

# Immigrant Newborn and Physiological Jaundice

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## Abstract

**Objective:** In Italy there are a growing number of infants born to non-Italian mothers. The aim of this study is to analyze the physiological trend of bilirubin in newborns from South-east Asia and South America, compared to Italian newborns.

**Method:** 60 newborns were enrolled: 20 Italian newborns, 20 South American newborns, 20 Southeast Asian newborns. All babies were born from normal pregnancies, delivered vaginally. There was no ABO and Rh incompatibility. Daily total serum bilirubin (TSB) levels were the main outcome.

**Results:** The bilirubin reached the peak on the third day of life in the Italian group ( $9.5 \pm 2.7$  mg/dL); on the fourth day of life in the Southeastern Asian group ( $9.9 \pm 3.0$  mg/dL) and on the fifth day of life in the South American group ( $10.9 \pm 2.4$  mg/dL).

On the fifth, sixth and seventh day of life South American newborns had significantly higher TSB levels compared to the Italian group and to the Southeastern Asian group.

**Conclusion:** The higher and delayed peak of bilirubin level in infants from Southeastern Asia and South America has epidemiological and health-care consequences. Dedicated nomograms should be processed to avoid the overtreatment and the discharge of newborns with a higher and later peak of bilirubin.

**Keywords:** Newborn; Physiological jaundice; Immigrant mother; Bilirubin

## Introduction

Nowadays in Italy, there are a growing number of infants born to non-Italian mothers, reflecting the increase of foreign residents in our country [1]. This trend is confirmed by the "A. Gemelli" hospital in Rome, where this study was conducted: infants born to foreign parents in the last five-years were between 20 and 25% of the total [2].

This trend has a significant role in clinical care, both for the mother and the newborn. Neonatal jaundice seems particularly relevant in some ethnic groups, such as Southeast Asian people and Latin American ones and less in others, such as in Africans [3-6].

The aim of this study was to analyze the physiological trend of bilirubin in the first seven days of life in newborns from Southeast Asia and in newborns from South America, in relation to the Italian population, to evaluate the differences between the populations concerned, and to minimize the overtreatment and the medicalization of normal newborns.

## Method

We studied 60 newborns: 20 Italian, 20 of Southeast Asian ethnicity, 20 from South America. These infants, delivered in Gemelli Hospital between October 2010 and August 2011, had the following characteristics: they were born from normal pregnancy, delivered vaginally, Birth weight  $>2,500$  g and appropriate for gestational age, Absence of ABO and Rh incompatibility, Direct Coombs test negative, Apgar score  $\geq 6$  at 1 min and at 5 min after birth, direct bilirubin (measured on the third day of life)  $<1$  mg/dL.

All patients included had both parents belonging to the same ethnic group. The countries of origin in groups of children of immigrant mother were respectively: Southeast Asia (Bangladesh, China, Philippines, India, Sri Lanka, Pakistan) and South America (Bolivia, Ecuador, Peru, Venezuela, Paraguay).

All infants were predominantly or exclusively breastfed. Newborns with a weight loss of  $>8\%$  were excluded from the study.

There were no statistically significant differences between the three groups studied with respect to gender, gestational age and birth weight.

Total serum bilirubin was measured every day for the first seven days of life, even after discharge, using a direct spectrophotometric method (Twin Beam Plus-Ginevri) and heparinized capillaries.

On the third day of life direct bilirubin was measured in all newborns, using the colorimetric method.

We considered the average of the maximum value of bilirubin reached by infants in the Italian population and in the immigrant groups, and the average hours of life when the maximum peak of bilirubin was reached.

All data were prospectively collected and stored on a database. Continuous variables were presented as mean  $\pm$  standard deviation (SD) and categorical variables as percentage. Comparisons with the variables were performed using Student's T-test in case of normal distribution. Significance was accepted at  $p < 0.05$ . Statistical analyzes were performed using the software Graph Pad 4.

Study protocol was approved by the Ethics Committee of the Gemelli Hospital.

Informed consent was obtained from all parents of infants enrolled in the study.

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Results

The trend of serum bilirubin in the first seven days of life in the entire population studied was similar to what has already been described in other medical reports: it highlights the classic biphasic trend of the levels of bilirubin. The mean maximum peak of bilirubin was 9.9 mg/dL and it was reached on the fourth day of life.

In the first phase, the rapid increase of the bilirubin is due to a higher rate of bilirubin production than adults, associated with a limited ability to conjugate bilirubin, which is the limiting step in this phase. During the slow decrease of serum bilirubin, the mechanisms of excretion is probably represented by a speed-limiting step, and it needs to be activated with an induction mechanism, as well as the conjugation [7,8].

Considering separately the three subpopulations, in the Italian group this trend was even more evident: the bilirubin increased rapidly to reach the peak on the third day of life, with mean values of 9.5 ± 2.7 mg/dL (Figure 1).

In the South-East Asian ethnic group, the peak of serum bilirubin occurred on the fourth day of life, with a mean of 9.9 ± 3.0 mg/dL, respecting the characteristic biphasic trend (Figure 1).

In the newborns of South American ethnicity, the maximum value of serum bilirubin was recorded on the fifth day, and the mean value was 10.9 ± 2.4 mg/dL (Figure 1). The peak of bilirubin was earlier and less pronounced in Italian infants, especially compared with infants from South America, who had a higher and later peak. Infants from South-East Asia are placed in an intermediate position compared to the other two groups.

Five Italian newborns (25%), six infants (30%) in the Southeast Asian group and six infants (30%) in the South American group had hyperbilirubinemia, defined as a level of total bilirubin ≥ 12 mg/dL [8].

The mean maximum value in infants who had a TSB level of >12 mg/dL was almost the same in the three ethnic groups (14.7 ± 1.0 mg/dL in Italian newborns, 14.1 ± 1.3 mg/dL in infants from Southeastern Asia, 14.7 ± 1.5 mg/dL in South American infants).

Two Italian newborns (10%), three newborns in the South American group (15%), two newborns in Southeast Asian group (10%) reached a bilirubin level of ≥ 15 mg/dL.

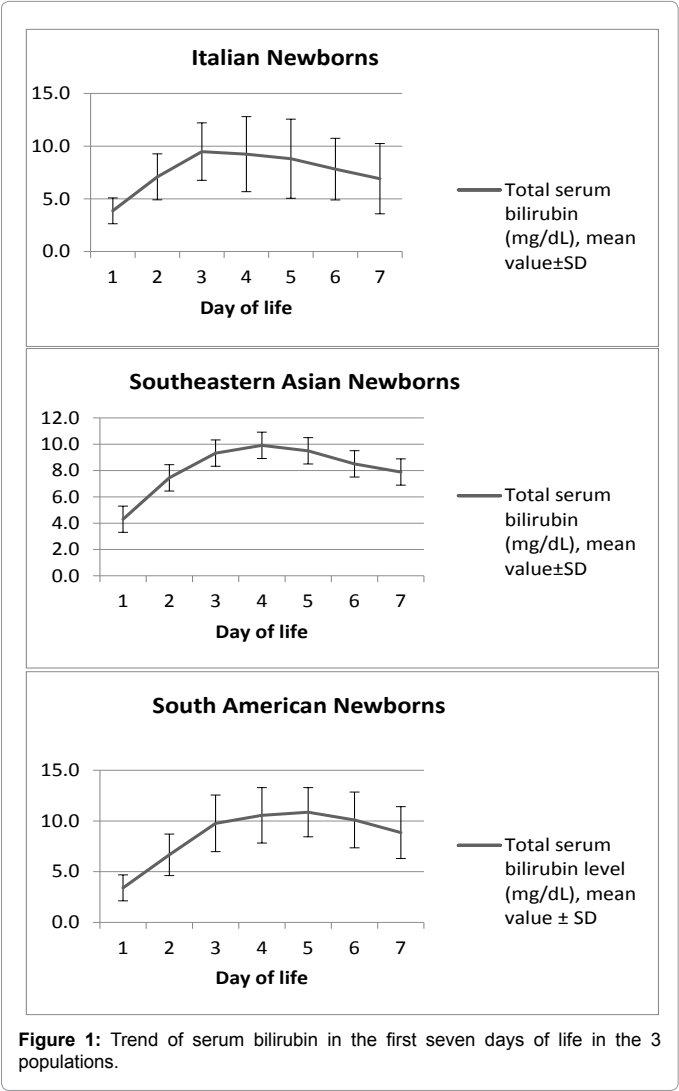
For none of the infants examined treatment with phototherapy and/or exchange transfusion was necessary.

Considering the daily values of bilirubin, on the fifth, sixth and seventh day of life in South American group had significantly higher TSB levels compared to the Italian group and to the Southeast Asian group. There were differences between the Italian group and the Southeastern Asian group, but they were not statistically significant (Table 1 and Figure 2).

Focusing on the number of hours when the peak of bilirubin was reached in the three groups, we observed that it occurred later in newborns from South America compared with Italian and Southeastern Asian populations (respectively 105 ± 19 h vs. 72 ± 20 h, p<0,0001 and 105 ± 19 h vs. 82 ± 20 h, p=0,0012).

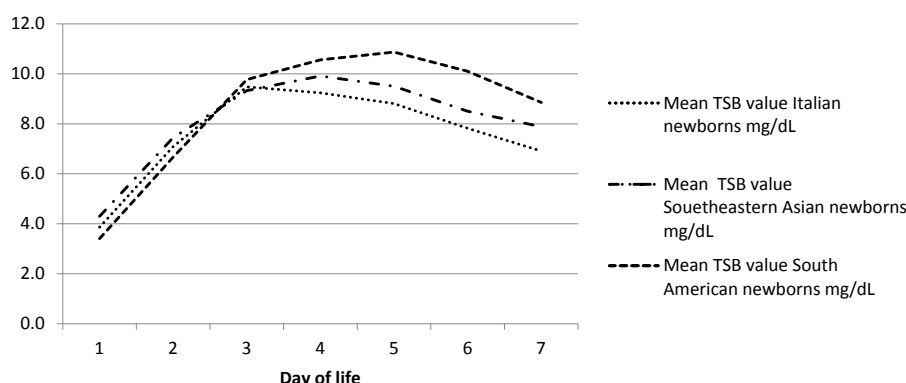
We performed multivariate regression analysis for confounding factors such as birth weight, gender, gestational age and type of lactation and we didn't find interference with the final results.

The trend of physiological weight loss was almost the same in the three groups, suggesting the absence of influence on physiologic neonatal jaundice: on the second day of life the mean weight loss was 3.5% in the Italian group, 3.4% in the Southeast Asian group and 3.7% in the South American group; on the third day after birth it was 5.9% in the Italian group, 5.4% in the Southeast Asian group and 6.1% in the South American group.



Total serum bilirubin (mg/dl) Mean value ± SD				p		
	A	B	C	A vs. B	B vs. C	A vs. C
	Italian (n=20)	South American (n=20)	Southeastern Asian (n=20)			
1° day	3.9 ± 1.2	3.4 ± 1.2	4.3 ± 2.2	ns	ns	ns
2° day	7.1 ± 2.1	6.7 ± 2.0	7.4 ± 2.8	ns	ns	ns
3° day	9.5 ± 2.7	9.8 ± 2.7	9.3 ± 2.4	ns	ns	ns
4° day	9.2 ± 3.5	10.6 ± 2.7	9.9 ± 3.0	ns	ns	ns
5° day	8.8 ± 3.7	10.9 ± 2.4	9.5 ± 2.9	0.04	0.04	ns
6° day	7.8 ± 2.9	10.1 ± 2.7	8.5 ± 2.9	0.01	0.01	ns
7° day	6.9 ± 3.3	8.9 ± 2.5	7.9 ± 3.1	0.03	0.03	ns

Table 1: Daily bilirubin values in the three ethnic groups.



**Figure 2:** Comparison between the three ethnic groups.

The mean maximum body weight loss in the entire population was 5.8%, and it was reached on the 3rd day of life.

## Discussion

Our data show that the trend of physiological jaundice in newborns from Southeast Asia and South America is different from Italian infants. In newborns born to immigrant mothers, there was a higher and more delayed peak of bilirubin than in Italian infants. This is even more evident examining data of the South America newborns, which had the maximum value of bilirubin higher (although not statistically significant) and later than Italian newborns and Southeast Asian infants (respectively 105 h vs. 72 h,  $p < 0.0001$  and 105 h vs. 82 h,  $p = 0.0012$ ).

There are many studies showing a higher incidence, extent and duration of neonatal jaundice in newborns of Asian ethnicity, while newborns from South America have not yet been studied.

In 1965, Brown and Wong in a study conducted on a population of four different ethnic origins (British, Chinese, Malay, Indian) reported a higher level of bilirubin, longer duration of hyperbilirubinemia and a later peak of TSB in the Asian population, suggesting that the reason could be the immaturity or the inhibition of the enzymatic system for the conjugation of bilirubin. The neonatal jaundice in Asian infants very often exceeds the limits of physiological jaundice in Caucasian infants, both in intensity and in duration; this phenomenon, however, cannot correlate to pathological conditions. Although the peak of bilirubin is higher and longer, TSB descends spontaneously, without the risk of neurological sequelae and without need for treatment [3].

In 1985 Linn, in a study of Caucasian, Black and Asian newborns showed that the Asian infants have a higher risk of hyperbilirubinemia and TSB level  $>15$  mg/dL compared to Caucasians [9].

In 2002 Setia et al. showed that Asian infants are 37% more likely to develop jaundice than Caucasians [10].

In recent years there was a lot of interest to research the specific causes of neonatal jaundice in the population of Asian ethnicity, but much less for infants from South America.

Akaba et al. in 1999 showed that the mutation Gly71Arg in the UGT (UDP glucuronosyl transferase) is prevalent in Japanese, Korean and Chinese populations. It is seen more frequently in patients with neonatal hyperbilirubinemia than in the control group [11].

Huang et al. in 2002 in a cohort study showed the impact of the presence of both the G6PD (Glucose-6-phosphate dehydrogenase)

enzyme deficiency and the A (TA) 7TAA variant of the promoter region of the gene of the enzyme UDP-glucuronosyl in the Taiwanese population, suggesting an additive role of the two genetic defects in hyperbilirubinemia [12].

In 2003, Weng et al. in a cohort study demonstrated that healthy infants at term born in Taiwan with G6PD deficiency have a higher incidence of hyperbilirubinemia (defined as TSB  $>15$  mg/dL) [13].

In 2004 Huang et al. showed that newborns with the 211 mutation of UGT1A1 and 388 of OATP2 (Organic anion transporting polypeptide 2) have a high risk of developing severe hyperbilirubinemia in the Taiwan population [14]. The G6PD deficiency may also explain the higher incidence of neonatal jaundice in South America populations. In 2006 Castro, Weber et al., in a study of 2799 infants, reported a total deficit of enzyme activity in 1.4% of patients, an intermediate form in 6.4%, while the remaining 92.2% had a normal G6PD [15]. The awareness that 7.9% of infants in southern Brazil have a deficit, absolute or partial, of the activity of G6PD is important to organize screening programs and a correct management of jaundice in the early days of life.

In the population we studied, the three groups of infants did not differ in the two most important risk factors for an accentuation of neonatal jaundice: all infants were breastfed, exclusively or predominantly, and weight loss in the three populations was similar [16-18].

The higher and delayed peak of bilirubin levels in infants from South-East Asia and South America has epidemiological and health care consequences: this can lead to later dismissal from hospital, especially in infants of ethnic South American compared with Italian infants.

Jaundice is the more frequent clinical event in the neonatal period: in a healthy infant the rate of hyperbilirubinemia is about 15-20% [19]. In most cases jaundice does not cause problems for a child's health. It requires monitoring, because it can cause serious neurological damage, or it can be the sign of a significant organic pathology [20].

In a recent study about the hyperbilirubinemia in newborns of immigrant mothers, Zuppa et al. showed that the hospitalization was significantly longer by approximately one day in infants from South-East Asia and South America than in Italian infants (4.5 days vs. 3.6 days,  $p < 0.0001$  and 4, 2 days vs. 3.6 days  $p = 0.0004$ ) [21].

There are nomograms for the bilirubin levels in the Italian population which are taken into consideration for a protected discharge and to determine the timing of the follow-up. Medical journals do not

show specific nomograms regarding other ethnic groups: it would be useful to adjust the curves of Italian newborns to infants of other ethnicity.

The other result of this study is related to the levels of bilirubin for which a treatment with phototherapy and/or exchange transfusion must start: since the newborns born to immigrant mothers seem to have a higher and later peak of bilirubin, it could be useful in clinical practice to start treatment at a greater number of hours after birth and for higher values of bilirubin, with the objective to avoid the overtreatment of normal newborns and the discharge of infants who may have a later peak.

## Conclusion

Therefore, physicians should be adequately informed and prepared to apply any new care protocols specific to immigrant ethnic groups. The results obtained with this study should be confirmed on broader and more homogeneous populations in order to process dedicated nomograms.

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