

Readmission of Preterm Infants Less Than 32 Weeks Gestation Into Early Childhood: Does Gender Difference Still Play a Role?

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Ralser Elisabeth, MD¹, Griesmaier Elke, MD, PHD¹, Neubauer Vera, MD¹,
Gnigler Maria, MD¹, Höck Michaela, MD¹,
and Kiechl-Kohlendorfer Ursula, MD, MSc¹

Abstract

The aim of the study was to investigate the frequency of and the predictors for rehospitalization in preterm infants into early childhood, focusing on gender differences. All preterm infants born at <32 weeks of gestation in North Tyrol between January 2003 and December 2005 were enrolled in this survey. About one fifth of all children were readmitted, showing an inverse downward trend with increasing age. The most common reason for readmission in the third (36.5%) and fourth (42.9%) years of life was respiratory infection, but changed to miscellaneous surgeries in the fifth (52.1%). Male sex showed significantly higher readmission rates and more miscellaneous surgeries. Additionally, male sex and chronic lung disease were risk conditions for rehospitalization in the multivariate analysis. Readmission rates and respiratory infections in preterm-born children showed an inverse downward trend with increasing age. In early childhood, gender difference still plays a role with regard to rehospitalization.

Keywords

hospital readmission, male sex, preterm infants, rehospitalization, respiratory infection

Introduction

During the past decades, quality in perinatal and neonatal care was enhanced as diagnostic methods, treatment, and prophylactic therapy advanced. Therefore, it is not surprising that the survival rate of preterm infants, particularly those born at <32 weeks gestational age (GA), is rising.^{1,2} However, long-term morbidity, including respiratory problems and rehospitalization, is still of great concern.^{3–5}

In the 1970s, Naeye et al⁶ already postulated the hypothesis of the “disadvantaged male,” in which they explained the increased perinatal morbidity of boys as compared to girls. Various other studies confirmed the fact that male infants are more frequently born preterm; suffer more often from respiratory distress syndrome, chronic lung disease (CLD), intracerebral hemorrhage (ICH), and necrotizing enterocolitis (NEC); and show an increased risk for adverse neurodevelopmental outcome and rehospitalisation.^{5,7} Male term-born children were also admitted more frequently to hospitals for respiratory infections⁸ or atopic asthma⁹ than are female children in various age groups up to 15 years. In a similar study

cohort of preterm infants, we have already shown a higher readmission rate in boys compared to girls during the first 2 years of life, but no differences between boys and girls were seen regarding neurodevelopmental outcome at the ages of 12 or 24 months.¹⁰

Previous studies also described risk predictors for readmission in general. However, most studies focused on health care costs,^{11,12} and only a few studies included sociodemographic data.^{5,13,14} The majority of the studies were conducted 20 to 30 years ago.^{15–18} Meanwhile, surfactant treatment, antenatal steroids, and deliberate ventilation are established procedures in neonatology and may have influenced outcome and readmission rates. It is proven that preterm infants have higher admission rates in the first year of life¹⁹ and more often suffer from

¹Department of Paediatrics II, Division of Neonatology, Innsbruck Medical University, Innsbruck, Austria

Corresponding Author:

Elisabeth Ralser, MD, Department of Paediatrics II, Division of Neonatology, Innsbruck Medical University, Anichstrasse 35, 6020 Innsbruck, Austria.
Email: elisabeth.ralser@i-med.ac.at.



respiratory infections^{15,17,20,21} leading to admission, whereas information on causes and risk conditions, specifically on gender differences, in later life needs further research.

This study investigated the incidence of and risk predictors for medical care as inpatients between the third and the fifth years of life in our study population of preterm infants born at <32 weeks gestation. It was conducted as a follow-up to a trial examining the rehospitalization rate and its contributing factors in the first 2 years of life in a similar cohort.²² Both surveys included participants from a defined geographic region and implied sociodemographic data in a current time frame. The present study aimed to identify changes in readmission rates into mid-childhood and the reasons for readmission, with the main focus being on gender differences.

Patients and Methods

Participants

The survey was conducted in North Tyrol, a state in western Austria with approximately 600 000 inhabitants and around 6300 live births per year. Between January 2003 and December 2005, all infants born before 32 weeks GA in this area were transferred to the neonatal intensive care unit (NICU) of the Department of Paediatrics of Innsbruck Medical University for further treatment and were prospectively enrolled. GA was calculated from the first day of the last menstrual period. This was compared with assessments of ultrasound scans. If the examination methods differed, the scan result was given preference. In Innsbruck, preterm infants were discharged when they were able to feed satisfactorily, while showing appropriate weight gain and did not show any desaturation or bradycardia for at least 5 days.

Data Collection

Sociodemographic data included maternal age (<23 years vs ≥ 23 years), maternal years of education (<12 years vs ≥ 12 years), smoking in pregnancy, siblings, antenatal steroid use, mode of delivery, multiple pregnancies, sex, birth weight (g), GA (full weeks), small for gestational age (SGA), postnatal surfactant treatment, and diagnosis of ICH, CLD, NEC, or infection. Antenatal steroids were deemed “yes” if even only one dosage was administered. Smoking habits in pregnancy were based on self-reported data. Those mothers who refused to provide information on their smoking status were considered smokers. SGA was defined as birth weight under the 10th percentile for sex and age, taking the growth charts of Alexander et al.²³ into account. ICH

was classified by the method of Papile et al.²⁴ Head ultrasound examinations were routinely performed on days 2 and 5 of life, thereafter weekly, and after 1 month every second or third week. CLD was defined as oxygen dependence at 36 weeks GA. NEC was defined according to Bell’s criteria²⁵ and was diagnosed either clinically (distended abdomen, bloody stool, and septic appearance plus evidence of pneumatosis intestinalis on abdominal X-ray or abdominal ultrasonography) or surgically (histologic proof of NEC in intestinal specimen). A diagnosis of early-onset (≤ 72 hours after delivery) or late-onset (≥ 72 hours after delivery) sepsis required signs of generalized infection, positive blood culture, and antibiotic therapy for 5 days or more.

Rehospitalization was defined as admission to any of the 5 hospitals with a pediatric department in North Tyrol from the second up to the fifth birthday. Rehospitalization data were obtained retrospectively from the computer databases of all children’s hospitals in the study area. Information on age (without correction for prematurity), diagnosis (according to ICD10), treatment, number of readmissions, duration of stay, and transfer to the pediatric intensive care unit (PICU) for each readmission was recorded. Diagnoses were divided into the following categories: respiratory infection (including acute infections of the upper airways, acute and chronic infections of the lower airways, pneumonia, other respiratory conditions), gastrointestinal disorder (including gastrointestinal infections, feeding problems, failure to thrive, and obstipation), other infection (other than respiratory or gastrointestinal, for example, urinary tract infection, other viral or bacterial infection), inguinal hernia repair, miscellaneous operation (including phimosis, orchidopexy, repair of hypospadias, vesicoureteral reflux or ventriculo-peritoneal shunt, adenoidectomy, paracentesis), disorders and injuries of the central nervous system (convulsions, cerebral concussion, head contusion, neurodegenerative disorders), diagnostic investigation and other diagnoses (endocrinologic disorders, animal bites, other genitourinary conditions, and other ear, nose, or throat conditions). Visits to outpatient clinics, physiotherapists, speech therapists, and other medical or social support were not included in the present study.

Statistical Analysis

Data analysis was performed using SPSS software, version 20.0 for Windows (SPSS Inc, Chicago, IL). Comparison of categorical data was made using the χ^2 or Fisher’s exact test as appropriate. Multivariate risk profiles for rehospitalization between the third and fifth years of life were computed by means of logistic regression analysis using a stepwise forward selection

Table 1. Rehospitalization According to Diagnosis Between the Third and the Fifth Years of Life.

Diagnosis	Third Year of Life (N = 50), n (%)	Fourth Year of Life (N = 44), n (%)	Fifth Year of Life (N = 32), n (%)
Respiratory infection	16 (32.0)	15 (34.1)	7 (21.9)
Gastrointestinal disorder	7 (14.0)	4 (9.1)	2 (6.3)
Infection (other than respiratory or gastrointestinal)	4 (8.0)	4 (9.1)	3 (9.4)
Inguinal hernia repair	2 (4.0)	1 (2.3)	0
Miscellaneous surgeries	11 (22.0)	15 (34.1)	13 (40.6)
CNS disorder	4 (8.0)	4 (9.1)	0
Diagnostic procedure	1 (2.0)	0	0
Other diagnosis	5 (10.0)	1 (2.3)	7 (21.9)

Abbreviations: N = number of admissions per year; CNS, central nervous system.

procedure with inclusion and exclusion criteria ($PI < 0.10$ and $PE > 0.15$).

Results

Between January 2003 and December 2005, 244 preterm infants born <32 weeks GA were admitted to the NICU at Innsbruck Medical University Hospital. Of the children 27 were not resident within the study area and had to be excluded. Furthermore, 31 preterm infants died before their fifth birthday. Thus, 186 participants were finally included in this study.

The mean GA of our cohort was 29.1 weeks (range = 23.9-31.9 weeks), and the mean birth weight was 1321 g (range = 530-2885 g).

The average length of hospital stay was 3.7 ± 2.6 (range = 1-14), 4.2 ± 2.7 (range = 1-12), and 3.9 ± 3.0 (range = 1-12) days in the third, fourth, and fifth years of life, respectively. Of all readmitted children only 2 (4.9%) in the third and 1 (2.9%) in the fourth years of life had to be transferred to the PICU. In the fifth year no child was critically ill, not needing intensive care.

Out of 186 preterm babies, 22% ($n = 41$) were rehospitalized in their third year of life: 35 patients were admitted once, 5 patients twice, and 1 patient 5 times. In the following years, 35 (18.8%) and 23 (12.4%) children were readmitted. The highest frequency of readmission was 3 and 5 times in the fourth and fifth years of life, respectively.

During the third year of life, respiratory infections were the leading reason for hospitalization (36.5%), followed by miscellaneous operations (26.8%) and gastrointestinal disorders (14.6%). A similar pattern was found throughout the fourth year of life. In the fifth year, respiratory infections lost predominance (21.7%) and miscellaneous operation became the main diagnosis leading to readmission (52.1%; Table 1).

Of the study population, 55.9% ($n = 104$) were male and 44.1% ($n = 82$) female ($P = .86$). No significant gender difference was found for sociodemographic and neonatal characteristics (Table 2). The majority of readmitted infants between the third and fifth years of life were male ($P = .003$). More males than females were admitted for respiratory infection although no significance was seen throughout the study period ($P = .12$). Of the other diagnostic groups only miscellaneous operations showed significantly higher readmission rates for males than for females ($P < .000$).

The univariate analysis of all 3 years together significantly related various risk predictors to rehospitalization: male sex ($P = .003$), CLD ($P = .02$), and NEC ($P = .04$; Table 3). The multivariate analysis using variables selected in a stepwise selection procedure showed male sex and CLD to be associated with rehospitalization between the third and the fifth years of life, respectively (odds ratio = 2.42; 95% confidence interval = 1.29-4.52; $P = .006$) and (odds ratio = 2.78; 95% confidence interval = 1.08-7.14; $P = .034$).

Discussion

Our study showed that in the third and fourth years of life almost one fifth of all children born <32 weeks of gestation were readmitted to a hospital, mainly because of respiratory infection. During the fifth year of life, respiratory infections were outpaced by miscellaneous surgeries as the leading reason for readmission. In contrast, during the first 2 years of life we could find a noticeable higher readmission rate of 40.1% in the first but already only 24.7% in the second year of life of a similar study population.²² This downward trend continued in the current study. Respiratory infections were the leading reason for readmission in the first 2 years too and were responsible for almost half of all hospital stays (42.1% and 47.4%, respectively).²² Boys

Table 2. Sociodemographic and Neonatal Characteristics of Preterm Infants According to Sex.

Variable	Female (N = 8), n (%)/ Mean \pm SD	Male (N = 103), n (%)/ Mean \pm SD	P Value ^a
Maternal age <23 years (vs \geq 23 years)	8 (9.6)	13 (13.1)	.50
Maternal education <12 years (vs \geq 12 years) ^b	46 (62.2)	58 (62.4)	1.00
Smoking in pregnancy yes (vs no)	18 (21.7)	32 (31.1)	.18
Siblings yes (vs no)	50 (61.0)	57 (55.3)	.46
Multiple pregnancy yes (vs no)	22 (26.5)	33 (32.0)	.43
Antenatal steroids yes (vs no)	72 (92.3)	89 (88.1)	.46
Vaginal delivery yes (vs no)	11 (13.4)	6 (5.8)	.12
Gestational age (weeks)	29.1 \pm 1.8	29.2 \pm 1.8	.86
Birth weight (g)	1296 \pm 390	1341 \pm 356	.41
SGA yes (vs no)	4 (4.9)	9 (8.7)	.39
Surfactant treatment yes (vs no)	38 (46.3)	58 (56.3)	.19
CLD yes (vs no)	7 (8.4)	15 (14.6)	.26
ICH yes (vs no)	11 (13.4)	22 (21.4)	.18
NEC yes (vs no)	5 (6.1)	12 (11.7)	.21
Early-onset sepsis yes (vs no)	2 (2.4)	2 (1.9)	1.00
Late-onset sepsis yes (vs no)	13 (15.9)	16 (15.5)	1.00

Abbreviations: SGA, small for gestational age; CLD, chronic lung disease; ICH, intracerebral hemorrhage; NEC, necrotizing enterocolitis.

^aP values are calculated from Fischer's exact test, χ^2 test, or t test, as appropriate; P values are significant if <.05.

^bMaternal education was available in 169 subjects; in all other variables, the proportion of missing data was <5%.

Table 3. Sociodemographic and Neonatal Characteristics of Preterm Infants According to Hospital Readmission Between the Third and the Fifth Years of Life.

Variable	Readmission (N = 74), n (%) / Mean \pm SD	No Readmission (N = 112), n (%) / Mean \pm SD	P Value
Maternal age <23 years (vs \geq 23 years)	6 (8.3)	15 (13.6)	.35
Maternal education <12 years (vs \geq 12 years) ^b	45 (67.2)	59 (59.0)	.33
Smoking in pregnancy yes (vs no)	20 (27.0)	30 (26.8)	1.00
Siblings yes (vs no)	44 (59.5)	63 (56.8)	.76
Multiple pregnancy yes (vs no)	22 (29.7)	33 (29.5)	1.00
Antenatal steroids yes (vs no)	65 (89.0)	96 (90.6)	.80
Vaginal delivery yes (vs no)	5 (6.8)	12 (10.8)	.44
Gestational age (weeks)	29.0 \pm 1.8	29.2 \pm 1.8	.41
Birth weight (g)	1300 \pm 372	1335 \pm 372	.53
SGA yes (vs no)	5 (6.8)	8 (7.1)	1.00
Male yes (vs no)	51 (68.9)	52 (46.4)	.003
Surfactant treatment yes (vs no)	41 (55.4)	55 (49.5)	.46
CLD yes (vs no)	14 (18.9)	8 (7.1)	.02
ICH yes (vs no)	15 (20.3)	18 (16.2)	.56
NEC yes (vs no)	11 (14.9)	6 (5.4)	.04
Early-onset sepsis yes (vs no)	2 (2.7)	2 (1.8)	1.00
Late-onset sepsis yes (vs no)	14 (18.9)	15 (13.5)	.41

Abbreviations: SGA, small for gestational age; CLD, chronic lung disease; ICH, intracerebral hemorrhage; NEC, necrotizing enterocolitis.

^aP values are calculated from Fisher's exact test, χ^2 test, or t test, as appropriate; P values are significant if <.05.

^bMaternal education was available in 169 subjects; in all other variables, the proportion of missing data was <5%.

Note. Bold indicates significant numbers.

showed a higher readmission rate than girls, with a nonsignificant trend for more respiratory infections and more admissions due to surgery. Overall, an inverse downward trend was seen in admission rates as well as admissions due to respiratory infection and rising age, which was also seen in various other surveys.^{12,26,27} Many studies have emphasized that respiratory infections are the main reason for readmission in the first years of life,^{5,26} with boys being more frequently readmitted than girls.²⁸ Selling et al²⁹ studied hospitalization in early childhood and adolescence and determined that former preterm infants still had higher admission rates than former term infants, while respiratory infections were no longer the most frequent cause. The importance of respiratory infections in childhood declines with age, most likely due to increased lung volume, larger diameter of airways, less air trapping, and decreased airway reactivity.^{4,26} However, another study showed a significant difference in FEV₁ (forced expiratory volume), FVC (forced vital capacity), and asthma or other respiratory conditions in preterm-born children as compared to term-born children leading to respiratory morbidity and rehospitalization beyond the first years of life.⁴

Even if readmission for respiratory infections declined in our current study, CLD remained a significant risk predictor for hospital readmission between the third and fifth years of life. In addition, Lamarche-Vadel et al described a significantly higher rate of readmissions due to respiratory conditions in her group of extremely preterm infants with CLD during the first 9 months of life.⁵ Moreover, CLD seems to be an attributing factor for asthma and recurrent wheezing, as well as for respiratory conditions needing rehospitalization in later life.⁴ A recent meta-analysis acknowledged the fact that all children born preterm, even those not developing CLD, show a significant reduction of FEV₁ in childhood (<18 years). The impact on health in later life and on health care systems is not quite clear yet.³⁰

In our study, male sex was determined to be significantly more compromised, as it showed more readmissions, more miscellaneous surgeries, and in general seems to be an independent risk predictor for hospital readmission. This is confirmed by other studies showing a gender difference in preterm infants with regard to respiratory conditions and readmission rates^{5,26,31} in the last 3 decades. Even male term infants suffer more often from respiratory problems than female term infants do.⁸ All this supports the opinion that male gender is far more vulnerable to immunologic disorders of the respiratory tract as respiratory infections are the number one cause of male readmission. Additionally, a large portion of miscellaneous operations are performed in the upper airways for underlying infections such as paracentesis, adenectomy, and so on. Jensen-Fangel et al⁸ observed in a

mega-study in Denmark that general-population boys were far more often rehospitalized for respiratory infection than were girls. This phenomenon was observed up to the age of 15 years, after which it reversed. One of their hypotheses was that after delayed lung maturation during the perinatal period, immune response among males might be poorer until an age where sex hormones interact positively as estrogen, progesterone, and dehydroepiandrosterone influence the secretion of several cytokines. However, to date no survey has considered gender-related immunological differences in children before puberty. Another survey¹⁵ acknowledged that surgical conditions took precedence over respiratory infections in the fifth year of life, that is, 54% versus 46%, respectively. Surgical conditions were mostly ear, nose, or throat surgeries, like in our study population.

One likely limitation of our study is a potential misclassification in the routine coding of diagnoses in readmitted children, as performed by various doctors. Furthermore, thresholds for admission might vary considerably between medical practitioners. By examining hospital admissions, this study viewed only a narrow health service area, neglecting additional health care facilities like outpatient clinics, outpatient pediatricians, social services, diverse therapies, and any form of remedial teaching.

The main strength of this 5-year follow-up study is the prospective enrolment of our study population from a well-defined geographical area, and findings may thus be considered representative, despite our limited cohort size. To our knowledge, no recent survey has investigated the general readmission rate of infants between their third and fifth years of life born <32 weeks of GA with regard to gender.

Conclusion

Admission rates and respiratory infections in preterm-born children showed an inverse downward trend with increasing age. CLD and male sex were meaningful risk predictors for later morbidity, reflecting the role of gender difference in early childhood. Neonatal intensive care should aim for further improvement of respiratory health in preterm infants, which might result in a decline of hospital readmission rates in girls as well as boys during childhood.

Declaration of Conflicting Interests

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