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ARTICLE

Improving Perinatal Regionalization by Predicting Neonatal Intensive Care Requirements of Preterm Infants: An EPIPAGE-Based Cohort Study

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ABSTRACT

OBJECTIVE. Perinatal regionalization has been organized into 3 ascending levels of care, fitting increasing degrees of pathology. Current recommendations specify that very premature infants be referred prenatally to level III facilities, yet not all very preterm neonates require level III intensive care. The objective of our study was to determine the antenatal factors that, in association with gestational age, predict the need for neonatal intensive care in preterm infants, to match the size of birth with the level of care required.

METHODS. Data were analyzed from a cohort of very preterm infants born in nine French regions in 1997. We defined the need for neonatal intensive care as follows: (1) the requirement for specialized management (mechanical ventilation for >48 hours, high frequency oscillation, or inhaled nitric oxide) or (2) poor outcome (transfer to a level III facility within the first 2 days of life or early neonatal death). Triplet pregnancies and pregnancies marked by fetal malformations or intensive care requirements for the mother before delivery were excluded.

RESULTS. We focused our study on 1262 neonates aged 30, 31 and 32 weeks' gestation, where the need for intensive care was 42.8%, 33.2%, and 22.8%, respectively. Multivariate analysis showed that the risk factors for intensive care requirement with low gestational age were twin pregnancies, maternal hypertension, antepartum hemorrhage, infection, and male gender. Antenatal steroid therapy and premature rupture of membranes were protective factors against intensive care requirement.

CONCLUSION. Infants <31 weeks' gestation should be referred to level III facilities. From 31 weeks' gestation, some infants can be safely handled in level IIb facilities. However, the quality of perinatal regionalization may only be fully assessed by long-term follow-up.

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Key Words
perinatal regionalization, NICUs, in utero transfer, very preterm, cohort study

Abbreviations
GA—gestational age
NIC—neonatal intensive care
IUGR—intrauterine growth restriction
OR—odds ratio
CI—confidence interval

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PROVIDING ADEQUATE CARE to preterm neonates is an important issue for perinatal medicine. The incidence of preterm deliveries has increased in all developed countries with quite similar trends.[1] In France, very preterm deliveries accounted for 1.9% of all pregnancies in 2003.[2] This increased incidence results from a variety of medical factors that also modify neonate adaptation to extrauterine life. Very preterm deliveries are also linked to social factors.[3]

To provide prompt and appropriate treatment to these premature infants, perinatal regionalization in France and other countries has organized care facilities in 3 ascending levels[4,5] corresponding with increasing degrees of pathology. These levels of care were well defined by the American Academy of Pediatrics.[6] Level I facilities offer neonatal care to healthy term newborns. Level II facilities have 2 subgroups: level IIa can care for preterm neonates >32 weeks' gestation and weighing >1500 g, and level IIb offers short-term mechanical ventilation for infants with respiratory distress syndrome. Finally, level III facilities are NICUs capable of handling very preterm infants and infants needing ventilatory support for a long period of time, high frequency ventilatory oscillation, or nitric oxide inhalation. Infants of all gestational ages (GAs) with severe malformations or morbidities requiring surgical management should also be referred to level III maternity units. It is noteworthy that these perinatal care facilities are defined by their highest level of care, although they also provide less complex care.

Because care provided to very preterm infants is essential from birth to avoid poor outcome,[7–9] it is mandatory that births be planned in facilities fitting the infant's level of pathology and care requirements.[10] Perinatal recommendations were based previously on birth weight. Nowadays, routine early fetal ultrasonography in France and other countries enables GA to be precisely defined. Recommendations for management of preterm infants now stress GA over birth weight. French perinatal regionalization suggests that births before 33 weeks' gestation, as high-risk births, be prenatally referred to level III facilities by in utero transfers.[11]

However, not all preterm neonates <33 weeks' gestation require intensive care. Thus, some very preterm deliveries could be managed in level IIb facilities closer to the parents' home, avoiding pointless in utero transfers, saturation of level III facilities, and higher costs of centers providing advanced technologies and very specialized staffs.

Indeed, GA alone does not provide sufficient information for prediction of the infant's state at birth, because many other factors modify infant adaptation and outcome.[10] Thus, the objective of our study was to determine the antenatal factors other than GA that are linked to the need for neonatal intensive care (NIC) in premature infants. To this end, we used the data of the EPIPAGE population-based cohort study.[5,12,13]

METHODS

Study Population

Data were analyzed from the French EPIPAGE (epidemiologic study of very preterm infants) cohort. The French EPIPAGE cohort included all preterm infants aged 22 to 32 weeks' gestation and a sample of preterm infants aged 33 to 34 weeks' gestation born in 1997 in 9 French regions. The aim of the EPIPAGE study was to assess mortality trends and neurologic outcomes of preterm infants at 5 years of age. The methodology of this study has been described in previous articles.[12,13]

We defined the study population as mother-infant pairs. These pairs were included in our study if the infants were of a GA at which <50% of the neonates required NIC. Below this limit, GA by itself indicates the need for antenatal transfer to a level III unit. Only infants who were living at birth and born in a maternity unit were included in this analysis.

Pregnancies needing specialized monitoring or management in level III facilities (ie, amnioinfusion, amnioreduction, and intrauterine fetal transfusion), triplet pregnancies, mothers suffering from diseases requiring care provided only in level III units (ie, dialyzed mothers and mothers suffering from drepanocytic anemia or from heart or lung insufficiency), infants with congenital malformations, and infants referred to a level III facility after 2 days of life were excluded from this analysis.

Because the objective of our study was to aid decision-making in the referral of pregnant women at risk of preterm delivery, both mother and infant were excluded when one met exclusion criteria. In the case of twin pregnancies, the sickest infant (ie, the one most likely to have led to an in utero transfer) was retained in the analysis.

Defining the Need for NIC

We defined the need for NIC as meeting 1 of the 2 following criteria: (1) the use of specialized management (mechanical ventilation for >2 days, ventilation by high-frequency ventilatory oscillation, or nitric oxide for refractory hypoxemia) or (2) poor outcome (early neonatal death or transfer from a level IIb to a level III neonatal unit during the first 2 days of life for more intensive care).

Risk Factors

Factors studied that were linked to the fetus included GA,[14,15] gender,[16] intrauterine growth restriction ([IUGR] defined as birth weight beneath the third percentile on Yudkin's curves[17] not associated with maternal hypertension),[12] and fetal distress (defined as abnormal Doppler or fetal heart rate before labor onset). Factors linked to the mother were severe hypertension[18] (defined as maternal hypertension associated with fetal IUGR or preeclamptic toxemia),[19] antepartum hemorrhage,[10] smoking,[20] and history of preterm delivery or early neonatal death. Finally, factors linked to the pregnancy included pregnancy induced by assisted reproductive technology, twin pregnancy,[21] antenatal steroid therapy,[22] premature rupture of membranes (PROM),[23] oligohydramnios or hydramnios, and infection (defined as probable infection suspected immediately after birth).

Data Analysis

We first performed a univariate analysis to identify factors associated with the need for NIC, using χ^2 tests. Then, known risk factors and variables for which $P \leq .05$ were selected for multivariate analysis. Multivariate associations were analyzed with logistic regression models. We looked for significant interactions among the factors entered in the multivariate models. We adjusted our models for the region and the care level of the maternity unit at birth. The results of the logistic models were expressed as odds ratios (OR) with 95% confidence intervals (CI). The fits of the logistic models were assessed with the Hosmer and Lemeshow goodness-of-fit test, with $P < .05$ taken as evidence of a statistically significant difference between observed and predicted need for NIC.

We then determined the frequency of the need for NIC among infants aged 31 and 32 weeks' gestation, according to the factors significantly associated with the need for NIC in the multivariate analysis. All of the analyses were performed with SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Description of the Cohort

Between January 1, 1997, and December 31, 1997, 3537 very preterm neonates were enrolled in the EPIPAGE study. According to our definition of requirement for NIC, >50% of infants aged ≤29 weeks' gestation required intensive care (Fig 1). Therefore, 1740 mother-infant pairs were selected for this study. All of these infants were aged 30 to 32 weeks' gestation, were living at birth, and received care in a delivery room and a neonatal unit.

Of the mother-infant pairs selected, 247 were excluded because of antenatal need for care in a level III facility (n = 58), triplet pregnancy (n = 71), infant congenital malformations (n = 49), severe maternal diseases (n = 21), or neonatal transfer after 2 days of life to a level III unit (n = 48). Of twin pregnancies, 231 infants were excluded to retain the sickest infant in the analysis or because the cotwin had met exclusion criteria. The remaining 1262 mother-infant pairs were included in this analysis.

The general characteristics of the study population are summarized in Table 1. Very few data were missing for

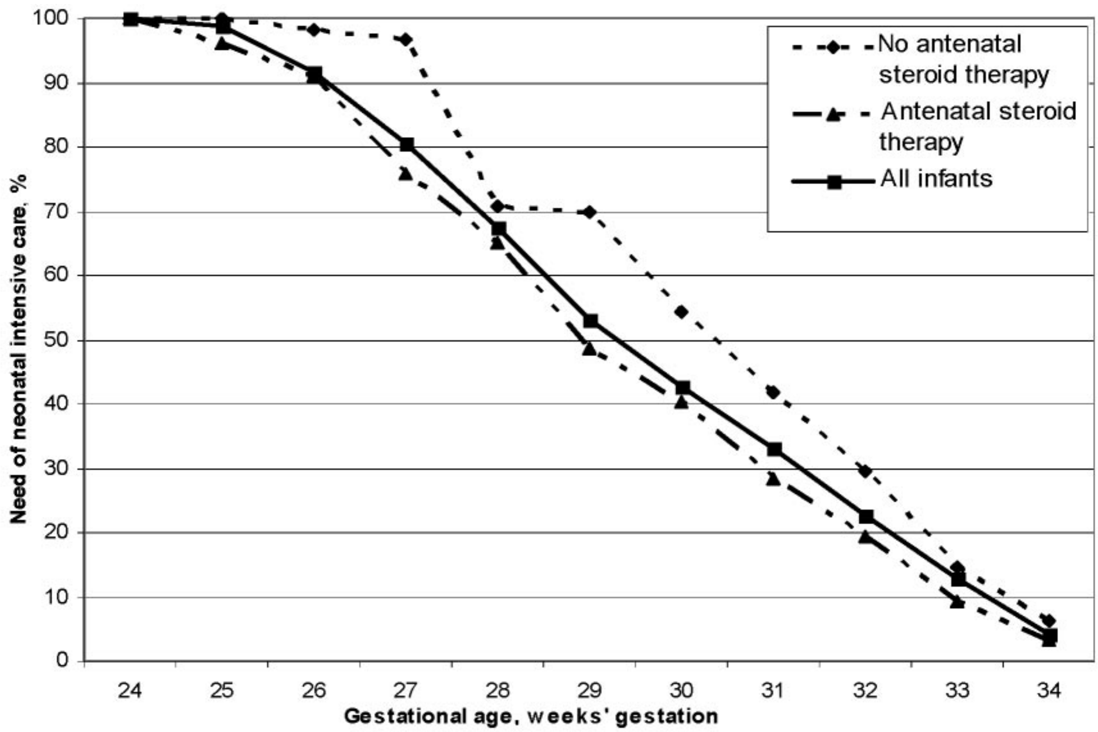

FIGURE 1
NIC requirements with gestational age and antenatal steroid maturation.

TABLE 1 Description of the Population Studied and the Need for NIC ($N = 1262$)

Variable	Population		Need of NICU Frequency
	N	Frequency	
Gestational age, wk gestation			
30	303	24.0	42.8
31	386	30.6	33.2
32	573	45.4	22.8
Factors related to pregnancy			
First child			
Yes	629	50.2	31.7
No	624		29.4
History of perinatal pathology			
Yes	142	11.2	26.6
No	1120		31.2
ART			
Yes	113	8.9	30.6
No	1149		30.7
Twin pregnancy			
Yes	191	15.1	41.4
No	1071		28.8
Oligohydramnios or hydramnios			
Yes	161	12.8	35.6
No	1099		30.1
PROM			
Yes	436	35.0	22.3
No	809		35.2
Infectious disease			
Yes	226	18.6	34.2
No	990		29.9
Antepartum hemorrhage			
Yes	110	8.7	42.4
No	1152		29.6
Antenatal steroid therapy			
Yes	879	72.0	27.2
No	342		38.5
In utero transfer to level III			
Yes	293	23.6	31.4
No	948		30.4
Level of maternity ward of birth			
I	271	21.5	35.3
IIa	127	10.0	34.4
IIb	158	12.5	24.8
III	706	55.9	29.6
Factors related to the mother			
Diabetes			
Yes	40	3.3	35.0
No	1161		30.0
Hypertension			
Yes	263	20.8	39.7
No	999		28.3
Smoking			
Yes	365	28.9	24.8
No	657		32.4
Factors related to the fetus			
Gender			
Male	665	52.7	34.6
Female	597		26.5
IUGR			
Yes	116	9.2	34.5
No	1146		30.3
Fetal distress			
Yes	487	38.6	34.2
No	775		28.5

ART indicates assisted reproductive technique.

the studied factors with the exception of tobacco use, for which 19% of the data were missing.

More than 70% of the preterm infants had antenatal steroid therapy. PROM was encountered in ~30% of pregnancies, maternal hypertension in 20%, and maternal diabetes in 4%. The prevalence of the different diseases studied did not differ with GA, with the exception of oligohydramnios and hydramnios, maternal diabetes, and maternal hypertension, which were significantly more frequent in the youngest preterm infants.

Prevalence of Intensive Care Requirement and Associated Factors

There was an inversely proportional linear trend for the need for intensive care with increasing GA: 42.8%, 33.2%, and 22.8% at 30, 31, and 32 weeks' GA, respectively (Fig 1). In the univariate analysis, factors associated with the need for NIC are detailed in Table 1 and their ORs presented in Table 2. The need for NIC was significantly increased in the youngest preterm infants, twin pregnancies, and males and in pregnancies marked by fetal distress syndrome, maternal severe hypertension, antepartum hemorrhage, and infection. Conversely, the need for NIC was significantly decreased with antenatal steroid therapy, PROM, and maternal smoking.

Multivariate analysis performed on the whole population showed that GA remained significantly linked to

TABLE 2 Relations Among Prenatal, Maternal, and Fetal Factors and the Need for NIC: Univariate Analysis ($N = 1262$)

Variable	Need of NIC	
	OR	95% CI
Gestational age		
30 weeks' gestation	1.88[a]	1.53–2.29
31 weeks' gestation	1.45[b]	1.18–1.79
Factors related to pregnancy		
First pregnancy	0.93	0.73–1.20
History of perinatal pathology	0.80	0.54–1.19
ART techniques	0.99	0.65–1.52
Twin pregnancy	1.74[b]	1.27–2.40
Hydro or oligoamnios	1.29	0.91–1.82
PROM	0.53[a]	0.40–0.69
Infectious disease	1.22	0.90–1.66
Antepartum hemorrhage	1.75[b]	1.17–2.63
Antenatal steroid therapy	0.60[b]	0.46–0.78
In utero transfer to level III	1.05	0.79–1.39
Birth in a level IIb maternity ward	1.07	0.96–1.18
Factors related to the mother		
Maternal diabetes	1.25	0.65–2.43
Maternal hypertension	1.67[a]	1.25–2.21
Maternal smoking	0.67[b]	0.51–0.92
Factors related to the fetus		
Male	1.47[b]	1.15–1.87
IUGR	1.201	0.80–1.83
Fetal distress	1.30[b]	1.02–1.66

ART indicates assisted reproductive technique.
[a] $P < .0001$.
[b] $P < .05$.

the need for NIC. The risk factors and protective factors were the same as in the univariate analysis with the exception of fetal distress syndrome, which was no longer associated with an increased NIC requirement in the adjusted model (Table 3). According to the multivariate analysis, among single infants aged 31 and 32 weeks' GA, the need for NIC was calculated as 14.8% and 14.4%, respectively, for infants with antenatal steroid therapy but without severe hypertension, antepartum hemorrhage, or infection.

Infants born of smoking women ($n = 356$) had a significantly decreased risk of intensive care requirement compared with infants born of nonsmokers (24.8% vs 32.4%; $P = .01$), but this protective effect disappeared when only infants with antenatal steroid therapy were taken into account (22.1% vs 27.1%; $P = .15$). Tobacco use had complex interactions with several medical factors. Risk factors for requirement of NIC among smokers are presented in Table 4. Among infants of smoking mothers, the need for NIC was significantly increased for the youngest preterm infants, twin pregnancies, male infants, and IUGR. This need was significantly decreased with PROM (Table 4).

DISCUSSION

Between 30 and 32 weeks' gestation, GA is an important factor predicting the need for NIC, yet it is not the only factor. Twin pregnancies, male fetuses, severe maternal hypertension, antepartum hemorrhage, and infectious disease were also linked with significant increases in the need for NIC. In contrast, antenatal steroid therapy and PROM were associated with significant decreases in intensive care requirement. Moreover, the requirement for NIC was not significantly higher among infants prenatally transferred to a level III facility.

Antenatal factors linked with respiratory distress syndrome or mortality in preterm infants have been considered in previous articles.[10,21] However, to the best of our knowledge this is the first study to determine antenatal factors that, in association with GA, modify the need for NIC.

Among medical factors under physician control, prenatal steroid therapy significantly prevents the need for NIC for very preterm neonates. In 1997, 30% of mothers who delivered between 30 and 32 weeks' gestation did not receive steroids, yet 33.8% ($n = 115$) of these women were admitted to the hospital ≥24 hours before delivery.

PROM seems to protect preterm infants from poor short-term outcome. However, women presenting with PROM are carefully monitored, which could at least partially explain the protective effect.

The results of the univariate analysis suggest a decreased intensive care requirement for infants born of smoking mothers. Moreover, it seems that antenatal steroid therapy, a well-known protective factor, could have decreased efficacy in smokers.[20] In contrast, IUGR in smokers is associated with an increased risk of intensive care requirement. Nevertheless, data concerning maternal smoking was lacking for 19% of the included pregnancies, so these analyses concerned only 1022 mother-infant pairs. This particular effect of tobacco use on preterm infants' immediate outcomes is not well understood and needs to be confirmed by additional studies. Multivariate analysis was performed separately for smokers. Finally, tobacco use may not be currently considered in the decision-making process to refer a pregnant woman to a level III unit.

The importance of perinatal regionalization has been emphasized in many studies. The concept of "critical mass"[24] guarantees expertise for preterm infants requiring specialized care. According to this principle, the sickest preterm infants should be born in facilities possessing the most advanced technologies and most experienced staffs. Yet the number of high-technology centers depends on the health care resources of the country. Therefore, the prenatal referral of infants to a level III

TABLE 3 Factors Associated With the Need for NIC: Multivariate Analysis ($N = 1176$)

Variable	[a]OR	95% CI
Gestational age, wk		
30	3.23[b]	2.29–4.55
31	1.72	1.25–2.38
Twin pregnancy	2.61[b]	1.81–3.77
Male	1.77[b]	1.34–2.33
Antenatal steroids	0.57[c]	0.42–0.77
PROM	0.54[c]	0.38–0.75
Infectious disease	1.83[c]	1.27–2.64
Antepartum hemorrhage	1.91[c]	1.19–3.06
Maternal hypertension	1.94[c]	1.34–2.82
IUGR	1.49	0.90–2.48
Fetal distress	1.11	0.81–1.52

[a] OR adjusted for region and level of maternity unit at birth.
[b] $P < .0001$.
[c] $P < .05$.

TABLE 4 Factors Associated With the Need for NIC Among Smokers ($N = 365$)

Variable	[a]OR	95% CI
Gestational age, wk		
30	3.96[b]	1.84–8.53
31	2.64	1.31–5.31
Twin pregnancy	4.73[b]	2.04–11.00
Male	2.01[b]	1.11–3.66
Antenatal steroids	0.62	0.34–1.15
PROM	0.39[b]	0.18–0.84
Infectious disease	1.82	0.83–3.98
Antepartum hemorrhage	2.08	0.90–4.81
Maternal hypertension	1.96	0.75–5.12
IUGR	2.83[b]	1.14–7.03
Fetal distress	1.50	0.75–2.98

[a] OR adjusted for region and level of maternity unit at birth.
[b] $P < .05$.

NICU should be closely linked with their needs to avoid saturation of level III maternity wards[2] and unnecessary expense.

In this study, 31% of infants born in a level III facility after in utero transfer needed intensive care. To improve the prediction of intensive care requirement at birth, it is important to focus on the complications and medical situations that increase the risk. Infants presenting with such medical conditions should then be referred prenatally to a level III facility.

A recent policy statement presented by the American Committee on Fetus and Newborn[6] uses both GA and birth weight as tools to define care provided at each neonatal facility level. Their definition of a level II facility is one that can care for infants aged >32 weeks' gestation or weighing >1500 g. However, our results showed that some neonates aged ≤32 weeks' gestation never require intensive care. In our study, only 14.6% (95% CI: 12.3–16.8) of single infants aged 31 and 32 weeks' gestation with antenatal steroid therapy but without severe hypertension, antepartum hemorrhage, or infection required intensive care, and the remainder could be handled in level IIb maternity units. Indeed, preterm infants aged 33 weeks' gestation are currently handled in level IIb units, and their requirement for intensive care reaches 13.1% (95% CI : 12.7–15.2). Moreover, in France, the requirements for physician presence and skills are the same in level IIb and III facilities.[25] Therefore, it is important for perinatal regionalization to take physician and staff abilities into account so as to maintain skills in the appropriate level of care. Reassignment of perinatal transfers for pregnancies at 31 or 32 weeks' gestation to level IIb facilities could participate to this purpose. It could also benefit health resources by providing care at a decreased distance from home. However, it should be kept in mind that ~14.6% of preterm infants at these GAs might require transfer to a level III unit after birth.

Currently, no clear definition of the need for NIC exists. The definition proposed in this study complies with physicians' current practice but may need to be revised according to perinatal care improvements and modifications in neonatal pathologies. In this definition, we excluded infants referred to level III facilities after 2 days of life, because it would have been difficult to distinguish the effects of antenatal factors from those of initial management.

Although we sought to determine antenatal factors associated with the need for NIC, IUGR and infectious disease were defined based on postnatal criteria, because prenatal information on these factors lacked precision. IUGR was, thus, defined based on birth weight criteria and infectious disease as probable infection, definitions commonly used in clinical practice. Infection and IUGR were not significantly associated with the need for NIC. Because these factors have been described in the literature to significantly increase respiratory distress syndrome,[23,26] they were included in the multivariate analysis.

In the multivariate analysis, associations between the factors and the need for NIC were adjusted for the level of the maternity unit at birth, because the intensity of the same complication and the quality of neonatal management may vary from one level to another. Because complications are also included in the models, an overadjustment can be feared. However, this would only weaken the association between a factor and the need for NIC. Medical practices may also experience regional variations. Thus, factors entered in the multivariate models were adjusted for the region of birth.

Our study was based on data from preterm infants born in 1997. In the years since, no major therapeutic modifications in neonatology have been introduced. The EPIPAGE study was conducted before the texts organizing French perinatal regionalization were promulgated.[4] However, even in 1997, high-risk births were routinely referred to level III facilities by in utero transfers, because 62% of births before 33 weeks' gestation took place in such maternity wards.[8] Finally, the quality of care in perinatal regionalization should focus not only on immediate outcomes of preterm neonates in level III and IIb facilities but also on long-term follow-up that needs to be performed both in level III and IIb facilities.

CONCLUSIONS

Short-term outcomes for preterm infants can be estimated before birth, allowing physicians to match the site of birth to the level of care required. Such predictions not only allow referral of sick infants to level III NICUs but also allow healthy preterm infants to be born and completely handled in level IIb facilities, optimizing the medical services available for very preterm neonates.

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