Predictors of Early-onset Neonatal Sepsis in Premature Newborns: Case Control Study

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Title: Predictors of early-onset neonatal sepsis in premature newborns: case control study

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Abstract:

Background: Early-onset neonatal sepsis (EOS) is difficult to diagnose clinically because the semiology of premature newborns is poor during the first days of life. This study aimed to identify predictive factors of EOS in neonates less than 37 weeks gestational age in neonatal care at Louis Mourier Hospital.

Method: This was a case-control study of all newborns <37 weeks of gestational age diagnosed and managed for EOS from January 1 to December 31, 2019. The main parameters studied were demographic characteristics, risk factors, biological and bacteriological characteristics. At the benchmarking level, the statistical tests used were the Mac Nemar test for qualitative variables and the paired Student's test for quantitative variables.

Results: A total of 50 mother-child pairs were included in this study (25 cases and 25 matched controls). The results showed a statistically significant relationship between the birth of a child suffering from an EOS and between a premature rupture of membranes (PRM)> 18 h (68% of cases versus 36% of controls (p: 0.042)); a positive culture of the placenta (p: 0.0002); a CRP> 6 mg / l (88% of cases against 20% of controls (p: 0.001)); a PCT> 0.6 ng / ml (72% of cases vs. 16% of controls (p: 0.001)). Grams negative including E. coli (44.5%) and Haemophilus Influenzae (14.8%) were the most common bacteria found.

Conclusion: The search for risk factors must be systematic. The dosage of PCT must be coupled with that of CRP and the clinic must remain at the center of the diagnostic process.

Keywords: Early bacterial neonatal infection, predictive factors, premature.

Background:

Early-onset neonatal sepsis is a disease of low incidence but at high risk of serious consequences, with 2 to 3% of deaths in term babies and 20 to 30% in premature infants in the United States [1]. The bacterial epidemiology of EOS has changed, but Streptococcus B remains the most common germ in term newborns, Escherichia coli is the bacterium most frequently identified in very premature newborns [2]. Newborns 34 - 36 weeks old have twice the risk of EOS unlike those born at term [3].

Recommendations for the management of newborns at risk for EOS have evolved in recent years. The American Academy of Pediatrics (AAP) and the Committee On Fetus and Newborn (COFN) published in 2012 a guide for the care of children suspected or suffering from a bacterial infection neonatal [4].

In France, the recommendations of the French Society of Neonatology (SFN) and the French Society of Pediatrics (SFP) of good practices underway in France are those of 2017 published

by the Haute Autorité de santé (HAS) in September 2017, relating to the management of newborns at risk of early-onset neonatal sepsis (≥34 WA). The questions addressed concern the identification of newborns at risk of EOS, who require clinical surveillance after childbirth, those who require additional examinations and those who require probabilistic antibiotic treatment at birth [5].

From these new recommendations, blood culture is still the gold standard for the diagnosis of EOS, and first-line empirical antibiotic therapy has been proposed by limiting the use of third generation cephalosporins from the outset. Antibiotic prophylaxis is supervised. This rational prescription of antibiotics aims to prevent the emergence of resistant and selective germs.

The incidence of EOS has decreased since the generalization of intra-natal antibiotic prophylaxis, 1.7 ‰ of streptococcal B EOSs in 1990, against 0.4 ‰ in 2008 in the United States [6], but this last is at the source of numerous biological assessments, as well as prescriptions of broad-spectrum antibiotics which may be at the origin of the emergence of resistant bacteria [7] and a disturbance in the implantation of the neonatal digestive flora with deleterious consequences at a distance from birth [8].

EOS is difficult to diagnose clinically because the semiology of the newborn is poor during the first days of life. The HAS recommendations published in 2017 take this specificity into account. The majority of the clinical signs of EOS evoked are not specific to an infection, but their presence within 48 hours of life should raise suspicion of early neonatal infection [5].

However, it is difficult to distinguish between a certain infection and a probable infection. In order to be able to distinguish a true EOS from a false one, we have undertaken this work which will allow us to research the predictive factors of early bacterial neonatal infection with evidence of the germ in the blood and / or the cerebrospinal liquid or in bacteriological samples from birth, in all cases associated with clinical or laboratory abnormalities.

This study aimed to identify the predictive factors of early bacterial neonatal infection in neonates under 37 weeks gestational age in neonatal care at Louis Mourier Hospital.

Patients and methods

Type and period of study

This was a case-control study of all newborns under 37 weeks gestational age diagnosed and treated for early-onset neonatal sepsis from January 1 to December 31, 2019, a period of 1 year, in the neonatology department of Louis Mourier hospital.

Study population

The study population consisted of newborns less than 37 weeks gestational age admitted to the neonatal unit at Louis Mourier Hospital with suspected early-onset neonatal sepsis.

Newborns were defined as cases when it comes to:

- A definite infection by showing the germ in the blood or cerebrospinal fluid, accompanied by clinical signs
- A probable infection by the demonstration of a clinical and / or biological abnormality associated with the isolation of a germ in bacteriological samples from birth and treated with antibiotic therapy for 7 days
- A possible infection by the demonstration of a clinical and / or biological anomaly without isolation of a germ in the bacteriological samples from birth and treated with antibiotic therapy for 7 days.

Newborns were defined as controls matched on gestational age with suspicion of unconfirmed infection in the case of simple colonization or negative bacteriological samples from birth with absence of biological anomaly and probabilistic antibiotic therapy stopped before 72 hours.

Included in the study were newborns born alive at a term of less than 37 weeks gestational age with definite, probable or possible bacterial neonatal infection during the first 3 days of life and newborns born alive at a term of less than 37 weeks gestational age suspected of bacterial neonatal infection during the first 3 days of life.

Parameters studied

The main parameters studied were demographic characteristics; risk factors for early bacterial neonatal infection; biological and bacteriological characteristics.

Data collection technique and tools

Identification of cases of neonatal bacterial infections meeting our inclusion criteria from reports from the neonatal service by searching on the ORBIS software and filling out questionnaires with maternal and neonatal data.

The data was collected on the basis of an elaborate questionnaire, filled in from the medical records of the newborns.

Statistical analysis

The entry of the validated collected data was done on the Epidata software version 3.1.. The statistical analysis was done with the R studio software in its version 3.3.2.

At the descriptive analysis level for the characteristics collected, the results were expressed as number and percentage for the qualitative variables or as the mean and standard deviation for the quantitative variables. At the benchmarking level, the statistical tests used were the Mac

Nemar test for qualitative variables and the paired Student's t test for quantitative variables. The study size did not allow multivariate analyzes to be performed. The chi-square test (X2) was used to look for possible differences between the percentages of qualitative variables with a significance level of 5%.

Results:

Demographic characteristics of mothers and newborns

A total of 50 newborns were included in this study (25 cases and 25 matched controls). No variable has missing values. Table 1 gives the results of the description and comparison of the different demographic characteristics in the cases and in the controls. Cases and controls were matched for gestational age (+/- 2 weeks) (n = 50).

Maternal risk factors

The results of the comparison of the various maternal risk factors found in mothers who gave birth to a child suffering from an early-onset neonatal sepsis (cases) and mothers who gave birth to an uninfected child (controls) (Table 2) .

There was a statistically significant relationship between premature rupture of membranes (PRM> 18h) and the birth of a child with early bacterial neonatal infection. In our study, 68.00% of children with early neonatal bacterial infection were born after prolonged premature rupture (PRM> 18h) compared to 36.00% of uninfected children (p value <0.05). The existence of intra-natal antibiotic therapy was significantly associated with EOS.

Neonatal risk factors

The results of the comparison of different risk factors in neonates with early-onset neonatal sepsis (cases) and uninfected neonates (controls) are shown in Table 3.

It can be verified that the cases and controls have the same Apgar score at the first, fifth and tenth minutes, the same birth weight of children. There was a statistically significant relationship between the duration of antibiotic therapy and the birth of a child with EOS.

The results of the description and comparison of clinical and laboratory diagnostic signs in the cases and in the controls are given in Table 4. There was a statistically significant relationship between positive cord procalcitonin (PCT) and the birth of a child with early-onset neonatal sepsis. As well as a statistically significant relationship between positive C-reactive protein (CRP) and the birth of a child with early-onset neonatal sepsis.

Bacteriological characteristics

The results of the distribution of pathogens associated with EOS in the 25 infected newborns are presented in Table 5.

We found an association of 2 germs in two of the newborns. A newborn baby with E. coli and Staphylococcus aureus, the other carrier of Staphylococcus aureus and Haemophilus influenzae. We found two cases of E. coli K1 whose mothers were from sub-Saharan Africa. Five mothers (20%) had been tested positive for group B streptococcus in prenatal care and had received intrapartum antibiotic prophylaxis. We found transmission of Group B Streptococcus in 2 newborns (40%) whose mothers had been treated with Amoxicillin.

There was a statistically significant relationship between the positivity of the bacteriological culture of the placenta, the positivity of the peripherals sampling and the birth of a child with EOS (Table 6).

Discussion:

This study enabled us to assess the factors most found in EOS in neonatology at Louis Mourier Hospital. Mothers with premature rupture of membranes rupture for more than 18 h, newborns with PCT> 0.6 ng / ml in cord blood and CRP> 6 mg / l at 12 hours of life had more risk of having EOS. The positivity of the bacteriology of the placenta and the positivity of the peripherals sampling were in favor of EOS. Negative grams including E. coli (44.5%) and Haemophilus Influenzae (14.8%) were the most common bacteria found. Transmission of group B streptococcus from mother to newborn was 40% despite treatment with amoxicillin.

The main limitation of this study was our modest size during the study period which did not allow multivariate analyzes to be performed. This was linked to the decrease in cases of EOS in the department. Given the limited staff, matching of controls was only at +/- 2 weeks gestational age. This "relative" match likely did not influence the results. However, this work has provided us with valuable information on the bacteriological profile and the characteristics leading to certain and probable infections.

The study looked at preterm infants with a gestational age of less than 37 weeks. Prematurity and low birth weight are risk factors for EOS, which we could not demonstrate due to the size of the sample in our study. These two factors remain independently associated with EOS in newborns under 28 and 32 weeks gestation [9]. Likewise, a systematic meta-analysis on the risk factors of neonatal infections carried out in India taking into account all types of gestational age had made it possible to find a gestational age <37 weeks which would in itself be a risk factor [10].

We found a relationship between prolonged premature rupture of membranes (> 8 hours) and the birth of a child with EOS. Premature rupture of membranes would be the most accurate infectious marker for the prediction of EOS in current use with a sensitivity> 90%, according to a prospective study conducted in two centers of all women admitted for premature rupture

of membranes ≥34 weeks gestation [11]. Another study reported the incidence and risk factors associated with premature rupture of membranes during EOS. Maternal fever, prematurity <34 weeks, low birth weight <1500 g were independent risk factors associated with culture-tested EOS during premature rupture of membranes [12].

PCT> 0.6 ng / ml and CRP> 6 mg / l, were arguments in favor of EOS in our work. While the predictive value of cord PCT has been well studied in the term newborn, few studies investigating PCT and CRP have looked at very low birth weights. A study based on a comprehensive review of the literature that identified 39 studies directly comparing PCT to CRP, including only 4 in very low birth weight infants, examining kinetics and performance for the diagnosis of neonatal sepsis by PCT and PCR. During INBP the mean sensitivity of PCT was 73.6% and that of CRP was 65.6%. Regarding the mean specificity during EOS, the specificity of PCT was 82.8% against 82.7% for CRP. PCT is arguably better than CRP for the detection of EOS [13].

Another PCT study investigated the value of PCT at different times during the first 3 days of life as part of the diagnosis of EOS, as well as the thresholds of PCT in the diagnosis of EOS with different gestational ages. Newborns with a gestational age <34 weeks had a significantly higher level of PCT than those with a gestational age ≥ 34 weeks ($p < 0.05$). The same criteria can be used for late preterm infants (with gestational age ≥ 34 weeks) and term infants, while early preterm infants (with gestational age <34 weeks) should be considered separately. PCT has different optimal cut-off values in diagnosing early bacterial neonatal infection in newborns of different ages, with a higher value than blood culture in diagnosing EOS within 36 hours after birth [14].

The study of PCT in extreme premature infants during EOS showed that elevation of PCT (> 0.5 ng / ml) in cord blood was significantly associated with EOS early in extreme premature but its sensitivity remains low (sensitivity 69%, specificity 70%). Its added value in combination with other early markers of EOS needs to be further investigated in this high risk population [15].

The combination of PCT and CRP alone improves the diagnostic accuracy of neonatal sepsis according to a meta-analysis and a systematic review of the literature. According to this study the appropriate cut-off value for PCT was 0.5 - 2 ng / ml and the cut-off value> 10 mg / l for CRP with high sensitivity and specificity for the diagnosis of EOS [16].

E. coli (44.5%) and Haemophilus influenzae (14.8), were the germs most frequently found during our work. In France, as in USA, E. coli is the first pathogen found in premature newborns. In a prospective study from the USA that included infants of at least 22 weeks

gestational age and birth weight greater than 400 g from 18 centers, the most common pathogens were Escherichia coli (36, 6%) and group B streptococcus (30.2%). E. coli infection occurred mainly in premature infants (68 of 131 [51.9%]); GBS infection had occurred primarily in term infants (54 of 104 [51.9%]), with 24 of 45 cases of GBS (53.3%) observed in infants born to mothers with clinical outcomes. GBS tests were negative. The rate of E. coli infection increased in very low birth weight infants (401-1500 g) (8.68 [95% CI, 6.50-11.60] vs. 5.07 [95% CI, 3.93) -6.53] per 1,000 live births (p = 0.008) [17].

This distribution of pathogens would depend on the geographic area in which the study was carried out. A recent study carried out in China on the pathogens responsible for EOS found in premature babies weighing more than 800 g Group B Streptococcus (18.3%), E. coli (18.1%) followed by Listeria monocytogen (12.1%) and Klebsiella pneumoniae [18].

Transmission of group B streptococcus was found in two newborns despite perpartum antibiotic prophylaxis based on Amoxicillin in mothers linked to antibiotic resistance. Hence the importance of choosing the appropriate antibiotic therapy for the germ. In Madagascar, a study on the acquisition of beta-lactamase-producing enterobacteria found E. Coli (34.1%), Klebsiella pneumoniae (24.4%) as the most common germ in infected newborns. Risk factors for acquiring extended spectrum beta-lactamase-producing Enterobacteriaceae were low body weight, cesarean section, and maternal use of antibiotics during childbirth [19]. Several other studies have looked at the effect of intrapartum antibiotics. Perinatal exposure to antibiotics in the mother and newborn had an impact on the microbiota of the mother and of the term or premature newborn with the risk of developing early bacterial neonatal infection [20].

Conclusion:

The predictors of early bacterial neonatal infection in neonates under 37 weeks gestational age that we found in this study were premature rupture of membranes of more than 18 hours; positive culture of the placenta; the positivity of diagnostic tests such as cord PCT and CRP after H12 in newborns. The pathogens found in the newborns in our study who were all premature were mainly E. coli and Haemophilus influenzae.

In view of these results, it seems essential for the clinician to distinguish between a true EOS and a false one in premature babies. The search for risk factors must be systematic and the clinic must remain at the center of the diagnostic process. The prevention of EOS by systematic screening for maternal genital infections has shown its effectiveness, but the emphasis should always be on the rational use of antibiotics. Antibiotic therapy should also be rational and limited in newborns.

No newborn baby with a negative culture of the placenta was infected during our study. Particular attention should be paid to the result of culture of the placenta in preterm infants suspected of EOS.

Abbreviations

AAP: American Academy of Pediatrics; CRP: C-reactive protein; COFN: Committee On Fetus and Newborn; EOS: Early-onset neonatal sepsis; GBS: Group B Streptococcus; HAS: Haute Autorité de Santé; PCT: Procalcitonin; PRM: Premature rupture of membranes; SFN: French Society of Neonatology; SFP: French Society of Pediatrics.

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Authors' contributions

OET conceived the study protocol. OET drafted the analysis plan and wrote the first draft of the manuscript. All authors contributed to data analysis through review and interpretation of the results. All authors read, revised and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Ethical approval for this study was obtained from the ethics committee of the UFR medical training and research unit of Paris Didérot - Paris VII. The study was approved for an end-of-training dissertation as part of the Specialized and Advanced Training Diploma in Pediatrics in Ile-de - France, University of Paris Diderot - Paris Vll.

Individual parental consent was obtained. All respondent signed an informed consent form before enrolment in the study. Patient's identification used in this study is hospital record number without name and address.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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