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Influence of glucocorticoid and betamimetic therapy on milk secretory IgA concentration produced by mothers delivering preterm infants

M. Martell, C. Oehninger, C. Scotti, L. Delgado, M. Martínez, I. Korc

Centro Latinoamericano de Perinatología y Desarrollo Humano (OPS/OMS), and Departamento de Bioquimica, Facultad de Medicina, Montevideo, Uruguay

1 Introduction

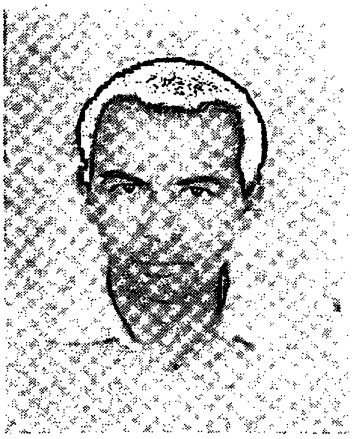
Nutritional and immunological requirements for growth and development of preterm infants are under continuous investigation [4, 6]. There are many reports stating that milk produced by mothers of term infants provides all the necessary nutritional requirements.

Recent reports have suggested that preterm infants may benefit from their mother's milk for their nutritional and immunological adaptation. Milk obtained from mothers of preterm neonates has increased contents of protein, fat, sodium and chloride, and lower concentration of lactose when compared with that of mothers of full term babies [1, 3, 8, 9]. The composition of saturated and unsaturated fatty acids is the same [14].

Besides its nutritional components, human milk contains many factors with bacteriostatic effects on the growth of many bacterial species including E. Coli [7, 10, 15]. Secretory IgA plays a major role in the protection of neonates from infection. In a longitudinal study of the effect of prematurity on the development of several components of the immunological system GOLDMAN [5] found that the concentration of lactoferrin and lysozyme were greater in preterm than in term infants. The secretory IgA was the predominant form in preterm mother's milk.

It is common in many obstetrical clinics to treat threatened premature labor by inhibiting uterine contractility with a betamimetic drug along with the administration of a glucocorticoid agent to prevent the respiratory distress syndrome in the neonate [11]. The aim of this study has been to find if these drugs given to mothers who delivered preterm infants had any influence on the secretory IgA concentration of maternal milk.

Curriculum vitae



MIGUEL MARTELL *was born in Uruguay in 1939. He received his Doctor of Medicine degree from the School of Medicine, University of Uruguay, Montevideo, Uruguay, in 1970. He specialized in pediatrics and works exclusively in neonatology. His main interest is in the field of growth, development and feeding of neonates which are preterm and low birth weight for gestational age. His work has been performed at the Latin American Center of Perinatology and Human Development (CLAP-PAHO/WHO) and at the Newborn Unit of the Hospital de Clinicas.*

2 Material and methods

Milk samples from three groups of mothers have been studied.

Group I: 11 mothers who delivered preterm neonates between 27 and 36 weeks of gestation

and not receiving any medication prior to delivery.

Group II: 10 mothers whose delivery occurred between 27 and 36 weeks gestational age and who received Fenoterol between 1 and 4 μg/minute I.V. or 20 mg daily orally, during 48 hours before delivery and a glucocorticoid agent (at least two doses of betametasone, 12 mg I.M., 48 and 24 hours before delivery).

Group III: 11 mothers giving birth at between 38 and 40 weeks of gestational age were considered as control group.

All the mothers aged between 18 and 32 years, were in apparently good health, good nutritional state and had no local inflammation of the breast. The ratio of nulliparous and multiparous women as well as the ratio of boys and girls in the offspring of each group were approximately equal. All mothers had ruptured membranes twelve or less hours before delivery. Gestational age was determined from the last menstrual period and by physical and neurological examination of the newborn. When the difference was greater than 15 days, the mothers were not admitted to the study.

The milk samples were collected with the following method: At 8 a.m. mechanical emptying of both breasts was performed and the milk was discarded. After three hours (11 a.m.) the same procedure was used to empty both breasts. This was done to establish a definite period of time and to avoid possible changes in concentration which may occur during the night. The milk from both breasts was mixed, the volume measured and an aliquot was removed and stored at $-20\,^{\circ}C$. The secretory IgA determination was performed between 20 and 30 days after obtaining the samples.

In each mother, the milk sample was obtained at three periods after delivery. The first one was collected between the 4th and 5th day, the second between the 8th and 10th day, and the last between the 14th and 15th day. Milk was not studied in the first three days after delivery, because mothers of preterm infants have little milk secretion at this time due to the fact that these infants are frequently nourished parenterally at this moment.

The quantitative determination of secretory IgA was carried out by the radial immunodiffusion technique of MANCINI et al. [13] using a specific antibody against the secretory piece (Bering Institute). The secretory IgA used for the reference standard was isolated and purified from colostrum and its protein concentration measured by microbiuret. All samples assayed, including the standard, were done in duplicate. A linear regression analysis was performed ($r^2 = 0.94$).

The analysis of variance was used to assess the concentration within the groups in every period studied. The STUDENT's paired test was used for the analysis of the evolution of the secretoy IgA concentration in each group at the different study periods.

3 Results

The gestational age in the preterm groups is shown in Tab. I. There was no significant difference between both groups, with and without drugs. Tab. II shows the concentration in the secretory IgA in the three groups.

The secretory IgA concentration in mothers who delivered at term was not significantly different, at any of the three periods, from mothers delivering preterm infants having or having not received glucocorticoid and betamimetic therapy (Fig. 1).

The concentration dropped abruptly at the beginning in the three groups and then remained unchanged. The differences were really important between the first and the second period ($p < 0.05$) but there was no significant difference between the second and third periods (Fig. 2).

Tab. I. Gestational age in weeks (mean and range) for the three groups

	Number of cases	Mean (weeks)	Range (weeks)
Group I	11	34	27–36 (*)
Group II	10	32	28–36 (*)
Group III	11	40	38–41

(*) Non significant between Group I and Group II

Tab. II. Secretory IgA concentration in grams/liter for the three groups in each period

	4–5 days			8–10 days			14–15 days		
	n	Mean	Range	n	Mean	Range	n	Mean	Range
Group I (Preterm without medication)	11	2.03	0.96–5.35	8	1.55	1.14–2.56	9	1.14	1.04–4.98
Group II (Preterm with medication)	10	3.17	1.55–5.35	9	2.03	1.55–5.35	8	1.47	0.96–2.03
Group III Full term	11	2.56	1.55–8.17	8	1.57	0.79–3.49	6	1.24	0.79–3.83

4 Discussion

The secretory IgA is the most concentrated immunoglobulin in human milk and provides it with anti-infection properties against a great variety of germs. Owing to its physical and chemical structure it is not affected by either digestive juices or pH changes. The quantification of milk secretory IgA, is a difficult technical problem and many kinds of methods have been used.

The previous mentioned values in human milk are expressed in different ways. These have been reported in arbitrary units, mg/g protein [15], g/l [10, 12] and mg/ml [5]. Our values are expressed in g/l, and they are quite similar to those reported by HANSON et al. [10] and GOLDMAN et al. [5].

We have not found differences in concentration in mothers with a full term delivery when compared with those who had a preterm delivery, having or having not received drugs. The same was found for colostrum, transitional and mature milk. This is a very important fact since drugs administered for the acceleration of pulmonary maturity and inhibition of uterine contractility in preterm labor would not produce modification in the secretory IgA concentration in maternal milk. This latter fact has not yet been pointed out regarding concentrations in preterm mother's milk.

Other authors, such as GROSS et al. [7] and LUCAS et al. [12] have found that the IgA secretory concentration is greater in preterm mothers. We have not been able to confirm this in our study. These authors do not mention whether the mothers were given any kind of medication.

According to the present study, it may be stated that glucocorticoid and betamimetic administration has no effects on the secretory IgA concentration in maternal milk.

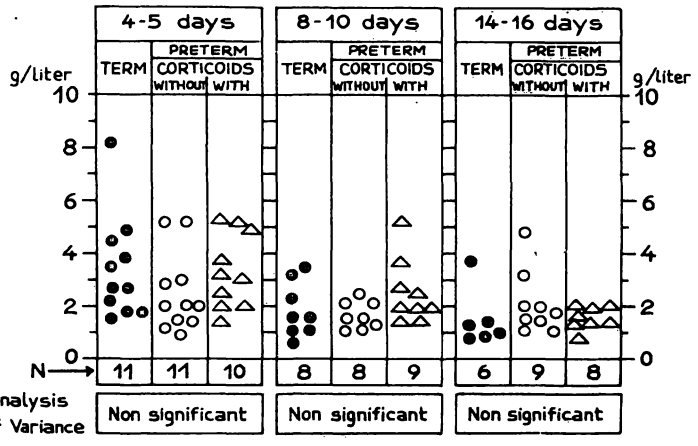


Fig. 1. IgA secretory concentration in milk from mothers with full and preterm delivery. There are no differences between the groups in the three periods.

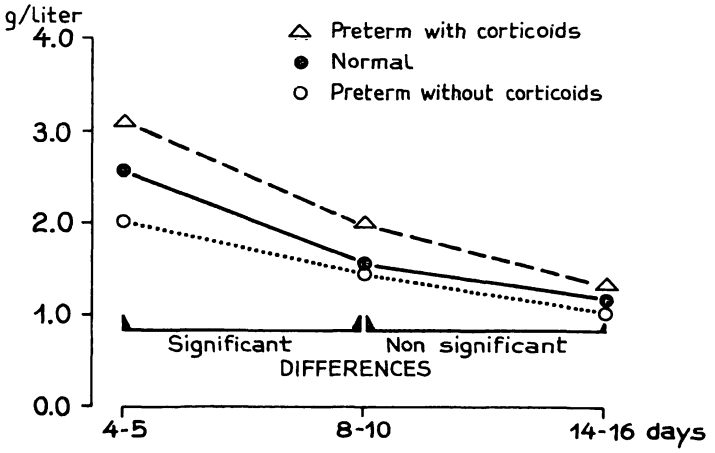


Fig. 2. The IgA secretory concentration is significantly greater in colostrum than in transitional milk. Between the latter and mature milk there are no differences.

Supporting the statements of other authors [1, 2, 3, 5, 7, 8, 9, 12, 14], we may conclude that the preterm infant's nutritional and immunological requirements could be met with milk from their own mothers. It therefore would be unnecessary to give formula or bank milk.

Summary

A prospective study was performed to find the possible difference in secretory IgA concentration in milk of mothers with term pregnancy labors and those delivering at earlier gestational ages. Since tocolytic drugs and/or glucocorticoid agents are usually given in cases of threatened premature labor, the pre-term group was divided into mothers with or without medication.
Thirty two mothers were distributed in three groups: Group I, mothers with preterm labors without any medication; Group II, preterm labors with previous treatment with betamimetics and glucocorticoids; Group III, term labors (see Tab. I). In each of the three groups, three periods were studied: colostral (4 to 5 days postpartum), transitional (8 to 10 days), and mature (14 to 15 days). All mothers were healthy, with good nutritional state, without local inflammation and membranes had been ruptured 12 hours or less before labor. There was no significant difference in the proportion of primiparas and multiparas in both groups. The gestational age was evaluated by amenorrhea and neonatal examination. In all mothers milk was extracted with a vacuum pump to empty the mammary gland. The determinations were made using a specific antibody against the secretory component. The concentration of free secretory component in these milks was practically insignificant.
No differences were found in the concentration of secretory IgA among the three groups (Tab. II, Fig. 1) in the periods that were studied, colostral, transitional or mature. The farther away from labor that milk extraction was made, in the periods considered in our study, there is a progressive decrease in the concentration of secretory IgA (Fig. 2).
No evidence has been found showing that medication given to the mother during the hours before delivery affects the concentration of secretory IgA in milk. This knowledge, together with other information previously described regarding composition of preterm mother's milk, supports the statement that preterm neonates may be fed with their own mother's milk.

Keywords: Betamimetics, glucocorticoids, human milk, preterm, secretory IgA.

Zusammenfassung

Einfluß von Corticoiden und Betamimetika auf die Konzentration von sekretorischem IgA in der Milch bei Müttern nach Frühgeburten
Wir führten eine prospektive Untersuchung mit folgender Fragestellung durch: gibt es Unterschiede zwischen den Konzentrationen von sekretorischem IgA in der Milch von Müttern mit Geburten am Termin und Müttern nach Frühgeburten? Da bei drohender Frühgeburt normalerweise wehenhemmende Mittel und/oder Corticoide verabreicht werden, mußte in der Frühgeburtengruppe weiter unterschieden werden zwischen Patientinnen mit und ohne Medikation.
32 Mütter wurden in 3 Gruppen aufgeteilt; Gruppe I: Patientinnen mit Frühgeburten ohne Medikation; Gruppe II: Frauen mit Frühgeburten, die vorher Betamimetika und Glucocorticoide erhalten hatten; Gruppe III: Frauen mit Geburten am Termin (Tab. I). In allen 3 Gruppen wurden 3 Phasen untersucht, in denen eine unterschiedliche Milch produziert wird: das Kolostrum (4–5 Tage p.p.), die Übergangsmilch (8–10 Tage p.p.) und die reife Milch (14–15 Tag p.p.). Alle Mütter waren gesund und in einem guten Ernährungszustand. Es lagen keine lokalen Entzündungszeichen vor und der Blasensprung war innerhalb von 12 Stunden ante partum erfolgt. Das Verhältnis von Erst- und Mehrgebärenden war in beiden Gruppen miteinander vergleichbar. Das Gestationsalter wurde durch die Dauer der Amenorrhoe sowie den neonatalen Reifezustand festgelegt. Die Milch wurde mit Vakuum abgepumpt, um so die Brustdrüse zu entleeren. Zur Konzentrationsmessung wurde ein spezifischer Antikörper gegen die sekretorische IgA-Komponente benutzt. Die Konzentration von freien sekretorischen IgA-Anteilen war bei allen Milchformen praktisch zu vernachlässigen. Zwischen allen 3 Gruppen gab es bezüglich der Konzentration von sekretorischen IgA innerhalb der einzelnen Phasen (Kolostrum, Übergangsmilch und reife Milch) keine Unterschiede (Tab. II, Fig. 1). Wir konnten feststellen, daß über unseren Beobachtungszeitraum das sekretorische IgA stetig abfiel, d.h., je länger die Geburt zurücklag, um so niedriger war das sekretorische IgA (Fig. 2).
Wir fanden keinen Anhalt dafür, daß eine der Geburt vorangegangene Medikation der Mutter die Konzentration von sekretorischem IgA beeinflußt. In früheren Arbeiten wurde die Zusammensetzung der Milch von Müttern nach Frühgeburten beschrieben. Das Ergebnis der vorliegenden Arbeit unterstützt die Forderung, daß Frühgeborene Muttermilch erhalten sollen.

Schlüsselwörter: Betamimetika, Corticoide, Frauenmilch, Frühgeburt, sekretorisches IgA.

Résumé

Influence des corticoïdes et des bétamimétiques sur la concentration des IgA secrétoires dans le lait des mères d'enfants prématurés

On a réalisé une étude prospective pour trouver une différence possible entre la concentration des IgA secrétoires dans le lait des mères ayant accouché à terme et des mères ayant accouché à des termes gestationnels plus précoces.

En raison du fait que l'on utilise habituellement des médicaments utéro-relaxants et/ou des corticoïdes en cas de menace d'accouchement prématuré, le groupe prématuré a été subdivisé en mères traitées et non-traitées.

Trente-deux mères ont été réparties en trois groupes: groupe I, mères avec accouchement prématuré sans traitement; groupe II, accouchement prématuré avec traitement antérieur par bétamimétiques et corticoïdes; groupe III, accouchement à terme (Tab. I). Dans les trois groupes, on a étudié trois périodes: colostrale (4 à 5 jours); transitionnelle (8 à 10 jours) et mature (14 à 15 jours).

Toutes les mères étaient bien portantes, avec un bon équilibre nutritionnel, sans inflammation locale et avec une rupture des membranes inférieure ou égale à 12 heures. Il n'y a pas eu de différence significative dans la proportion de primipares et de multipares entre chaque groupe. L'âge gestationnel a été déterminé par la durée de l'aménorrhée et l'examen néonatal. Chez toutes les mères, le lait a été extrait à l'aide d'une pompe à aspiration afin de vider la glande mammaire. L'analyse a été effectuée à l'aide d'un anticorps spécifique contre les composants secrétoires. La concentration des composants secrétoires libres dans ces laits était pratiquement insignificante.

On n'a pas trouvé de différence dans la concentration des IgA secrétoires entre les 3 groupes (Tab. II, Fig. 1), au cours des 3 périodes étudiées, colostrale, transitionnelle et mature. Aussi longtemps que l'on a poursuivi les prélèvements de lait après l'accouchement, il y a eu dans les périodes de notre étude une diminution progressive de la concentration des IgA secrétoires (Fig. 2).

On n'a pas trouvé d'arguments en faveur d'un retentissement des médications données à la mère au cours des heures précédant l'accouchement sur la concentration d'IgA secrétoires dans le lait.

Cette connaissance, jointe aux autres informations préalablement décrites sur la composition du lait des mères d'enfants prématurés, conforte l'idée que les nouveaux-nés prématurés doivent être nourris à l'aide du lait de leurs propres mères'

Mots-clés: Accouchement prématuré, bétamimétiques, corticoïdes, IgA secrétoire, lait humain.

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Dr. Miguel Martell
Centro Latinoamericano de Perinatología
y Desarrollo Humano
Casilla de Correo 627
Montevideo, Uruguay