndrome; ROP: Retinopathy of prematurity.

	ACS (n = 168)		p[1]	No ACS (n = 42)		p[2]	p[3]
IVH (Gr ≥ 3) ‡	Male (n = 90)	8 (9)	0.780	Male (n = 23)	0	-	0.138
	Female (n = 78)	6 (8)		Female (n = 19)	0		0.212
NEC (any stage)‡	Male (n = 90)	21 (23)	0.518	Male (n = 23)	3 (13)	0.613	0.282
	Female (n = 78)	15 (19)		Female (n = 19)	1 (5)		0.141
BPD (moderate/severe)‡	Male (n = 90)	22 (24)	0.056	Male (n = 23)	0	0.452	**0.008**
	Female (n = 78)	10 (13)		Female (n = 19)	1 (5)		0.352
ROP (treatment required)‡	Male (n = 90)	1 (1)	0.159	Male (n = 22)	1 (4)	0.420	0.416
	Female (n = 78)	2 (3)		Female (n = 19)	0		0.733
Mortality‡	Male (n = 90)	10 (11)	**0.038**	Male (n = 23)	9 (39)	0.207	**0.001**
	Female (n = 78)	18 (23)		Female (n = 19)	4 (21)		0.850
Duration of hospitalization (d)*	Male (n = 90)	41.2 ± 26.8	0.235	Male (n = 23)	28.2 ± 24	0.877	**0.029**
	Female (n = 78)	36.4 ± 25		Female (n = 19)	27 ± 22.1		0.118

*mean ± SD; †median (IQR); ‡number (%).

p[1]: Comparision of male and female infants received ACS; p[2]: Comparision of male and female infants did not receive ACS; p[3]: Comparision of infants received and did not received ACS.

ACS: antenatal corticosteroid; BPD: Bronchopulmonary dysplasia; IVH: Intraventricular haemorrhage; NEC: Necrotizing enterocolitis; PDA: Patent ductus arteriosus; RDS: Respiratory distress syndrome; ROP: Retinopathy of prematurity.

In the analysis of only ANS received group depending on sex distribution, there was a significant decrease in mortality rate in male infants compared with female infants (11% vs. 23%, p = 0.038), whereas the incidence of BPD (moderate/severe) was higher in male infants (49% vs. 23%, p = 0.005). Of the infants who did not received ANS, the rates of mortality and BPD rate were according to gender (p = 0.207, and p = 0.280) (Table 2).

Discussion

In this study, the rate of complete course ANS was 80% which is similar to many countries over the world [9]. We have demonstrated that ANS was associated with a greater reduction in mortality in male infants compared with female infants who received ANS and male infants who did not receive ANS. On the other hand, in ANS received group, we reported a higher rate of BPD in male infants compared to female ones.

The complications in the neonatal period have been evaluated not individually, but also according to gender. Different results have emerged in both groups. Compared to the female, male sex is a risk factor for adverse pregnancy outcomes [10]. In our study population, with similar GA and BW distribution according to gender, the mortality rate was similar, but the incidence of moderate/severe BPD was found to be higher in male infants.

There is varying evidence in the literature about which gender benefits more from ANS treatment. In animal studies involving long-term neurological development outcomes, the varied influence of ANS in relation to sex has been documented. Female infants showed higher levels of stress activity and more behavioral issues [11, 12]. Fetal sex is related to noticeable differences in fetal development, the transition from fetus to newborn, and postnatal morbidity and mortality. Although male sex fetuses are protected in utero, females show a higher degree of maturation during fetal to newborn transition and later in the newborn period which results in a stronger ability to stabilize, lower rates of short-term prematurity associated morbidities, and better long-term outcomes [3, 13–15]. The two recently published studies on ANS and the influence of sex reported different information. Ramos-Navorro et al. found a positive effect of ANS in male infants born before 29 weeks' gestation [7], whereas Lee et al. demonstrated the beneficial effect of ANS in female infants compared to males in reducing death before discharge [8]. Of infants who received ANS in present study, the rate of mortality was lower with a higher rate of BPD in male infants compared to female ones.

Our study has some limitations. First the rate ANS use was lower than some countries worldwide, but higher than many centers in our country. Secondly, this is a retrospective single center study with a small number of patients which may affect the incidences of both mortality and morbidities according to sex distribution.

In conclusion the associated influence of ANS in premature infants in our population is seems to be gender dependent. ANS is related with lower mortality but higher BPD in male infants born before 32 weeks' gestation. Further research is currently needed to evaluate advantage of antenatal steroids in different populations.

Declarations

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University Ankara (Date:2021/No :17).

Written informed consent was obtained from the parents.

Statements and Declarations

Authors' contributions

Study concept and design: Erdal Şeker, Elvis Kraja and Emel OKulu. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: Erdal Şeker and Yasemin Ezgi Köstekçi. Critical revision of the manuscript for important intellectual content:all authors. Statistical analysis: Acar Koç and Maide Seiln Çakır. Study supervision: Ömer Erdeve, Begüm Atasay, Saadet Arsan.

Declarations Competing interests

The authors declare no competing interests

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Our Research Ethical Committee approved the study (Approval no. 21/2017). Ethical approval was obtained from Ankara University.

The informed consent was obtained.

References

1. Kent, A.L., et al., *Mortality and adverse neurologic outcomes are greater in preterm male infants*. Pediatrics, 2012. **129**(1): p. 124–31. DOI: 10.1542/peds.2011-1578.
2. Zisk, J.L., et al., *Do premature female infants really do better than their male counterparts?* Am J Perinatol, 2011. **28**(3): p. 241–6. DOI: 10.1055/s-0030-1268239.
3. Stevenson, D.K., et al., *Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage*. Arch Dis Child Fetal Neonatal Ed, 2000. **83**(3): p. F182-5. DOI: 10.1136/fn.83.3.f182.
4. Saigal, S. and L.W. Doyle, *An overview of mortality and sequelae of preterm birth from infancy to adulthood*. Lancet, 2008. **371**(9608): p. 261–9. DOI: 10.1016/s0140-6736(08)60136-1.
5. *Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes*. JAMA, 1995. **273**(5): p. 413–8. DOI: 10.1001/jama.1995.03520290065031.
6. Roberts, D., et al., *Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth*. Cochrane Database Syst Rev, 2017. **3**(3): p. CD004454. DOI: 10.1002/14651858.CD004454.pub3.
7. Ramos-Navarro, C., et al., *Antenatal corticosteroids and the influence of sex on morbidity and mortality of preterm infants*. J Matern Fetal Neonatal Med, 2020: p. 1–8. DOI:

10.1080/14767058.2020.1819977.

8. Lee, R., et al., *Influence of antenatal corticosteroids and sex on the mortality and morbidity of extremely prematurely born infants*. J Matern Fetal Neonatal Med, 2021: p. 1–4. DOI: 10.1080/14767058.2021.1940941.
9. Helenius, K., et al., *Survival in Very Preterm Infants: An International Comparison of 10 National Neonatal Networks*. Pediatrics, 2017. **140**(6). DOI: 10.1542/peds.2017-1264.
10. Di Renzo, G.C., et al., *Does fetal sex affect pregnancy outcome?* Gend Med, 2007. **4**(1): p. 19–30. DOI: 10.1016/s1550-8579(07)80004-0.
11. Rodriguez, J.S., et al., *Prenatal betamethasone exposure has sex specific effects in reversal learning and attention in juvenile baboons.* Am J Obstet Gynecol, 2011. **204**(6): p. 545 e1-10. DOI: 10.1016/j.ajog.2011.01.063.
12. Kemp, M.W., et al., *Efficacy and safety of antenatal steroids*. Am J Physiol Regul Integr Comp Physiol, 2018. **315**(4): p. R825-r839. DOI: 10.1152/ajpregu.00193.2017.
13. Braun, F., et al., *Sex-specific and lasting effects of a single course of antenatal betamethasone treatment on human placental 11β-HSD2*. Placenta, 2018. **69**: p. 9–19. DOI: https://doi.org/10.1016/j.placenta.2018.07.007.
14. Lorente-Pozo, S., et al., *Influence of Sex on Gestational Complications, Fetal-to-Neonatal Transition, and Postnatal Adaptation*. Front Pediatr, 2018. **6**: p. 63. DOI: 10.3389/fped.2018.00063.
15. Kotecha, S.J., J. Lowe, and S. Kotecha, *Does the sex of the preterm baby affect respiratory outcomes?* Breathe (Sheff), 2018. **14**(2): p. 100–107. DOI: 10.1183/20734735.017218.