original article

Antenatal care of mothers and morbidity and mortality disparities among preterm Saudi and non-Saudi infants less than or equal to 32 weeks' gestation

Mountasser Al-Mouqdad,[a] Adli Abdelrahim,[a] Nabeel Abdullah Alodhaidan,[a] Haider Hussein Sumaily,[a] Thanaa Mustafa Khalil,[b] Yasmeen Asfour,[c] Suzan Suhail Asfour[d]

From the [a]Neonatal Intensive Care Unit, Hospital of Pediatrics, King Saud Medical City, Riyadh, Saudi Arabia; [b]Obstetric and Gynecology Department, Maternity Hospital, King Saud Medical City, Riyadh, Saudi Arabia; [c]Obstetrics and Gynecology Department, Family Care Hospital, Riyadh, Saudi Arabia; [d]Clinical Pharmacy Department, Pharmaceutical Care Service, King Saud Medical City, Riyadh, Saudi Arabia

Correspondence: Dr. Mountasser Al-Mouqdad · Neonatal Intensive Care Unit, Hospital of Pediatrics, King Saud Medical City, Riyadh 12417, Saudi Arabia · M.almouqdad@ksmc.med.sa · ORCID: https://orcid.org/0000-0002-0424-4833

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BACKGROUND: Premature non-Saudi infants comprise a significant proportion of neonatal intensive care unit admissions in Saudi Arabia. Any differences in antenatal care of mothers and neonatal outcomes compared with premature Saudi infants are unreported.

OBJECTIVE: Assess antenatal care of mothers and neonatal outcomes among premature Saudi and non-Saudi infants, and investigate possible reasons for disparities.

DESIGN: Retrospective cohort study.

SETTING: Tertiary care center in Riyadh.

PATIENTS AND METHODS: All neonates of gestational age ≤32 weeks and birthweight <1500 g admitted from 2015 to 2019 were included.

MAIN OUTCOME MEASURES: Antenatal care of mothers and rates of neonatal mortality and morbidity in premature Saudi and non-Saudi infants.

SAMPLE SIZE: 755 premature infants, 437 (57.9%) Saudi, 318 (42.1%) non-Saudi.

RESULTS: Saudi mothers received more antenatal steroids and were more likely to have gestational diabetes mellitus (*P*=.01 and .03, respectively). Non-Saudi mothers were more likely to have pregnancy-induced hypertension (*P*=.01). Non-Saudi infants had significantly higher rates of intraventricular hemorrhage, patent ductus arteriosus, pulmonary hemorrhage, bronchopulmonary dysplasia and necrotizing enterocolitis compared with Saudi infants (*P*=.03, <.001, .04, .002, and <.001, respectively). There were no significant differences in mortality rate, early-onset sepsis, and late-onset sepsis between Saudi and non-Saudi infants (*P*=.81, .81, and .12, respectively).

CONCLUSIONS: Disparities exist in the antenatal care of Saudi and non-Saudi women and in the neonatal morbidities of their premature infants. There was no difference in the neonatal mortality rate. More quality improvement initiatives are required to reduce differences in antenatal and neonatal outcomes.

LIMITATIONS: Retrospective, socioeconomic disparities not identified.

CONFLICT OF INTEREST: None.

Although the rate of premature deliveries is decreasing, prematurity is still the main reason for neonatal morbidity and the second leading cause of infant mortality.[1] A large proportion of the population in Saudi Arabia is non-Saudi (about 37% of the total population).[2] Interestingly, all the studies that have investigated the short- and long-term outcomes of term and preterm infants have overlooked the fact that the non-Saudi population is responsible for a significant proportion of total neonatal intensive care units' admissions.[3-6] Therefore, we do not know the precise rates of neonatal mortality and morbidity such as respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC) among the Saudi population; we also do not know the factors that may contribute to these differences, if they exist.

The aim of our study was to detect the rates of neonatal mortality and morbidity in Saudi and non-Saudi premature infants who were less than or equal to 32 weeks' gestation and less than 1500 grams, admitted at our unit over a 5-year period from 2015 to 2019, and investigate the possible reasons for any disparities.

PATIENTS AND METHODS

This study was a retrospective review of the charts of infants (gestational age ≤32 weeks; birthweight <1500 grams) who were admitted to level 3 of the neonatal intensive care unit (NICU) of King Saud Medical City (KSMC) tertiary referral center from January 2015 to December 2019. We excluded patients who transferred out within the first two days, patients born outside KSMC, and patients whose data we could not retrieve. The NICU had an average annual admission of 1100 patients, including NICU levels 2 and 3. This study was conducted in accordance with the Declaration of Helsinki, the Good Pharmacoepidemiology Practices guidelines,[7] and was approved by the medical ethical review committee of our institution with a waiver of consent (Reference number H1RI-21-Dec17-01).

Patient charts from NICU admission until discharge or death were reviewed. Data retrieved included birthweight, gestational age, Apgar score at 1 and 5 minutes, and small for gestational age status. Neonatal outcomes included patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), seizure, retinopathy of prematurity, necrotizing enterocolitis (NEC), surfactant use, length of hospital stay, pulmonary hemorrhage, pneumothorax, early-onset sepsis (EOS), late-onset sepsis (LOS), ingestion of expressed breast milk (EBM), omeprazole, ranitidine, analgesia; cholestasis; and mortality. Maternal data included booking status, mode of delivery, antenatal steroid treatment, presence of gestational diabetes mellitus (GDM), prolonged rupture of membrane, pregnancy-induced hypertension (PIH), and hypothyroidism.

EOS was defined as sepsis caused by pathogens transmitted vertically from mother to infant on or before the third day of life.[8,9] LOS was sepsis caused by horizontally-acquired pathogens that occur after day 3 of life.[9,10] NEC included stage II and above according to the Bell Staging Criteria.[11] NEC medical were cases not treated by surgery.[11] NEC surgical were cases treated by surgery.[11] PDA pharmacological was treated with either indomethacin, ibuprofen, or acetaminophen.[12] IVH was classified into grades I to IV according to Papile et al's IVH classification.[13] BPD involved any supplemental oxygen use at 36 weeks postmenstrual age, or on oxygen at discharge at 34 to 35 weeks if transferred or discharged before 36 weeks gestation.[14] Mortality was death before hospital discharge. NICU interventions given by the NICU staff may have included the use of a non-invasive ventilator, an invasive ventilator, insertion of umbilical arterial catheter (UAC) line, an umbilical venous catheter line, a peripherally inserted central catheter (PICC) line or a central venous catheter line, use of nitric oxide, ranitidine, omeprazole, EBM, analgesia and sedation, inotropes, and hydrocortisone.

Data were analyzed using IBM SPSS version 25.0 (Armonk, NY: IBM Corp). Descriptive statistics, including median, interquartile range (IQR), frequency, and percentages were used to describe the maternal and neonatal variables. We calculated the cumulative incidence of maternal morbidities, NICU interventions for Saudi or non-Saudi mothers and neonates, and birth year, along with confidence intervals. The cumulative incidence of neonatal morbidities and mortality for Saudi and non-Saudi neonates and birth year along with confidence intervals were also calculated.

Fisher's exact test was used to determine the association between categorical variables. Mann-Whitney U-test was used for ordinal qualitative variables (gestational age, and Apgar score). For continuous variables, the unpaired *t* test was used; when data were not normally distributed, Mann–Whitney U-test was performed. The Kolmogorov–Smirnov test and a visual inspection of histograms were performed to verify the normality of distribution of the quantitative variables. Rates were calculated by division of the number of cases divided by the total cases for each nationality group. Statistically significant differences are visible on the graphs as the nonoverlapping areas of the confidence intervals. All statistical tests were 2-tailed, and *P* values of <.05 were considered to be statistically significant.

RESULTS

There were 2810 admissions to the NICU (level 3) between January 2015 and December 2019, of which 2055 cases were excluded, leaving a total of 755 infants who were included in the final analysis (**Figure 1**). Saudi infants accounted for 57.9% of 755 infants admitted to KSMC. Maternal and neonatal demographic characteristics nationality are described in **Table 1**. More Saudi mothers had prenatal care than non-Saudi mothers (21.3% vs 8.2%) (*P*<.001). Furthermore, the rate of booking remained constant over the years in both groups (**Figure 2**, upper left). There were statistically significant differences in the use rates of non-invasive ventilators, insertion of UAC lines, insertion of PICC lines, and use of omeprazole and EBM (**Figure 3**). The use of non-invasive ventilators was significantly higher among non-Saudi than among Saudi infants (*P*=.002). This difference remained almost constant over the years 2015-2019. In addition,the use of PICC lines over time increased among non-Saudi infants. The use of EBM and omeprazole was lower in Saudi infants (*P*≤.001 and *P*=.02, respectively) and these remained almost constant over time (**Table 2; Figure 3**).

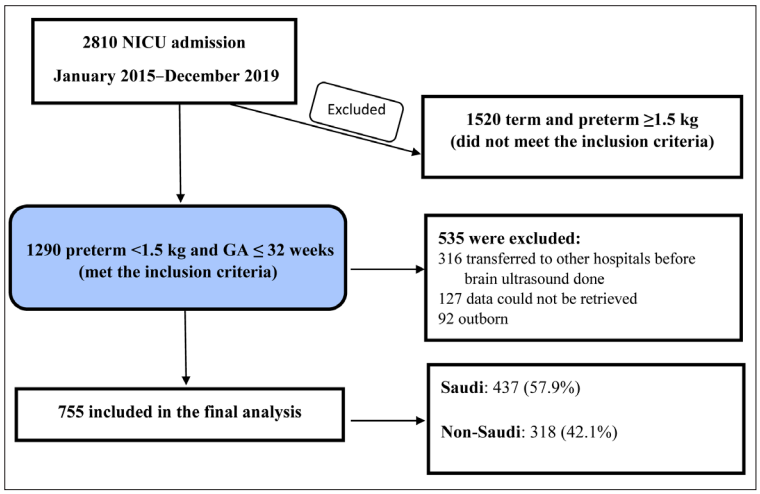

Figure 1. Flow chart of patient selection GA: gestational age, NICU: neonatal intensive care unit.

Mortality and pulmonary hemorrhage increased during the first year of our study (2015); subsequently, these decreased and remained almost constant until 2018. In 2019, the mortality rate and pulmonary hemorrhage increased again, almost reaching the previous rate in 2015 (**Figure 4**).

Overall, non-Saudi infants had significantly higher rates of IVH, PDA, pulmonary hemorrhage, BPD, NEC, and NEC medical (*P*=.03, <.001, .04, .002, <.001, and <.001, respectively) (**Table 3**). The differences in the

Table 1. Demographic and clinical characteristics of Saudi and non-Saudi mothers and neonates of very low birthweight and ≤32 weeks gestation status (n=755).

	Saudi (n=437)	Non-Saudi (n=318)	*P* value
Appointment booked	93 (21.3)	26 (8.2)	**<.001**
Antenatal steroid	242 (55.4)	146 (45.9)	**.01**
Pregnancy induced hypertension	76 (17.4)	79 (24.8)	**.01**
Gestational diabetes mellitus	28 (6.4)	9 (2.8)	**.03**
Prolonged rupture of membrane	53 (10.7)	36 (4.8)	.73
Hypothyroidism	10 (2.3)	5 (1.6)	.79
Caesarean delivery	166 (38)	130 (40.9)	.45
Gender (Male)	225 (51.5)	165 (51.9)	.94
Gestational age, wk	28 (26,30)	28 (26,30)	.12
Birth weight, g	1050 (795,1292)	1060 (822.5,1350)	.2
Small for gestational age	213 (48.7)	168 (52.8)	.27
Apgar score at 1 min	5 (3,6)	5 (3,6)	.44
Apgar score at 5 min	7 (6,8)	7 (6,8)	.89
Length of hospital stay	21 (6,45)	40 (18,64)	**<.001**

Data are median (25th, 75th percentile) or number (%).

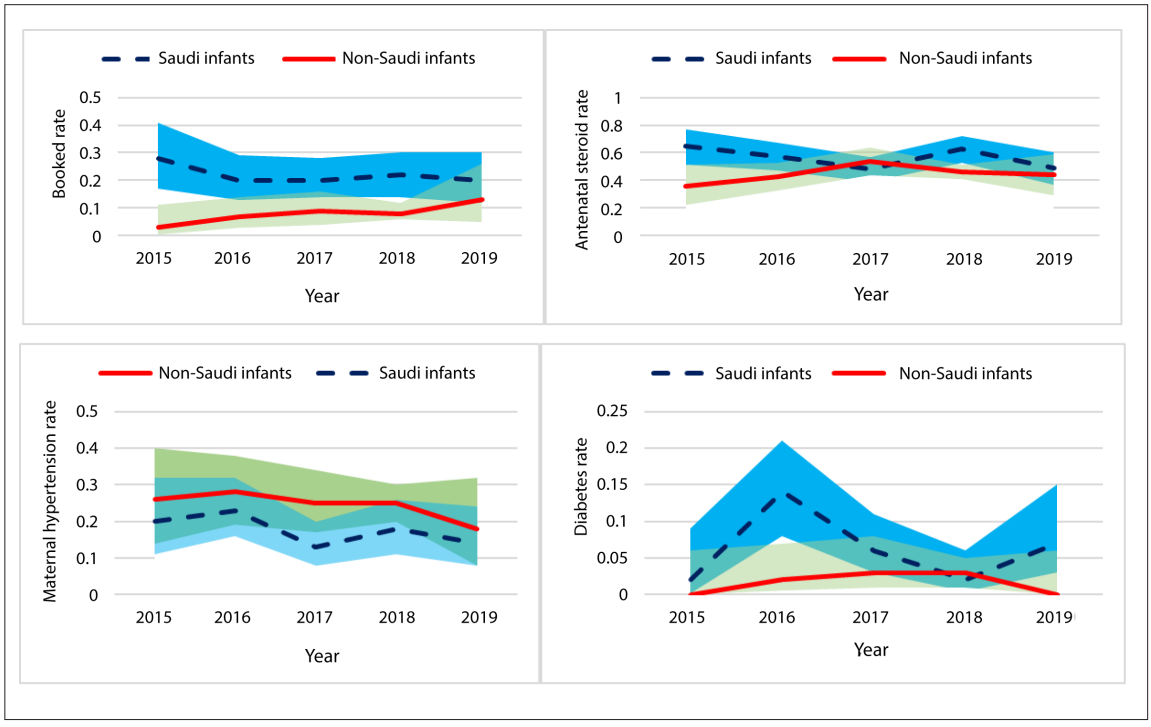

Figure 2. Rates of antenatal care and maternal complications among Saudi and non-Saudi infants by birth year. The blue line represents mothers of Saudi infants, the red line represents mothers of non-Saudi infants, shading represents 95% confidence intervals.

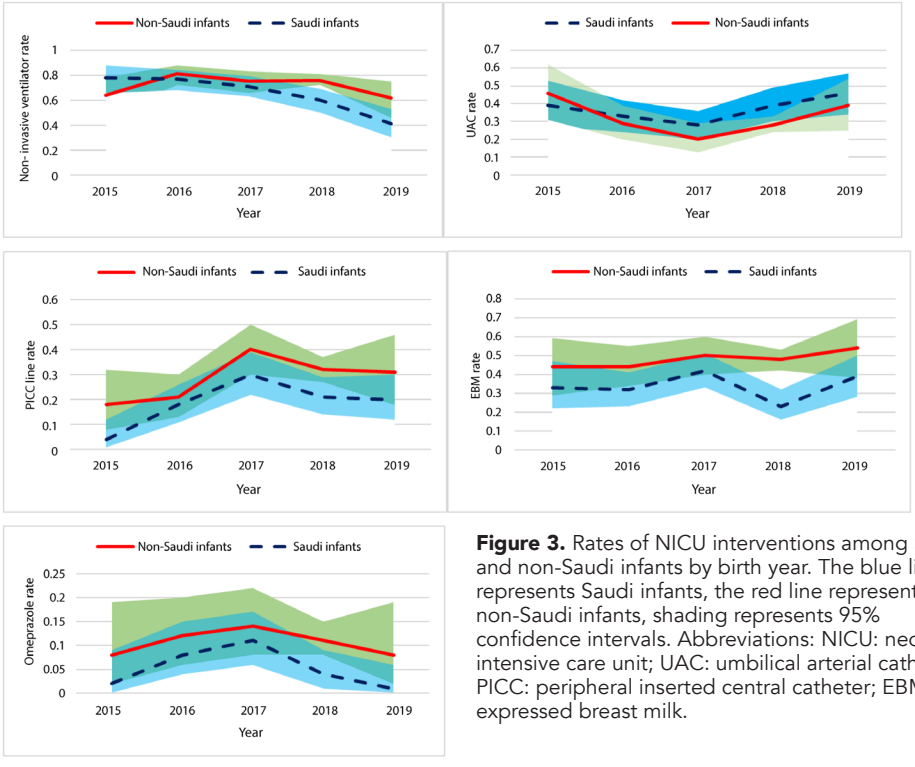

Figure 3. Rates of NICU interventions among Saudi and non-Saudi infants by birth year. The blue line represents Saudi infants, the red line represents non-Saudi infants, shading represents 95% confidence intervals. Abbreviations: NICU: neonatal intensive care unit; UAC: umbilical arterial catheter; PICC: peripheral inserted central catheter; EBM: expressed breast milk.

Table 2. Neonatal intensive care unit interventions among Saudi versus non-Saudi infants (n=755).

	Saudi (n=437)	Non-Saudi (n=318)	*P* value
Non-invasive ventilator	288 (65.9)	243 (76.4)	**.002**
Invasive ventilator	327 (74.8)	224 (70.4)	.18
Surfactant	288 (65.9)	196 (61.6)	.25
Nitric oxide	12 (2.7)	8 (2.5)	.999
Umbilical arterial catheter	156 (35.7)	90 (28.3)	**.03**
Umbilical venous catheter	344 (78.7)	238 (74.8)	.22
Peripherally inserted central catheter	90 (20.6)	102 (32.1)	**<.001**
Central venous catheter	16 (3.7)	18 (5.7)	.21
Ranitidine	18 (4.1)	21 (6.6)	.14
Omeprazole	27 (6.2)	35 (11)	**.02**
Expressed breast milk	148 (33.9)	152 (47.8)	**<.001**
Analgesia and sedation	228 (52.2)	179 (56.3)	.27
Inotropes	179 (41)	144 (45.3)	.26
Hydrocortisone	94 (21.5)	79 (24.8)	.29

Data are number (%).

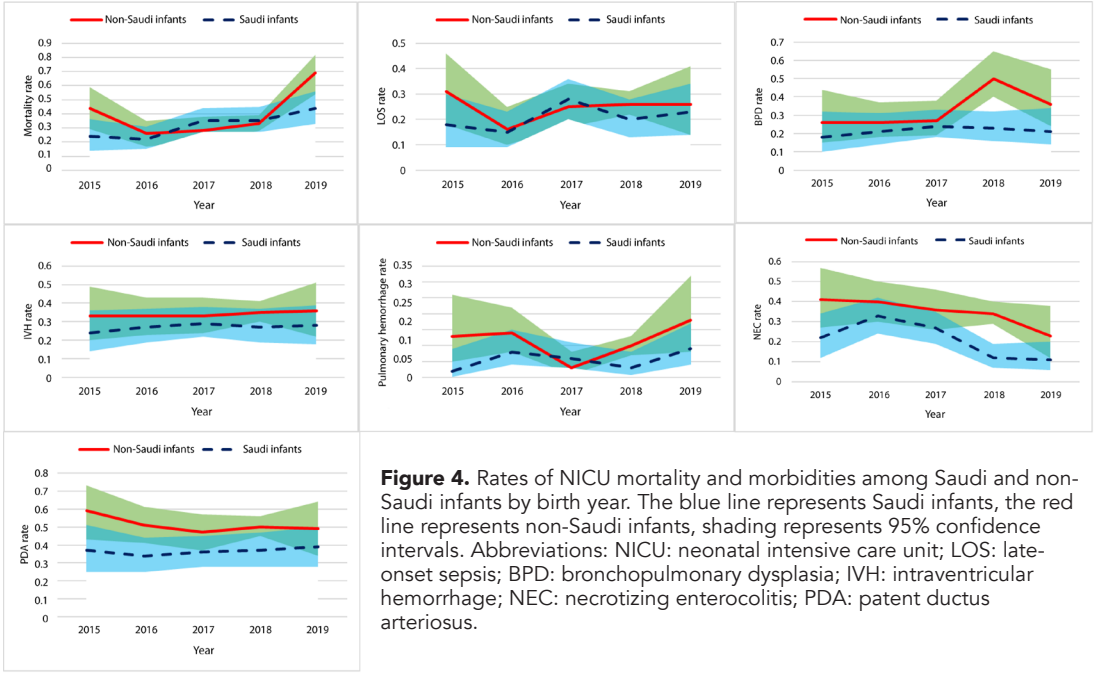

Figure 4. Rates of NICU mortality and morbidities among Saudi and non-Saudi infants by birth year. The blue line represents Saudi infants, the red line represents non-Saudi infants, shading represents 95% confidence intervals. Abbreviations: NICU: neonatal intensive care unit; LOS: late-onset sepsis; BPD: bronchopulmonary dysplasia; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus.

rates of neonatal morbidities including IVH, BPD, presence of PDA, and NEC remained higher for non-Saudi infants throughout the study period. However, the rate for NEC decreased over the last year (**Figure 4**). However, there were no significant differences in mortality rate, EOS, LOS, NEC surgical, and treatment of PDA between Saudi and non-Saudi neonates.

DISCUSSION

In our study, we reviewed 755 premature infants who were less than or equal to 32 weeks' gestation, and admitted at our unit over 5 years. We found that there were disparities in certain neonatal outcomes between Saudi and non-Saudi premature infants. Compared with non-Saudi mothers, Saudi mothers had more booking dates and received more antenatal steroids; their infants developed less IVH, PDA, pulmonary hemorrhage, BPD, and NEC. Non-Saudi infants received more EBM, stayed longer on non-mechanical ventilation, and stayed longer in the hospital, with no differences in EOS and LOS rates.

The rate of antenatal care among Saudi mothers, though suboptimal, was significantly higher than among non-Saudis over the 5 years, from 2015 to 2019. The main reason is that the majority of pregnant non-Saudi mothers cannot be followed up at the government health facilities for free, because they are not eligible; therefore, they resort to private medical centers that might have a different quality of care. It is conceivable that pregnant non-Saudi mothers may go to private clinics where the cost of care is high and later decide to go to the government health facilities to continue with their follow-up plan, which they then pay for.

Although the rate of antenatal care was higher

Table 3. Differences in infant mortality and morbidity outcomes among Saudi versus non-Saudi infants (n=755).

	Saudi (n=437)	Non-Saudi (n=318)	*P* value
Mortality	142 (32.5)	106 (33.3)	.81
Bronchopulmonary dysplasia	96 (22)	102 (32.1)	**.002**
Pneumothorax	27 (6.2)	19 (6)	.999
Pulmonary hemorrhage	25 (5.7)	31 (9.7)	**.04**
Seizure	52 (11.9)	41 (12.9)	.74
Retinopathy of prematurity	20 (4.8)	12 (3.8)	.71
Intraventricular hemorrhage	120 (27.6)	112 (35.2)	**.03**
Severe Intraventricular hemorrhage	58 (13.3)	52 (16.3)	.25
Endocarditis	7 (1.6)	8 (2.5)	.43
Necrotizing enterocolitis	94 (21.5)	109 (34.3)	**<.001**
Necrotizing enterocolitis, medical	74 (16.9)	92 (28.9)	**<.001**
Necrotizing enterocolitis, surgical	20 (4.6)	17 (5.3)	.73
Spontaneous perforation	5 (1.1)	1 (.3)	.41
Cholestasis	52 (11.9)	42 (13.2)	.65
Early-onset sepsis	12 (2.7)	7 (2.2)	.81
Late-onset sepsis	92 (21.1)	83 (26.1)	.12
Dysmorphic	8 (1.8)	7 (2.2)	.79
Patent ductus arteriosus	159 (50)	159 (63.4)	**<.001**
Patent ductus arteriosus, pharmacological	20 (4.6)	25 (7.9)	.06
Congenital heart disease	3 (.9)	4 (1.3)	.46
Congenital gastrointestinal tract anomalies	3 (.7)	2 (.6)	.999

Data are number (%).

among pregnant Saudi women, antenatal steroid therapy fluctuated in the two groups over the years. This may be due to the fact that most of the pregnant Saudi women go to the hospital uncertain of their date of delivery; therefore, they may not have had sufficient time to have received the antenatal steroid treatment. However, overall, the Saudi women were more likely to receive antenatal steroids than the non-Saudis.

With regards to respiratory diseases, a recent systematic review reported that the premature infants who were exposed antenatally to corticosteroids therapy developed respiratory distress syndrome less frequently than others, without alteration in the BPD rate.[15] Our study showed no differences in invasive ventilator use and surfactant application. However, there was a significantly lower BPD rate in Saudi infants. Although BPD is multifactorial, there was no difference in the gestational age, birthweight, invasive ventilation use, surfactant application rate, EOS, and LOS. Therefore, this difference in BPD rate may be attributed to genetic factors. Genetic factors in Saudi populations potentially contribute to determining the BPD rate in premature infants; in contrast, non-Saudi infants are a more heterogeneous group. Multiple studies have shown that the treatment of BPD and its response are widely affected by gene-environment interaction.[16-18] These studies found specific links between certain genes and progressing BPD in certain races and ethnic populations.

Regarding intraventricular hemorrhage, we assessed risk factors for IVH in premature infants who were less than 32 weeks' gestation and found that antenatal steroids are among the most common factors that reduce the incidence of severe IVH.[19] However, we did not examine whether the outcome would be affected by whether the patients were Saudi or not. In this study, we found that premature Saudi infants developed IVH less frequently than non-Saudis. This may likely have occurred because their mothers were followed up by their perinatologists and were more likely to have received antenatal care including antenatal steroid therapy.

The most interesting finding was related to NEC. It was clear that premature Saudi infants developed NEC less frequently than non-Saudis, although they received less EBM. A new meta-analysis concluded that any volume of human milk is better than formula milk in reducing the rate of NEC among premature infants.[20] The main cause of the higher NEC rate among non-Saudi patients despite the high rate of EBM feeding among them is unknown. However, this high rate of NEC was associated with a high rate of PDA, IVH, PICC line, and prolonged hospital stay. Information was not available on the quantity of EBM for the two groups. Interestingly, when we considered the rate of NEC and EBM use over the years for both groups, we found that there was an inverse relationship between the two. Furthermore, the cumulative incidence curve of NEC among non-Saudis showed a steeper decline (from 41% to 23%) from 2015 to 2019 compared to that among Saudi patients (from 22% to 11%).

Although there are significant disparities between the two groups in most of the important neonatal morbidities, there was no significant difference in mortality rates. There are several possible explanations for this. First, there were no differences in the gestational age, birthweight, and the rates of EOS and LOS between the two groups; it is known that these factors play a crucial role in determining the neonatal mortality rate. In addition, although premature Saudi infants had a lower cumulative incidence of RDS, IVH, and BPD, they showed less tendency toward reducing the NEC rate and received less EBM than non-Saudis. This could have created some sort of balance between the two groups.

This study highlighted the neonatal morbidity and mortality rates in Saudi and non-Saudi premature infants. It is important to identify the risk factors for each group so that appropriate measures can be taken to minimize potential complications. We recommend improving evidence-based practices through quality improvement projects, as these initiatives improve neonatal care and reduce the morbidity rate.[21-23] Initiatives involve emphasizing antenatal care for both Saudi and non-Saudi mothers and educating pregnant women that antenatal care is not only for the monitoring of their conception, but also for addressing the high-risk factors that negatively affect their babies. It also involves encouragement of both groups of mothers to provide breast milk and apply kangaroo care for their babies.[24,25] We recommend several measures to reduce the rate of BPD, such as the implementation of clear guidelines on applying early continuous positive airway pressure for avoiding intubation, optimizing caffeine administration, gentle ventilation, and reducing the duration of mechanical ventilation.[26] Most private sector organizations provide basic healthcare coverage for their employees through private insurance companies. Many insurance companies follow inconsistent policies towards Saudi and non-Saudi patients. We recommend modifying the insurance policy to cover emergency medical cases of pregnant women, regardless of whether they are Saudi or non-Saudi, especially in the private sector.

One limitation of our study was that it was a retrospective cohort study that only analyzed the premature infants who were born in our center. However, ours is the only center in the central region of the country that

receives a large number of pregnant non-Saudi mothers for delivery; therefore, we can generalize the results to a large extent. Furthermore, we could not determine any socioeconomic disparities between the two groups, which could have played an essential role in determining the outcome. The strength of our study is that it is, to our knowledge, the first report in Saudi Arabia to show the potential disparities in neonatal outcomes between Saudi and non-Saudi premature infants. In conclusion, we found that between 2015 and 2019, compared with non-Saudis, pregnant Saudi women were more likely to be followed up antenatally and their premature infants had lower rates of RDS, IVH, PDA, NEC, and BPD without differences in the mortality rates. These disparities emphasize the need to improve the quality of antenatal and neonatal care.

Ethical Approval

This study was approved (Reference number H1RI-21-Dec17-01) by the institutional review board of the hospital.

Competing interests

No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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