Prevalence of Intrahepatic Cholestasis of Pregnancy in Chile

HUMBERTO REYES, M.D.; MANUEL C. GONZALEZ, M.D.; JOSÉ RIBALTA, M.D.; HECTOR ABURTO, M.D.; CLAUDIO MATUS, M.D.; GERMAN SCHRAMM, M.D.; RICARDO KATZ, M.D.; and ERNESTO MEDINA, M.D., M.P.H.; Santiago, Arica, and Valdivia, Chile

The prevalence of intrahepatic cholestasis of pregnancy was studied immediately postpartum in 869 women from three distant Chilean cities differing in climate and food supply. Cholestatic jaundice of pregnancy was detected in 2.4% and pruritus gravidarum in 13.2%, without significant differences between the three cities. Every woman was then ethnically classified as predominantly Caucasoid, Araucanian Indian, or Aimara Indian. A significantly higher prevalence of cholestatic jaundice of pregnancy (5.5%) and pruritus gravidarum (22.1%) was found in Araucanians than in Caucasoids (2.5% and 12.6% respectively) or in the Aimaras (0 and 11.8% respectively). The prevalence of intrahepatic cholestasis of pregnancy in Araucanians increased directly with the degree of "ethnic purity." Recurrence of the disease in multiparous women was also greater in Araucanians (13.8%) than in Caucasoids (5.5%) or in the Aimaras (3.9%). We propose that an ethnic predisposition to develop intrahepatic cholestasis of pregnancy is present in Araucanian women and that the high prevalence of the disease in Chile is mainly influenced by ethnic admixture with this South American Indian (ethnic) group.

INTRAHEPATIC CHOLESTASIS OF PREGNANCY is a rare disease of unknown etiology. The first description has been attributed to Ahlfeld in 1883 (1), but a detailed study of its clinical, biochemical, and histologic features began in 1954, with the reports by Svanborg (2) and Thorling (3). Initially the diagnosis was restricted to women who, during the second half of several pregnancies, developed mild jaundice, dark urine, and generalized pruritus lasting until delivery and disappearing in the first days postpartum ("recurrent idiopathic jaundice of pregnancy") (1-10). These symptoms are accompanied by a cholestatic laboratory profile (increased serum total and direct reacting bilirubin, alkaline phosphatase, 5' nucleotidase, bile acids, with a mild rise in serum transaminases, and serum lipoprotein X). The liver biopsy shows a mild nonspecific cholestasis (1-10, 13, 14, 16-27). Although recurrence in several pregnancies strongly reinforces the diagnosis of idiopathic cholestatic jaundice of pregnancy, it may also be diagnosed in primiparous women and in multiparous women with an overtly affected pregnancy preceded by asymptomatic gestations.

The term "pruritus gravidarum" is applied to pregnant women complaining of a persistent generalized itching, without hyperbilirubinemia, but with the other biochemical abnormalities characterizing a cholestatic syndrome, all of which disappear rapidly after delivery and tend to recur in future pregnancies (11-27). Pruritus gravidarum and cholestatic jaundice may alternate in different pregnancies of the same woman. Alterations in estrogen metabolism by the liver have been observed in both. Neither functional nor histologic hepatic sequelae have been detected. Thus, pruritus gravidarum and cholestatic jaundice of pregnancy are currently considered to be two clinical forms of the same disease (12-27), and they may be included under the name of "idiopathic intrahepatic cholestasis of pregnancy."

The influence of genetic factors in the pathogenesis of intrahepatic cholestasis of pregnancy is supported by several examples of a familial case aggregation (1, 4-9, 13, 15, 17, 23-25, 28-30). Whereas in most European countries and in North America recurrent cholestatic jaundice of pregnancy is detected in less than one case per 1000 pregnancies (5-9, 17), frequencies more than 10 times greater have been reported from Sweden (1-4, 13-15, 25), Finland (13, 20), Poland (27), and Chile (31, 32). This still unexplained and peculiar geographic distribution may be due to genetic or environmental factors, or both. The present study was designed to estimate the current prevalence of intrahepatic cholestasis of pregnancy in Chile and to assess the role of ethnic characteristics in the high prevalence of the disease in this country.

▶ From the Departments of Medicine and Experimental Medicine (Eastern Campus) and Public Health (Northern Campus), University of Chile School of Medicine; and Hospital del Salvador; Santiago; Hospital Juan Noé; Arica; and Hospital John F. Kennedy; Valdivia, Chile.

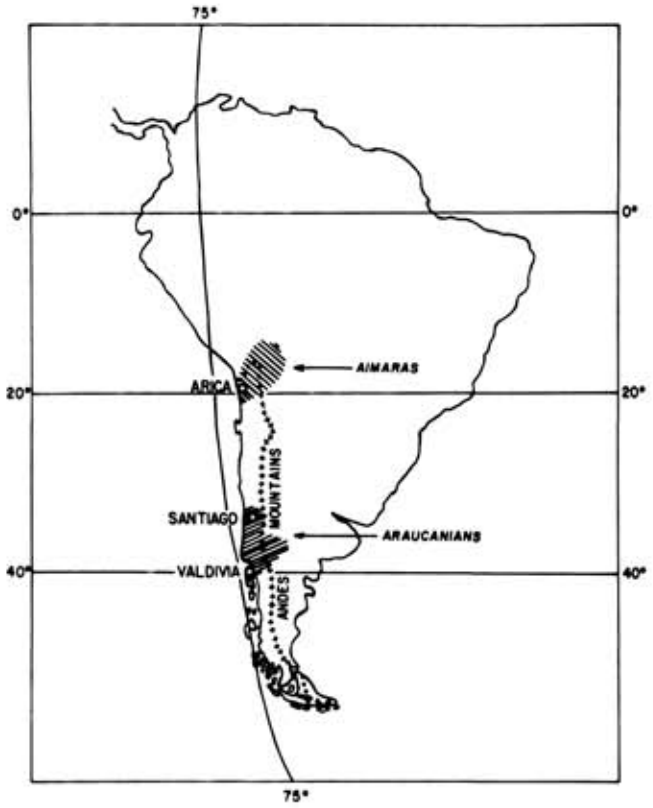

Figure 1. Geographic site of the cities of Arica, Santiago, and Valdivia, the Chilean boundaries, and the zones where Aimara and Araucanian Indians were originally located.

Material and Methods

The prevalence of intrahepatic cholestasis of pregnancy in Chilean women was prospectively studied in the cities of Arica, Santiago, and Valdivia. In Arica and Valdivia the study was done in the obstetric wards of the local general hospitals, where about 95% of the deliveries occurring in each city are attended. In Santiago, the study was done in the Department of Obstetrics, Hospital del Salvador, where about 80% of the deliveries occurring in the Eastern District of Santiago are attended.

ENVIRONMENTAL CHARACTERISTICS

Arica (latitude 18° 28′ S; longitude 70° 19′ W), in the northern end of Chile (Figure 1), is a seaport with a desert coastal climate. It has some small fertile valleys in the vicinity but is geographically separated from other Chilean cities by the Atacama desert. Santiago (latitude 33° 27′ S; longitude 70° 40′ W; altitude 600 m above sea level), in the central part of Chile and close to the Andes mountains, has a moderate climate with a dry summer. Valdivia (latitude 39° 49′ S; longitude 73° 15; W) is a southern city near the Pacific ocean, with a moderate but rainy climate. Santiago and Valdivia are located near both ends of Chile's main agricultural zone, where about 70% of the current Chilean population lives.

The main foodstuffs available in these three cities (wheat, corn, meat, milk and mild derivatives, rice, sugar) come from the agricultural provinces in Chile's central zone or are imported from common foreign sources. A local supply of fruits, vegetables, and other agricultural products is proportionally greater in Arica than in Santiago or Valdivia.

ETHNIC ANTECEDENTS

The current Chilean population results mainly from an ethnic admixture between Spanish colonizers and native South American Indian groups, initiated in the 16th Century. Since 1835, the Chilean population has increased from one to 10 million, mostly by internal growth (33, 34). Several groups of Araucanian Indians (Mapuches, Picunches, Huilliches, Pehuenches) who originally inhabited the central zone of Chile have been the predominant South American Indian groups participating in the ethnic admixture of the Chilean population (34, 35). The extinction of the original Araucanian Indian population plus their progressive ethnic admixture with Europeans left only a small number of individuals with close to a pure indian ancestry, living in southern communities and in rural isolates (36, 37). In the recent decades, a certain number of individuals with overt Araucanian descent have migrated to Santiago and other urban and industrial centers.

The origin of the population in Arica county has some distinctive characteristics: [1] the local South American Indian groups are mainly the Aimaras with a smaller proportion of Quechuas and Changos (34, 35, 38); [2] during the seventeenth and eighteenth centuries, a small ethnic contribution of African negroes and some Asiatics was added to the European-American admixture, in a comparatively greater extent than in the rest of Chile (34, 38); [3] during the nineteenth and twentieth centuries, an increasing flow of individuals coming from central and southern Chile has settled in this county. The current population of Arica includes only about 30% of individuals born from ancient local families.

METHODOLOGY

From July 1974 until October 1975, every pregnant woman who delivered between 0 and 24 h on randomly chosen days was examined 15 to 40 h after delivery. The following information was registered in individual charts.

[1] Patient's surnames, age, birthplace and place of residence.

[2] Length and outcome of the recent pregnancy, presence or absence or pruritus gravidarum or cholestatic jaundice of pregnancy; sex and weight of the newborn. In multiparous women the same information was filled in for their previous pregnancies. In every woman a past history of jaundice or pruritus, or both, in nonpregnant periods was sought.

[3] ABO blood groups, Rh factor, and the presence of "shovel-shaped teeth" were investigated in every individual. Shovel-shaped upper frontal teeth is a morphologic characteristic transmitted as an autosomal dominant trait, highly prevalent in Mongoloid populations in Asia. It has been found in 80% to 100% of persons from most South American Indian groups and in 0 to 20% of individuals from Caucasian populations in Europe (39-42).

[4] Blood samples for liver function tests were obtained from every patient who appeared clinically affected by intrahepatic cholestasis of pregnancy. Thirty-nine women who recently had an uncomplicated pregnancy with no itching, no history suggesting a hepatic disorder, no past history of intrahepatic cholestasis of pregnancy, and normal physical examination served as control subjects. The distribution of the women according to age and parity was the same in both groups. All maternal blood samples were obtained 15 to 40 h after delivery, and serum bilirubin, alkaline phosphatase, and glutamic-pyruvic transaminase were measured by standard laboratory methods.

CLASSIFICATION IN ETHNIC GROUPS

Every person was ethnically classified as Aimara, Araucanian, or Caucasoid. A woman was classified as Aimara when she was born in Arica county, had facial indian traits, Aimara surnames, and her native language was the Aimara. A woman was classified as Araucanian when she was born in the central part of Chile, had facial indian traits, and Araucanian surnames. All the other persons, without overt recent indian admixture as judged by their facial traits and European surnames, were classified as Caucasoids.

ABO blood groups, Rh factor, and shovel-shaped teeth were used to estimate the degree of ethnic admixture in each group

after every individual had been classified using the aforementioned criteria.

Based on previous observations, we expected to find a higher prevalence of intrahepatic cholestasis of pregnancy in Araucanians than in Caucasoids. The number of Araucanians identified in the total sample of women studied at random during 16 months was still too small to allow a reasonable statistical comparison between groups representing different degrees of Indian admixture. We then enlarged this sample by studying every consecutive woman showing Indian facial traits and Araucanian surnames who had a delivery attended in the Hospital del Salvador (Santiago) during the 3-month period that followed the nonselected sample study.

DIAGNOSTIC CRITERIA FOR INTRAHEPATIC CHOLESTASIS OF PREGNANCY

The diagnosis of pruritus gravidarum was made when the following characteristics were met.

[1] Generalized pruritus, without jaundice, that appeared during pregnancy, lasted until delivery, and was clearly attenuated in the subsequent hours.

[2] Absence of skin lesions, except those due to scratching.

[3] Absence of biliary colicky pain during pregnancy.

[4] Absence of widespread pruritus, with or without jaundice, in nonpregnant periods.

[5] Absence of symptoms and physical signs of other liver diseases.

Cholestatic jaundice of pregnancy was diagnosed in patients with jaundice, dark urine, and generalized pruritus, all appearing during the second half of pregnancy, with a clear decline of itching immediately after delivery. A serum bilirubin higher than 1.2 mg/dl in the blood sample taken after delivery was required to document a declining jaundice. As with pruritus gravidarum, the absence of jaundice and pruritus in nonpregnant periods and of symptoms or physical signs suggesting other liver diseases were mandatory requisites.

STATISTICAL ANALYSIS

The Yates correction of the chi-square test was used in the statistical analysis of the data (43). Differences with a P value equal to or smaller than 0.05 were accepted as statistically significant. According to Snedecor and Cochran (44), we considered that the chi-square test is accurate enough if the smallest expectation number is at least 1.

Results

The samples studied in Arica, Santiago, and Valdivia represent 3% to 8% of the deliveries attended in each hospital during the 16 months covered by this study. As shown in Table 1, 2.4% of these 869 women had cholestatic jaundice in their last pregnancy and 13.2% had pruritus gravidarum. Among 84 multiparous women with intrahepatic cholestasis of pregnancy, 33 (39%) had recurrent cholestasis during previous pregnancies. No significant differences in the prevalence of the disease were observed between the three cities.

Table 1. Prevalence of Intrahepatic Cholestasis of Pregnancy in Three Cities in Chile

City	Sample Size*	Cholestatic Jaundice	Pruritus Gravidarum
	no. (%)	%	
Arica	212 (5.3)	2.8	12.3
Santiago	418 (3.6)	2.2	12.9
Valdivia	239 (8.2)	2.5	14.6
Total	869	2.4	13.2
X^2 test between the three cities: P		N.S.†	N.S.

* Numbers in parenthesis indicate the proportion of deliveries represented by the samples, in relation with the total number of deliveries attended in each hospital during the 16-month period covered by this study.
† N.S. = not significant.

Table 2. Age and Parity in Women with or without Intrahepatic Cholestasis of Pregnancy

	Cholestatic Jaundice (n=21)	Pruritus Gravidarum (n=115)	Without Intrahepatic Cholestasis (n=733)
Age, *yrs.*			
Mean	28.9	25.1	23.7
Median	28	24	23
Range	17 to 45	15 to 43	14 to 46
Parity			
Mean	2.4	2.4	2.4
Median	2	2	2
Range	1 to 5	1 to 11	1 to 12
Primiparous Women, %	28.9	40.8	35.1

Age, parity, and the proportion of primiparous women were comparable in women with pruritus gravidarum and without intrahepatic cholestasis of pregnancy (Table 2). Women with cholestatic jaundice had higher mean and median age and a smaller proportion of primiparity than the other two groups. The age by parity distribution, studied in 5-year periods, was not significantly different in the three groups. In 62% of the affected women, pruritus appeared during the second trimester of pregnancy. In the remaining cases it started during the seventh or eighth month of gestation. The onset of jaundice could not be stated retrospectively with the same confidence but most cases noticed it 2 to 4 weeks after the beginning of pruritus. No patient reported jaundice preceding pruritus.

Figure 2 shows serum total bilirubin, alkaline phosphatase, and glutamic-pyruvic transaminase (SGPT) values in blood samples obtained 15 to 40 h after delivery. Women classified as having cholestatic jaundice during their recent pregnancy still had slightly or moderately raised levels in both total and direct reacting bilirubin in the early puerperium. No cases of hyperbilirubinemia were detected among the 39 control subjects. Mean and median alkaline phosphatase and SGPT values were higher in the groups with cholestatic jaundice of pregnancy or pruritus gravidarum than in the control subjects.

Among the total sample of 869 women, 777 appeared as predominantly Caucasoids. The prevalence of intrahepatic cholestasis of pregnancy (cases with cholestatic jaundice plus cases with pruritus gravidarum) in them was 15.1%. In 34 Aimaras examined in Arica, the frequency of pruritus gravidarum was 11.8%, and no cases of cholestatic jaundice were detected among them. Fifty-eight women (6.7% of the total sample) had an overt Araucanian descent; one was identified in Arica and the others were evenly distributed among the women examined in Santiago and Valdivia. Intrahepatic cholestasis of pregnancy was detected in 24.1% of these Araucanian women.

The number of Araucanians was enlarged as described

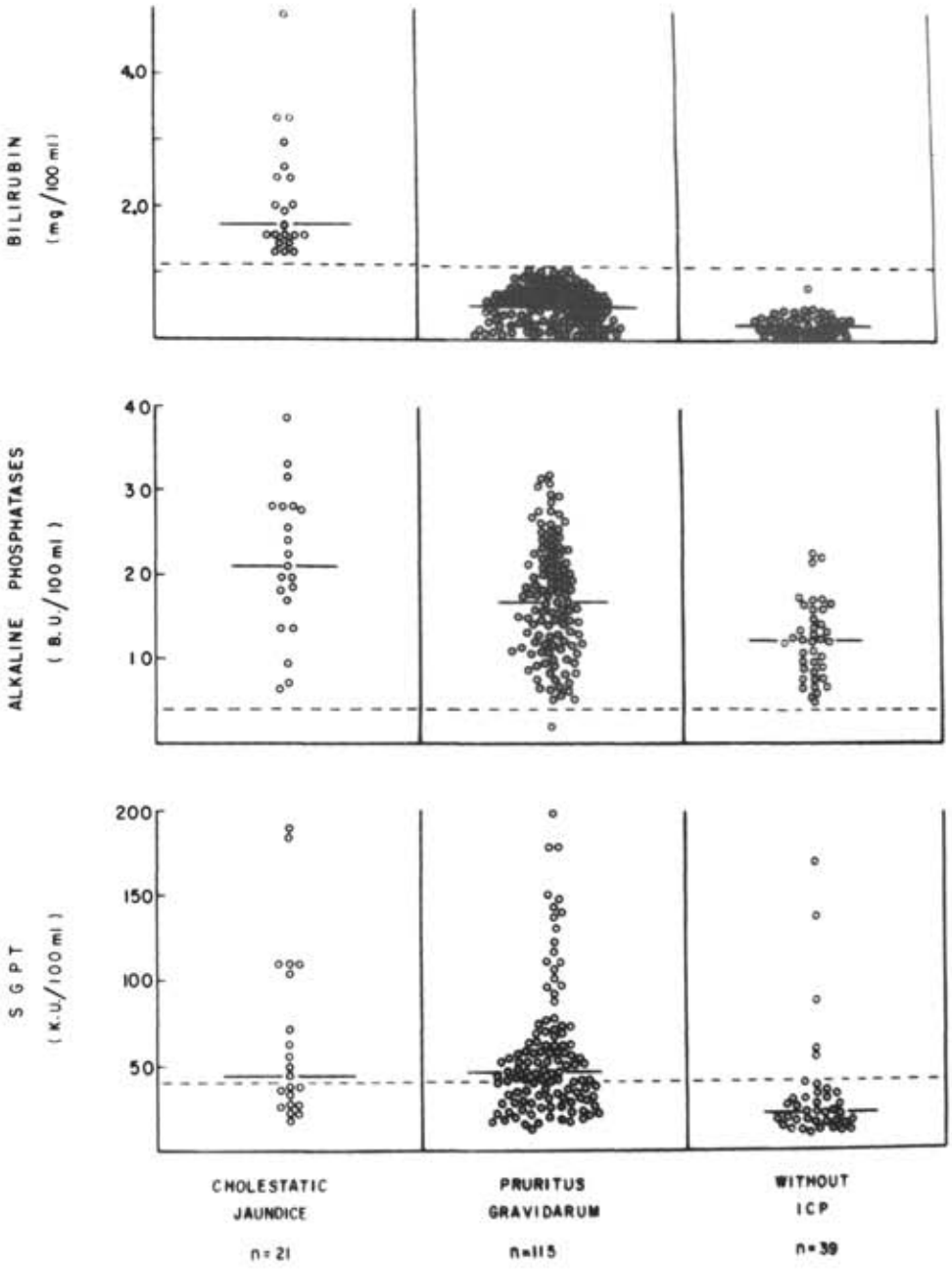

Figure 2. Serum total bilirubin, alkaline phosphatase, and glutamic-pyruvic transaminase (*SGPT*) measured 15 to 40 h after delivery in women with and without intrahepatic cholestasis of pregnancy (*ICP*). The broken horizontal lines indicate upper normal limits in nonpregnant women. In each group, the continuous horizontal lines show the medians.

in Material and Methods. One hundred five women with overt Araucanian descent were thus added. Age and parity were similar to the initial sample and also comparable to Caucasoids and Aimaras. As shown in Table 3, both cholestatic jaundice of pregnancy and pruritus gravidarum had a significantly higher prevalence in Araucanians than in Caucasoids or Aimaras. The prevalence of pruritus gravidarum in Aimaras appeared similar to Caucasoids.

Table 4 shows that a past history of intrahepatic cholestasis in two or more pregnancies could be detected in 6.6% of the 631 multiparous women. The proportion of cases with recurrent intrahepatic cholestasis of pregnancy was significantly higher in Araucanians (13.8%) than in Caucasoids (5.5%) or Aimaras (3.9%) ($P < 0.01$).

Women with overt Araucanian descent were separated into two groups, using ethnic and genetic markers to estimate their degree of admixture with Europeans. Group A includes 63 women having both maternal and paternal indian surnames, O blood group, Rh-positive factor, and shovel-shaped teeth. The remaining 100 Araucanians were classified in Group B, either because they had only one parent with indian surnames or they lacked any other characteristic required to belong in Group A. The distribution frequencies of ABO blood groups, Rh-factor (D), and shovel-shaped teeth in Aimaras, Caucasoids, and Araucanians (Groups A and B) are compared in Table 4. As shown in this table, cholestatic jaundice of pregnancy and pruritus gravidarum were more frequent in both groups of Araucanians than in Caucasoids or Aimaras.

Araucanian women classified in Group A—in whom ethnic admixture with Europeans among their ancestors may be estimated to be comparatively small—showed the highest prevalence of both clinical forms of intrahepatic cholestasis of pregnancy.

Discussion

In this study, the diagnosis of intrahepatic cholestasis of pregnancy was primarily based on clinical characteristics of the disease. Serum bilirubin measurements documented the persistence of jaundice a few hours after delivery and showed that it was due to a direct-reacting hyperbilirubinemia. The median and mean values of alkaline phosphatase and SGPT were higher in women with a past history of recent cholestatic jaundice or pruritus gravidarum than in women without cholestatic symptoms during their recent pregnancy. However, overlapping of individual values reduces the importance of these last two tests—when done in the early puerperium—for the differential diagnosis of intrahepatic cholestasis of pregnancy. The moderate rise in SGPT in intrahepatic cholestasis of pregnancy was helpful to minimize the risk of misdiagnosing other forms of acute liver disease, such as viral hepatitis, which occasionally may present in late pregnancy a pattern of mixed hepatocellular-cholestatic jaundice.

Confusion with other forms of benign intrahepatic cholestasis (for example, Summerskill's disease) (45, 46) is improbable in women whose first cholestatic episode appeared during a pregnancy between the second and fourth decade of life. It is also difficult to sustain this diagnosis in multiparous women with several cholestatic episodes occurring exclusively during pregnancies and disappearing immediately after delivery. None of the women considered by us as having an intrahepatic cholestasis of pregnancy gave a past history of jaundice and pruritus during childhood, nor had they been recently exposed to drugs or other known factors able to induce a cholestatic syndrome.

By examining hospitalized women immediately after delivery instead of pregnant women under control in outpatient clinics, we pursued the following methodologic advantages: [1] to suppress the risk of selection by morbidity, which may happen when asymptomatic pregnant women fail to attend ambulatory controls, [2] to evaluate a full-length past history of the recent pregnancy and at the same time to verify by physical examination the presence or absence of signs indicating other diseases that are able to mimic cholestatic jaundice of pregnancy or pruritus gravidarum, [3] to identify every patient affected by intrahepatic cholestasis of pregnancy, even when symptoms started 3 or 4 weeks before delivery.

Table 3. Prevalence of Intrahepatic Cholestasis of Pregnancy in Chilean Women with Indian Descent and in Caucasoids*

Ethnic Group	Sample Size	Cholestatic Jaundice	Pruritus Gravidarum
	no.	*%*	
Aimaras	34	. . .	11.8
Araucanians	163	5.5	22.1
Caucasoids	777	2.5	12.6

* X^2 test between Araucanians and Caucasoids: cholestatic jaundice, $P = 0.02$ to 0.05; pruritus gravidarum: $P < 0.01$.

Table 4. Frequency of Ethnic Markers and Prevalence of Intrahepatic Cholestasis of Pregnancy in Chilean Women with Indian Descent and in Caucasoids*

	Araucanians		Aimaras ($n=31$)	Caucasoids ($n=633$)
	Group A ($n=63$)	Group B ($n=100$)		
	←	%	→	
Blood Groups				
AB	0	0	0	2.1
A	0	31	5.9	32.3
B	0	10	2.9	7.4
O	100	59	91.2	58.2
Rh-factor (D)	100	96	100	96.1
Shovel-shaped teeth	100	64.7	77.4	43.1
Cholestatic jaundice	9.5	3.0	0	2.5
Pruritus gravidarum	30.1	17.0	11.8	12.6

	*X^2 Test for Cholestatic Jaundice	Pruritus Gravidarum
	P	
Between the four ethnic groups†	0	<0.001
Between Araucanians Group A and B	<0.05	<0.025
Between Araucanians Group A and Caucasoids	<0.05	<0.001
Between Araucanians Group B and Caucasoids	>0.1	>0.1
Between Araucanians Group A and Aimaras†		0.05-0.1

† X^2 test for intrahepatic cholestasis of pregnancy (cholestatic jaundice plus pruritus gravidarum), $P < 0.02$.

In 1968, we estimated the prevalence of cholestatic jaundice of pregnancy as 2.4% and of pruritus gravidarum as 11% among 3100 women examined in every general hospital attending the population of the cities of Santiago and Valdivia, and also in Panguipulli, a small rural community in southern Chile (32). The figures obtained were uniform in these three geographic locations, although the disease appeared to be more frequent in women with overt Araucanian Indian descent than in Caucasoid Chilean women. No attempts were made in that survey to correlate the prevalence of intrahepatic cholestasis of pregnancy with different degrees of Indian admixture. In the present work, the prevalence of the disease was studied again in Santiago and Valdivia, and now compared with Arica. Both studies followed the same methods and diagnostic criteria, and in both a similar prevalence of cholestatic jaundice of pregnancy and of pruritus gravidarum was found. These observations suggest that the factors influencing a high prevalence of intrahepatic cholestasis of pregnancy in Chile have not varied in the past 8 years and are shared by the populations living in quite distant cities. Furthermore, the finding of a similar prevalence of the disease in women from urban communities with geographic and climatic differences, and with some important differences in the sources of food supplied, indicates that these environmental characteristics do not influence the epidemiology of intrahepatic cholestasis of pregnancy in Chile. However, individual differ-

ences in eating habits and in specific food consumption tendencies were not sought and these aspects deserve future study.

In contrast, when women were classified according to their ethnic origin, intrahepatic cholestasis of pregnancy had a higher prevalence and a greater recurrence rate in women with overt Araucanian descent than in the Aimaras or in the predominantly Caucasoids. Cholestatic jaundice of pregnancy and pruritus gravidarum were even more frequent in the group of Araucanians where several ethnic markers concurred to indicate a smaller proportion of European admixture than in the remaining Indian-mixed women.

The main markers used to identify women with overt Indian descent were facial traits and surnames. Mongoloid facial traits are a common characteristic of every Indian group living in Chile. Indian surnames are notoriously different from the Spanish ones because they are a phonetical adaptation of the original Indian names and not a translation into a European language (38, 47). Araucanian surnames are also clearly different from the Aimara ones (34, 38, 47). Adoption of European surnames has historically occurred in a certain proportion of the Indians in Chile (38). On the contrary, adoption of Indian surname by Europeans has been exceptional. Thus, an individual with Indian traits bearing Indian maternal and paternal surnames, has a high probability of a predominantly Indian descent.

Historical data, as well as the few ethnic studies done in Chile with inclusion of several genetic markers, indicate that the Indian population currently living in urban communities has a certain degree of European admixture. Only in some small rural isolates are a scarce number of "almost pure" Indians still found (36-38, 41, 42, 48-50). European admixture is greater among the Araucanians living in agricultural zones in Chile than in the case of the Aimaras, scattered in the highplains close to the Bolivian Andean Plateau (37, 38).

As in most other South American Indian groups, a nonmixed Araucanian person is expected to have O blood group, positive Rh factor, and shovel-shaped teeth (36, 37, 41, 42, 48-50). In the present study, the concurrence of these characteristics in women with Indian facial traits and surnames was considered as a greater probability of having less European admixture than in individuals showing similar phenotypical and sociocultural characteristics but with A or B blood groups, a negative Rh factor, or the absence of shovel-shaped teeth. These criteria were used to separate Araucanian women into two groups, estimating the probability of ethnic admixture with Europeans among their ancestors. It cannot be used to measure the exact degree of admixture in every individual. Thus, to calculate a correlation coefficient between degrees of Araucanian admixture and the prevalence of intrahepatic cholestasis of pregnancy was not feasible.

Eighty-nine percent of the women examined at random were classified as Caucasoids because they did not show overt Indian traits. However, the frequency of O blood group and shovel-shaped teeth in them was higher than the expected figures in Spain or in other Caucasian populations (36, 37, 39-42, 48-50). This observation suggests that the predominantly Caucasoid population in Chile has an important degree of admixture with the Indian groups who originally inhabited the country.

From our results, we propose that an unidentified factor or factors preferentially predisposes women with Araucanian descent to develop intrahepatic cholestasis of pregnancy and that the high prevalence of the disease in the Chilean general population is highly influenced by ethnic admixture with this South American Indian group. This hypothesis is further reinforced by the following observations. [1] Caucasoid women born in Arica, descendants from ancient families settled in this county, had a slightly lower prevalence of intrahepatic cholestasis of pregnancy (1.6% had cholestatic jaundice of pregnancy and 10.6% had pruritus gravidarum) than the Caucasoid women born in the central and southern zones of Chile. This difference might be related to a selective admixture with Aimaras and Quechuas, instead of Araucanians, among their ancestors. [2] Although isolated case reports indicate that intrahepatic cholestasis of pregnancy is well recognized in Spain and in some Latin American countries (51-56), no indication of a high prevalence of the disease has yet been documented, except in Chile. A few South American countries have environmental similarities with Chile and almost all share a Spanish ancestry as a main ethnic contribution to their current population. In contrast, the Araucanian Indians participated exclusively in the ethnic admixture in Chile and in a small zone in the south of Argentina.

Whether the nature of the predisposing factor is primarily genetic or not requires further clarification. The increasing prevalence of intrahepatic cholestasis of pregnancy in Araucanian women as their European admixture decreases suggests the influence of a genetic factor, mainly because the samples of urban population that we studied share important environmental characteristics. A better understanding of the basic alterations leading to intrahepatic cholestasis during pregnancy and a diagnostic test capable of identifying every individual affected by the "predisposing trait" are essential to solving this problem.

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▶ Requests for reprints should be addressed to Humberto Reyes, M.D.; Universidad de Chile; Facultad de Medicina, Sede Oriente; Casilla 16038; Santiago 9, Chile.

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