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The FLIP-2 Study: Risk and Protector Factors Linked to Respiratory Syncytial Virus Infection Requiring Hospitalization in Premature Infants Born at a Gestational Age of 32^1 to 35^0 Weeks in Spain.

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ABSTRACT

Background and Objective. The objective of this study (FLIP-2 study) was to validate the risk factors previously found in the FLIP study and related to the occurrence of a respiratory infection due to RSV which involved hospitalization in premature infants born at a gestational age of 32^1 to 35^0 weeks. The protective influence of the prophylactic administration of palivizumab was also analyzed.

Methods. It was a two cohort prospective study: premature infants hospitalized for RSV infection (202) and the remaining premature infants of the same age who did not require any hospitalization for respiratory causes (5239). The children came from 37 participating Spanish hospitals during the 2005-2006 RSV seasons (October 2005 to April 2006) and the 2006-2007 RSV season (October 2006 to April 2007).

Results. 1.3% of infants who received prophylactic palivizumab were hospitalized and 4.1% of those who did not receive it ($p < 0.001$). 17.8% of the cases were admitted to the ICU, and 7.4% required mechanical ventilation. None of the patients died. Logistic regression analysis demonstrated that the risk of RSV-related respiratory infection requiring hospital admission in preterm infants 32^1-35^0 WGA was most often associated with absolute chronological age at start of RSV season $\leq$10 weeks (OR: 2.99; 95%CI: 2.23-4.01), presence of $\geq$1 school-age siblings or day care attendance (OR: 2.04; 95%CI: 1.53-2.74), and smoking during pregnancy (OR: 1.61; 95%CI: 1.16-2.25). Prophylactic administration of palivizumab showed a protective effect (OR: 0.25; 95% CI: 0.13-0.49).

Conclusions. In premature infants born 32^1-35^0 WGA certain underlying risk factors (being born between 15 July and 15 December, presence of $\geq$1 school-age siblings or day care attendance, and smoking during pregnancy) significantly increase the risk of RSV-related respiratory infection and hospitalization. RSV prophylaxis with palivizumab reduces the probability of hospitalization.

INTRODUCTION

Ex-premature infants are more predisposed to complicated primary RSV infections. Those with 33-35 WGA represent 70% of premature infants[1], and it is important to identify both the risk factors that increase the likelihood of hospitalization due to RSV infection and the possible protective effect of anti-RSV monoclonal antibodies (palivizumab). A case-control study had already been carried out in our community to define the association between certain risk factors and the requirement for hospitalization due to RSV LRTI in prematures 33-35 WGA (FLIP study)[2]. The factors that were found to be related were: absolute chronological age at start of RSV season ≤10 weeks, breastfeeding ≤2 months, some school-age siblings, residents and/or visitors at home ≥4 and history of wheezing in the family. A cohort study was designed with the purpose of validating these results that would overcome the characteristic limitations of case-control studies, with the participation of 37 of the 50 hospitals of the IRIS study group. This group of hospitals has also published several national epidemiologic studies on RSV severity in preterm infants ≤32 WGA[3, 4].

The current study intends to identify risk factors for hospitalization due to RSV infection in a cohort study that includes all prematures with 32^{1}-35^{0} WGA (***FLIP-2*** study) seen in the participating hospitals during two consecutive seasons, and also to verify the prophylactic usefulness of palivizumab in this GA group.

PATIENTS AND METHODS

The collection of the cases and controls of this cohort study was carried out in 37 of the hospitals of the Spanish Iris group for two consecutive RSV seasons (October 2005 to April 2006 and October 2006 to April 2007). The selection and definition of variables and study design were very similar to that of the FLIP study[2], since it intended to validate its results. It was submitted for approval to the Clinical Research Ethical Committee of two of the centers participating in the study (Hospital Clínic, Barcelona; Hospital La Paz, Madrid).

Case definition. Cases were defined as preterm infants born between 32^{1} and 35^{0} WGA (as determined at each participating site), of either sex, discharged during the infectious RSV season, or aged 6 months or less at the start of the season (October 1st in Spain). The patients were to have been born at–or transferred immediately after birth to– a participating hospital. Patients considered cases were admitted to hospital with an RSV proven lower respiratory tract infection (IF, ELISA, virus culture).

Control definition. Controls were the remaining prematures seen (born at– or transferred immediately after birth to–) one of the participating hospitals within the same time period and within the same GA limits as cases. Controls could not have been previously hospitalized for any acute respiratory illness during the RSV season.

Exclusion criteria for cases and controls. Patients were excluded for the following reasons: previous inclusion in the study; nosocomial RSV infection (appearing more than five days after admission); known renal impairment, hepatic dysfunction or immunodeficiency; chronic seizure disorder; congenital heart disease with cyanosis or heart failure; chromosomal anomalies, congenital metabolic diseases, or major congenital anomalies. Subjects who participated in clinical trials with blind treatments, those previously hospitalized for acute respiratory illness, or patients with other chronic lung diseases except for bronchopulmonary dysplasia (BPD) were also excluded.

Sample size estimation. The calculation for the required sample size was based on the correct determination of the prophylactic effect of palivizumab. In a cohort study, in order to detect a protective effect that reduces the figure of hospitalization due to RSV infection by 50% (from 4.7% to 2.3%, based on the data obtained in the IRIS Group study 1999-2000[3, 4,] and on the FLIP-1[2] results) at least 654 cases are required with the protective factor and 1962 controls without it in order to achieve $\alpha=0.05$ and $1-\beta=0.8$. Both samples must show comparable prevalence of risk factors, or higher in the group with the protective factor.

Definitions for Risk Factors and other variables of interest. In order to avoid bias as far as feasible, questioning about risk factors and other variables of interest was carried out according to the following criteria:

- Chronological age in weeks at the start of the RSV season (October 1st in Spain) was calculated by the equation “(date of the start of RSV season - date of birth)/7”

- >=1 school-age siblings or day care attendance: a variable that jointly analyses having siblings of school-age or who attend nursery school, or that the child itself attends nursery school. The probability of exposure to RSV would increase in all these cases.

- Tobacco smoke exposure at home[5]: Children were considered exposed if at least one family member living with the child declared smoking at home or if at least one of the persons who usually cared for the child declared smoking in its presence.

- Smoking during pregnancy: When during pregnancy the mother smoked any number of cigarettes daily.

- History of wheezing: Presence of wheezing lasting 2 or more consecutive days, forcing treatment with inhaled bronchodilators in any of the parents or siblings.

- Habitual residents at home were defined as those usually sleeping every night in the family home.

- Respiratory infection attributable to RSV: A respiratory infection was attributed to RSV if an RSV test was performed on the child between 7 days before and 72 hours after admission, and proved positive. No attempt was made to standardize RSV testing methodology.

Study design. The parents were informed of the study to be carried out at the time of hospital admission of premature infants born from April 1st, and they were requested consent. If affirmative, data was collected on kinship and risk factors. Once each RSV season was over, during the month of May all the participating families were contacted (visit or telephone call) completing the report of risk factors and recording data for possible hospitalizations (or rehospitalizations) for respiratory causes (positive RSV or not). If the family did not give initial consent, was not located or refused performing the final survey at the end of May, the child was excluded.

Statistical analysis. The dependent variable was admission for respiratory infection attributable to RSV in this group of children. Independent variables included the following: chronological age at the start of the RSV season, smoking during pregnancy, exposure to tobacco smoke at home, family history of wheezing, the presence of school-age siblings, nursery school or daycare site attendance, breastfeeding and its duration, number of residents at home (discounting school-age siblings and the case/control him/herself), and the prophylactic administration of palivizumab.

Variables are described as mean and standard deviation (SD) for continuous variables. Statistical tests used included the Student's t test for continuous variables, and chi square test for categorical variables. Cut-off points of continuous variables converted to categorical (absolute chronological age at start of RSV season, school-age siblings, breastfeeding and residents and visitors at home) were the same used in FLIP-1 study[2].

Since the primary objective of the study was to determine the potential risk factors for developing RSV respiratory infection requiring hospitalization in preterm infants of 32^{1}-35^{0} WGA or in order to protect from said hospitalization, the main endpoint was the odds ratio (OR) for RSV infection according to the different risk characteristics. Bivariate calculation of ORs was used to determine the rates of each risk factor for cases and controls (point estimate and 95% CI) [6]. Any variable for which a $P \leq 0.10$ in any of the bivariate analyses was considered for entry into the multivariate model (logistic regression analysis). Finally, adjusted ORs were determined within the multivariate model to estimate each factor's contribution after controlling for other factors in the model.

RESULTS

In the two years considered a total of 6473 children complied with the inclusion criteria. Of these 777 were excluded due to refusal to participate or loss to follow-up, 235 due to respiratory admissions that were not RSV positive, 3 due to death during the lactation period not related to respiratory processes and 15 due to incomplete data. Thus, 5441 children were valid to analyze the risk factors, 202 of these considered cases since they were RSV positive admissions and 5239 controls. Five of the cases exhibited also RSV positive rehospitalizations. Of the cases, 17.8% required ICU admission, and 7.4% needed mechanical ventilation. There were no deaths. Median length of stay in hospital was 7 days (IQR: 4-10) and in ICU 5 days (IQR: 3-10.8). Regarding the prophylactic administration of palivizumab, 1.3% of those who received it and 4.1% of those who did not were admitted due to serious RSV infection.

Perinatal characteristics of cases and controls can be seen in Table 1. Table 2 shows the OR for each individual risk factor. For all risk factors, $P \leq .10$, except for breastfeeding <=2 months, >=4 adult residents at home, history of wheezing, and day care attendance. However, the joint variable ">=1 school-age siblings or day care attendance" was present in 61.4% of the cases and in 44.1% of controls ($p<0.001$). Variables with $P \leq .10$ were included in the logistic regression analysis. Gender was also considered as covariable because $P \leq .10$ after comparing case and control groups. Logistic regression analysis (Table 3) demonstrated that independent risk factors of RSV-hospitalization in preterm infants 32^1-35^0 WGA included: absolute chronological age at start of RSV season ≤10 weeks (i.e. born between July 15th and December 15th), presence of school-age siblings (≥1) or day care attendance, and tobacco smoking during pregnancy. According to the estimated model, with other risk factors being equal, children with school-age siblings or attending nursery school, and whose mother also smoked during pregnancy, with respect to children who do not have any of these two factors, exhibit an odds ratio of hospitalization due to RSV infection of 3.30 (1.77-6.15). This is the combination of the presence of two risk factors with a lower OR. Children born between July 15th and December 15th who also have school-age siblings or who attend nursery school, against those who do not have these two factors, exhibit an OR for hospitalization due to RSV infection of 6.12 (3.41-10.98), the greatest in combinations of two factors. The presence of the three risk factors, against children who do not have any of them, implies an OR of hospitalization due to RSV infection of 9.89 (3.96-24.67). All other risk factors being equal, the OR for hospitalization due to RSV+ of children who received prophylaxis with palivizumab versus those who did not receive it is 0.25 (0.13-0.49).

The comparative study between children who received prophylactic palivizumab and those who did not receive it is summarized in table 4. 1.3% of those who received palivizumab and 4.1% of those who did not receive it were hospitalized due to serious RSV infection ($p<0.001$).

DISCUSSION

The results of this study (FLIP-2) have not confirmed the same risk factors found in the FLIP -1 study[2]some years earlier. There are two essential differences between both studies: 1/ the FLIP-1 study had a case-control design (189 cases and 378 controls), whereas the FLIP-2 study has been a prospective study with 2 cohorts including all premature infants seen who complied with the inclusion criteria. 2/ The FLIP-1 study included premature infants at a gestational age of33^0 to 35^6 weeks, whereas FLIP-2 included children who were 6 days more immature (32^1 to 35^0 weeks). This change was performed in order to accommodate the FLIP-2 study to the new guidelines of the Spanish Neonatology Society[7]. Despite premature infants being slightly more immature in the FLIP-2 study, the median length of stay of those hospitalized, the need of admission to ICU and its duration, and the need for mechanical ventilation were similar to those of FLIP-1. The fact that 17.8% required hospitalization in ICU and 7.4% mechanical ventilation supports that RSV lower respiratory tract illness in 33-35 WGA preterm infants requiring hospitalization can be severe[8] and comparable to that observed in preterm infants ≤32 WGA[9] and in the study published by Horn et al.[10]

Because of the low admission rates for this group for RSV respiratory infection (5.7%)[11] the cohort study obliged the inclusion of a large amount of children. The number reached is sufficient to assess the prophylactic usefulness of palivizumab. Our conclusions may be limited by a selection bias introduced by the methods used to contact candidates in the months of May in order to perform the final survey, in many cases by telephone. The relatively high number of losses to follow-up is due to the difficulties in contacting the families (changes in telephone numbers) and sometimes due to language difficulties (immigrants who do not speak Spanish well). The modest predominance of males in the case group was expected, because males are known to have more severe RSV illness[12,13].

As in the FLIP-1 study[2], it was demonstrated that infants with a chronological age of 10 weeks or less at the onset of RSV season were at high risk of hospitalization for RSV LRTI. The finding coincides with our previous studies[3,4] and with the conclusions of Joffe and colleagues[14] which demonstrated that chronological age <3 months immediately prior to RSV season was a risk factor for RSV hospitalization. An additional risk factor for RSV disease, also found in the FLIP-1 study[2] was living with a school-age sibling, a fact described in previous studies[3,4], and accepted by

the AAP[15,16], which includes it as a risk factor. The limited utilization of day care centers in our population (less than 5%) may mask the true impact of day care as a risk factor in countries where day care attendance is common. However, the joint use as a risk factor of “living with a school-age sibling or day care attendance” increases the odds ratio of the variable.

Maternal smoking during pregnancy and following delivery or smoke exposure in general have also been associated with increased LRTI and wheezing in early childhood[17]. Most studies about lower respiratory infections in the first year of life have found an association with maternal or household smoking[18,19]. Smoking in the expectant mother causes lesions in the fetal lung[17,20]. In our study, only maternal smoking in the pregnancy was associated (*P*= .004) with a higher risk of RSV hospitalization, both in the bivariate analysis and in the multiple logistic regressions. In the FLIP-1 study[2] this variable was only significant in the bivariate analysis but did was not considered in the logistic regression model. The factor exposure to tobacco smoke at home (>=2 smokers) in the present study has been higher in the cases than in controls (20% vs. 14%; p=0.011) but it was not considered in the logistic regression model. From previous studies in Spain, it appears that exposure to tobacco smoke at home (>=2 smokers) has decreased during the last few years in Spain (52% in 1999-2000 RSV season[3] versus 30% in FLIP-1 study[2] and 14% in the current study). This reduction may be a result of anti-smoking campaigns and better health education.

In contrast to of the FLIP-1 study[2], breastfeeding during more than the first 2 months does not show a protective effect against RSV-infection, in contrast with the studies by Holdberg et al[21] and Bulkow et al[22] who described a decreased risk of RSV hospitalization in breastfeeding infants. Furthermore, the presence of 4 additional residents at home did not increase the risk for RSV hospitalization, either. Neither did a history of wheezing in the family (parents and siblings) reach statistical significance as a risk factor in the present study. In the other cohort study performed to date (PICNIC study), the family history of asthma was not significant, either[23]. All this suggests that bronchial hyperreactivity, rather than predisposing towards a serious form of RSV infection, would be a consequence thereof.

The present study proves the prophylactic efficacy of palivizumab for reducing hospitalizations due to RSV infection in this group of premature infants (1.3% vs. 4.1%). It is also of note that, as expected, the risk factors were significantly higher in the group that received palivizumab than in the group that did not receive it, which makes the significant improvement achieved from the administration of palivizumab even worthier of mention. The fact that they received more palivizumab than those born between July 15th and December 15th, or those who had school-age siblings or a history of wheezing in parents or siblings, was in agreement with the guidelines of the Spanish Neonatology Society[7], whereas its priority administration to a lower gestational age or a lower birth weight is only due to decisions of the doctors.

In a review of the studies performed from 1970 through April 2003, the risk factors for development of severe RSV LRTI[13] were: male gender, young age, birth in the first half of the RSV season, day care attendance, crowding in the home, and siblings. The PICNIC study performed in Canada is very similar to ours since it prospectively analyses two consecutive RSV seasons (2001-2002 and 2002-2003) aiming to identify independent factors for hospitalization due to RSV in expremature infants of 33-35 WGA. Respiratory diseases were identified by telephone calls. 1760 breastfeeding infants were followed, of which 66 were hospitalized due to proven RSV infection. Independent predictors for hospitalization for RSV infection were: day care attendance, November through January birth, preschool age siblings, birth weight <10th percentile, male gender, >= 2 smokers in the home, and households with >4 people, excluding the subject; family history of eczema was protective[23] . The results from the PICNIC study were consistent with those of the FLIP study[24]. It is likely that there is an additive effect when several risk factors are present in the same infant, which may have practical prophylaxis implications[24].

In the present study (FLIP-2), the independent risk factors for the development of severe RSV LRTI, in descending order according to ORs, were: absolute chronological age at start of RSV season ≤10 weeks, some school-age siblings (≥1) or day care attendance, and history of smoking during pregnancy. Premature infants 32^1-35^0 WGA should be screened for such factors and those at high risk for RSV hospitalization (especially those with 2 or more risk factors present) should be considered for palivizumab administration.

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Table 1. Perinatal characteristics in 32^1-35^0 WGA study subjects.

	CASE (n=202)	CONTROL (n=5239)	*P*
Birth weight (g)	2047 (360)	2020 (400)	NS (.304)
Gestational age (w)	33.8 (0.8)	33.9 (0.9)	NS (.774)
- 32^1-33^0 weeks	49 (24.3%)	1229 (23.5%)	NS (.965)
- 33^1-34^0 weeks	68 (33.7%)	1790 (34.2%)	
- 34^1-35^0 weeks	85 (42.1%)	2220 (42.4%)	
Gender (male)	121 (59.9%)	2800 (53.4%)	NS (.083)
Multiple pregnancy	76 (37.6%)	2052 (39.2%)	NS (.711)
Bronchopulmonary dysplasia	0	4 (0.07%)	NS (.352)

Number (%), Mean (SD)

Student's t test, chi^2 test

Table 2. Bivariate analysis of risk factors related to RSV hospitalization in 32^1-35^0 WGA study subjects

	CASE (n=202)	CONTROL (n=5239)	0R (95% CI)	*P*
Absolute chronological age at start of RSV season (weeks) ≤10 weeks	126 (62.4%)	1944 (37.1%)	2.81 (2.10-3.75)	.0000
≥2 tobacco smokers at home	41 (20.3%)	721 (13.8%)	1.59 (1.12-2.26)	.0119
Smoking during pregnancy	51 (25.4%)	907 (17.3%)	1.62 (1.17-2.24)	.0046
History of wheezing	60 (29.7%)	1346 (25.7%)	1.22 (0.89-1.66)	NS (.236)
≥1 school-age siblings	119 (58.9%)	2211 (42.3%)	1.96 (1.47-2.60)	.0000
Day care attendance	11 (5.4%)	229 (4.4%)	1.25 (0.67-2.34)	NS (.581)
Breastfeeding ≤ 2 months	152 (75.6%)	3738 (71.4%)	1.24 (0.89-1.72)	NS (.225)
≥4 residents at home (without school-age siblings and subject)	20 (9.9%)	388 (7.4%)	1.37 (0.85-2.20)	NS (.238)
Prophylaxis with palivizumab:	9 (4.5%)	670 (12.8%)	0.32 (0.16-0.62)	.0006

Number (%), Mean (SD).

Student's t test, chi^2 test

Table 3. Logistic regression analysis of risk factors related to RSV hospitalization in 32^{1}-35^{0} WGA study subjects.

	Coefficients (standard error)	OR (95% CI)	*P* value
Absolute chronological age at start of RSV season ≤10 weeks *	+ 1.0965 (0.1494)	2.99 (2.23-4.01)	$2.11*E^{-13}$
Some school-age siblings or day care attendance *	+ 0.7156 (0.1486)	2.04 (1.53-2.74)	$1.47*E^{-6}$
Tobacco smoking during pregnancy *	+ 0.4795 (0.1684)	1.61 (1.16-2.25)	.0044
Prophylaxis with palivizumab *	- 1.3884 (0.3457)	0.25 (0.13-0.49)	$5.91*E^{-5}$
(Intercept)	- 4.1679 (0.1530)	-----	$<2*E^{-16}$

* No=0, Yes=1

Table 4. Characteristics of 32^{1}-35^{0} WGA study subjects according to prophylactic palivizumab administration.

	Palivizumab (679)	No palivizumab (4758)	p
Gestational age	33.3 (0.9)	33.9 (0.8)	<0.001
Birthweight	1813 (398)	2050 (391)	<0.001
Absolute chronological age at start of RSV season ≤10 weeks	53.2%	35.9%	<0.001
Some school-age siblings or day care attendance	48.6%	42.1%	0.0015
Tobacco smoking during pregnancy	20.7%	17.2%	0.03
History of wheezing in family	31.2%	25.1%	0.0009
RSV + hospital admissions	9 (1.3%)	193 (4.1%)	<0.001

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