High cord blood IL-10 levels in preterm newborns with respiratory distress syndrome

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ABSTRACT

Background: The development of respiratory distress syndrome (RDS) is closely related to fetal immaturity, although the participation of inflammatory mechanisms also seems to be likely. We previously reported high interleukin-10 (IL-10) levels in cord blood from preterm infants. In the present study, we investigate the possible role of IL-10 and IL-12 in preterm newborns with RDS, a disease that is also closely related to gestational age.

Patients and methods: Cord blood levels of IL-10 and IL-12 (p70 + p40) were determined by ELISA in 20 preterm infants who later developed RDS, in 21 preterm infants without RDS and in 31 full term newborns. In 11 patients follow-up samples could be also obtained between 2 and 14 days of life.

Results: Preterm infants with RDS showed higher IL-10 (27 vs 10.8 pg/mL; p: 0.0003) and lower IL-12 (188 vs 384; p: 0.002) levels in cord blood than premature infants without RDS and full term newborns (IL-10: 3.2 pg/mL, p: 0.0001; IL-12: 352 pg/mL; p: 0.002). The differences remained statistically significant after correction for the effect of gestational age between both preterm groups.

Conclusions: The results obtained may be related to an immature cytokine response in premature infants, but the IL-12/IL-10 imbalance found in our patients also supports the hypothesis that inflammation plays a role in RDS.

Key words: Cytokines. Hyaline membrane disease. IL-12/IL-10. Preterm newborns. Respiratory distress syndrome. Th1/Th2 lymphocytes.

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RESUMEN

Antecedentes: La aparición del Síndrome de Distress Respiratorio (SDR) se relaciona muy estrechamente con la inmadurez fetal aunque también es probable la participación de mecanismos inflamatorios. Previamente hemos publicado niveles elevados de interleucina 10 (IL-10) en sangre de cordón de niños prematuros. Aquí, investigamos el posible papel de la IL-10 e IL-12 en recién nacidos prematuros con SDR, que también se relaciona con la edad de gestación.

Métodos y enfermos: Se determinaron los niveles de IL-10 e IL-12 (p70 + p40) en sangre de cordón mediante ELISA en 20 niños prematuros que después desarrollaron SDR, 21 prematuros sin SDR y 31 recién nacidos a término. En 11 casos también pudimos conseguir muestras de sangre del seguimiento entre 2-14 días de vida.

Resultados: Los niños pretérmino con SDR presentaron niveles más altos de IL-10 (27 vs 10,8 pg/mL; p: 0.0003) y más bajos de IL-12 (188 vs 384; p: 0.002) en sangre de cordón que los prematuros sin SDR y que los recién nacidos a término (IL-10: 3,2 pg/mL p: 0.0001 y IL-12 352 pg/mL; p: 0.002). Las diferencias siguieron siendo significativas tras la corrección del efecto de la edad de gestación entre los dos grupos de prematuros.

Conclusiones: Los resultados obtenidos pudieran relacionarse con una respuesta inmadura de las citocinas en los prematuros, pero el disbalance IL-12/IL-10 encontrado en nuestros pacientes también apoya la hipótesis según la cual la inflamación juega algún papel en el SDR.

Palabras clave: Citocinas. Enfermedad de membrana hialina. IL-12/IL-10. Recién nacidos prematuros. Síndrome de distress respiratorio. Linfocitos Th1/Th2.

Abbreviations: IL-12/IL-10: interleukin-12/interleukin-10; RDS: respiratory distress syndrome; Th1/Th2: T1/T2 helper lymphocyte; NK: natural killer cells; TNF: tumour necrosis factor; IFNγ: interferon gamma.

INTRODUCTION

IL-10 has a potent activity in immunosupression, specially directed to Th1 cells, by inhibiting both IL-12 and IFNγ synthesis[1]. The feto-placental unit synthesizes IL-10, involved in the suppression of cellular immunity and induction of HLA-G expression in the human trophoblast, therefore protecting the fetus from rejection[2,3]. By contrast, at the time of delivery there is a Th1 response with increased IL-12 levels, as occurs in graft-versus-host reactions[4]. IL-12 has a potent Th1 effect, involved in defence mechanisms against intracellular pathogens and in delayed-type inflammatory reactions. Moreover, IL-12 induces IFNγ synthesis by T and NK cells[5]. The predominance of Th2 cytokines is associated to normal pregnancy, whereas Th1 is involved in recurrent spontaneous abortions[2,4]. The fetal Th2 predominance remains in the newborn for several weeks postdelivery[6].

Serum IL-10 levels are increased in preterm infants and we have previously reported an inverse correlation between IL-10 cord blood levels and gestational age[7]. Here, we investigate the possible role of this interleuklin in preterm newborns with respiratory distress syndrome (RDS), which it is also related to gestational age. Besides, the imbalance between IL-10 (antiinflammatory) and IL-12 (proinflammatory cytokine) are also studied.

PATIENTS AND METHODS

Patients

The study was performed in 41 preterm infants with a mean gestational age of 32 weeks (range 25-37). Weight at birth ranged between 480 to 3,160 gr. Only one newborn had low weight for gestational age (< Pc10). Respiratory distress syndrome (RDS) was shown in 20 cases, and the diagnosis was reached by clinical and radiological findings and the course of the disease. All newborn with RDS were ventilated with a continuous positive airway pression (CPAP). The severity of the distress was assessed according to days of assisted ventilation, and referred as mild when less than 5 days, moderate between 5-10 days, and severe when more than 10 days. Antenatal steroid therapy was not administered to any case included in the study.

Neonatal sepsis was found in 5/20 cases and 7 premature infants died. There were differences affecting gestational age (median 29.5 vs 32 w; p: 0 > 0.5) and weight (mean 1230 vs 1720 gr; p: < 0.05) between groups, premature with and without RDS, but the type of delivery and the frequency of sepsis were similar (table I). Analysis determinations could be repeated in 11 preterm infants with 2 to 14 days of life, and without signs of infection or respiratory distress at that time. The results were compared to those obtained from a group of 31 healthy full term infants. The delivery was vaginal in all but 18 cases undergoing a caesarean section due to different problems: 5 had RDS, 6 without RDS and 7 full-term controls. None of the cases included in the study developed bronchopulmonary dysplasia.

The study was approved by the Ethical Research Committee of the Faculty of Medicine of University of Valladolid and performed according to ethical procedures.

Techniques

Blood samples were obtained from umbilical cord. After centrifugation for 10 minutes, serum samples were separated and frozen at –20 °C until the study was performed. Cytokines were measured by an ELISA test (Endogen, USA), using two no-competitive monoclonal antibodies reacting against different

Table I

Birth weight, gestationals age and interleukin levels of all included cases

	Delivery	Weight (gr)	Gest. age (w)	IL12 (pg/mL)	IL10 (pg/mL)	IL12/IL10
RDS						
1	Vagin.	1,140	28	10	35	0.3
2	Vagin.	625	25	10	27	0.4
3	Caesar.	1,740	33	10	17	0.6
4	Caesar.	950	27	20	19	1.1
5	Vagin.	1,430	35	368	257	1.4
6	Caesar.	950	27	140	71	2.0
7	Caesar.	950	27	281	101	2.8
8	Vagin.	2,650	37	38	9.1	4.2
9	Vagin.	1,120	30	128	29	4.4
10	Vagin.	1,800	30	331	71	4.7
11	Vagin.	1,260	29	56	12	4.7
12	Vagin.	1,800	30	336	67	5.0
13	Caesar.	950	27	188	27	7.0
14	Vagin.	2,200	35	634	84	7.5
15	Vagin.	2,470	35	292	27	10.8
16	Vagin.	2,200	35	165	13	12.7
17	Vagin.	1,070	28	395	31	12.7
18	Vagin.	850	26	188	14	13.4
19	Vagin.	2,200	35	286	16	17.9
20	Vagin.	1,200	28	733	13	56.4
Mean		**1,478**	**30.4**	**230**	**47**	**8.5**
St. dev.		**606**	**3.8**	**202**	**56**	**12.4**
Median		**1,230**	**29.5**	**188**	**27**	**4.7**
No-RDS						
1	Vagin.	1,400	30	66	12.5	5
2	Caesar.	2,330	37	212	26	8
3	Vagin.	3,160	36	247	22	11
4	Vagin.	1,700	31	368	17.0	22
5	Vagin.	1,900	32	358	16.2	22
6	Vagin.	1,570	32	511	22.8	22
7	Caesar.	2,450	33	541	22.1	24
8	Vagin.	1,910	35	607	24.3	25
9	Vagin.	1,680	33	506	18.4	28
10	Vagin	480	23	309	11.1	28
11	Vagin.	1,500	31	331	10.5	32
12	Vagin.	1,750	32	258	7.0	37
13	Vagin.	2,400	37	328	8.8	37
14	Caesar.	2,300	35	479	10.8	44
15	Vagin.	1,720	35	489	9.6	51
16	Vagin.	1,680	32	436	7.0	62
17	Caesar.	1,600	32	529	8.4	63
18	Caesar.	2,600	35	451	7.0	64
19	Caesar.	2,250	33	309	4.5	69
20	Vagin.	1,470	31	777	6.0	130
21	Vagin.	1,570	32	384	1.8	213
Mean		**1,877**	**32.7**	**405**	**13.0**	**48**
St. dev.		**557**	**3.0**	**155**	**7.2**	**47**
Median		**1,720**	**32.0**	**384**	**10.8**	**32**

Table I

Birth weight, gestationals age and interleukin levels of all included cases *(continuation)*

	Delivery	Weight (gr)	Gest. age (w)	IL12 (pg/mL)	IL10 (pg/mL)	IL12/IL10
Controls						
1	Vagin.	3,560	39	392	11.5	34
2	Vagin.	3,050	40	352	9.7	36
3	Vagin.	3,400	39	199	4.6	43
4	Vagin.	3,030	40	394	8.4	47
5	Vagin.	3,200	39	455	8.6	53
6	Caesar.	3,230	40	179	3.2	56
7	Vagin.	3,670	40	291	4.9	59
8	Vagin.	3,830	41	475	7.7	62
9	Vagin.	3,595	40	331	5.3	62
10	Vagin.	2,900	40	270	4.3	63
11	Caesar.	3,750	40	395	5.4	73
12	Caesar.	3,200	39	379	4.3	88
13	Vagin.	4,085	40	191	2.1	91
14	Vagin.	2,995	40	391	3.7	106
15	Vagin.	3,435	40	354	3.2	111
16	Vagin	3,350	38	1,178	9.7	121
17	Caesar.	3,390	39	133	1.0	133
18	Vagin.	3,035	40	309	2.2	140
19	Vagin.	3,970	41	496	3.5	142
20	Vagin.	3,235	38	472	2.4	197
21	Vagin.	3,155	39	334	1.4	239
22	Vagin.	2,900	40	412	1.7	242
23	Vagin.	2,900	40	254	1.0	254
24	Vagin.	3,200	42	433	1.7	255
25	Vagin.	3,370	41	270	1.0	270
26	Cesar.	2,525	39	299	1.0	299
27	Vagin.	3,170	40	439	1.4	314
28	Vagin.	3,460	41	327	1.0	327
29	Caesar.	4,055	40	346	1.0	346
30	Caesar.	3,230	42	473	1.0	473
31	Vagin.	3,160	42	292	*	*
Mean		**3,324**	**40.0**	**371**	**3.9**	**158**
St. dev.		**363**	**1.0**	**177**	**3.1**	**116**
Median		**3,230**	**40.0**	**352**	**3.2**	**116**

epitopes of the IL-10 or IL-12 molecules. The IL-12 kit measure total IL-12 (p40 + p70). Using these tests, no cross-reactions with other cytokines, such as IL-1, IL-2, IL-6, tumour necrosis factor (TNF) or interferon gamma (IFNγ) are detected. The inter- and intra-assay variations were below 10 %. The final sensibility of the tests was 1 pg/mL for IL-10, and 3 pg/mL for IL-12.

Statistical analysis

The values showed a non-parametric distribution, so results are expressed as median and the Mann-Whitney U-test and the Spearman coefficient were used to assess differences and correlations between two groups, respectively. The Bonferroni ANOVA was used for comparing preterm with RDS group, preterm without RDS and term newborn controls. For age matching, differences between preterm groups were repeated after suppressing cases with less than 26 gestational weeks, 28 w., 32 w. and so on. A logistic regression model, using logarithmic transformation, was used for calculating the RDS risk variation according to the IL-12/IL-10 ratio. Sensibility and specificity value and OR (95 % CI) were calculated for groups with high and low gestational age (> 32 w. <), IL-10 (> 10 pg/mL <) and IL-12 value (> 300 pg/mL <). Differences were considered significant when p value was < 0.05.

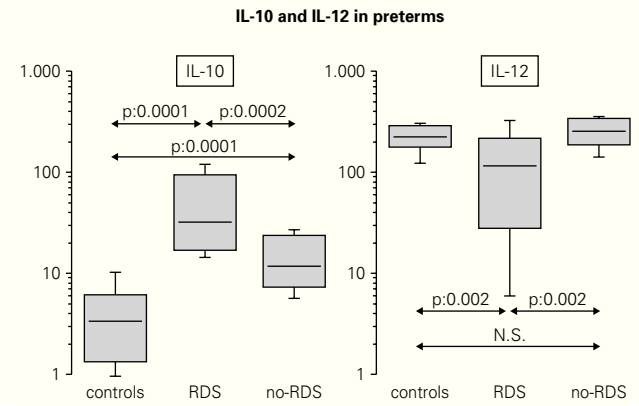

Figure 1.—Preterm infants with RDS showed higher IL-10 and lower IL-12 levels in cord blood compared to premature infants without RDS. Similar results were found when compared to full term infants.

RESULTS

General results

At birth, preterm infants with RDS showed higher IL-10 (27 vs 10.8 pg/mL, p: 0.0002) and lower IL-12 levels (188 vs 384 pg/mL, p: 0.002) than premature newborns without (table I). Similar results were found when compared to full term infants (IL-10: 3.2 pg/mL, p: 0.0001 and IL-12: 352 pg/mL, p: 0.002) (fig. 1). These results were confirmed by ANOVA Bonferroni test, assesing the three groups (IL-10, p: 0.0001 and IL-12, p: 0.005). No significant differences were found according to the severity of the RDS, although IL-10 and IL-12 levels were higher in cases with severe forms as compared to mild forms. No signficant differences were found in the group of 5 cases with sepsis. Children who died later showed higher IL-10 levels (p: 0.05) and a lower IL-12/IL-10 ratio (2.3 vs 11.0; p: 0.03) compared to survivor children. The IL12/IL10 ratio was lower in preterm newborns with RDS (4.6 vs 32; p: 0.0001) than in cases without RDS.

We found that the best discrimination was obtained setting up the cut-off point of the IL-12/IL-10 ratio at 20 value. Only 1/20 (5 %) child with RDS and 18/21 (86 %) without RDS showed levels above this point (sensibility 0.95; specificity 0.86) (fig. 2). Similar results were found when the cut-off point for IL-10 was raised to 10 pg/mL (sensibility 0.95 and specificity 0.77), nevertheless they were lower with IL-12 for a cut-off point at 300 pg/mL (sensibility 0.70 and specificity 0.73). The risk of RDS related to cord blood IL-10 level > 10 pg/mL (OR 69; CI 95 %: 7.8-546) was higher than the risk for IL-12 levels < 300 pg/mL or the gestational age < 32 weeks (table II)

The gestational age showed a strong negative correlation with IL-10 levels in the overall group of newborns (Z:-6.18; p: 0.0001) and in both preterm groups (Z:-4.56; p: 0.0001), but there was no correlation with IL-12 levels. On the other hand, IL-10 and IL-12 levels show no correlation with each other in any of the three groups. In the following days after delivery, the most striking finding in the 11 followed-up cases was

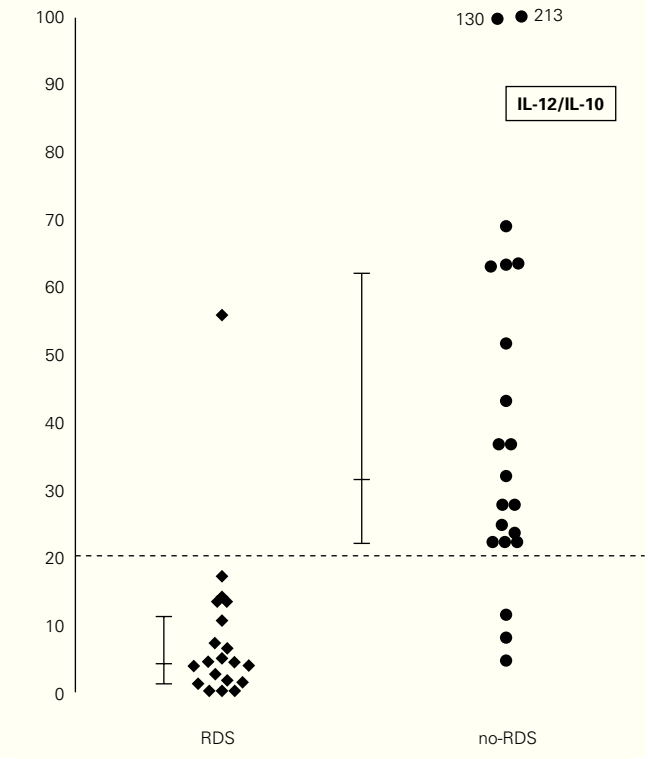

Figure 2.—The IL-12/IL-10 ratio was lower in preterm newborns with RDS (p:0.0001). A cut-off point at 20 showed a sensibility of 0.95 and specificity of 0.86.

Table II

Risk of respiratory distress syndrome (RDS) in the total newborn group

	No. (RDS/no-RDS)	OR (95 % CI)
Gestational age		
< 32 w	(13/11)	6.9 (2.2-21.5)
> 32w	(7/41)	
IL-10		
> 10 pg/mL	(19/11)	69 (7.8-546)
< 10 pg/mL	(1/38)	
IL-12		
< 300 pg/mL	(14/14)	6.33 (2.0-19.7)
> 300 pg/mL	(6/38)	

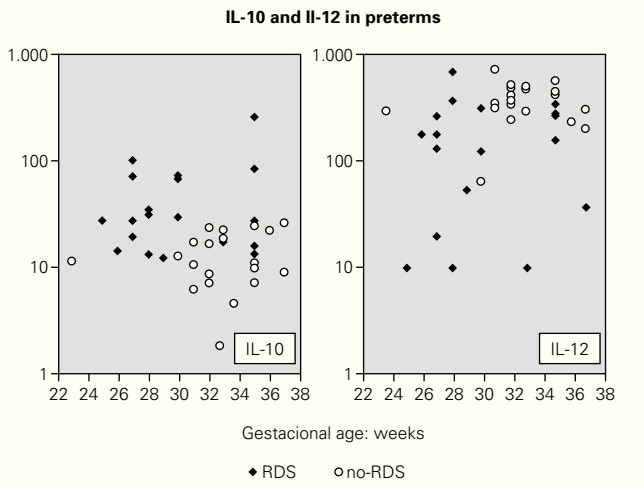

Figure 3.—The gestational age was lower in cases with RDS compared to those without RDS, but results did not change after a correction of the gestational age, by suppressing cases with less than 30 weeks.

the decrease in IL-12 levels, particularly in those with RDS (p: 0.0007) but also in premature infants without RDS (p: 0.004). By contrast, IL-10 levels decreased only in the group with RDS (p: 0.04) but not in those without RDS. No differences were found on weight, gestational age or cytokine levels among the group of infants born by caesarean delivery.

Results after correcting the gestational age

Newborns with RDS were younger than those without RDS (30 vs 32 weeks; p: 0.04), and they had lower body weight (1,230 vs 1,720 gr; p: 0.04). Nevertheless, these circumstances do not justify the strong difference found in IL-10 and IL-12 levels, because results did not change after correcting the gestational age effect (fig. 3). When a stratified study by gestational age was performed for groups > 28 and > 30 weeks, the birth weight and the gestational age were no different between RDS and non-RDS groups, whereas differences in IL-10 and IL-12 levels maintained the statistical significance (table III). Using a regression model with logarithmic data we found that the increase of 1 log unit of IL-10 levels was equivalent to the increase 12.01 times the RDS risk. On the contrary, the risk decreases 1.42 times for every 50 units of IL-12 increase.

DISCUSSION

We had previously reported high cord blood IL-10 levels in normal preterm infants, and an inverse correlation with gestational age[7], in agreement with other studies. The increased IL-10 expression in placenta in a gestational age-dependent manner followed by down-regulation at term may be underlying the mechanism of the delivery[8].

It is well known that RDS is strongly associated to gestational age. According to these findings, high cord blood IL-10 levels in RDS infants may be the expression of a biological immaturity of the fetus, independently of gestational age. By contrast, cord blood IL-12 levels were not related with gestational age, even though it tends to increase. Both premature and full term infants showed very high IL-12 levels at the time of delivery with a trend to decrease in the following days after birth[7].

An alternative explanation may be related to the antiinflammatory role of IL-10, manifested by its potent inhibitory effect on a vast array of cells and cytokines, particularly on Th1-type cytokines[9]. Surfactant deficiency in preterm infants leads to RDS, although some data also suggest a participation of local inflammation[10]. The study of inflammation in RDS is currently a matter of great interest. An interstitial inflammation was observed by immunohistochem-

Table III

Differences betwewn RDS and nom-RDS groups. Cases are stratified by gestational age

	No*	Birth weight	Gestational age	IL-12	IL-10	IL-12/IL-10
All cases	(20/21)	0.034	0.029	0.002	0.0002	0.0001
> 26 w	(19/21)	0.022	0.018	0.003	0.0004	0.0001
> 28 w	(14/21)	NS	NS	0.035	0.0001	0.0001
> 30 w	(10/20)	NS	NS	0.031	0.003	0.0001
> 32 w	(7/16)	NS	NS	NS	NS	0.0007
> 33 w	(7/10)	NS	NS	NS	NS	0.003
> 35 w	(6/7)	NS	NS	NS	NS	0.022

*(RDS/non-RDS).
The figures express the "p value" obtained by Mann-Whitney U-test. NS: no significant difference.

istry in 40 infants who died due to acute RDS in the first week of life, with a maximal process at 72 hours of age, though it began within hours of birth[11]. Moreover, circulating polymorphonuclear leukocytes are activated in preterm infants with RDS and this seems to play a role in pathogenesis, with leukocyte activation present only two hours after birth[12-14]. Nevertheless, the inflammation is transient, vanishing by day 7-10 unless chronic lung disease is developed[13]. Nevertheless, at present there is little evidence supporting a prominent antiinflammatory role of IL-10 in the prevention of chronic lung disease[15]. After LPS injection, IL-10 knock-out mice undergo a chronic disease similar to human ulcerative colitis, with cachexia, anaemia and shock[16,17] but it is striking that they do not develop lung disease, as it occurs in TGF-β knock-out mice[18]. IL-10 seems to be not related to airway inflammation, on the contrary, it has been found associated to recurrent wheezing and bronchial hyperresponsiveness in different experiment models[19-21]. In summary, an antiinflammatory role of IL-10 in fetal lung is not proved.

The main general stimuli for IL-10 secretion are proinflammatory cytokines, such as IL-1, IL-12, IFNγ, or TNFα[22] and it is noteworthy that steroids have an inhibitory effect on IL-10, though it is not clear whether this is the result of a direct effect on the cytokine, or a consequence of the depression of proinflammatory cytokines, which are very active in IL-10 stimulation[22,23]. During pregnancy, the regeneration and tolerance factor (RTF) expressed by tissue at the maternal interface and all the pregnancy-specific glycoproteins (PSGs) induce IL-10 secretion[23-25].

In an early study using bronchoalveolar lavage samples from preterm infants, no soluble IL-10, or IL-10 mRNA cellular expression were detected, whereas most samples from full term infants had positive results[26]. However, later studies showed detectable IL-10 levels in 50 % of bronchoalveolar samples from 17 premature infants[15]. These contradictory results are not relevant to our findings because bronchoalveolar lavage samples were obtained several days after birth. We have found increased serum IL-10 levels just at the time of delivery, decreasing later in postnatal life and becoming undetectable in a high percentage of samples. We should probably have to consider the delivery as a challenge test, when the feto-placental unit produces high amounts of different cytokines, due to a potent stimulus, which later disappears.

None of the infants included in our study developed bronchopulmonary dysplasia, and therefore we were unable to draw conclusions on this interesting aspect. We are planning a different experimental design to address this issue.

As occurs with other cytokines, the effect of IL-10 might be not exclusively anti-inflammatory, and different and even contradictory effects of IL-10 in particular situations are known. In adult healthy volunteers, it has been reported that after the injection of endotoxin, a high dose of IL-10 increases the effect of proinflammatory cytokines[27]. Others have shown that the tracheal instillation of IL-10 in animals highly increases bronchial hyperresponsiveness, and *knock-out* mice do not show bronchial response induced by allergens[28].

In conclusion, decreased IL-12 and, very specially, increased IL-10 levels were found in cord blood from the premature newborns, which developed RDS. The results were independent of gestational age, therefore the IL-12/IL-10 ratio give us more useful information on RDS risk than age or weight. Nevertheless, it remains unclear whether the increased IL-10 levels, besides reflecting functional immaturity of the newborn, has any role in the inflammatory process affecting the development of RDS.

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