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Biologic substances present in human colostrums demonstrate the evolution of this essential nutrient for growth and development: Insulin-like growth factor-I and prolactin[☆]

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Abstract

The aim of the present study was to see whether the level of both insulin-like growth factor-I (IGF-I) and prolactin (PRL) present in the colostrums of women coming from fairly different environmental conditions showed any significant difference. To this end, the IGF-I and PRL levels of African and Italian women still living in their countries of origin were determined. The IGF-I levels of African women turned out to be lower than those of Italian women (11.53 ± 8.67 vs 29.16 ± 14.39 ng/mL) and, in addition, significantly and progressively decreased within the first 3 days after delivery. The IGF-I levels in the colostrums of Italian women who delivered by cesarean delivery were comparable to that of African women who delivered by spontaneous delivery. However, because the colostrum volume and the IGF-I level of African women are larger and lower, respectively, than those typical of Q3 Italian women, Italian and African newborns end up receiving roughly the same amount of IGF-I on day 1 after birth. Prolactin levels in Italian and African women were comparable (85.16 ± 29.14 and 74.88 ± 27.97 ng/mL) and were significantly reduced in 10 Italian women 2 days after the cesarean

☆ Each author contributed to this study in equal manner and no conflict of interest exists.

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delivery (59.22 ± 12.96 ng/mL). The progressive decrease of IGF-I level detected in the first 3 days of life demonstrates the crucial role of IGF-I in the development of both gastrointestinal and immune systems. In addition, the stability of PRL levels in the first 3 days of life underlines the essential role of this hormone in the switching on of lactation as well as in the regulation of immune response.

Keywords: IGF-I; Prolactin; Colostrums; African women; Italian women

1. Introduction

Milk, originally regarded as a food furnishing essential nutrients to infant growth, is nowadays known to contain a large number of chemicals that provide immune protection to suckling newborns and that may also promote the development of neonatal immune competence [1]. In addition, these specialized components are 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 (ie, epidermal growth factor, fibroblast growth factor, platelet-derived growth factor, and transforming growth factors α and β) to induce either growth stimulation or growth inhibition, as well as differentiation, preservation, and apoptosis [3,4]. Q4

Insulin-like growth factor-I (IGF-I) and prolactin (PRL), protein hormones present at the start of lactation, subserve also as immunoregulatory mediators [5,6]. In fact, IGF-I is mainly involved in the growth and development of newborns' gastrointestinal tract [7,8]. Moreover, IGF-I can stimulate milk yield and blood flow in goats when directly infused into the mammary gland, suggesting that it plays an important role in supporting lactation [8].

Prolactin is generally associated with the start of lactation; however, there are evidences clearly indicating that milk PRL is also involved in a variety of physiological functions including differentiation and maturation of neonatal neuroendocrine and immune systems [1-9].

The role of IGF-I and PRL in the immune system derives from the identification of IGF-I and PRL receptors immunocompetent cells, leading to the hypothesis that PRL and IGF-I possess a direct effect on the immune system [5,6]. Based on this statement, the function of IGF-I and PRL in the human milk may be particularly determinant for neonates who are born in the African countries by spontaneous delivery, considering the environmental conditions and the absence of elementary hygienic norms.

The aim of the present study was to determine PRL and IGF-I in colostrum of African women compared with Italian women living in Europe, to evaluate differences, if any, between these 2 groups, and to correlate these parameters to the neonate requirements.

2. Methods and materials

2.1. Colostrum sample collection

Fifty-three African women (Centre Medical St Camille Maternity, Ouagadougou, Burkina Faso) and 30 Italian women (S. Bambino Maternity, Catania, Italy) were investigated. The characteristics of the 2 groups are listed in Table 1. Italian and African women were orally

Table 1
Characteristics of the women investigated

Women	Age (y)	No. of delivery	Colostrum volume		
	Median (range)	Median (range)	Day 1	Day 2	Day 3
African (n = 53)	26 (17-40)	4 (1-9)	6.0 ± 0.5*	8.0 ± 0.5*	10 ± 0.5*
Italian (n = 30)	27 (20-30)	2 (1-3)	2.0 ± 0.1*	4.0 ± 0.1*	6.0 ± 0.1*

* $P < .0001$ (milliliters of colostrums collected in 10 minutes).

informed about the aim of this study. Written informed consents were obtained from Italian women only.

The average age of African women was 26 years (range, 17-40 years). African women had on the average 4 pregnancies [1-9] and they all delivered at the end of the 40th week except 2 who had premature deliveries (36 weeks) and were consequently treated separately in the statistical evaluation. It is important to underline that all African women investigated in the present study had spontaneous deliveries. The median age of Italian women was 27 years (range, 20-30 years); Italian women had on the average 2 pregnancies [1-3]. Of the 30 Italian women, 10 delivered by cesarean delivery and were therefore considered separately in the statistical evaluation. The living condition of African women was clearly different from that of Italian women living in Europe. They all came from poor villages with little comforts and often lacked drinkable water. The 2 groups followed the traditional eating habits of their countries of origin (ie, millet, vegetables, fruit, and little meat for African women, and wheat, vegetables, fruit, fish, and meat for Italian women). Colostrum samples were collected by the same teams both in Italy and in Burkina Faso according to a standardized procedure: colostrum was collected by manual expression into a sterile polystyrene tube in the morning after awakening and before baby breast-feeding. Manual expression was carried out for 10 minutes and this operation was repeated for 3 consecutive days at 6:00 AM ± 30 minutes. Colostrum samples, kept over ice, were immediately rushed to the local laboratory and were frozen at −20°C. These samples were then transported (over dry ice) to the Institute of Biochemistry and Clinical Biochemistry (School of Medicine, Catholic University, Rome, Italy). After thawing, colostrums were firstly centrifuged (680 × g for 10 minutes) at 4°C. The supernatants were removed and the sample was recentrifuged (10 000 × g for 30 minutes) at 4°C. Colostrum serum samples thus obtained were stored in 1.5-mL polypropylene tubes and were frozen at −20°C until assayed for IGF-I and PRL. Colostrum samples from Italian women were collected and stored by following the same procedure and were also sent to Rome for analysis.

2.2. IGF-I and PRL assays

Insulin-like growth factor-I was assayed by IGF-I Chemiluminescence Immunoassay (Nichols Advantage, San Juan Capistrano, Calif) by using a Liaison equipment (Nichols Advantage). The intra-assay variation coefficient (repetitivity) was ±4.8%; the inter-assay variation coefficient (reproducibility) was ±6.7%; the smallest single value that can be distinguished from zero at 95% confidence (sensitivity) was 6 ng/mL. A standard sample was added to each plate; the reported results were the mean of 2 determinations.

Table 2
Levels of IGF-I and PRL in the colostrums of African and Italian women

	Women	IGF-I (ng/mL)			PRL (ng/mL)		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
A (n = 53)	African	11.53 ± 8.67*	6.08 ± 2.91*	4.07 ± 1.57*	74.88 ± 27.97	75.54 ± 25.17	66.69 ± 24.02†
B (n = 20)	Italian	29.16 ± 14.39¶	34.1 ± 16.95¶	9.51 ± 6.54*	85.16 ± 29.14	93.03 ± 32.43	80.74 ± 25.37
C (n = 2)	African (preterm)	7.75 ± 1.28	3.33 ± 0.54§	3.65 ± 1.68	65.25 ± 12.65	60.23 ± 18.46	58.45 ± 22.03
D (n = 10)	Italian (cesarean delivery)	11.04 ± 6.54	10.50 ± 5.89$^{\Vert}$	8.13 ± 3.87	95.64 ± 29.98	59.22 ± 12.96$^{\Vert}$	77.77 ± 26.34

A, Day 1 → day 2→ day 3 (*P < .0001; $^{\dagger}P$ = .067). B, Day 1 → day 2→ day 3 (*P < .0001). C, Day 1 → day 2→ day 3 ($^{\S}P$ = .046). D, Day 1 → day 2→ Day 3 ($^{\Vert}P$ < .061).

A→ B, *P < .0001; A→ C, not significant; B→ D, $^{\P}P$ = .0001.

Prolactin was assayed by an electro-chemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany) by using a Modular Analytics E 170 (Roche Diagnostics). The intra-assay and inter-assay variation coefficients were ±2.9% and ±4.0%, respectively, whereas the sensitivity was 0.47 ng/mL (see above).

2.3. Statistical analysis

Data were presented as mean ± SD. Statistical comparison of PRL and IGF-I concentrations among the samples collected over 3 consecutive days were performed using paired and unpaired Student *t* test or Mann-Whitney *U* test (when appropriate) and were considered statistically significant when $P < .05$. All computations were performed using SPSS-10 program for Windows (SPSS, Inc, Chicago, Ill).

3. Results

Table 1 summarizes the characteristics of African and Italian donors. The colostrum volume collected from African women was about 2 to 3 times larger than that of Italian women. The results of IGF-I and PRL determinations (ng/mL) are reported in Table 2.

Insulin-like growth factor-I concentration in the colostrums of African women was 11.53 ± 8.67 ng/mL in the first day and these values progressively and significantly decreased in the second day (6.08 ± 2.91 ng/mL, $P < .0001$) and in the third day (4.07 ± 1.57 ng/mL, $P < .0001$) (Fig. 1). Insulin-like growth factor-I concentration in the colostrums of Italian women in the first day was higher (29.16 ± 14.39 ng/mL) than in African women, remained stable for the first 2 days from the delivery, and decreased in the third day (9.51 ± 6.54 ng/mL) (Table 2).

Prolactin levels in the colostrums of African women were comparable to those found in Italian women. Unlike IGF-I concentration, these levels remained stable over the first 3 days (Table 2).

Insulin-like growth factor-I concentration of Italian women (10 of 30) who had cesarean deliveries was found to be significantly lower than that detected in women who had full-term

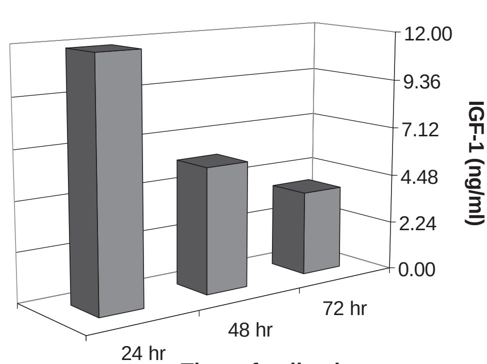

Fig. 1. Values of IGF-I in the colostrums of African women.

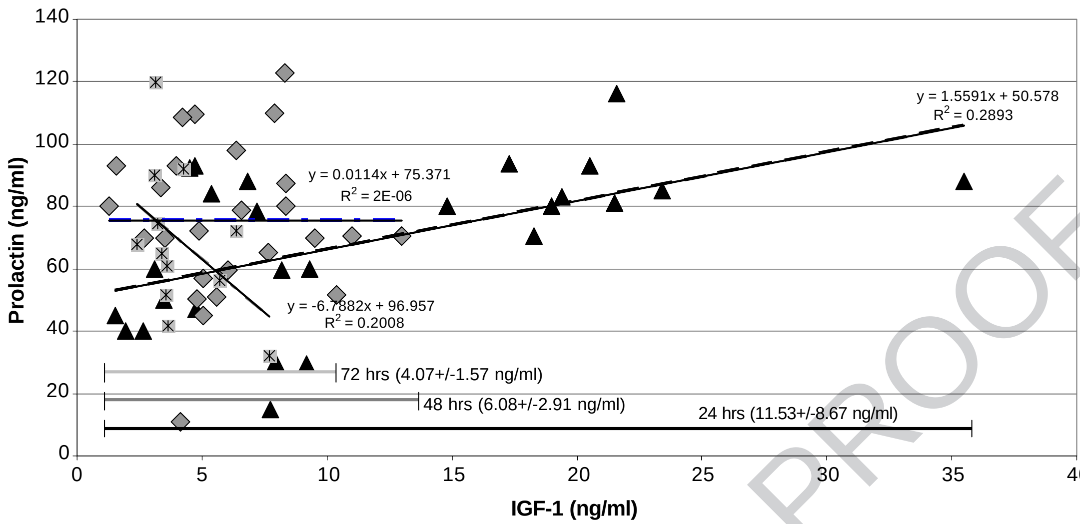

Fig. 2. Correlation between IGF-I and PRL in the colostrums of African women.

delivery (11.04 ± 6.54 vs 29.16 ± 14.39 ng/mL); their PRL was also found to be lower and decreased significantly in the second day (59.22 ± 12.96 ng/mL, $P < .0001$).

The colostrum IGF-I and PRL concentrations of 2 African women who delivered prematurely were found to be lower than that of women who had full-term delivery (IGF-I concentrations were 7.75 ± 1.28, 3.33 ± 0.54, and 3.65 ± 1.68 ng/mL in the first, second, and third day, respectively; PRL concentrations were 65.25 ± 12.65, 60.23 ± 18.46, and 58.45 ± 22.03 ng/mL in the first, second, and third day, respectively) (Table 2).

A positive correlation ($r^2 = 0.29$) between colostrum IGF-I and PRL levels was found in the first day only. Such a correlation was no longer detectable in the second day and became negative in the third day ($r^2 = -0.20$) (see Fig. 2).

No significant correlation between IGF-I and PRL was found for Italian women in any of the 3 days.

Interestingly, IGF-I and PRL levels could not be correlated with anthropologic parameters such as age and number of deliveries.

4. Discussion

The IGF-I levels obtained for African and Italian women were always lower than those reported in the literature [10] whereas the PRL values, observed in both African and Italian women, were higher than those reported in similar studies [11]. The reason for this is not entirely clear and might be because of the different assay technique or method of colostrum expression (manual or electric pump); however, a soft technique such as manual expression together with the use of an external standard should further support the statistical significance of the present results.

Previous studies performed on Italian women demonstrated that both growth factor content and mitogenic activity in colostrums are high but decrease considerably during lactation [10]. The IGF-I levels in the colostrums of Italian women who had full-term delivery were significantly higher than those found for African women in the first 2 days; however, this difference became statistically irrelevant in the third day. It is noteworthy that the IGF-I levels of Italian women who had cesarean delivery were significantly lower in the second day already. The IGF-I levels of Italian women who delivered by cesarean delivery were comparable to that of the African women in the first day but were significantly higher on the second and third day after delivery. However, because the colostrum volume and the IGF-I level of African women are larger and lower, respectively, than those of Italian women, Italian and African newborns end up receiving roughly the same amount of IGF-I on day 1 after birth. The PRL levels in African women were comparable to those of Italian women. Nevertheless, taking into account that the colostrum volume was fairly larger for African women than for Italian women, the amount of PRL ingested was significantly larger in African newborns than in Italian newborns [12], and this turns out to be crucial for the development and maturation of the immune system [9]. Moreover, it is noteworthy that both the colostrum volume and PRL concentration detected in Italian 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 [13].

On the other hand, the IGF-I and PRL levels in the colostrums of African women who delivered prematurely were lower than those of women delivering at term, suggesting that the lower levels of IGF-I and PRL in preterm lactation are mediated, at least in part, by (1) the stress-induced suppression of PRL secretion [13], (2) the maturity stage of the newborn, (3) the energy intake, and (4) the type of lactation [14].

The decrease (from day 1 to day 3) of IGF-I level in the colostrums of African women suggests that this hormone plays a crucial role mainly in the first 24 hours. The correlation between IGF-I and PRL (positive on day 1 and negative on the following days), observed in African women only, would support the hypothesis that in African women the high PRL levels are essential to maintain high milk production. Insulin-like growth factor-I and prolactin would be present in the colostrums not only to promote the growth of the newborn but also to prepare the mammary gland for lactation. The elevated volumes of colostrums (2 to 3 times larger in African women) and, consequently, the elevated IGF-I and PRL amounts ingested by the African newborns are crucial for metabolic performance, endocrine, health status, and growth performance [15]. Our results point out the great benefit of spontaneous delivery on lactation, which appears to be declining in Italian women nowadays. In fact, the nutrition and the protection of the infant represent the primary role of breast-feeding after delivery. The growth and differentiation of the intestinal epithelium are very likely influenced by IGF-I milk content [3,4] because the gastrointestinal cells of the newborn are the first cells to come in contact with colostrums. In addition, the function of the small intestine is to absorb nutrients from colostrums and to provide a barrier to the sensitization to extraneous substances [16]. Colostrums also facilitate the establishment of gut flora that, in turn, inhibit colonization by many pathogens and stimulate the growth of beneficial microorganisms [17]. Therefore, breast-fed babies are better protected against various infections for some years and also show an enhanced response to vaccines [18]. A long-lasting protection against certain immunologic diseases, such as allergies and celiac disease, has also been found [19,20]. Moreover, IGF-I improves the use of the relatively small protein content of milk by acting locally on the gut mucosa [21]. In addition to this classic functions, we suggest that IGF-I may also be involved in the development and proliferation of the mucosal immune system and may contribute to the migration and activation of intestinal T lymphocytes that, in turn, enhance mucosal immunity during the early neonatal period. This hypothesis is supported by the following evidences: (1) IGF-I is involved in T-lymphocyte and B-lymphocyte proliferations [22]; (2) activated T cells and B cells possess receptors for IGF-I; (3) IGF-I is chemotactic for activated T cells [23]; and (4) pretreatment of murine thymic epithelial cell with IGF-I increases their adhesion to thymocytes [24]. An increase in the frequency of $CD4^{-}CD8^{-}CD90^{+}$ T cells, which adhered to pretreated thymic epithelial cells after IGF-I administration, has also been observed, which further supports the idea that IGF-I may also act indirectly on intrathymic T-cell differentiation and migration through the thymic epithelium [24].

Prolactin, like IGF-I, is an important factor for the growth and development of the mammary gland [25] and it is essential for lactogenesis and the start of lactation. Increasing evidence has shown PRL to be involved in a series of physiological functions, including osmoregulation, and behavioral modifications [26]. Prolactin response has been demonstrated in numerous extrapituitary tissues, including endothelial [27], neuronal [28], and immune cells (ie, thymocytes, lymphocytes, and mononuclear cells) [29,30]. Prolactin is currently being thought to be both a circulating hormone and cytokine [29,30]. The role of PRL as a cytokine is further established by studies demonstrating its structural similarity to members of the cytokine/hematopoietin receptor superfamily [31]. In addition, PRL receptors are expressed in the lympho-hemopoietic system [32], confirming the important role of PRL in the development of the immune system [33,34]. Likely, both IGF-I and PRL carry out very important functions in the complex network of the immune system. In conclusion, our results demonstrate that these components of colostrums influence the maturity of newborn immune competence that is of particular relevance to the newborn health, especially in very harsh environmental conditions.

5. Addendum

After the last revision of this paper, Qin et al [35] found in 118 serial samples of human Chinese colostrums (lactation 1-4 days postpartum) that IGF-I concentration on the first lactation day was significantly higher than that on the fourth day ($P < .01$), decreasing from 25.9 ± 2.7 to 5.6 ± 1.3 μg/L. This confirms our data and supports the indispensable function of IGF-I in the normal growth and development of infants.

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References

[1] Ellis LA, Mastro AM, Picciano MF. Milk-borne prolactin and neonatal development. J Mammary Gland Biol Neoplasia 1996;1(3):259-69.

[2] Neville MC, Morton J. Physiology and endocrine changes underlying human lactogenesis II. J Nutr 2001;131:3005S-8S.

[3] Hirai C, Ichiba H, Saito M, Shintaku H, Yamano T, Kusuda S. Trophic effect of multiple growth factors in amniotic fluid or human milk on cultured human fetal small intestinal cells. J Pediatr Gastroenterol Nutr 2002;34(5):524-8.

[4] Wagner CL, Forsythe DW. Effect of human milk and recombinant EGF, TGFalpha, and IGF-1 on small intestinal cell proliferation. Adv Exp Med Biol 2000;478:373-4.

[5] Kooijman R, Hooghe-peters EL, Hooghe R. Prolactin, growth hormone and insulin-like growth factor-I in the immune system. Adv Immunol 1996;63:377-454.

[6] Clark R. The somatogenetic hormones and insulin like growth factor-I: stimulators of lymphopoiesis and immune function. Endocr Rev 1997;18:157-79.

[7] Burrin DG. Is milk-borne insulin-like growth factor-I essential for neonatal development? J Nutr 1997;127(5 Suppl):975S-9S.

[8] Prosser CG. Insulin-like growth factor in milk and mammary gland. J Mammary Gland Biol Neoplasia 1996;1(3):297-306.

[9] Ellis LA, Mastro AM, Picciano MF. Do milk-borne cytokines and hormones influence neonatal immune cell function? J Nutr 1997;127(5 Suppl):985S-8S.

[10] Suikkari AM. Insulin-like growth factor (IGF-I) and its low molecular weight binding protein in human milk. Eur J Obstet Gynecol Reprod Biol 1989;30(1):19-25.

[11] Ho Yuen B. Prolactin in human milk: the influence of nursing and the duration of postpartum lactation. Am J Obstet Gynecol 1988;158(3 Pt 1):583-6.

[12] Hennart PF, Brasseur DJ, Delogne-Desnoeck JB, Dramaix MM, Robyn CE. Lysozyme, lactoferrin, and secretory immunoglobulin A content in breast milk: influence of duration of lactation, nutrition status, prolactin status, and parity of mother. Am J Clin Nutr 1991;53(1):32-9.

[13] Chatterton Jr RT, Hill PD, Aldag JC, Hodges HR, Belknap SM, Zinaman MJ. Relation of plasma oxitocin and prolactin concentrations to milk production in mothers of preterm infants: influence of stress. J Clin Endocrinol Metab 2000;85(10):3661-8.

[14] Diaz-Gomez NM, Domenech E, Barroso F. Breast-feeding and growth factors in preterm newborn infants. J Pediatr Gastroenterol Nutr 1997;24(3):322-7.

[15] Rauprich AB, Hammon HM, Blum JW. Influence of feeding different amounts of first colostrum on metabolic, endocrine, and health status and on growth performance in neonatal calves. J Anim Sci 2000;78(4):896-908.

[16] Farhadi A, Banan A, Fields J, Keshavarzian A. Intestinal barrier: an interface between health and disease. J Gastroenterol Hepatol 2003;18(5):479-97.

[17] Wold AE, Adlerberth I. Breast feeding and the intestinal microflora of the infant—implications for protection against infectious diseases. Adv Exp Med Biol 2000;478:77-93.

[18] Pickering LK, Granoff DM, Erickson JR, Masor ML, Cordle CT, Schaller JP, et al. Modulation of the immune system by human milk and infant formula containing nucleotides. Pediatrics 1998;101(2):242-9.

[19] Hanson LA. Breastfeeding provides passive and likely long-lasting active immunity. Ann Allergy Asthma Immunol 1998;81(6):523-33; quiz 533-4, 537. Review. Erratum in: Ann Allergy Asthma Immunol 1999;82(5):478.

[20] Persson LA, Ivarsson A, Hernell O. Breast-feeding protects against celiac disease in childhood—epidemiological evidence. Adv Exp Med Biol 2002;503:115-23.

[21] Sanderson IR. Dietary regulation of genes expressed in the developing intestinal epithelium. Am J Clin Nutr 1998;68:999-1005.

[22] Clark R, Strasser J, Mc Cabe S, Robbins K, Jardieu P. Insulin-like growth factor stimulation of lymphocytes. J Clin Invest 1993;92:540-8.

[23] Shimoda N, Tashiro T, Yamamori H, Takagi K, Nakajima N, Ito I. Effects of growth hormone and insulin-like growth factor-1 on protein metabolism, gut morphology, and cell-mediated immunity in burned rats. Nutrition 1997;13(6):540-6.

[24] de Mello Coelho V, Villa-Verde DM, Farias-de-Oliveira DA, de Brito JM, Dardenne M, Savino W. Functional insulin-like growth factor-1/insulin-like growth factor-1 receptor-mediated circuit in human and murine thymic epithelial cells. Neuroendocrinology 2002;75(2):139-50.

[25] Cox DB, Owens HA, Hartmenn PE. Blood and milk prolactin and the rate of milk synthesis in women. Exp Physiol 1996;81(6):1007-20.

[26] Bole-Feysot C, Goffin V, Edery M, Binart N, Kelly PA. Prolactin (PRL) and its receptor: actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. Endocr Rev 1998;19(3):225-68.

[27] Malaguarnera L, Pilastro MR, Quan S, Ghattas MH, Yang L, Mezentsev AV, et al. Significance of heme oxygenase in prolactin-mediated cell proliferation and angiogenesis in human endothelial cells. Int J Mol Med 2002;10(4):433-40.

[28] Grattan DR. Behavioural significance of prolactin signaling in the central nervous system during pregnancy and lactation. Reproduction 2002;123(4):497-506.

[29] Malaguarnera L, Musumeci M, Licata F, Di Rosa M, Messina A, Musumeci S. Prolactin induces chitotriosidase gene expression in human monocyte-derived macrophages. Immunol Lett 2004;94:57-63.

[30] Malaguarnera L, Imbesi RM, Scuto A, D'Amico F, Licata F, Messina A, et al. Prolactin increases HO-1 expression and induces VEGF production in human macrophages. J Cell Biochem 2004;93:197-206.

[31] Cosman D, Lyman SD, Idzerda RL, Beckmann MP, Park LS, Goodwin RG, et al. A new cytokine receptor superfamily. Trends Biochem Sci 1990;15(7):265-70.

[32] Dogusan Z, Hooghe R, Verdood P, Hooghe-Peters EL. Cytokine-like effects of prolactin in human mononuclear and polymorphonuclear leukocytes. J Neuroimmunol 2001;120(1-2):58-66.

[33] Horseman ND, Zhao W, Montecino-Rodriguez E, Tanaka M, Nakashima K, Engle SJ, et al. Defective mammopoiesis, but normal hematopoiesis, in mice with a targeted disruption of the prolactin gene. EMBO J 1997;16(23):6926-35.

[34] Bouchard B, Ormandy CJ, Di Santo JP, Kelly PA. Immune system development and function in prolactin receptor–deficient mice. J Immunol 1999;163(2):576-82.

[35] Qin YD, Luo X, Huang DL, Xu CZ. Dynamic changes of enzyme activities and growth factors contents in human colostrums. Zhonghua Fu Chan Ke Za Zhi 2004;39(7):449-52.