Short-term outcomes of inborn v. outborn very-low-birth-weight neonates (<1 500 g) in the neonatal nursery at Groote Schuur Hospital, Cape Town, South Africa

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Background. The Groote Schuur Hospital (GSH) neonatal nursery provides level 3 care for the Metro West Health District in the Western Cape Province of South Africa. Worldwide, very-low-birth-weight (VLBW) neonates delivered in level 3 neonatal units have better outcomes than those transported from other facilities.

Objectives. To identify the characteristics and outcomes of VLBW neonates at GSH, with emphasis on differences between inborns and outborns.

Methods. This was a retrospective cohort study. VLBW neonates admitted to the GSH neonatal nursery between 1 January 2012 and 31 December 2013 were enrolled on the Vermont Oxford Network database and reviewed.

Results. Of 1 032 VLBW neonates enrolled, 906 (87.8%) were delivered at GSH and 126 (12.2%) were outborn. Access to antenatal care, antenatal steroids and inborn status were statistically significant predictors of mortality and survival without morbidity. The mothers of inborn patients were more likely than those of outborn patients to have received antenatal care (89.1% v. 57.9%; $p<0.0001$) and antenatal steroids (64.2% v. 15.2%; $p<0.0001$). Inborns required less ventilatory support (16.2% v. 57.9%; $p<0.0001$) and surfactant administration than outborns (25.3% v. 65.1%; $p<0.0001$), and developed less late infection (8.8% v. 23.4%; $p<0.0001$), severe intraventricular haemorrhage (3.7% v. 13.9%; $p<0.0001$) and chronic lung disease (5.3% v. 13.4%; $p=0.003$). The incidence of necrotising enterocolitis was similar in the two groups (5.9% v. 8.7%; $p=0.227$). The mortality rate was 18.4% for inborns and 33.3% for outborns ($p<0.0001$). Mortality declined as birth weight increased. Of the survivors, 85.0% of inborns and 70.2% of outborns did not develop serious morbidity ($p=0.003$).

Conclusions. VLBW neonates delivered at GSH had better outcomes than their outborn counterparts. Perinatal regionalisation is beneficial to our patients, with antenatal care, timeous transfer *in utero* and antenatal steroids contributing to excellent outcomes.

S Afr Med J 2017;107(10):900-903. DOI:10.7196/SAMJ.2017.v107i10.12463

The 75-bed Groote Schuur Hospital (GSH) neonatal nursery admits >2 000 neonates per year, ~500 of whom are of very low birth weight (VLBW). The neonatal nursery offers intensive care facilities, with 8 beds for invasive ventilation and 12 beds with non-invasive ventilatory facilities. It provides level 3 specialist care to the Metro West Health District in the Western Cape Province, South Africa (SA). Level 2 care is provided by Mowbray Maternity Hospital and New Somerset Hospital, and level 1 care by several midwife obstetric units and district hospitals.

Outborn neonates tend to be less mature and more ill than their inborn counterparts.[1] It is recognised that optimising maternal conditions, transfer *in utero* and delivery at level 3 centres contribute to improved perinatal outcomes for premature neonates.[2] Based on the literature, the place of delivery policy in the Metro West was revised and implemented in May 2012.

Before May 2012, place of delivery was based on maternal condition, resulting in many infants requiring tertiary care being born to low-risk mothers in level 1 and 2 units. The new policy stipulates that threatened preterm deliveries at 26 - 30 weeks, or with an expected birth weight of 700 - 1 200 g, be transferred to the perinatal service at GSH. Although transfer *in utero* is preferred, infants delivered at level 1 units within the referral network weighing 700 - 1 200 g should also be transferred to the GSH nursery. Deliveries of infants weighing <700 g or at <26 weeks' gestation are discussed with the consultant prior to transfer, and mothers of infants with an anticipated gestational age of at least 30 weeks, or expected to weigh ≥1 200 g, are referred to level 2 hospitals prior to delivery.

The initial resuscitation and stabilisation of preterm infants after delivery affects their morbidity and mortality,[3] and it has been suggested that some outborn preterm infants die shortly after delivery or before transport to a level 3 facility can be arranged.[4] Those who are transported by less experienced teams and over greater distances have also been found to have poorer physiological outcomes.[5]

Maternal social and behavioural factors play a role in location of delivery.[4] Lack of antenatal steroids has been associated with lack of prenatal care and outborn status,[6] and all are statistically significant factors contributing to mortality.[7] The administration of antenatal steroids seems to be of more significance than outborn status itself,[8] and can be an independent predictor of outcome.[9]

In a Canadian study enrolling >6 000 premature neonates, 37% survived without serious morbidities. Predictors for morbidity included lower gestational age, physiological condition on admission, outborn status, prenatal steroids, ventilatory support and surfactant administration on day 1 of life.[9]

A meta-analysis of literature between 1976 and 2010, with a total study population of 104 944 patients, showed an overall odds ratio of 1.62 of mortality for VLBW neonates born outside level 3 facilities. When the analysis was restricted to nine high-quality articles, enrolling a total of 46 318 patients, a 60% increase in the odds of mortality was still demonstrated in the outborn population. Five

studies documenting the mortality of extremely-low-birth-weight (ELBW) neonates, weighing <1 000 g, were combined (N=13 093) and showed an 80% increased risk of mortality in outborns. Despite the 35-year span of the analysis, the association between place of delivery and mortality did not change over time.[10]

Objectives

To identify the characteristics of the VLBW neonates admitted to the GSH neonatal nursery, with emphasis on the differences in outcomes between inborn and outborn patients, and identify focus areas for improvement of these outcomes.

Methods

This was a retrospective cohort study of neonates weighing ≤1 500 g admitted to the GSH nursery between 1 January 2012 and 31 December 2013, and subsequently enrolled in the Vermont Oxford Network (VON) database. A database analysis was performed.

Data were collected using the VON data capture form, and stored on the VON database. Definitions used were based on those specified by the VON database.

The VON database comprises >1 000 neonatal units worldwide. Established in 1988, this non-profit organisation aims to improve the quality of care of premature neonates through research and quality improvement projects. The GSH neonatal nursery became a member in 2012, and submits data on >500 patients per year. Data are collected by medical officers and registrars working in the unit by means of a standardised data collection sheet, and verified by an overseeing consultant who enters the data into the password-protected database.

Ethical considerations

Each patient is allocated a number on the database to maintain confidentiality, and the data are stored in a password-protected database only accessible to registered users. The hard copies of the capture forms are stored in a lockable cupboard accessible only to investigators. As the study was retrospective, informed consent was not required from the parents of participants.

Ethical approval was granted by the Human Research Ethics Committee of the University of Cape Town Faculty of Health Sciences on 19 November 2014 (ref. no. 853/2014), and permission to conduct the research was granted by the CEO of GSH.

Data analysis

Data were captured manually using the VON data capture form, and entered into the VON database. Relevant parameters were documented on an Excel 2013 spreadsheet (Microsoft, USA) and analysed using SPSS software (IBM, USA).

Wilcoxon rank-sum tests were used to compare the distributions of gestational age and weight between in- and outborn infants (skewed continuous valued variables) and χ^2 tests of association to determine whether there was any association between birth location and various categorical variables. Significance was assessed at the 5% level.

Results

Study cohort

Of a total of 1 032 infants enrolled, 906 (87.8%) were delivered at GSH and 126 (12.2%) were outborn, i.e. delivered outside GSH and transported to our facility.

Maternal characteristics

Of mothers of inborn infants, 89.1% had received antenatal care, compared with 57.9% of mothers of outborn infants (p<0.0001); 64.2% and 15.2%, respectively, had received antenatal steroids (p<0.0001). The provision of antenatal care and antenatal steroids were statistically significant factors predicting survival without morbidity and mortality.

Of the mothers at GSH, 54.6% were treated for hypertension, compared with 3.2% of mothers from other centres (p<0.0001). This finding is in keeping with the fact that hypertensive pregnant women in the Metro West area are referred for specialist care at GSH. Of inborn deliveries, 74.1% were via caesarean section, compared with 17.5% of outborn deliveries (p<0.0001). The outborn caesarean section deliveries took place at level 2 hospitals.

Chorioamnionitis was reported in 6.4% of inborns and 7.5% of outborns. Data were missing for 39 patients (3.8% of the cohort). This finding was not statistically significant (p=0.659).

Infant characteristics

During their admission at GSH, 16.2% of inborn neonates and 57.9% of outborns received invasive ventilation (p<0.0001). Clinically unstable neonates may be intubated and ventilated for ambulance transfer, accounting for part of the large proportion of ventilated outborns.

Endogenous surfactant was needed by 25.3% of inborns, compared with 65.1% of outborns (p<0.0001).

Fifty-one infants (4.9%) did not have documented temperatures within 1 hour of admission. Of the remainder, 44.4% of inborns and 40.8% of outborns were hypothermic on admission (p=0.465). This is recognised as a problem, and has subsequently been addressed by increasing the temperature in operating theatres where caesarean sections are performed.

Outcomes

Culture-positive late infection developed in 8.8% of inborns and 23.4% of outborns (p<0.0001), and 5.9% of inborns and 8.7% of outborns developed clinical and radiological necrotising enterocolitis. The difference was not statistically significant (p=0.227).

One hundred and forty infants (13.6%) did not have a cranial ultrasound scan in the first 28 days of life. Many died before a scan could be done, or were transferred to another facility before they were scanned. Of those who did have an ultrasound scan, 3.7% of inborns and 13.9% of outborns were found to have severe (grade 3 or 4) intraventricular haemorrhage (IVH) (p<0.0001).

Of the infants who survived to discharge, 2.0% of inborns and 6.3% of outborns had severe IVH (p=0.039). In the cohort who died, 17.2% of inborns and 35.7% of outborns who had cranial ultrasound scans before their death were found to have severe IVH (p=0.02).

Of the infants who survived to discharge, 5.3% of inborns and 14.1% of outborns developed chronic lung disease (p=0.003), which was calculated by an algorithm used by the VON database based on oxygen requirement at 36 weeks' corrected gestational age and/or 28 days of life.

Survival without serious morbidity, as defined by VON, indicated that the patient survived to discharge without developing severe IVH, periventricular leucomalacia, chronic lung disease, necrotising enterocolitis or any late infection; 85.0% of inborn and 70.2% of outborn survivors did not develop serious morbidity (p=0.003), with increased weight being associated with improved outcomes (Fig. 1). Access to antenatal care, antenatal steroids and inborn status were predictive of survival without morbidity (p<0.0001).

Of the total cohort, 18.4% of inborns and 33.3% of outborns died (p<0.0001), mostly in the first 2 days after admission. In the cohort weighing ≤800 g, 53.6% of inborns and 87.5% of outborns died. For infants weighing >800 g, the mortality of inborns and outborns was comparable, with a significant decrease in mortality with increasing

birth weight (Fig. 2). Predictors of mortality included antenatal steroids and birth location ($p<0.0001$), as well as antenatal care ($p=0.004$).

The above outcomes are summarised in Table 1.

Discussion

The concept of perinatal regionalisation was initially proposed in the USA in 1976, in the March of Dimes publication 'Towards improving the outcome of pregnancy'.[10] It recommended that at-risk premature infants be delivered in level 3 hospitals with specialised perinatal services, and implementation of the model showed improvements in neonatal mortality rates throughout the USA. Over the past few decades, the outcomes of VLBW and ELBW neonates have improved significantly, particularly since the introduction of exogenous surfactant therapy in 1990[11] and the increased administration of antenatal steroids since the mid-1990s.[8,9] However, delivery outside a level 3 centre has remained a poor prognostic factor, largely as a result of less skilled resuscitation and initial care of premature neonates[3] and the fact that outborn mothers are less likely to have received antenatal care and steroids.[6]

In May 2012, the Metro West Health District adopted a policy of perinatal regionalisation, aiming to increase *in utero* transfer of premature infants to our level 3 unit for delivery. Unfortunately, many deliveries still take place at level 1 and 2 units, and the neonates are subsequently transferred to the GSH nursery for continued specialised care. Of the 1 032 patients recruited to this study, 87.8% were born at GSH and 12.2% were transferred in from other facilities.

In keeping with the literature, and reflecting the findings of SA case-controlled studies of preterm neonates born before arrival in KwaZulu-Natal Province[12] and Johannesburg,[13] compared with mothers of inborn infants, fewer of our mothers of outborn infants received antenatal care. They were also less likely to receive timeous antenatal steroids, which play a significant role in improving lung maturity and thus decreasing the development of chronic lung disease, as well as being protective against IVH.[14] The consequences of not receiving antenatal steroids were evident in our cohort, with outborn neonates requiring more exogenous surfactant, and having a higher incidence of chronic lung disease and severe IVH, than their inborn counterparts.

Neonates weighing ≥800 g are eligible for invasive ventilatory support at the GSH nursery. Clinically unstable neonates are often intubated by inexperienced staff and ventilated for ambulance transfer, accounting for part of the large number of ventilated outborn infants. Not only is intubation and ventilation difficult, risky and costly, but it also increases the risk of hypotension and the need for surfactant[15] (another expensive procedure), as well as the risk of

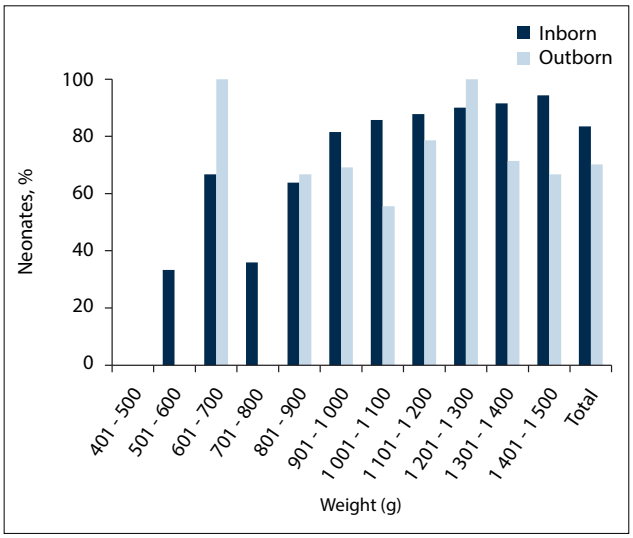

Fig. 1. Survival without morbidity of inborn v. outborn neonates at Groote Schuur Hospital.

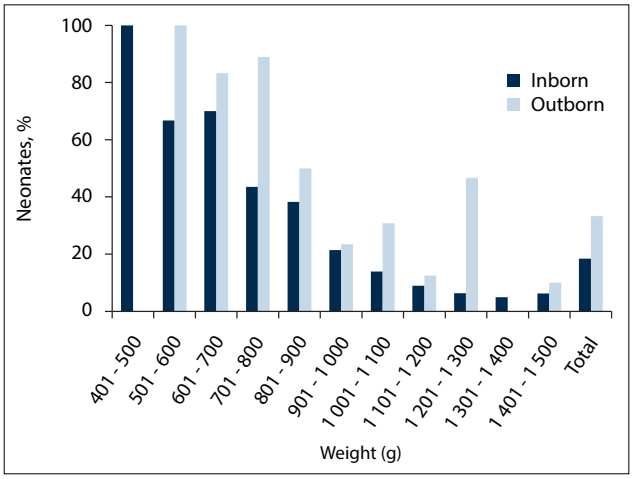

Fig. 2. Mortality of inborn v. outborn neonates at Groote Schuur Hospital.

Table 1. Summary of results

	Inborn, *n* (%)	Outborn, *n* (%)	*p*-value
Antenatal care	807/906 (89.1)	73/126 (57.9)	<0.0001
Steroids	582/906 (64.2)	19/126 (15.2)	<0.0001
Hypertension	495/906 (54.6)	4/126 (3.2)	<0.0001
Chorioamnionitis	57/887 (6.4)	8/106 (7.5)	0.659
Caesarean section	671/906 (74.1)	22/126 (17.5)	<0.0001
Ventilation	143/893 (16.2)	73/126 (57.9)	<0.0001
Surfactant	229/906 (25.3)	73/126 (65.1)	<0.0001
Hypothermia	382/860 (44.4)	49/120 (40.8)	0.465
Late infection	73/827 (8.8)	26/111 (23.4)	<0.0001
NEC	53/892 (5.9)	11/126 (8.7)	0.227
Severe IVH	29/784 (3.7)	15/109 (13.9)	<0.0001
Chronic lung disease	41/747 (5.3)	12/85 (13.4)	0.003
Survival without morbidity	628/739 (85.0)	59/84 (70.2)	0.003
Mortality	167/906 (18.4)	42/126 (33.3)	<0.0001

NEC = necrotising enterocolitis; IVH = intraventricular haemorrhage.

developing severe IVH and nosocomial sepsis.[16] Inborn neonates admitted directly to the GSH nursery have immediate access to non-invasive respiratory support, primarily continuous positive airway pressure (CPAP) ventilation, which is associated with fewer adverse events, decreased surfactant requirements and potentially a decreased incidence of chronic lung disease.[15]

In a resource-limited setting such as ours, it is particularly important that patients who survive do so with no morbidity, especially with regard to respiratory and neurodevelopmental outcomes. In comparison with the Canadian Neonatal Network database, our cohort had a higher rate of survival without morbidity (82% v. 37%), but at the cost of higher mortality (20% v. 10%).[9] Access to antenatal care, antenatal steroids and inborn status were independent predictors of mortality and survival without morbidity.

An increased birth weight was associated with improved survival and outcomes, with outborn infants weighing >800 g having outcomes comparable with their inborn counterparts. In the group weighing ≤800 g, however, inborns fared far better; 53.6% of inborns weighing <800 g died, compared with 87.5% of outborns. Of the two outborn patients weighing <800 g who survived, only one did so without developing serious morbidity.

Most of the neonates who died did so in the first 2 days after admission. When outborn infants are transferred to level 3 care, they are often separated from their mothers, sometimes for several days. In the sub-800 g group this is particularly traumatic, as these babies often die before being reunited with their parents. Given the high cost of transport and treatment for these patients, the emotional burden on their families and their ultimate poor outcome, we recommend a revision of the current referral protocol. These babies may benefit from remaining with their mothers, with specialist advice provided telephonically to the centres caring for them, adequate counselling of their families, and a 'comfort care' or palliative care approach being taken to ensure that they are treated with dignity during the hours or days they are alive.

Study strengths and limitations

The large sample size was a strength and advantage. We were limited by the fact that this was a retrospective study. Also, as the VON is an international entity, locally relevant factors such as maternal HIV status and congenital infections were not routinely recorded.

Conclusions and recommendations

This study has demonstrated that perinatal regionalisation is beneficial to our patients, with timeous identification of at-risk pregnancies, administration of antenatal steroids and *in utero* transfer to level 3 care leading to excellent outcomes. Despite the referral protocol in place, many high-risk VLBW and ELBW deliveries still do not take place at GSH. We must continue to strive to strengthen regionalisation to ensure that more premature infants are delivered at appropriate facilities.

We also recommend allocation of resources to the training of midwives, ambulance staff and paramedics on resuscitation and early management of VLBW neonates who are delivered outside level 3 care to improve their ultimate outcomes.

The Western Cape Province Department of Health Decision Support Framework was revised in February 2017. Neonates with a gestational age of <27 weeks or weighing 500 - 650 g are only eligible for CPAP if inborn but may not receive surfactant, with an emphasis on palliative measures. Neonates weighing 650 - 799 g may receive CPAP and one dose of surfactant if inborn, and outborns are eligible for transfer to level 3 care on a case-by-case basis. Given the high morbidity and mortality of outborn neonates in these groups, the emotional and financial costs of transfer are often not warranted. It may be more beneficial for them to remain with their mothers at level 1 and 2 facilities for the short duration of their lives, with an emphasis on comfort care. Those who are still clinically stable beyond the first day of life may be considered for transfer after discussion with a senior clinician at a level 3 hospital.

Training and support of staff at level 1 and 2 facilities regarding resuscitation and management of extremely premature neonates, counselling of their families and provision of appropriate palliative care may prove extremely beneficial, not only to the patients affected but to the overburdened system as a whole.

Acknowledgements. None.

Author contributions. MCH acted as academic supervisor of the MMed project on which this article is based. He conceptualised the project, designed the questions and provided support with data interpretation, analysis of the work, and completion of the thesis and subsequent article. Each step of the process was directly overseen by him. LT oversees the VON database at GSH. He aided with the design of the project, as well as the acquisition and analysis of data. He reviewed the data presented in the thesis and article, and contributed significantly to the final article. LG embarked on this project as an MMed thesis, forming part of her paediatrics qualification. She worked with MCH and LT on the design and conceptualisation of the article. She collected data for the VON database in 2012 and 2013, and used these data for her article. Interpretation of the data was primarily done by her, and the article is her own work.

Funding. None.

Conflicts of interest. None.

1. Chien L, Whyte R, Aziz K, Thiessen P, Matthew D, Lee SK. Improved outcome of preterm infants when delivered in tertiary care centres. Obstet Gynecol 2001;98(2):247-252. https://doi.org/10.1097/00006250-200108000-00012
2. Yeast JD, Poskin M, Stockbauer JW, Shaffer S. Changing patterns in regionalization of perinatal care and the impact on neonatal mortality. Am J Obstet Gynecol 1998;178(1):131-135. https://doi.org/10.1016/s0002-9378(98)70639-8
3. Lorch S, Baiocchi M, Ahlberg CE, Small DS. The differential impact of delivery hospital on the outcomes of premature infants. Pediatrics 2012;130(2):270-278. https://doi.org/10.1542/peds.2011-2820
4. Dooley SL, Freels SA, Turnock BJ. Quality assessment of perinatal regionalization by multivariate analysis: Illinois, 1991-1993. Obstet Gynecol 1997;89(2):193-198. https://doi.org/10.1016/s0002-9378(97)80473-5
5. Eliason SHY, Whyte H, Dow K, Cronin CM. Variations in transport outcomes of outborn infants among Canadian neonatal intensive care units. Am J Perinatol 2013;30(5):377-382. https://doi.org/10.1055/s-0032-1324706
6. Chien L, Ohlsson A, Seshia MMK, et al. Variations in antenatal corticosteroid therapy: A persistent problem despite 30 years of evidence. Obstet Gynecol 2002;99(3):401-408. https://doi.org/10.1097/00006250-200203000-00007
7. Moro M, Figueras-Aloy J, Fernández C, et al. Mortality for newborns of birthweight less than 1500 g in Spanish neonatal units (2002 - 2005). Am J Perinatol 2007;24(10):593-601. https://doi.org/10.1055/s-2007-992175
8. Palmer KG, Kronsberg SS, Barton BA, Hobbs CA, Hall RW, Anand KJS. Effect of inborn versus outborn delivery on clinical outcomes in ventilated preterm neonates: Secondary results from the NEOPAIN Trial. J Perinatol 2005;25:270-275. https://doi.org/10.1038/sj.jp.7211239
9. Ge WJ, Mirea L, Yang J, Bassil KL, Lee SK, Shah PS. Prediction of neonatal outcomes in extremely preterm neonates. Pediatrics 2013;132(4):e876-e885. https://doi.org/10.1542/peds.2013-0702
10. Lasswell S, Barfield W. Perinatal regionalization for very low-birth-weight and very preterm infants: A meta-analysis. JAMA 2010;304(9):992-1000. https://doi.org/10.1001/jama.2010.1226
11. Boo N-Y, Neonatal Data Collection Group. Outcome of inborn compared with outborn very low birth weight infants admitted to level 3 Malaysian nurseries. Med J Malaysia 1995;50(1):42-51.
12. Parag N, McKerrow NH, Naby F. Profile of babies born before arrival at hospital in a peri-urban setting. S Afr J Child Health 2014;8(2):45-49. https://doi.org/10.7196/SAJCH.681
13. Bassingthwaighte MK, Ballot DE. Outcomes of babies born before arrival at a tertiary hospital in Johannesburg, South Africa. S Afr J Child Health 2013;7(4):139-145. https://doi.org/10.7196/SAJCH.671
14. Arad I, Gofin R, Baras M, Bar-Oz B, Peleg O, Epstein L. Neonatal outcome of inborn and transported very-low-birth-weight infants: Relevance of perinatal factors. Eur J Obstet Gynecol Reprod Biol 1999;83(2):151-157. https://doi.org/10.1016/s0301-2115(98)00336-4
15. Levesque BM, Kalish LA, LaPierre J, Welch M, Porter V. Impact of implementing 5 potentially better respiratory practices on neonatal outcomes and costs. Pediatrics 2011;128(1):e218-e226. https://doi.org/10.1542/peds.2010-3265
16. Aziz K, McMillan DD, Andrews W, et al. Variations in rates of nosocomial infection among Canadian neonatal intensive care units may be practice-related. BMC Pediatr 2005;5:22. https://doi.org/10.1186/1471-2431-5-22

Accepted 30 May 2017.