Predicting Nonhemolytic Neonatal Hyperbilirubinemia

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abstract

BACKGROUND: Before hospital discharge, newborn infants should be assessed for the risk of excessive hyperbilirubinemia. We determined maternal and obstetric risk factors for hyperbilirubinemia in infants born at term (gestational age ≥37 weeks) to form an individualized risk assessment tool for clinical use.

METHODS: This was a population-based study with data from the Swedish Medical Birth Register from 1999 to 2012, including 1 261 948 singleton infants. Outcome was defined as infants diagnosed with hyperbilirubinemia (*N* = 23 711), excluding all cases of hemolytic (immune-mediated or other specified hemolytic) diseases of the newborn.

RESULTS: Risk factors with an adjusted odds ratio (aOR) for neonatal hyperbilirubinemia of ≥1.5 (medium-sized effect or more) were gestational age 37 to 38 weeks (aOR = 2.83), failed vacuum extraction (aOR = 2.79), vacuum extraction (aOR = 2.22), Asian mother (aOR = 2.09), primipara (aOR = 2.06), large-for-gestational-age infant (aOR = 1.84), obese mother (aOR = 1.83), and small-for-gestational-age infant (aOR = 1.66). Planned cesarean delivery (CD) was associated with a reduced risk (aOR = 0.45). Without any of these risk factors (normal birth weight infant delivered vaginally at 39 to 41 weeks' gestation by a non-Asian, nonobese, multiparous mother) the rate of nonhemolytic neonatal hyperbilirubinemia was 0.7%. In relation to the combined load of different risk factors, rates of neonatal hyperbilirubinemia ranged from 0.2% to 25%.

CONCLUSIONS: Collection of a few easily available maternal and obstetric risk factors predicts >100-fold variation in the incidence of neonatal hyperbilirubinemia. The information provided herein enables individualized risk prediction with interactions between different risk factors taken into account.

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WHAT'S KNOWN ON THIS SUBJECT: The American Academy of Pediatrics recommends that every newborn should be assessed for the risk of developing severe hyperbilirubinemia before hospital discharge. However, currently listed risk factors for neonatal hyperbilirubinemia are based on old and small studies.

WHAT THIS STUDY ADDS: This large, population-based study enables individualized hyperbilirubinemia prediction, taking interactions between different (known and new) risk factors into account. Collection of a few easily available maternal and obstetric risk factors predicts >100-fold variation in the incidence of neonatal hyperbilirubinemia.

Newborn infants often develop transient hyperbilirubinemia that requires no treatment, that is, physiologic jaundice.[1–3] In some infants, also in the absence of hemolytic or other diseases, there is a more pronounced imbalance between bilirubin production and excretion, resulting in excessive bilirubin levels.[3,4] High levels of unconjugated bilirubin could be associated with brain dysfunction and even permanent brain damage, known as kernicterus.[5,6]

In light of the recurrence of kernicterus in healthy term infants,[7–9] prediction and early detection of infants at risk have received high priority. Different guidelines and approaches[8–16] have been issued, among which that of the American Academy of Pediatrics (AAP)[17] is the most commonly used worldwide. This guideline was based on a comprehensive literature review by the US Department of Health and Human Services' Agency for Health Care Research and Quality, New England Medical Center Evidence-Based Practice Center.[18] The AAP guideline recommends that every newborn, particularly those who are discharged from hospital before the age of 72 hours, should be assessed for the risk of developing severe hyperbilirubinemia.[17] Besides blood group determinations and neonatal bilirubin measurements, collecting information on common risk factors most frequently associated with an increase in the risk of severe hyperbilirubinemia is stated as an important part of the predischarge assessment. However, the listed[17] maternal and obstetric risk factors for neonatal hyperbilirubinemia are based on studies executed in the 1970 to 1990s,[12,19–22] with limited numbers of patients (24–127) with hyperbilirubinemia.[12,19,20,22] Different cutoff values for hyperbilirubinemia were also used, ranging from what could be considered physiologic (maximum serum bilirubin >12.9 mg/dL or >219 μmol/L)[21] to dangerously high levels (maximum serum bilirubin >25 mg/dL or >425 μmol/L).[12] Therefore, current best available knowledge is limited by imprecise estimates of size and direction of significant risk factors. In addition, recommendations based on older data may not take recent changes in the reproductive epidemiology landscape, mainly increased maternal age,[23] BMI,[24] and rates of operative deliveries,[25] into account. Finally, there is no previous study with sufficient power to disentangle interactions between different risk factors, which is necessary for individualized risk prediction.

To form a robust and contemporary risk assessment tool targeting hyperbilirubinemia prediction, we performed a large population-based cohort study. The aim was to identify and characterize selective contributions of maternal and obstetric risk factors in 23 711 term newborn, singleton infants treated for nonhemolytic neonatal hyperbilirubinemia.

METHODS

Study Population

This study was based on data from the Swedish Medical Birth Register from 1999 to 2012. During this period, there were 1 330 421 deliveries in Sweden. We included all live-born, singleton infants in a nonbreech presentation at birth, born at ≥37 weeks + 0 days (n = 1 261 948). Forceps was rarely used (3.3 per 1000 births), and births by forceps were therefore excluded. Because of a completely different risk factor profile for hemolytic hyperbilirubinemia, we also excluded infants who were diagnosed according to the *International Classification of Diseases, 10th Revision* (ICD-10, from 1997 and onward) with the codes P55 (hemolytic disease of fetus and newborn, n = 6464) and P56 (hydrops fetalis due to hemolytic disease, n = 16). Finally, we excluded cases with a diagnosis of kernicterus (ICD-10 code P57, n = 26) because the registry did not provide data on the underlying cause (hemolytic or nonhemolytic hyperbilirubinemia) in 22 out of 26 of these cases. The study was approved by the Regional Ethical Review Board in Stockholm (Dnr 2008/1322-31).

Risk Factors or Exposures

Maternal risk factors or covariates included maternal country of birth (Sweden, Asia, or other), maternal age, weight, height, BMI, parity, and diabetes mellitus (ICD-10 code O24.0-9). BMI was calculated from measured height and weight, obtained from the first antenatal care visit at 8 to 10 gestational weeks, and categorized according to the World Health Organization as underweight (BMI <18.5 kg), normal (BMI 18.5–24.9), overweight (BMI 25–29.9), or obese (BMI ≥30.0). Obstetric risk factors or covariates included induction of labor; mode of delivery, characterized as spontaneous vaginal delivery, planned or emergency CD, vacuum extraction (VE), or CD after a trial of vacuum extraction (VE + CD); and gestational age (GA). Infant characteristics known immediately after birth, such as gender, birth weight, and large for GA (LGA) or small for GA (SGA) were also included in the analyses. LGA was defined as a birth weight >2 SD above and SGA was defined as a birth weight >2 SD below the mean for GA and gender in a Swedish reference for normal fetal growth.[26]

Outcome

The outcome variable, neonatal hyperbilirubinemia, was classified according to the ICD-10 codes P58 (neonatal jaundice due to other excessive hemolysis) and P59 (neonatal jaundice from other unspecified causes). In Sweden, newborn infants received a diagnosis of neonatal hyperbilirubinemia only if they were admitted for neonatal care,

before or after discharge and up to a postnatal age of 28 days, and were actively treated with phototherapy or exchange transfusion to reduce serum bilirubin levels. The cutoff values for treatment have been formulated in national guidelines, the most recent version being from 2008.[27] According to these guidelines, the maximum serum bilirubin tolerated without initiation of bilirubin-reducing treatment in term newborn infants was 20 mg/dL (corresponding to 340 μmol/L) before 2008 and 20.6 mg/dL (350 μmol/L) from 2008 and onward.

Statistical Methods

We performed statistical analysis by using SPSS 20.0 (IBM SPSS Statistics, IBM Corporation). Descriptive statistics (numbers, frequencies, and proportions) were used to describe the distributions within the study population. Logistic regression analyses were used to calculate odds ratios (ORs) with 95% confidence intervals, first in bivariate analyses, followed by multiple logistic regression including all risk factors. The data were then stratified for GA, and the proportions of infants with neonatal hyperbilirubinemia with 1 or different combinations of clinically relevant maternal or obstetric risk factors, defined as an adjusted OR (aOR) ≥1.5 or ≤0.5 (medium-sized or larger effects), were calculated.

RESULTS

Altogether, 1.88% (n = 23 711) of term infants in the study cohort received a diagnosis of nonhemolytic (no immune-mediated or no diagnosis of specific hemolytic disease) neonatal hyperbilirubinemia. The distributions of different risk factors in the study population in relation to neonatal hyperbilirubinemia are shown in Table 1.

In the adjusted analyses, maternal factors associated with increased risk for neonatal hyperbilirubinemia were Asian mother, maternal age ≥30 years, maternal overweight and obesity, and maternal diabetes. Maternal age <20 years was associated with a decreased risk for neonatal hyperbilirubinemia.

Obstetric factors associated with an increased risk for neonatal hyperbilirubinemia included primiparity, induction of labor, delivery by VE, and delivery at 37 to 38 weeks' gestation, whereas CD, both emergency and elective, and GA >41 weeks were associated with reduced risks. Boys were more often diagnosed than girls, and neonatal hyperbilirubinemia was more common in SGA and LGA infants compared with infants whose birth weight was appropriate for GA.

Risk factors with an aOR for neonatal hyperbilirubinemia of ≥1.5 (medium-sized or larger effects), in order from highest to lowest aOR, were GA 37 to 38 weeks, failed VE, VE, Asian mother, primiparous mother, LGA infant, obese mother, SGA infant, and induction of labor. The only risk factor with an aOR <0.5 was planned CD (Table 1).

Without any risk factor (infant birth weight appropriate for GA, delivered vaginally without induction of labor at 39 to 41 weeks' gestation and by a non-Asian, nonobese, multiparous mother), the rate of nonhemolytic neonatal hyperbilirubinemia was 0.7%. The highest incidence for hyperbilirubinemia was seen in infants delivered at 37 weeks' gestation with emergency CD after VE had failed (26%), and the lowest incidence was found in infants delivered at 41 weeks' gestation with planned CD (0.2%).

Figure 1 uses the identified risk factors to create a sheet targeting individualized prediction of nonhemolytic neonatal hyperbilirubinemia for a given GA and for different modes of delivery. Incidences of neonatal hyperbilirubinemia (percentages) are presented for different combinations of maternal and obstetric factors identified to be clinically relevant (to have a medium-sized or larger effect) for the risk of developing significant neonatal hyperbilirubinemia in need of treatment. Neonatal hyperbilirubinemia was classified as very common if >10% infants had been diagnosed (very high risk, depicted in dark red in Figure 1), common if 5% to 10% were diagnosed (high risk for hyperbilirubinemia, red), less common if >1% but <5% were diagnosed (moderate risk, yellow), or rare if ≤1% had been diagnosed with neonatal hyperbilirubinemia (low risk, green).

DISCUSSION

This study provides solid and contemporary estimates of neonatal hyperbilirubinemia in term newborn infants in relation to a set of perinatal risk factors. Our main finding was that a simple collection of common maternal and obstetric risk factors, as well as infant birth weight, predicted >100-fold variation in the incidence of neonatal hyperbilirubinemia already at birth. By disentangling the selective contributions from these risk factors, predictions of hyperbilirubinemia specific for GA and mode of delivery could be constructed for a given maternal ethnicity, BMI, and parity and for birth weight. This new information enables individualized risk prediction in developed health care systems, and perhaps in clinical setting with limited or no resources for blood type or bilirubin screening programs, if the bilirubin epidemiology in these settings is similar to that of Sweden.

We found that 1.9% of term infants in Sweden were treated for neonatal nonimmune hyperbilirubinemia. Given that national Swedish guidelines recommend starting treatment at a total serum bilirubin level >20.6 mg/dL (>350 μmol/L) in infants born at ≥37 weeks' gestation and without other complicating morbidity,[27] our findings are in line

TABLE 1 Incidence, Crude and Adjusted ORs for Nonhemolytic, Neonatal Hyperbilirubinemia by Maternal and Obstetric Risk Factors, and Infant Anthropometry at Birth

	Total, *N* = 1 261 948	Neonatal Hyperbilirubinemia,		Crude OR (95% CI)	aOR (95% CI)
		N = 23 711	%		
Maternal region of birth					
Sweden	993 958	18 179	1.8	1.0	1.0
Asia	30 892	1253	4.1	2.27 (2.14–2.41)	2.09 (1.97–2.22)[a]
Other	237 098	4279	1.8	0.99 (0.95–1.02)	1.02 (0.99–1.06)
Maternal age (y)					
<20	21 712	453	2.1	1.05 (0.95–1.15)	0.86 (0.79–0.95)
20–29	548 045	10 932	2.0	1.0	1.0
30–34	438 931	7701	1.8	0.88 (0.85–0.90)	1.05 (1.02–1.08)
>34	253 188	4623	1.8	0.91 (0.88–0.95)	1.18 (1.14–1.22)
Missing	72	2	2.8	1.40 (0.34–5.73)	1.37 (0.33–5.66)
Maternal BMI					
Underweight (<18.5)	18 435	300	1.6	1.03 (0.92–1.16)	0.89 (0.79–1.00)
Normal (18.5–24.9)	452 430	7145	1.6	1.0	1.0
Overweight (25–29.9)	184 653	3806	2.1	1.31 (1.26–1.36)	1.39 (1.33–1.45)
Obese (≥30.0)	79 577	2144	2.7	1.73 (1.64–1.81)	1.83 (1.74–1.92)[a]
Missing	526 853	10 316	2.0	1.24 (1.21–1.28)	1.25 (1.21–1.29)
Maternal diabetes					
No	1 244 162	23 020	1.9	1.0	1.0
Yes	17 786	691	3.9	2.14 (1.98–2.32)	1.35 (1.24–1.46)
Parity					
Multipara	713 823	9205	1.3	1.0	1.0
Primipara	548 125	14 506	2.6	2.08 (2.03–2.14)	2.06 (2.00–2.12)[a]
Induction of labor					
No	148 292	4394	3.0	1.0	1.0
Yes	1 113 656	19 317	1.7	1.73 (1.67–1.79)	1.53 (1.48–1.59)[a]
Mode of delivery					
Vaginal delivery	1 000 612	16 816	1.7	1.0	1.0
VE	97 561	4353	4.5	2.73 (2.64–2.83)	2.22 (2.15–2.31)[a]
VE converted to CD	4310	243	5.6	3.50 (3.07–3.98)	2.79 (2.45–3.19)[a]
Emergency CD	88 596	1426	1.6	0.96 (0.91–1.01)	0.67 (0.63–0.71)
Planned CD	70 869	873	1.2	0.73 (0.68–0.78)	0.45 (0.42–0.48)[a]
GA (wk)					
37–38	235 533	8750	3.7	2.57 (2.50–2.64)	2.83 (2.75–2.92)[a]
39–41	930 142	13 749	1.5	1.0	1.0
>41	96 273	1212	1.3	0.85 (0.80–0.90)	0.63 (0.59–0.67)
Infant gender					
Girl	612 969	9503	1.6	1.0	1.0
Boy	648 774	14 208	2.2	1.42 (1.39–1.46)	1.41 (1.37–1.45)
Infant birth weight (g)					
<3000	123 617	3573	2.9	1.65 (1.59–1.71)	1.06 (1.02–1.11)
3000–4000	878 436	15 617	1.8	1.0	1.0
4001–4500	205 990	3489	1.7	0.95 (0.92–0.99)	0.99 (0.95–1.04)
>4500	51 161	999	2.0	1.10 (1.03–1.17)	0.98 (0.90–1.07)
Missing	2744	33	1.2	0.67 (0.48–0.95)	0.70 (0.50–0.99)
SGA					
No	1 238 858	22 849	1.8	1.0	1.0
Yes	23 090	862	3.7	2.06 (1.93–2.21)	1.66 (1.54–1.80)[a]
LGA					
No	1 216 413	22 216	1.8	1.0	
Yes	45 535	1495	3.3	1.82 (1.73–1.92)	1.84 (1.72–1.98)[a]

CI, 95% confidence interval.

[a] aORs depict risk factors with a medium-sized or larger effect (aORs ≥1.5 or ≤0.5) on the risk of neonatal hyperbilirubinemia.

with US data suggesting that a total serum bilirubin level of ≥20 mg/dL (≥342 μmol/L) is seen in ~1% to 2% of infants born at a GA of ≥35 weeks.[12,28]

The risk factors for development of severe hyperbilirubinemia identified herein add new knowledge to current standards. In the AAP guidelines from 2004, a GA of 35 to 36 weeks was identified as a major risk factor for severe hyperbilirubinemia, whereas a GA of 37 to 38 weeks was listed as a minor risk factor.[17] In the update from 2009,[29] infants born after 35 to

Non-overweight, non-Asian mother

Primipara

Mode of delivery	Gestational age, weeks 37	38	39	40	41	>41
VE	16	10	6	4	3	2
Vaginal	7	4	2	2	1.4	1.4
Emergency CS	5	3	2	1.3	1.1	1.0
Planned CS	3	1.0	0.9	2	0.2	1.1

Multipara

Mode of delivery	Gestational age, weeks 37	38	39	40	41	>41
VE	13	7	4	3	1.4	1.4
Vaginal	4	2	1.0	0.8	0.7	0.8
Emergency CS	3	2	1.1	1.0	1.1	0.9
Planned CS	2	1.2	0.7	0.6	0.3	0.5

Overweight/obese mother

Mode of delivery	Gestational age, weeks 37	38	39	40	41	>41
VE	19	10	6	4	3	3
Vaginal	8	4	2	1.5	1.2	1.2
Emergency CS	5	3	2	2	1.4	1.3
Planned CS	3	2	0.8	2	1.0	1.2

LGA-infants

Mode of delivery	Gestational age, weeks 37	38	39	40	41	>41
VE	22	17	8	6	2	2
Vaginal	12	6	3	2	1.2	0.7
Emergency CS	6	4	2	2	1.0	2
Planned CS	5	2	1.2	0.7	0.0	0.0

Asian mother

Mode of delivery	Gestational age, weeks 37	38	39	40	41	>41
VE	22	14	8	7	8	7
Vaginal	8	5	4	3	3	2
Emergency CS	6	3	4	3	2	1.2
Planned CS	3	1.0	0.6	1.0	2	3

SGA-infants

Mode of delivery	Gestational age, weeks 37	38	39	40	41	>41
VE	16	12	7	5	5	5
Vaginal	8	5	3	2	2	2
Emergency CS	7	6	4	4	2	2
Planned CS	5	3	4	6	1.0	4

FIGURE 1

Risk factor sheet targeting prediction of nonhemolytic hyperbilirubinemia in term newborn infants. Each colored cell contains the incidence (%) of neonatal hyperbilirubinemia for different combinations of maternal and obstetric risk factors based on a cohort of 1 261 948 infants with 23 711 patients. The incidence of neonatal hyperbilirubinemia was classified as very high if >10% (dark red), high if 5%–10% (red), moderate if >1% but <5% (yellow), or low if ≤1% infants developed hyperbilirubinemia after birth (green).

37 weeks were characterized as being at increased risk for severe hyperbilirubinemia. However, infants born at 38 weeks' gestation were categorized as low-risk infants,[29] possibly because of observations (n = 48 patients treated for hyperbilirubinemia) of no significant difference in rates of hyperbilirubinemia between infants born at 38 to 39 weeks and infants born at ≥40 weeks' gestation.[30] Our study confirms several smaller (n = 73–270 patients) US studies[12,31–33] documenting an impact of each decreasing week of gestation on the risk of developing severe hyperbilirubinemia. Given that infants born not only after 37 but also after 38 weeks' gestation were, in most combinations of other perinatal risk factors, found to be at moderate to high risk for hyperbilirubinemia (Figure 1), we suggest that a GA of 38 weeks should be listed as a major risk factor in coming updates of neonatal hyperbilirubinemia guidelines.

Whereas the previously known risks associated with a cephalohematoma, probably in the causal pathway of the association between VE and hyperbilirubinemia, and with an East Asian mother could be confirmed, our findings suggest that maternal obesity, primiparity, and LGA (also identified by Newman et al[12]) and SGA infants should be added to the list of major risk factors.[17] In line with AAP recommendations, maternal diabetes and infant male gender were associated with increased risks, but the effect sizes were small. And we could not find support for the recommendation that advanced maternal age (defined in AAP guidelines as ≥25 years) is a risk factor for neonatal hyperbilirubinemia:[17] although maternal age ≥30 years was significantly associated with hyperbilirubinemia in our study, the effect size (aOR = 1.05) was very small and without clinical significance. Finally, the evidence behind the recommendation that GA ≥41 weeks is associated with a decreased risk for hyperbilirubinemia[17] was only partially supported in our study. In Asian women and in SGA infants delivered with VE, the risk for significant hyperbilirubinemia remained high to very high across the GA range, underlining the need to take interactions between different risk factors into account.

Even though a majority of infants in our study did not reach a bilirubin level that necessitated treatment, a >10% incidence of the need for acute treatment within hours or days to detect and prevent a potentially disabling disease is very high (depicted dark red in Figure 1). By convention, side effects from drugs are classified as very common (≥10%), common (≥1%, <10%), and less common (≥0.1%, <1%). We used a slightly more conservative classification.

Today, most infants born at term will have their peak bilirubin concentration after discharge from hospital, and hyperbilirubinemia has become one of the most common reasons for readmission to hospital in the neonatal period.[22] The problem is not readmission per se; given that hyperbilirubinemia peaks at home after early discharge from hospital, increased readmission rates are expected in a health care system focused on patient safety. The concern is that some readmitted infants have been reported to exhibit dangerously elevated bilirubin levels, >25 mg/dL (>425 μmol/L).[34] This development calls for an even more thorough predischarge risk assessment of all newborn infants. Knowledge about maternal and obstetric risk factors is an important

part of such an assessment, and the use of checklists may be helpful.[10,17] An individualized score sheet available at birth, as suggested herein, may take hyperbilirubinemia risk assessment several steps forward in terms of accuracy of risk prediction. Such an individualized risk prediction can be useful for parental counseling, planning of optimal timing for hospital discharge and follow-up visits, and timing of bilirubin determinations, before and after hospital discharge.

Besides the risk factors studied herein, a history of older sibling with neonatal hyperbilirubinemia (especially if intervention was needed), a family history of hemolytic disease, and maternal blood group (information not available in the Swedish Medical Birth Registry) will add important information to the overall risk assessment at birth.

Most of the newborn infants diagnosed with hyperbilirubinemia in our study (and not mediated by hemolytic disease) will have been treated with phototherapy. As judged from our data, phototherapy to reduce bilirubin appears to be more frequently used in the United States[35] and other countries[36] than in Sweden. Besides our exclusion of hemolytic diseases and late preterm infants, higher rates of phototherapy may be explained by lower bilirubin thresholds for initiating treatment in other countries than in Sweden.[17,27] Population differences in the distribution of some maternal and obstetric risk factors, such as ethnicity (2.4% of mothers in our study had an Asian origin vs 6.7% of all births in the United States[37]), overweight and obesity (21% of the women in our study vs >50% in the United States[38]), and rates of delivery in weeks 37 to 38 (19% among term deliveries in our study vs 28% among term deliveries in the United States[37]), may also contribute to the explanation of higher rates of phototherapy in the United States than in Sweden. In addition, the risk of neonatal hyperbilirubinemia is affected by postnatal management. The most important management issue relates to feeding practices. In Sweden, all women are instructed and encouraged to breastfeed their infants. Early and frequent breastfeeding decreases the risk, whereas inadequate breastfeeding can contribute to severe hyperbilirubinemia.[15]

We excluded patients with hemolytic hyperbilirubinemia because we assumed that they would have a different risk factor profile (determined mainly from maternal and fetal blood groups) than infants with nonhemolytic hyperbilirubinemia. We also excluded patients with a registry diagnosis of kernicterus because the registry did not provide data on the underlying cause (hemolytic or nonhemolytic hyperbilirubinemia) in most cases and because we did not have access to any case records to validate the kernicterus diagnoses. Nevertheless, in the database, 26 term newborn infants had received a diagnosis of kernicterus, giving a crude estimation of the kernicterus incidence of 26 out of 1 261 974, or 20.6 infants per million. Although not the aim of this study, we note with great concern that our crudely estimated incidence is high compared with estimates of kernicterus in term infants reported previously.[7,14,39] Our observation warrants additional validation of the kernicterus diagnosis in the Swedish Medical Birth Register and more information on background, clinical course, and outcome in these patients.

Exclusion of the patients with registry diagnosis kernicterus does not invalidate the results or interpretations of this study. The patients diagnosed with kernicterus constituted a minute fraction of the whole cohort treated for hyperbilirubinemia, and there is no obvious reason to anticipate that the maternal and obstetric risk factor profile for patients with kernicterus should differ from that of the included patients (all treated for severe hyperbilirubinemia and at risk for kernicterus). Applying the prediction sheet created herein (Figure 1) to the 3 excluded infants documented in the birth registry with a diagnosis of kernicterus and nonhemolytic hyperbilirubinemia would have categorized all 3 of them at birth as being at moderate risk (incidence >1% but <5%) for developing postnatal hyperbilirubinemia in need of treatment. This observation has several important implications. First, it shows that prediction of a nonexisting risk for kernicterus cannot be made. Second, one has to keep in mind that our grading of predicted incidences of severe hyperbilirubinemia, from low to very high, is not a grading of the severity of hyperbilirubinemia, once this complication has occurred. Third, this observation clearly indicates that a clinical risk assessment at birth, based on the maternal and obstetric risk factors studied herein or on other sources of information, can never be foolproof alone. Successful hyperbilirubinemia prediction and kernicterus prevention build on a system approach in which accurate risk assessment immediately after birth could serve as a good starting point that must be combined with other actions in the neonatal period. Finally, our study design, including a large (>20 million of data points) registry database, can be a valuable tool for creating precise risk factor estimates for as accurate prediction as possible. But it is unsuitable for analysis of rare and serious adverse events such as kernicterus; our data set did not provide information on the postnatal course of the infants with kernicterus, on the duration of their hospital stay, on how follow-up was organized and executed, whether these infants suffered from additional significant neonatal morbidity

(besides severe hyperbilirubinemia) before or after discharge from the hospital, and whether kernicterus in these patients represented a system failure or occurred despite proper detection and treatment of hyperbilirubinemia.

The major strengths of this study are the large study population and the high quality of the Swedish Medical Birth Register (98% of all pregnant women in Sweden included). The size of the sample (23 711 cases of hyperbilirubinemia) played a crucial role in avoiding errors, in estimating effect size and significant interactions between different risk factors, that may occur in smaller studies or by intuitive prediction based on case series. The major limitation is that the register lacks information on important covariates such as family or sibling history of neonatal hyperbilirubinemia, blood group, number and duration of tractions using VE, and bruising. In addition, we do not have information on neonatal outcomes such as maximal serum bilirubin levels and clinical picture.

Finally, the proposed sheet of hyperbilirubinemia prediction based on risk factors should optimally be cross-validated, assessing how the results of our study would generalize to an independent data set or in other settings. Unfortunately, other Swedish population-based registers do not contain the set of risk factors studied herein, excluding the possibility of validation using other Swedish data sets. We see 2 possibilities for future validation: to perform a similar study to ours using a sufficiently large data set generated in another country or population or to use the proposed prediction sheet and prospectively study to what extent the prediction of significant hyperbilirubinemia mirrors the outcome.

CONCLUSIONS

Collection of a few easily available maternal and obstetric risk factors predicts >100-fold variation in the incidence of neonatal hyperbilirubinemia. While confirming part of the evidence derived from older and smaller studies, this study challenges some other currently listed risk factors for neonatal hyperbilirubinemia. We suggest that a GA of 38 weeks, maternal obesity, primiparity, and LGA and SGA infants should be added and that maternal age ≥25 years should be excluded from the list of major risk factors for neonatal hyperbilirubinemia. The risk factors identified and quantified herein enable simple and individualized risk prediction immediately after birth. Such assessment may be a good starting point for parental counseling and for professional decision-making on additional management in the neonatal period, targeting early detection of severe hyperbilirubinemia and thereby effective prevention of kernicterus.

ABBREVIATIONS

AAP: American Academy of Pediatrics
aOR: adjusted odds ratio
CD: cesarean delivery
GA: gestational age
ICD-10: *International Classification of Diseases, 10th Revision*
LGA: large for gestational age
OR: odds ratio
SGA: small for gestational age
VE: vacuum extraction

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