Levels of IgG, IgA and IgM in cord blood of Latin American newborns from different ecosystems [1]

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ABSTRACT: Cord serum levels of IgG, IgA and IgM were determined by the radial immunodiffusion technique in five groups of newborns and in their mothers. Mothers of Group 1 were selected from a developed Peruvian urban society and received medical attention during pregnancy.

Mothers of the other four groups (2 to 5) correspond to less developed urban and rural societies of Peru and Guatemala, where very poor sanitary conditions prevail, and no medical attention is provided during pregnancy. Cord blood samples where admixture with maternal blood was suspected, were dicarded from the study.

Mean levels of IgM in the cord blood of Groups 2 to 5 were significantly higher than those of Group 1 (t test, $p < 0.01$). In the latter, only 6 per cent of infants had IgM values above 0.20 mg/ml, a situation similar to that reported for American infants born in environments with good sanitation. On the other hand, 40 to 60 per cent of infants from Groups 2 to 5 showed high IgM levels in cord blood, a result which is remarkably comparable to that reported in infants with suspected intrauterine infection or born of mothers infected during pregnancy. Considering the high risk of infection under which the mothers studied live, in all probability the main contributing causes to the high IgM levels observed are: maternal infection during pregnancy and/or intrauterine infection. The latter possibility should be explored in the light of the known cause-to-effect relatioship that exists between intrauterine infection and impaired physical and mental development.

INTRODUCTION

Several studies have shown that a high percentage of newborns with high levels of IgM in cord serum have suffered from infection *in utero.* [2] This finding is interpreted as a production of fetal antibody since the human placenta cannot transport this immunoglubulin from the blood of the mother to the child [3], [35]. Based on this knowledge, several surveys have been conducted in countries with a high degree of technical development to determine the levels of IgM in newborns [4, 9, 15, 19, 22, 24, 28, 32-34]. However, there is no information available in regard to the situation of infants born in urban and rural areas of technically underdeveloped countries. These data would be of interest, not only because of the high risk of infection prevailing in the ecosystem in which such populations live, but also because approximately two-thirds of the children of the world are born in technically underdeveloped countries. The purpose of the present study was to determine the serum levels of the G, A, and M immunoglobulins in cord blood of Peruvian and Guatemalan infants born in environments with different levels of sanitation and socio-economic conditions.

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MATERIAL AND METHODS

Populations

The main characterictics of the five groups of population studied are summarized in Table 1. These were integrated as follows:

Group 1. Sixteen infants born at the "Hospital Central del Seguro Social del Empleado", in Lima, Peru, of mothers from urban areas with satisfactory sanitary conditions, all of whom had received medical attention during pregnancy.

Group 2. Twenty infants born at the "Maternidad de Lima", also in the capital of Peru, of mothers from peripheral urban areas (slums) with poor sanitation. In this case, no medical attention had been provided to the mothers during pregnancy.

Group 3. Sixteen infants born at hospitals or in their own homes in the central highlands of Peru.

Group 4. Seventy infants from a Mayan highland village of Guatemala born in their own homes. These are from a cohort studied prospectively [20].

Group 5. Twenty-three infants born at the clinics of two Mayan villages located also in the Guatemalan highlands.

All of the infants included in Groups 3, 4 and 5 were born of mothers who had not received medical attention during pregnancy. Furthermore, they lived in rural areas with very poor sanitation.

Collection of Blood Specimens

Blood was collected from the umbilical cord (mother's side) immediately after birth. Specimens from Groups 1, 2 and 3 were drawn by a physician who took special care in avoiding any admixture of cord blood with maternal blood. Specimens from Group 4 were collected by folk midwives. Mayan Indian traditions preclude an adequate collection of cord blood. Since admixture of blood could not be avoided in all cases, the procedure followed was that of discarding specimens when the IgM/IgA ratio was. below 1.5.

In the case of Group 5, cord blood was carefully collected by physicians, and the IgM/IgA ratio determined. In addition, infants were bled (femoral vein) at three days of age. All subjects with a ratio above 1.5 in cord sera showed similar or higher IgM levels three days after birth, a finding which suggests that the IgM/IgA ratio is a satisfactory index to detect admixture of cord blood with mother's blood. This is particulary useful when postdelivery samples cannot be obtained from the infants.

Venous blood samples were collected also from the mothers of all newborns except from those in Group 4.

Measurements of Ig Levels

IgG, IgA and IgM were determined by radial immunodiffusion utilizing agar-antibody plates (Hyland, Los Angeles, Calif.). The technique used was that recommended by FAHEY and MCKELVEY [11] as standardized for sera from populations with a high risk of infection and malnutrition [18]. The coefficient of variation of this technique was from 5 to 15 per cent for the three Ig classes. The highest variability of the IgM determination was observed at levels below 0.1 mg/ml, as expected.

RESULTS

The average levels of IgG, IgA and IgM in cord sera, compared with sera of the corresponding mothers, are shown in Table 2. No differences were noted in the average concentrations of IgG in cord blood among the five groups studied. Otherwise, levels of this Ig in cord serum were remarkably similar to those of the corresponding mothers. The average concentration of IgA was found to be higher only in the infants from one the highland Mayan villages (Group 4) than in the other groups. However, IgM concentration was significantly higher in infants from all environments with a high risk of infection, whether urban or rural. As shown in Figure 1, where the mean Ig concentration in Group 1 (with a low risk of infection) is compared with the pooled values

Table 1

Composition of the five groups studied

Country	Population	Number of infants: Total collected	Number of infants: Total studied*	Site of delivery	Sanitary conditions	Medical atention during pregnancy	Period of collection of cord blood samples
1. Peru	Urban	20	16	Hospital	Satisfactory	Adequate	1969
2. Peru	Urban (peripheric)	21	20	Hospital	Very poor	None	1969
3. Peru	Rural **	16	16	Hospital & Health Units	Very poor	None	1969
4. Guatemala	Rural ***	127	70	Home	Very poor	None	1964-1966
5. Guatemala	Rural ***	30	23	Hospital	Very poor	None	1969-1970

* Total number studied after discarding those infants in whom possible admixture with maternal blood was suspected.
** Located at an altitude of 11,375 feet above sea level.
*** Located at an altitude of 6,500 feet above sea level.

Table 2

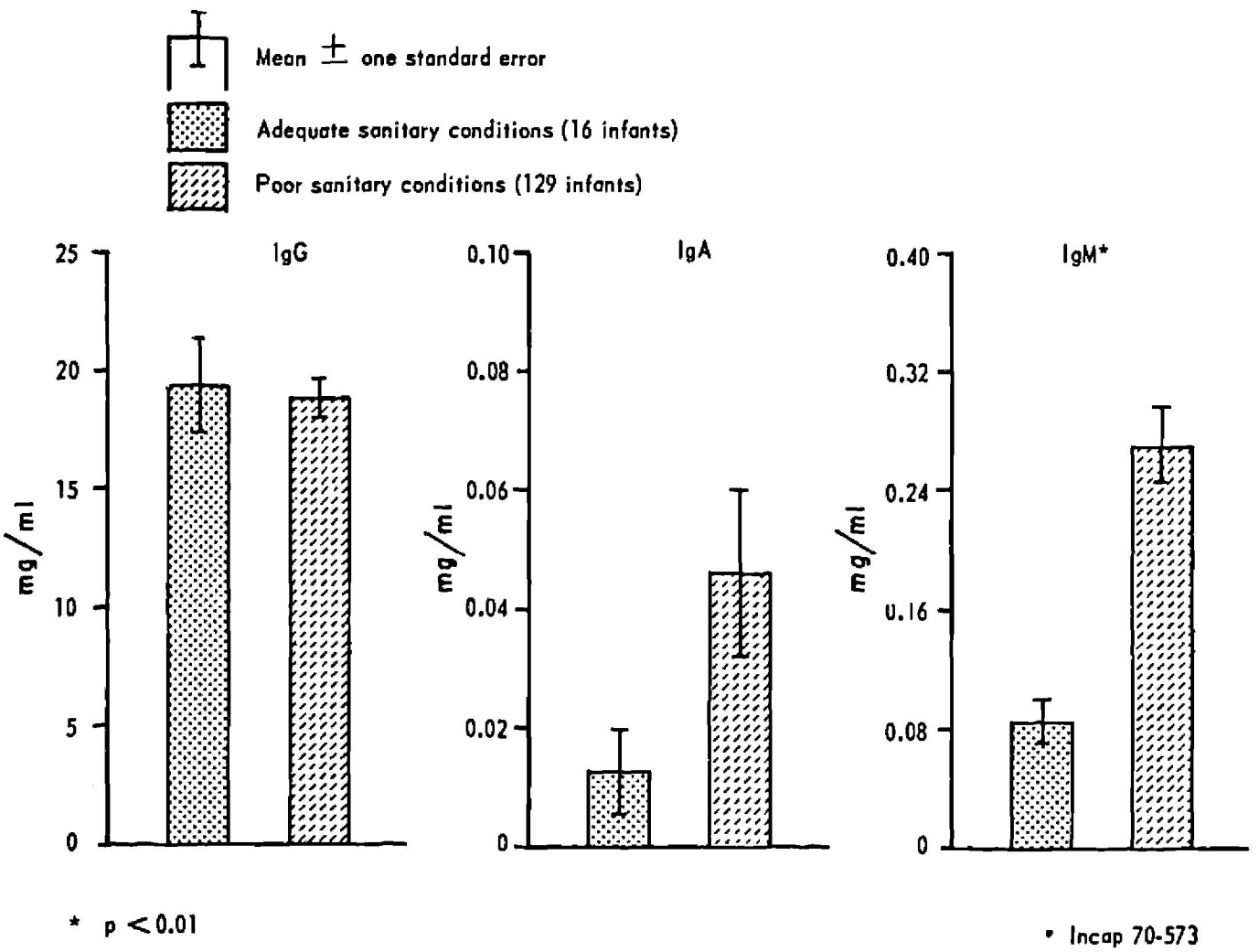
Inmonuglobulin levels in cord and maternal sera (mg /ml)

Groups Studied	Ig G		Ig A		Ig M	
	Cord	Maternal	Cord	Maternal	Cord	Maternal
1. Urban, high environmental sanitation, Peru	19.40 ± 1.90* (9.50 - 32.50)	17.30 ± 2.70 (7.00 - 40.50)	0.01 ± 0.01 (0 - 0.09)	4.00 ± 0.56 (1.42 - 6.70)	0.12 ± 0.04 (0 - 0.61)	1.76 ± 0.27 (0.56 - 4.10)
2. Urban, low environmental sanitation, Peru	28.30 ± 2.90 (7.60 - 47.50)	24.80 ± 2.40 (4.90 - 47.50)	0.02 ± 0.01 (0 - 0.07)	4.31 ± 0.04 (1.55 - 8.40)	0.34 ± 0.05 (0 - 0.66)	1.97 ± 0.33 (0.61 - 7.00)
3. Rural, low environmental sanitation, Peru	22.70 ± 2.70 (7.10 - 40.50)	22.70 ± 2.60 (10.30 - 47.50)	0.02 ± 0.01 (0 - 0.08)	4.83 ± 0.71 (0.45 - 7.90)	0.30 ± 0.05 (0.10 - 0.85)	3.07 ± 0.40 (0.85 - 7.20)
4. Rural, low environmental sanitation, Guatemala	15.70 ± 6.20 (4.00 - 32.00)		0.07 ± 0.01 (0 - 1.55)		0.26 ± 0.04 (0.02 - 2.35)	
5. Rural, low enrironmental sanitation, Guatemala	17.70 ± 1.10 (9.20 - 29.00)	17.20 ± 1.20 (10.00 - 29.00)	0.02 ± 0.01 (0 - 0.18)	3.50 ± 0.30 (2.10 - 8.50)	0.24 ± 0.05 (0 - 0.95)	1.94 ± 0.26 (0.49 - 5.60)

* Mean ± one standard error. Range values given in parentheses.

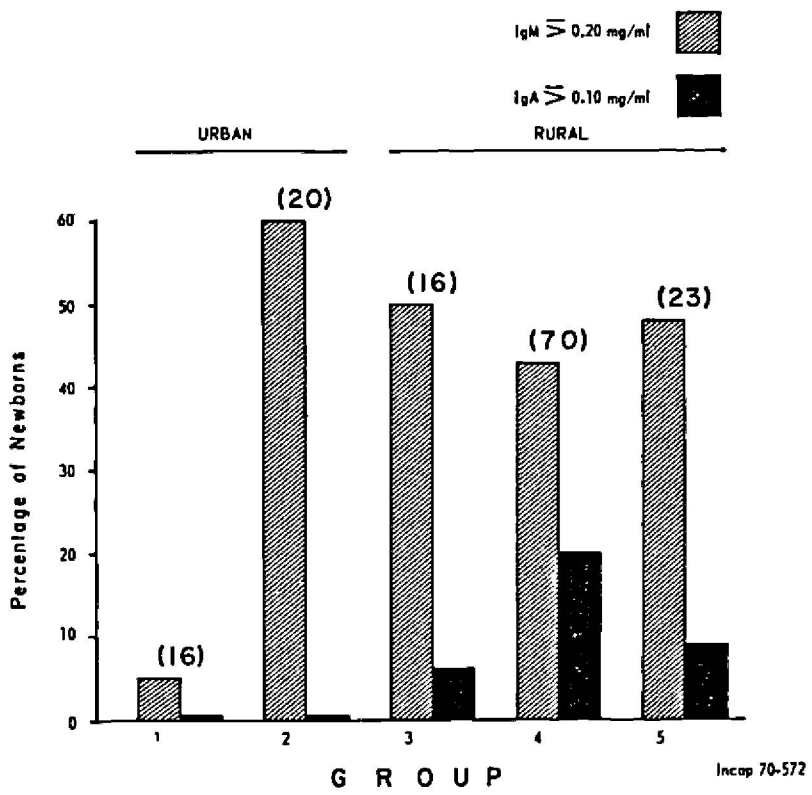
26.

Fig. 1. Inmunoglobulin levels in cord sera of infants from environments with varying sanitary conditions.



* $p < 0.01$. Group 1: adequate sanitary conditions; Groups 2-5: poor sanitary conditions.

Fig. 2. Frequency of high levels of IgM and IgA in cord sera of infants included in the five study groups.



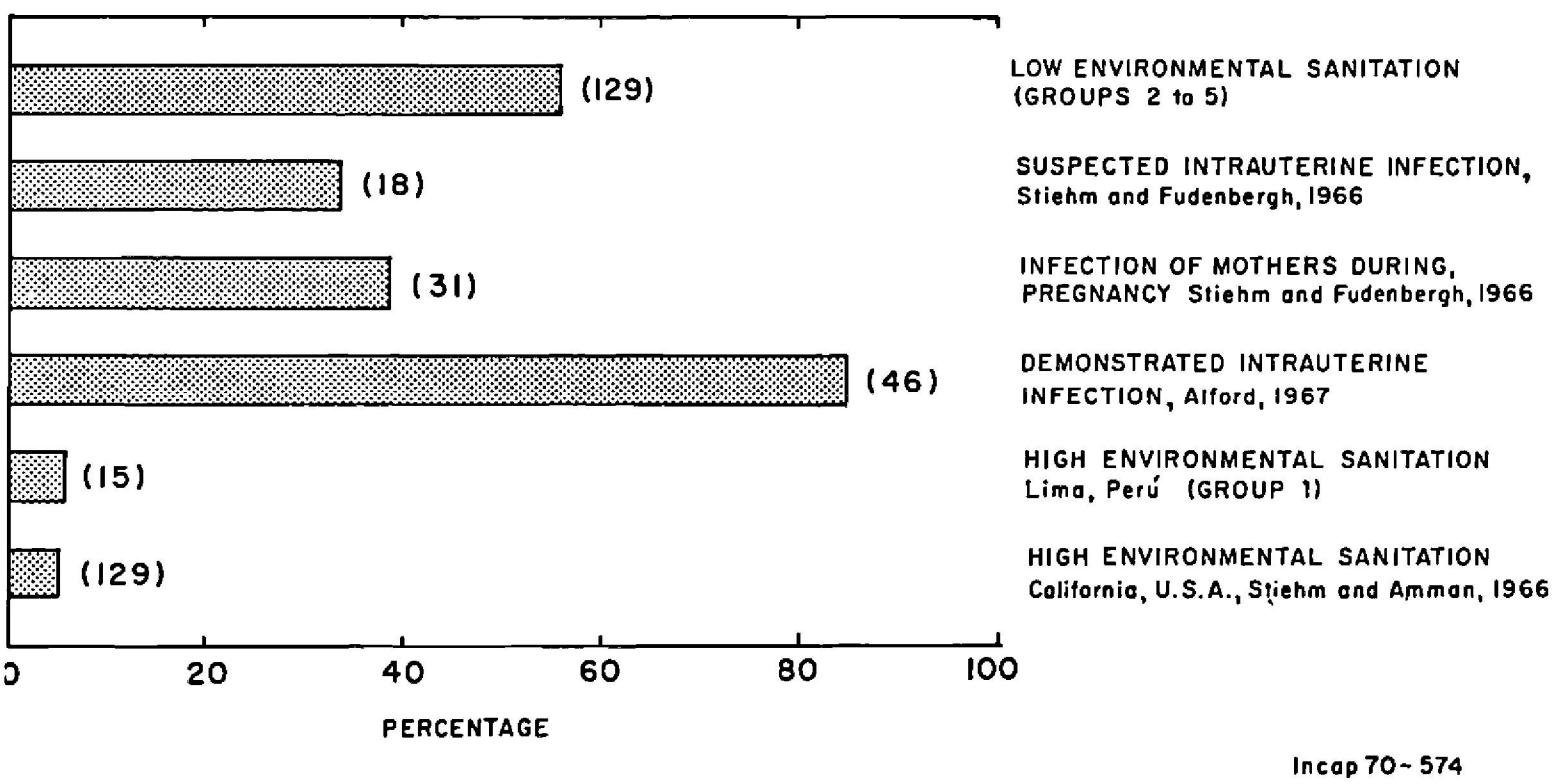
Figures on top of columns represent the number of cases.

of Groups 2 to 5 (with a high risk of infection), it is evident that IgM was significantly higher in the pooled groups (2 to 5) than in Group 1 (t test, $p < 0.01$).

Of greater importance than average values in the population groups studied, was the proportion of high values found. In the present case, IgA and IgM levels were considered "high" when they were 0.10 and 0.20 mg/ml, or greater, respectively. These criteria were proposed by STIEHM and AMMAN [31], and found to be adequate by ALFORD and associates [4], as well as by the authors of the present paper. The relative frequencies of high values of IgA and IgM in cord blood of the various groups studied are shown in Figure 2. High IgM levels were detected in only 6 per cent of urban infants from a low-infection-risk environment (Group 1), and no cases of high IgA values were found in the same group. These results are in agreement with those of STIEHM and FUDENBERG [32], in their studies in California. On the other hand, sixty per cent of the urban infants from a high-infection-risk environment (Group 2) presented high IgM levels, but the frequency of high IgA values in this group was low. In Groups 3, 4 and 5, all of them rural populations from a high-infection-risk ecosystem, the proportion of high IgM values was more than 40 per cent, and high IgA levels were found in 6 to 20 per cent of the cases.

Figure 3 shows a comparison of Group 1 and Groups 2 to 5, combined, with newborns from the United States. The frecuency of high IgM values in Latin American newborns from underdeveloped areas, was remarkably similar to that of American newborns with suspected intrauterine infection, or born of mothers infected during pregnancy. IgM levels in infants with confirmed infection *in utero* were found elevated in a proportion one-and-a-half larger than that of infants comprising Groups 2 to 5.

Fig. 3. Frequency of high cord IgM values ($\geq$ 0.20 mg/ml) in infants from different ecosystems.



Figures in parentheses represent the number of cases.

Discussion

Transport of immunoglobulins through the human placenta is a highly selective process [13]. The only immunoglobulin transported from the mother to the fetus is IgG. Thus, IgG levels in cord serum tend to reflect maternal values. In the present study, IgG concentrations in cord and maternal blood were virtually of the same magnitude, but the levels were higher than those observed in technically developed countries. It is probable that the finding of these concentrations of IgG in Latin American populations may be due to their history of greater exposure to infection.

Although it is generally accepted that IgM is not transported from the mother to the fetus, Gitlin and associates [13] report very low amounts of maternal IgM in ten per cent of newborns from Mexico. On the other hand, the human fetus has been shown to be capable of producing IgM, IgA and IgG as of the fourth month of life in response to adequate stimulation [6, 35]. Antigenic stimulation *in utero* could be induced by complexes of maternal origin, such as allotypes and histocompatibility antigens carried by leukocytes, as Brasher and Hartley [9] have suggested occurs in the case of Caucasian heterogeneous populations. However, this situation does not apply to infants of Groups 2 to 5 in the present study since they belong to societies that range from closed communities with a high frequency of cross-linked unions (the Guatemalan Indian villages) to open heterogeneous societies (Lima, Peru). Therefore, if the hypothesis of Brasher and Hartley is to be considered, antigenic differences of genetic origin would not explain the consistently high values observed in Groups 2 to 5.

Another possible source of antigenic stimulation is the presence of infection in the pregnant mother. Such infection could lead to liberation of microbial antigenic components in the mother's blood which are capable of passing the placental barrier and then stimulate the fetal immunologic system. Figure 3 shows evidence in favor of this hypothesis. Stiehm and associatees [31], for example, found that 39 per cent of infants born of mothers who suffered from infection during pregnancy, had high IgM levels in their cord serum.

Another explanation for the high cord IgM values reported in the present study could be the presence of infectious agents invading fetal tissues and resulting in clinical or subclinical infection. Immunologic responses could be elicited as a consequence of this infection. In this regard, Alford [3] showed that 75 per cent of infants suffering from congenital rubella had high cord IgM levels. Later, other workers also reported high IgM cord values in 20 to 100 per cent of cases with this disease [5, 14, 24]. Similar findings have been described in intrauterine infection caused by other agents, particularly cytomegaloviruses [2, 7, 25], *Toxoplasma* [2], herpes simplex [29] and bacteria [2, 8]. However, some investigators have described clinical and subclinical intrauterine infections with low values of IgM, as measured in cord serum [1, 24].

In 1967, Alford and associates [4] reported that 85 per cent of children born with viral or bacterial infections had high levels of IgM in cord sera. More recently, the same authors [2], demonstrated by means of a prospective study, that infants born with high levels of IgM, had 40 times more intrauterine and perinatal infections than those born with normal values.

Adequate environmental conditions, including medical attention during pregnancy, were present only in Group 1, where only one infant showed high IgM values in cord blood. As stated previously, Groups 2 to 5 belong to ecosystems that differ insofar as geographic location, ethnic background and other environmental conditions. Nevertheless, they share one common characteristic: the particular sociocultural factors which are typical of technically underdeveloped societies, and that favor the presence of infection.

In all these groups with a high risk of infection the prevalence of high IgM levels in cord sera resembled that described for children of technically developed areas, in whom there was clinical or microbiological evidence of intrauterine infection, or proven maternal infection during pregnancy. As this study revealed, no differences were determined between the IgM values of Latin American and American infants, provided they were born of mothers living in environments with adequate sanitary conditions.

In summary, the frequent high IgM levels found in cord sera collected in technically underveloped areas of Latin America, suggest the presence of maternal infection, intrauterine infection, or both. The implication of these findings deserves consideration because of two main reasons: (a) clinical or subclinical intrauterine infection carries with it a high risk of fetal damage and long-term effects on physical and mental development of the child [2, 12, 16, 23, 27, 30]. (b) On the other hand, children from areas with poor environmental sanitation

of Latin America and similar regions of the world, exhibit a high frequency of fetal growth retardation and prematurity. Furthermore, retardation in physical growth and deficiencies in mental performance, when compared with children living under better environmental conditions, have been observed [10, 17, 21, 26].

WINICK [36] has shown that malnutrition during the fetal stage and the first year of life results in a decreased number of brain cells and a smaller cranial circumference. The changes described by the same author in relation to deprivation of nutrition can be induced as well by intrauterine infection. Therefore, the role of infection and its interaction with nutrition during the fetal period must be explored in terms of its effect on physical and mental development.

LECHTIG, A. & MATA, L. J. Inmunoglobulinas séricas en recién nacidos provenientes de diferentes sistemas ecológicos en Latinoamérica. *Rev. lat-amer. Microbiol., 13:* 173-179, 1971.

RESUMEN: Se determinaron los niveles séricos de IgG, IgA é IgM en sangre del cordón umbilical de 5 grupos de recién nacidos y sus respectivas madres. El grupo 1 proviene de una población urbana del Perú con adecuada higiene ambiental y atención médica. Los otros 4 grupos (2 a 5) provienen de poblaciones urbanas y rurales de Perú y Guatemala que se hallan bajo deficientes condiciones de saneamiento ambiental y carecen de cuidados médicos adecuados. Los casos en los que se sospechó mezcla de la sangre del cordón con sangre materna fueron descartados del estudio.

La concentración promedio de IgM en el suero del cordón de los grupos 2 a 5 fue significativamente mayor que en el grupo 1 (prueba t, $p < 0.01$). En este último, sólo el 6 por ciento de los niños mostraron valores de IgM mayores de 0.20 mg/ml y tal proporción de valores altos de IgM es similar a la encontrada en recién nacidos provenientes de poblaciones tecnológicamente desarrolladas con satisfactorias condiciones de higiene ambiental. Por otro lado, 40 a 60% de los niños de los grupos 2 a 5 mostraron valores de IgM mayores de 0.20 mg/ml, un hecho que probablemente denota elevada prevalencia de infección materna durante el embarazo y de infección intrauterina. Ambas posibilidades deben ser exploradas, debido al alto riesgo de retardo en el desarrollo físico y mental, y de otras secuelas que acarrea la infección *in utero*.

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