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Biologic Substances Present in Human Colostrums

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Abstract

Colostrum is nowadays known to contain a large number of chemical substances that provide immune protection to suckling newborns and that may also promote the development of neonatal immune competence. The primary components, divided into two classes, include immune factors and growth factors. These specialized components partecipate to hormone-regulated events that prepare the breast to lactation and protect the mammary gland from pathogen colonization. In addition to the hormonal function, colostrum represents a source of essential substances, important for the development of infants such as lipids for the brain development, oligosaccharides for the development of intestinal flora to modulate the immune response, endorphin and S100B proteins to protect the infant during the postnatal adaptation. The study of this fascinating aspect of human nutrition has been developed only recently, considering the human milk as the gold standard to build new updated formulas. The opportunity to collect colostrums during the first three days from delivery in mothers living in Burkina Faso, one of the poorest country of Sub-Saharan area, gives us an instrument to trace the evolution of breast milk. The determination of IGF and prolactin in colostrum of Sicilian mother compared to colostrum of African women demonstrate a significant difference, according the necessity of newborn adaptation after the intrauterine life. The endorphin levels were found elevated in African colostrum and correlated with the degree of asphyxia and difficulty in the delivery. This protection was also demonstrated by analyzing the oligosaccharide in the African colostrum which show a characteristic secretion of 2-FL more early than that found in Sicilian colostrums. These studies confirmed that a genetic selection is operating in colostrum and supports that the difference between African and Sicilian is due to the needs of African newborns, born in precarious conditions of life.

Keywords: Colostrum, Biologic Substances, Sicily, Burkina Faso

List of Abbreviation

- **IGF:** Insulin Growth Factor
- **NS:** Nervous System
- **NK:** Natural Killer
- **2-FL:** 2-fucosyl Lactose
- **LNFP:** Lacto-N-FucoPentaose
- **sIGA:** surface Immunoglaaaaassszobulin A

Introduction

Colostrum, secreted 2-4 days after delivery, is originally regarded as a food supplying essential nutrients to newborn growth. It is, nowadays, known to contain a large number of chemical substances that provide immune protection to suckling newborns and that may also promote the development of neonatal immune competence [1]. It has a mild laxative effect, encouraging the passing of the baby's first stool, which is called meconium.

There are over 90 known components in colostrum. The primary components, divided into two classes, are immune factors and growth factors. Colostrum also contains a precise balance of vitamins, minerals and amino acids. All of these factors work together in perfect synergy to restore and maintain health.

Immune Factors in colostrum have been shown to help the body to fight off harmful invaders such as viruses, bacteria, yeast and fungi. Each factor plays a specific role in the body defense against these attackers. In addition, colostrum contains over 20 antibodies to specific pathogens including E coli, salmonella, rotavirus, candida, streptococcus, staphylococcus, H pylori, and cryptosporidia.

These specialized components are also essential to hormone-regulated events that prepare the breast to lactation and protect the mammary gland from pathogen colonization [2]. They also cooperate or compete with other growth factors (e.g., epidermal, fibroblast, platelet-derived, and transforming growth factors α and β) to induce either growth stimulation or inhibition, as well as differentiation, preservation, and apoptosis [3]. In addition to the hormonal function, colostrum represents a source of essential substances, important for the development of infants such as lipids for the brain development, oligosaccharides for the development of intestinal flora to modulate the immune response, endorphin and S100B protein to protect the infant during the postnatal adaptation. However, the study of this fascinating aspect of human nutrition has been developed only recently, considering the human milk as the gold standard to build new updated formulas.

The opportunity to collect colostrum during the first three days from delivery in mothers living in Burkina Faso, one of the poorest country of Sub-Saharan area, gives us an instrument to trace the evolution of breast milk. The discovery of stem cells in colostrum has properties that go beyond what one can imagine. Stem cells in human infant milk differentiate not only into mammary cells but also into macrophage cells, including neutrophil-like cells of other tissue types. Stem cells migrate from milk to infant. Given their accessibility they could be used in patients with damage to the central nervous system [4].

Analysis of Human Colostrum during the Infant Development

We started this study collecting human colostrum, which represents the first infant aliment. This first period of life is absolutely important for the immunological imprinting of newborns. The determination of IGF and prolactin in colostrum of Sicilian mother compared to colostrum of African women demonstrate a significant difference, according the necessity of newborn adaptation after the intrauterine life [5]. The composition of lipid in colostrum of African mothers compared to Sicilians suggest that this difference could be due to the special needs of nervous system (NS) during its development [6]. This characteristic is supported also by elevated levels of S100B in African colostrums compared to Sicilian [7].

The endorphin and S100B levels were found elevated in African colostrums and correlated with the degree of asphyxia and difficulty in the delivery [8]. This result demonstrates that physiologically the endorphin represents an effective protection on NS especially in newborn with asphyxia. This protection was also demonstrated by analyzing the oligosaccharide in the colostrum which show a characteristic secretion of 2-FL more early than that found in Sicilian colostrums [9]. This oligosaccharide shows an immuno-modulant effect on the macrophage activity, in culture, when stimulated with LPS [10]. This seems another function of colostrum in the immunological imprinting that protects the NS from the abnormal production of cytokines, associated to newborn asphyxia. The effect of colostrum in the protection against fungal infections is due to the elevated chitotriosidase (Chit) level, a chitinase that digests the chitin lining of Candida species [11]. These studies confirmed that a genetic selection is operating also in colostrum and supports that the difference between African and Sicilian colostrums is due to the needs of African newborns who born in precarious conditions.

Prolactin (PRL) and IGF-1

The IGF-I levels found both in colostrum from African and Sicilian women were lower, whereas the PRL values, observed in colostrums from African and Sicilian women, were higher than those reported in similar studies [5]. Previous studies performed on Italian women demonstrated that both growth factor content and mitogenic activity in colostrum are high but decrease considerably during lactation [12]. The IGF-I levels in the colostrums of Sicilian women, who had full-term delivery, were significantly higher than those found for African women in the first 2 days (see Figure 1). It is noteworthy that the IGF-I levels of Sicilian women who had cesarean delivery were significantly lower in the second day. The PRL levels in African women were comparable to those of Sicilian women. Nevertheless, taking into account that the colostrum volume was fairly larger for African women than for Sicilian women, the amount of IGF-1 and PRL ingested was significantly larger in African newborns than in Sicilian newborns , and this turns out to be crucial for the development and maturation of the immune system [5, 13]. Moreover, both the colostrum volume and PRL concentration detected in Sicilian women submitted to cesarean delivery were significantly reduced in the second day from the cesarean delivery. This phenomenon could be attributed very likely to the surgery trauma and the anesthetic drugs and highlights the negative effect on the hormonal balance induced by the stress [5].

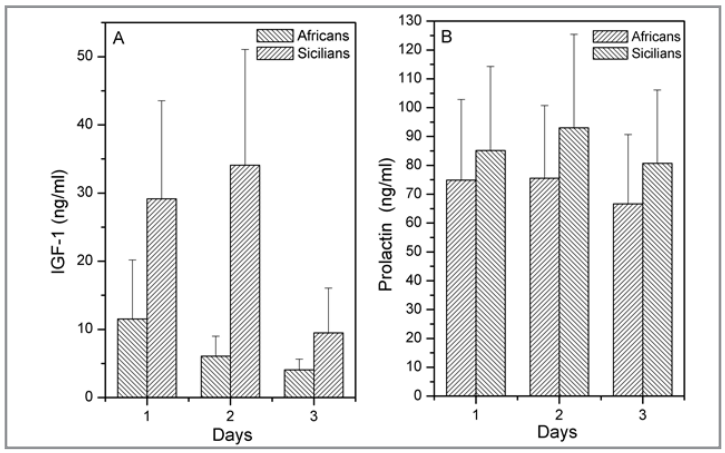

Figure 1: IGF-1 and Prolactin levels (mean +/- SD) in colostrum of African and Sicilian mothers in the first three days after delivery (IGF-1 in Africans 1° versus 2° versus 3° day, P< 0.0001; in Sicilians 1° versus 2° versus 3° day P< 0.0001; Africans versus Sicilians P< 0.0001)

Lipids

Differences in the fatty acid composition of colostrum samples from African and Sicilian women were more evident in the first 24-48 hours, however the levels converged progressively in the following days, where the differences became insignificant (see Table I) [6]. Slight differences in the levels of saturated fatty acid were found in the first days comparing Sicilian to African colostrum. Also monounsaturated fatty acids, arachidonic acid (AA, 20:4n-6), docosahexaenoic acid (DHA, 22:6n–3) and long-chain n-3 polyunsaturated fatty acids (LC n–3 PUFA) levels were lower in the colostrums of African women than in the colostrum of Sicilian women. The α-linolenic acid (LNA, 18:3n-3) content was lower in the first day, while the linoleic acid (LA, 18:2n-6) was higher in African colostrum. Consequently, the 18:2n-6/18:3n-3 and LCn-6/LCn-3 ratios were higher in the colostrum of African women than in the Sicilian women. In a previous study on the fatty acid composition of mature breast milk from African women, Rocquelin et al, 2001 detected an elevated level of saturated fatty acids due to the typical maternal diet, rich in cereals, that contains high quantities of linoleic acid oils (cotton seed and peanut oil) [14]. In fact the same authors, by comparing the milk lipid composition of women living in Burkina Faso with that of women living in Brazzeville (Congo), demonstrated a higher weight gain in children from Congo during the first 5 months of life, due to the characteristic diet of Congolese mothers, based essentially on fish instead of vegetables as in Burkina Faso, ensuring a more balanced 18-2n-6/18n3-n3 (between 5:1 and 15:1) ratio [15].

Table 1: Fatty acid composition (% w/wt) in colostrum of Sicilian and African mothers in the first three days after delivery.

	Italian (colostrum) 1° day	P	Italian (colostrum) 2° day	P	Italian (colostrum) 3° day	Burkinabe (colostrum) 1° day	P	Burkinabe (colostrum) 2° day	P	Burkinabe (colostrum) 3° day
Total Lipid content (g/dl)	**2.20±1.30***	**0.029**	**3.00±1.40**	**NS**	**3.70±1.50**	**2.90±1.20**	**0.019**	**3.50±1.40**	**0.009**	**4.30±1.70**
Saturates										
C8:0	0.10 ± 0.03	NS	0.09± 0.03*	NS	0.10± 0.03*	0.10 ± 0.01	0.0001	0.20± 0.03	0.0001	0.30± 0.02
C10:0	0.63 ± 0.30	NS	0.64 ± 0.35	NS	0.71 ± 0.38	0.51 ± 0.32	0.0027	0.70±0.35	NS	0.78± 0.37
C12:0	3.51 ± 1.50	NS	3.52 ±1.48	NS	3.74± 1.55*	3.01 ± 1.40	0.002	3.98± 1.75	0.0001	4.95 ±2.00
C13:0	0.03 ± 0.01	NS	0.04 ± 0.01	NS	0.04 ± 0.01	0.02 ± 0.01	NS	0.02 ±0.01	NS	0.03 ±0.01
C14:0	6.42 ± 1.25	NS	6.50 ± 1.30	NS	6.85 ± 1.40	5.86 ± 1.30	0.0004	6.87± 1.51	NS	7.23± 1.65
C15:0	0.16 ± 0.04	NS	0.10 ± 0.03	NS	0.10 ± 0.03	0.10 ± 0.03	NS	0.10± 0.03	NS	0.10 ±0.03
C16:0	30.1±2.51	NS	28.62 ±2.48	NS	27.89 ±2.35	33.09 ±3.01	NS	32.66±3.25	NS	29.92±3.15
C17:0	0.30 ±0.09*	0.0007	0.20 ±0.08*	0.023	0.15 ±0.05*	0.41 ±0.09	0.0003	0.34 ±0.10	0.0001	0.25± 0.08
C18:0	4.90 ±2.00	NS	4.61 ±2.10	NS	4.32 ±2.12	5.26 ±2.40	NS	5.04 ±2.51	0.018	3.98 ±2.01
C19:0	0.01 ±0.01	NS	0		0	0.02 ± 0.01	NS	0		0
C20:0	0.20 ± 0.01	NS	0.20 ±0.012	NS	0.20 ±0.01	0.20± 0.01	NS	0.20±0.01		0.15 ±0.01
C21:0	0.15 ±0.09	NS	0.10 ±0.08	NS	0.10 ±0.09	0.18 ±0.12	NS	0.15 ±0.11	0.0001	0.10±0.09
C22:0	0.10 ±0.08	NS	0.10 ±0.07	NS	0.10 ±0.08	0.10 ±0.09	NS	0.10 ±0.09	NS	0.10 ±0.09
C24:0	0.20 ±0.01	NS	0.20 ±0.01	NS	0.20 ±0.01	0.20 ±0.01	NS	0.20 ±0.01	NS	0.20 ±0.01
Monosaturates	39.19±4.14*	NS	39.13±4.89*	NS	40.89±4.20*	34.35± 4.49	0.003	31.91±3.58	NS	32.72±4.07
PUFA										
18:2(n – 6)	12.09± 3.89	NS	12.3± 1.93	NS	12.57±2.90*	13.48± 5.73	NS	12.96±3.02	0.002	15.02±3.55
20:4(n – 6)	0.35 ± 0.14*	0.002	0.47± 0.14*	NS	0.45± 0.15*	0.17 ± 0.10	0.001	0.26 ±0.08	0.025	0.30 ±0.10
LC (n – 6) PUFA	1.11± 0.35*	0.001	1.47± 0.27*	0.001	1.17 ± 0.33	0.87 ± 0.40	0.005	1.07 ±0.32	0.001	1.21 ±0.34
18:3(n – 3)	0.63± 0.25*	NS	0.65 ± 0.34	0.028	0.50 ± 0.13	0.29 ± 0.02	0.001	0.57 ±0.18	NS	0.53 ±0.07
22:6(n – 3)	0.11± 0.04*	0.001	0.19± 0.11*	NS	0.15± 0.07*	0.06 ± 0.03	0.001	0.06 ±0.03	0.001	0.08 ±0.03
LC (n – 3) PUFA	0.16± 0.05*	0.001	0.30± 0.17*	0.011	0.21± 0.08*	0.07 ± 0.05	0.014	0.09 ±0.03	0.001	0.12 ±0.04
Ratios										
18:2(n-6)/18:3(n-3)	21.79±11.1*	NS	23.33± 9.23	NS	26.48±7.15*	47.30±28.02	0.001	25.71±7.97	0.001	30.36±5.34
LC (n – 6)/LC(n– 3)	7.17 ± 2.37*	NS	6.31± 3.04*	NS	6.15± 2.18*	15.09± 8.64	NS	13.00±4.56	NS	11.51±4.48

Also in Italy, Scopesi et al, 2001 demonstrated that maternal dietary saturated and monounsaturated fatty acids intake was significantly correlated with milk levels of these fatty acids during the transitional milk phase (P<0.01), while the total polyunsaturated (PUFAs) content correlated only in the mature milk phase (P<0.01) [16].

The lower concentration of arachidonic acid (AA, 20:4n-6) observed in the colostrum of African women in the first days, could provide the African children of a protective mechanism for modulating the inflammatory responses, since arachidonic acid is a prostaglandin precursor. Moreover, low quantities of arachidonic acid in breast milk could accelerate the Botallo duct closure in African infants, with documented benefits for newborns [6].

On the contrary the higher concentration of linoleic acid (LA, 18:2n-6) in colostrum of African women could influence the infant neurological and immune development. It is known that ethnic differences in metabolism rates may correct the effects of dietary deficiencies and vice versa. In fact, rural African women consuming few animal fats tend to have high levels of long-chain n-6 polyunsaturated fatty acids (LC n–6 PUFA) in milk, regardless of the maternal dietary intake of preformed LCP (long chain polyunsaturated fatty acids) [6]. In fact the breast milk fatty acid composition of Fulani women, living in Northern Nigeria has been found lacking in a-linolenic (18:3n–3) and docosahexaenoic (DHA, 22:6n–3) acids; notwithstanding their poor eating habits and a nomadic lifestyle, Fulani children develop and grow normally without specific pathologies linked to dietary unbalance.

Finally, it is worth noting the anomalous pattern of lipid composition found in the colostrums of Sicilian women, who delivered by a scheduled caesarean section. Their lipid composition was characterized by a significant decrease of fatty acid levels, not explained by maternal diet or socio-economic status. Only the monosaturated fatty acid levels were found increased. This unexpected result suggests that both the stress of caesarean delivery and the effect of anaesthetic drugs could influence the lipid metabolism and, consequently, the breast milk lipid composition [6].

Endorfin (EPs)

Beta-EPs levels assessed in African colostrum were significantly higher than those found in Sicilian mothers during the first 3 days of lactation [8]. Beta-EPs content in human colostrum may be important in overcoming birth stress and in postnatal foetal adaptation. These considerations help to explain the elevated Beta-EPs levels in colostrum of African women that, in turn, could ensure a major protection to newborns in the postpartum. On the contrary, Beta-EPs concentration in colostrum of Sicilian women was lower, probably due to the better assistance level to mothers from the obstetricians during delivery and to active child birth preparation, with the consequent minor labour stress. In fact the longer the delivery periods/the stronger the pain/the higher the stress, the higher would be the risk of neonatal tissue injury with the subsequent requirement of "stress adaptation", role that could be assigned to Beta-EPs.

The effect of Beta-EPs is not limited to the nervous cells, but also on cells of the immune system. In particular, some studies reported the presence of Beta-EPs receptors in immune system cells. Beta-EPs was found to interact specifically with T lymphocytes, enhancing in vitro mitogen-induced T cell proliferation and augmenting human natural killer (NK) cell cytotoxic activity [17]. Beta-EPs derived peptides may be considered as selective agonists of non-opioid receptors for Beta-EPs and this effect is particularly relevant for neonates, born in African countries, ensuring them a better adaptation to extauterine life.

The higher Beta-EPs levels measured in colostrum of full term delivery African women dropped by approximately 25% from day 1 to day 3, while those lower found in Sicilian women decreased to a much lesser extent.

The relation between the role of child birth preparation in the pathogenesis of stress has been documented by the lower Beta-EPs secretion in Sicilian mothers. In fact it is significant the correlation between Beta-EPs and the length of stage II.

All data obtained in these studies suggest that the elevated Beta-EPs amount ingested by African newborns may have a relevant role in the adaptation of newborn to extra-uterine life in the unfavorable condition where the delivery is realized.

S100B

The S100B levels in the colostrum of full term delivery African and Sicilian women show that S100B levels assessed in African were significantly higher than those found in Sicilian colostrum only during the first day of lactation [7]. Moreover, our data showed that the levels of S100B in the colostrum of Sicilian woman during the first three days are higher than that found by Gazzolo et al, 2003, and only after third day the values in ng/ml should be comparable between the two different studies [18]. These differences could be due to different modalities of execution, including thaw or freeze or to different kits. Thus, the elevated content of S100B in African colostrum could be important in overcoming birth stress, favouring the brain maturation, giving major protection to newborns in postpartum because its neurotropic role. After this period the level of S100B decreased reaching similar concentration of Sicilians. On the contrary, S100B concentrations in colostrum of Sicilian women could be lower in the first day of lactation, probably due to the better assistance levels (lengh of stage II) to mothers during delivery and to child birth preparation, with the consequent minor labour stress. However no correlation was found among Beta-EP and S100B both in African and Sicilian colostrum confirming that any relationship exist among these two proteins with regard to their regulation and gene expression.

The progressive increment of S100B levels from colostrum to transition milk and mature milk demonstrate that this protein is important during the brain maturation of infants feed at breast, while in formulae milks the S100B is at the lowest level reported in human milK, probably due to the protein epitopes modification during the production process [19].

The S100B levels are comparable in the colostrum of second and third days in African and Sicilian mothers, but African women produce more colostrum (2-3 times) and their newborns so receive a higher S100B amount. This could promote the brain maturation in the precarious nutritional condition of African mothers, whose colostrum contain lower levels of DHA 22:6n–3 (Docosahexaenoic acid) and LC n–3 PUFA (long-chain n-3 polyunsaturated fatty acids), a risk factor for future infant development [6].

Moreover, ethnic factors may impact the timing of lactogenesis stage II and it is possible that the African mothers secreted milk sooner and in larger quantities than the Sicilian women, with the aim of major protection of their newborn.

These could be convincing explanations for volume difference and S100B content between African and Sicilian colostrum in the first day of lactation.

Oligosaccharides

On a qualitative level, the analysis of colostrum from African and Sicilian mothers, indicating a comparable oligosaccharide composition in women classified as secretor ABH/Lewis a-b+, suggests that the oligosaccharide secretion is maintained in ontogenesis [9]. However, a difference in the proportion of some oligosaccharides clearly distinguishes colostrum of African from that of Sicilian women (Figure 2). The 2' FL is the first and prevalent oligosaccharide in African colostrum and its appearance is followed by the appearance of LNFP-1. Since the volume of the colostrum in African mothers is greater than that of Sicilian mothers, African newborns receive in absolute more 2'-FL by breast milk than Sicilian newborns. The reason for a delay in the appearance of 2'-FL in Sicilian mothers is not clear. The results obtained by Chaturvedi et al, 2001, in secret or ABH/Lewis a-b+ Mexican women, where the predominant oligosaccharide during the first few months lactation was 2'-FL followed by LNFP-I, support the hypothesis that this delay may be attributed to racial factors [20].

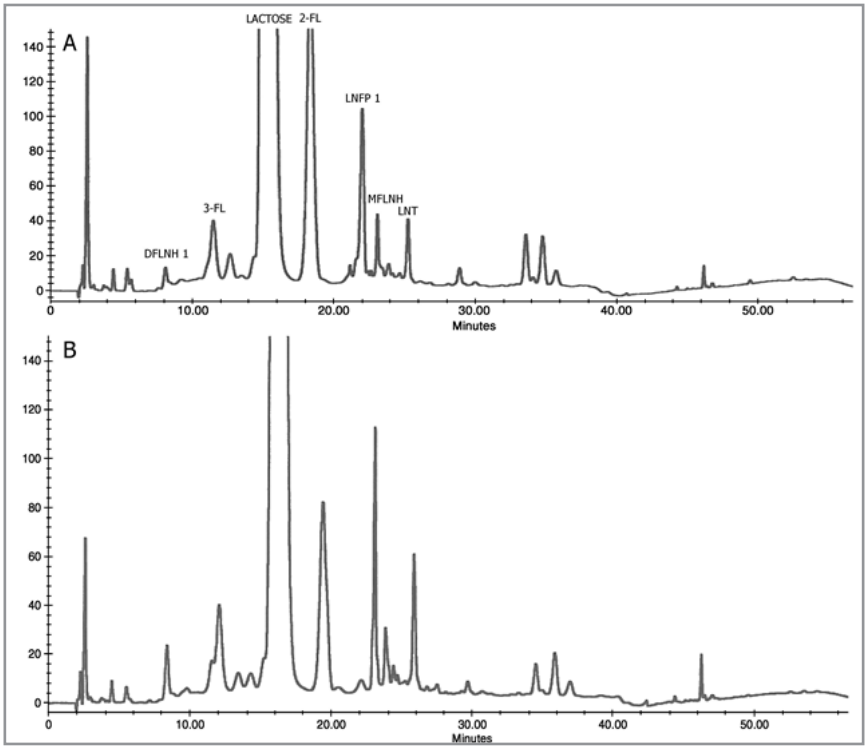

Figure 2: Oligosaccharides in colostrum of African (A) and Sicilian (B)mothers in the third days after delivery (DFLNH 1, disialyllactose-N-tetraose; 3-FL, 3-fucosyllactose; 2-FL, 2-fucosyllactose; LNFP 1, lacto-N-fucopentaose; MFLNH, monofucosyllacto-N-hexaose; LNT, lacto-N-tetraose.

There are differences in concentration and temporal changes for each oligosaccharide, which seem to characterize breast milk in different geographical and ethnical areas. Erney et al, 2000 by studying the fucosyl-oligosaccharides of human milk in different populations, found that 100% of Mexican samples and only 46% of Philippine ones contained 2'-FL, which may be explained by non-uniformly distribution of genetically-determined traits [21]. Interestingly, Newburg et al (Newburg et al, found that the variable expression of a1,2-linked fucosyl-oligosaccharides in milk of Mexican women significantly relates to lower incidence of diarrhoeal disease among breastfed infants [22]. Thus, the protection against diarrhoeal diseases afforded by human milk could depend on the fucosyl-oligosaccharide secretion and, particularly, on the different content of 2'-FL. In fact, Coppa et al, 2003 recently demonstrated that complex fucosyl-oligosaccharides of human milk inhibit the adhesion of Listeria monocytogenes to the adenocarcinoma cell line of the human colon by means of a selective receptor-like mechanism, mimicking intestinal receptors for pathogens [23]. In the aboriginal Mestizo Mexicans, the very low prevalence (1% or less) of non-secretor mothers could be a consequence of the greater vulnerability of infants receiving milk with low content of protective a1,2-linked fucosylated-oligosaccharides [24]. In fact, individuals of O blood group type have greater susceptibility to cholera and to other virus strains, suggesting a basis for selecting a genotype that provides the highest protection against pathogens.

The protective function of oligosaccharides may relate not only to competition with epithelial ligands on the intestinal mucosa aimed at preventing the attachment of several pathogens, but also to the potential effect exerted by their binding to the mannose-fucose receptors on the macrophage surface. Then 1,2-linked fucosylated-oligosaccharides contained in human colostrum may have yet several undefined functions in the cascade of events following the appearance of lactation.

Chiotriosidase (Chit)

The mean levels of Chit activity are increased in the colostrum of the African women, especially in the first two days after delivery [25]. Interestingly, Chit decreases in the third day, confirming that the secretion of colostrum in addition to its important role for the newborn nutrition, has an important protective function especially during the first days of life (see Figure 3). This enzyme, produced by activated macrophages of breast milk could influence both the growth and differentiation of the intestinal epithelium and at the same time facilitates the establishment of a gut flora that inhibits colonization by many pathogens and stimulates the growth of beneficial micro-organisms.

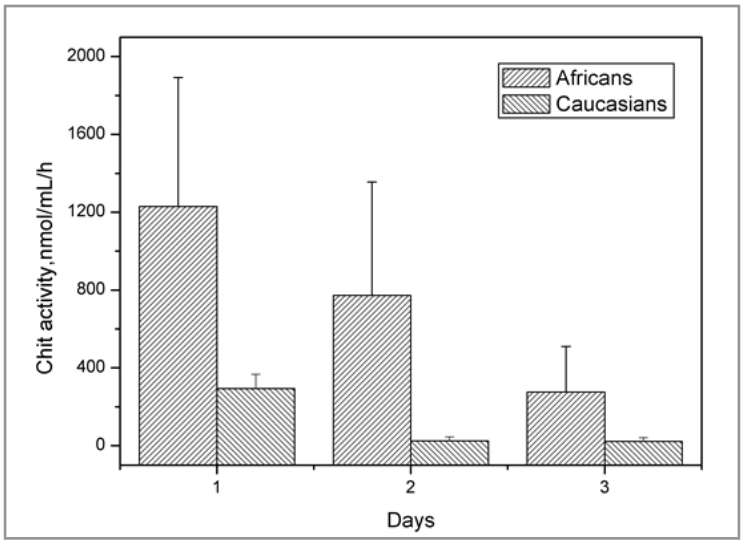

Figure 3: Chitotriosidase (Chit) activity (mean +/- SD) in colostrum of African and Sicilian mothers in the first three days after delivery (Africans versus Sicilians P< 0.001; 1° versus 2° versus 3° day P< 0.001).

The level of Chit in African women is higher in accordance with the genetic polymorphism of CHIT gene in Sub-Saharan areas. Our study performed in Benin and in Burkina Faso, both endemic regions for plasmodium falciparum malaria and infections due to intestinal parasites, a low incidence of CHIT mutation for the duplication of 24 base pairs in exon 10 (heterozygous 0% and 2% respectively) was found and no subject homozygote for Chit deficiency were identified [26]. In Sicily and in Sardinia, the heterozygote frequency for the duplication was 44 % and 32.71 % respectively, whereas homozygous Chit deficient were 5.45 % and 3.73 %. As a direct consequence of the elevated frequency of the 24 base pair mutation, the Chit level was lower in the breast milk of Sicilian women since the first days, while the level of Chit activity in plasma of African women were higher than Sicilian women.

In human plasma, Chit activity have been proposed as a biochemical marker of macrophage activation and our results confirm that, also in colostrums, Chit has a relevant role in the protection of newborn against pathogens species in the first days of life. The ratio between Chit activity in colostrum and in plasma suggests an active production of Chit from macrophages of human milk. As a direct consequence of this fact, the oral candidiasis is very rare in the first month of life in African infants, despite a large diffusion of oral and intestinal candidiasis in the following months (personal observation).

The role of human Chit in the protection against Candida albicans and nematodes it has been sustained by the consideration that this enzyme shows a chitinase activity on artificial chitin substrate and it could be considered an endo-cellular antibiotic. Nevertheless, contrasting results about a presumptive anti parasitic activity of Chit have been reported. Masoud et al, 2002 did not find any difference in the percentage of homozygotes for the defective Chit allele among survivors of Candida sepsis with respect to the control population [27]. Hise et al, 2003 studying the polymorphism of three innate immunity genes suspected of contributing to the susceptibility to infections and lymphatic pathologies, showed in residents of Papua New Guinea that CHIT mutation and polymorphisms of toll-like receptors-2 and toll like receptor-4 genes did not correlate with human Wuchereria bancrofti filarial infection [28]. These results are clearly in contrast with previous paper of Choi et al, 2001 who showed that the homozygous condition for defective allele and the consequent decreased Chit activity was associated with the elevated susceptibility to human Wuchereria bancrofti filarial infection [29].

However the low level of Chit in colostrums of Sicilian women, which is in accord with the high heterozigote frequency of the mutated allele (medially 44%) in Sicilian population, suggests that Chit enzyme could be redundant (i.e. not essential for defence mechanism), in Sicilians with respect to Africans.

Based on these studies, it appears that genetic and environmental features could be responsible for diversity of colostrum Chit activity among Sicilian and African populations.

HIV load and Cytokines

The mechanism which is responsible of HIV load decreasing in colostrum it is not clear. It is possible that the reduction of the

HIV load in colostrums must be due to the reduced replication of HIV and to the progressive reduction of macrophages in the colostrums, that are present at high concentration in the first days for the defence of newborn from pathogens contaminating the breast milk [30].

However the virus, which is now present in colostrum at lower concentration, as in other similar situations, increases its infectivity for the presence of cytokines favouring the CD4+ receptors expression on the lymphocytes surface. An example of this is the more infectivity of mothers which are affected by mastitis because the colostrum is more rich of cytokines, which favour the infectivity of colostrums or HIV. The colostrum contains significantly higher levels of IL-18 compared with early milk and mature milk, which correlates with preterm delivery and pregnancy complication and plays an important role in host defense of high-risk neonates. The increased content of IL-16 a chemo-attractant factor present in breast milk may be responsible for the traffic of leukocytes from the maternal circulation to the breast milk (Figure 4). The stable presence of IL-12 shows that in breast milk pro-inflammatory cytokines are essential in the protection of newborns from the pathogens especially in the first days of life. In addition to the regulation of late inflammatory functions such as INF-gamma production, IL-12 and IL-18, alone or in combination, regulate early inflammatory events such as T cell adhesion to inflamed sites. On the contrary the presence of TGF beta1 and TGF-beta2 balance the increase of pro-inflamatory cytokines in colostrum.

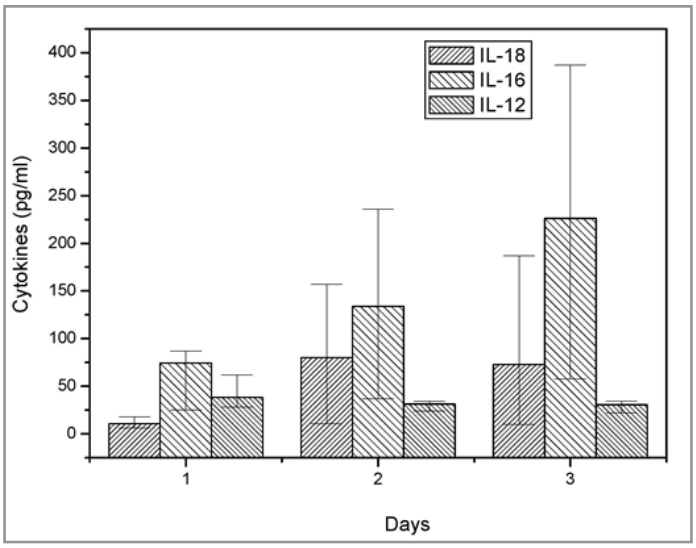

Figure 4: Median and range levels of cytokines (IL-18, IL-16 and IL-12) in colostrum of 20 HIV infected African mothers in the first three days after delivery (IL-18, 1° versus 2° day P <0.05; IL-16, 1° versus 2° versus 3° day P< 0.001).

In conclusion, IL-18, IL-16 and IL-12 increase the risk of HIV infection for the newborn receiving colostrum since the first day and stimulate the maturation of immune system, favoring both the penetration of HIV inside the CD4+ cells. Since it is no possible modify the composition in cytokines of human colostrum and considering that HIV load decrease also for effect of Nevirapine profilaxis, it is advisable to interrupt the administration of colostrum in this critical period of lactation. In developed countries the mother-to-child transmission has been dramatically reduced by the use of antiretroviral treatment and avoidance of breastfeeding. However these regimens including highly active antiretroviral therapy are not praticable in under developed countries, where a possible strategy is suspending for three days the colostrum administration.

In this way the death rate of babies and the vertical transmissions is nearly to zero [14].

Immunoglobulins and Hyperimmune Colostrum

Newborns have very small digestive system, and colostrum delivers its nutrients in a very concentrated low-volume form. Colostrum is known to contain immunoglobulins such as IgA, IgG, and IgM. IgA are absorbed through the intestinal epithelium, travels through the blood, and are secreted onto other Type 1 mucosal surfaces. They are the major components of the adaptive immune system [31]. Colostrum is very rich in proteins, vitamin A, and sodium chloride, but contains lower amounts of carbohydrates, lipids, and potassium than normal milk. The most pertinent bioactive components in colostrum are growth factors and antimicrobial factors. The antibodies in colostrums provide passive immunity, while growth factors stimulate the development of the gut.

Hyperimmune colostrum was an early attempt to boost the effectiveness of natural bovine colostrum by immunizing cows with a specific pathogen and then collecting the colostrum after the cow gave birth. This, initially, appeared very promising as antibodies did appear towards the specific pathogens or antigens that were used in the original challenge. However, upon closer examination and comparison, it was found that IgG levels in natural colostrum towards 19 specific human pathogens were just as high as in hyperimmune colostrum, and natural colostrum nearly always had higher antibody titers than did the hyperimmune version [32]. Colostrum contains a multitude of components that

can, or may, provide immune protection to the suckling offspring and that also may promote development of neonatal immune competence. Moreover, these specialized factors are essential for the protection of the mammary gland, the offspring's food source, from pathogen colonization and lactation failure. Colostrum also facilitates the establishment of a gut flora that inhibits colonization by many pathogens and stimulates the growth of beneficial microorganisms. Maternal immunity can be transferred to the infant via antibodies, primarily of the sIgA type in humans, as well as by leukocytes including effector and memory T lymphocytes. In this way, protection is provided passively against the pathogens to which the mother has been exposed. Currently, there is much interest in determining the protective efficacy of oral supplementation with immunoglobulins from the colostrums of lactating animals hyperimmunized against specific pathogens [33]. An array of immunostimulatory components in milk, notably cytokines, may be protected against intestinal proteolysis, thereby providing the offspring with a prepackaged immune response system. These components may help to boost the infant's immature immune system. At the same time, anti-inflammatory factors (IL-10) in colostrums help to modulate cytokine responses to infection, thereby facilitating defense and minimizing tissue damage such as that which occurs in infants with necrotizing enterocolitis. Undoubtedly, the many components constituting the repertoire of immune and immunomodulating agents in colostrum interact synergistically to protect both the mammary gland and the offspring from invading pathogenic microorganisms [34, 35].

Conclusion Remarks

Milk contains a multitude of biological substances that can provide immune protection (chitotriosidase and immunoglobulins) to the suckling newborn and that also may promote development of neonatal immune competence (cytokines and interferon). In addition, these specialized factors are also essential for the protection of the mammary gland from pathogen colonization and lactation failure. Moreover colostrum also favours the establishment of a gut flora and inhibit colonization by many pathogens. Maternal immunity can be transferred to the infant via antibodies, primarily of the IgA type in humans, as well as by leukocytes including memory T lymphocytes. Currently, there is much interest in the protective efficacy of oral supplementation with immunoglobulins from colostrum of lactating animals hyperimmunized against specific pathogens. Colostrum protect immunostimulatory components, notably cytokines, against intestinal proteolysis. These biological substances contained in colostrums may help to mature the infant's immature immune system. At the same time, anti-inflammatory factors present in colostrum (IL-10) help to modulate cytokine responses to infection, thereby minimizing tissue damage such as that which occurs in newborn with necrotizing enterocolitis. Undoubtedly the biological substances contained in colostrum interact in synergy to protect both the mammary gland and the offspring from invading pathogenic microorganisms. Moreover the endorphin and S100B protect the brain of newborn from the consequence of asphyxia in African newborns while the lipid contents of African colostrum favour the brain development. In addition the presence in colostrum of growth factors (IGF-I) favour the intestinal maturation and the body development, while the prolactin regulates the breast function. These substances are contained in more elevated quantity in African colostrum since the precarious condition of people living in Africa determine a selective pressure to preserve the newborn.

Key Facts

- Colostrum is nowadays known to contain a large number of chemical substances that provide immune protection to suckling newborns and that may also promote the development of neonatal immune competence.
- The primary components in colostrum include immune factors and growth factors, both partecipate to hormone-regulated events that prepare the breast to lactation and protect the mammary gland from pathogen colonization.
- Colostrum represents a source of essential substances, such as lipids for the brain development, oligosaccharides for the development of intestinal flora to modulate the immune response, endorphin and S100B protein to protect the infant during the postnatal adaptation.
- The opportunity to collect colostrums during the first three days from delivery in mothers living in Burkina Faso, one of the poorest country of Sub-Saharan area, gives us an instrument to trace the evolution of breast milk.
- These studies demonstrate a significant difference between African and Sicilian colostrums, according the necessity of newborn adaptation after the intrauterine life, due to a genetic selection of African newborns who born in precarious conditions of life.

Summary Points

- Colostrum contains a multitude of biological substances which provide immune protection to sucking newborn and that also may promote development of neonatal immune competence.
- These specialized factors are also essential for the protection of the mammary gland from pathogens and the offspringing from invasive pathogenic microorganism. Moreover, colostrum also favours the establishment of a gut flora and inhibits colonization by many intestinal pathogens.
- Maternal immunity can be transferred to infant via antibodies, primary of the sIgA type, as well as by leukocytes and macrophages including memory T lymphocytes. Chitotriosidase is also present in human colostrum.
- Anti-inflammatory factors present in colostrum (IL-10) help to modulate cytokine responses to infection, thereby minimizing tissue damage such as that which occurs in newborn with necrotizing enterocolitis.
- Currently, there is much interest in the protective efficacy of oral supplementation with immunoglobulins from colostrum of lactating animals hyperimmunized against specific pathogens.
- Colostrum protect immunostimulatory components, notably cytokines, against intestinal proteolysis.
- The endorphin and S100B protect the brain of newborn from the consequence of asphyxia in African newborns, while the lipid contents of African colostrum favour the brain development.
- In addition the presence in colostrum of growth factors (IGF-I) favour the intestinal maturation and the body development while the prolactin regulate the breast function.
- These substances are contained in more elevated quantity in African colostrum since the precarious condition of people living in Africa determine a selective pressure to preserve the health of newborn.

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