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The Enigma of Intrahepatic Cholestasis of Pregnancy: Lessons from Chile

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CLINICAL SPECTRUM OF THE DISEASE

The main symptom of intrahepatic cholestasis of pregnancy (ICP) is pruritis which appears during pregnancy, lasts until the end of gestation, and disappears a few hours or days after delivery (1-3). Patients often notice "dark urine" from the onset of pruritus; only a small proportion have jaundice which is slight or moderate and is characterized by predominantly direct-reacting hyperbilirubinemia. Most pregnant women with pruritus have normal or slightly increased serum total bilirubin concentrations which are clinically undetectable. Patients with hyperbilirubinemia are usually diagnosed as having cholestatic jaundice of pregnancy (CJP); those with pruritus and other biochemical abnormalities except hyperbilirubinemia are diagnosed as having pruritus gravidarum (PG). In both entities, biochemical characteristics are those of a cholestatic syndrome and include a moderate increase in serum fasting total bile acids, cholesterol and other lipids, alkaline phosphatases and 5'nucleotidase activities, and lipoprotein-X. These laboratory alterations return to normal within a few days after parturition; only the serum alkaline phosphatase activity may remain elevated for several months. Examination of liver biopsy specimens by light microscopy reveals mild cholestasis (i.e., intracellular bile pigment and canalicular bile plugs) (4-6). Electron microscopic study reveals nonspecific intracellular abnormalities in hepatocytes and enlargement of bile canaliculi with loss of microvilli; these changes occur in most cholestatic syndromes (6). As previously summarized by Haemmerli (7), in ICP, "cholestasis is clinically marked, biochemically moderate and histologically minimal."

The diagnosis of ICP requires—or is reinforced by—absence of biliary colic, other manifestations of gallstone disease, fever, and general malaise. Exceptionally, the liver is enlarged, soft, smooth, and slightly tender. Liver function tests never show prominent signs of liver cell necrosis, inflammation, or failure. Vitamin K deficiency due to malabsorption secondary to cholestasis may lead to hypoprothrombinemia; this complication particularly occurs in women receiving cholestyramine. Patients have no past history of cholestasis during nonpregnant periods except when taking estrogen-containing oral contraceptives. The disease usually recurs in multiparous women; a past history of pruritus during pregnancy, with or without jaundice, strongly supports the diagnosis of ICP.

ICP was first described by Ahlfeld in 1883 (8). A vague reference to its clinical manifestations appears in Eppinger's textbook (9). Notwithstanding, major interest in the disease started in 1954 after Svanborg's (1) and Thorling's (2) classic papers. Since then, ICP has been identified in several countries with epidemiologic characteristics which will be discussed subsequently.

A distinction between CJP and PG is sometimes difficult and is often unnecessary (4, 10-13). In jaundiced patients, serum total bilirubin concentrations usually range between 2 and 5 mg per dl; when higher values are reached, concomitant diseases, such as urinary tract infection, may be contributory factors (2). Weekly follow-up shows fluctuation in serum bilirubin concentrations which occasionally return to normal despite persistence of pruritus. Serum levels of other clinical parameters of liver cell function and bile secretion (i.e., total bile acids, alkaline phosphatases, glutamic-pyruvic transaminase, lipoprotein-X) may also show major fluctuations and often superimpose on values expected in normal pregnancy at the same gestational age (Glasinovic et al., unpublished observations; Reyes et al., unpublished observations) (Figure 1). The severity of pruritus often varies. Whether or not these clinical and biochemical fluctuations reflect changes in the intensity of the cholestatic phenomenon at a subcellular level is hypothetical. Jaundiced patients tend to have greater alterations in most of the aforementioned biochemical parameters than do patients with pruritus and persistently low serum bilirubin values. In icteric cases, we have also detected abnormal stool fat excretion (ranging from 8 to 30 gm/24 h) in the absence of cholestyramine treatment; in these patients, stool fat excretion returned to normal within 3 months after delivery, long after other biochemical tests became normal (Reyes et al., unpublished observations).

A review of consecutive pregnancies in multiparous women reveals major variations in the severity of the disease and its onset during each gestation (6, 10, 14).

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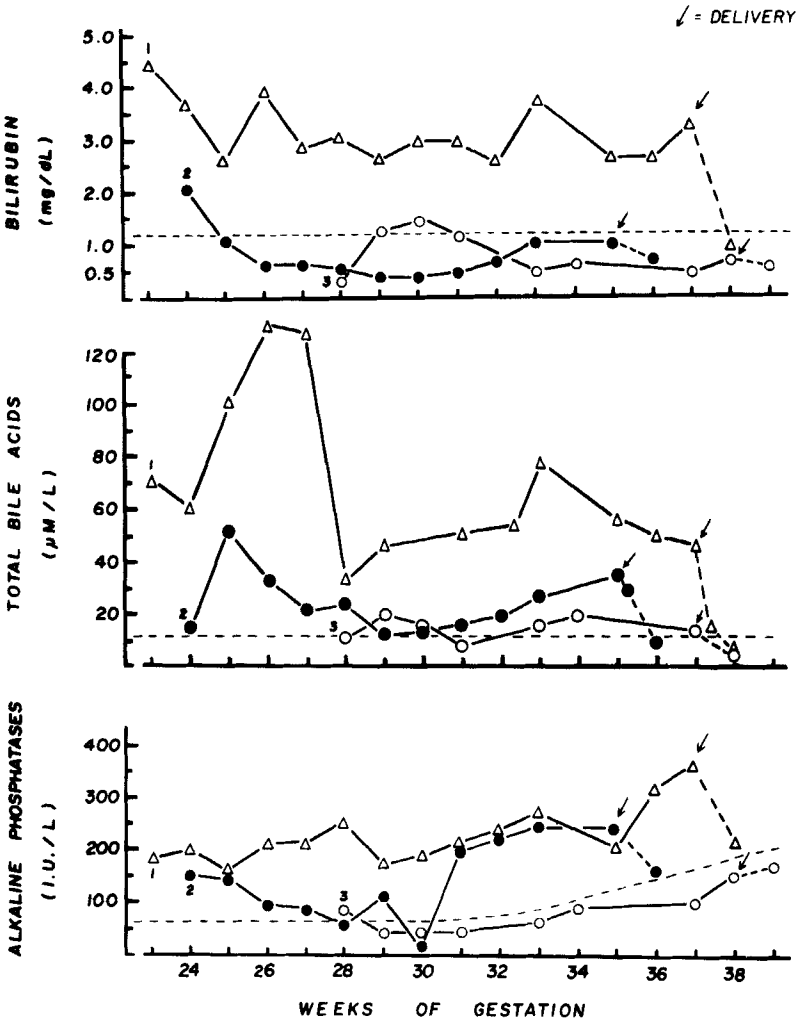

Fig. 1. Weekly follow-up of serum total bilirubin, bile acids, and alkaline phosphatases in three cases of ICP. The *broken horizontal lines* show the upper limits in uncomplicated pregnancies of the same gestational ages. Case 1 (classified as CJP) illustrates wide fluctuations with time which were significantly raised over normal values during the last 15 weeks of pregnancy. Cases 2 and 3 (classified as PG) show transient increases in serum total bilirubin; bile acids and alkaline phosphatases were often superimposed on values detected in normal pregnancies. A rapid fall toward normal occurred in each case and laboratory test immediately after delivery.

Some patients have recurrent ICP from their first pregancy, others have one or more asymptomatic gestations before ICP appears. Some women have recurrent PG and in others, PG and CJP alternate in consecutive gestations without a predictable sequence. A few cases have asymptomatic pregnancies after one or more gestations were affected by ICP. When a woman develops overt jaundice with intense pruritus and biochemical alterations during one pregnancy, the disease usually recurs in future gestations, but its precocity and severity can vary. There is no simple rule correlating the early onset of the disease with biochemical severity. We have not seen cases of ICP in which jaundice began in the first trimester; however, as described previously (15, 16), most of our patients experienced pruritus in the second or third month of pregnancy. The description of ICP as a disease characteristically appearing during the third trimester of pregnancy includes only about 70% of the patients. Variability in the clinical and biochemical characteristics of ICP has to be emphasized to understand the limitations of epidemiological, biochemical, and experimental data regarding its etiology and pathogenesis.

PATHOPHYSIOLOGY

Earlier studies of ICP suggested that female sex hormones, mainly estrogens, may play a pathogenetic role (1–3, 7, 8, 17). Clinical, epidemiological, and experimental data support this hypothesis: the disease develops exclusively during pregnancy, with a tendency to recur in every gestation; clinical and biochemical manifestations follow a "temporal profile" which grossly parallels changes in several sex hormones during pregnancy and after delivery. Initially, attention was called to the resemblance between ICP and the intrahepatic cholestasis induced by chlorpromazine, methyltestosterone, and other related steroid hormones (17). Later, the resemblance between ICP and cholestatic hepatitis produced by contraceptive pills which contain a synthetic estrogen and a progestagen was noted (8, 18). Many cases of gestagen-induced jaundice have a past history of ICP, and a high prevalence for both diseases occurs in some countries (19, 20). Natural and synthetic estrogens alter liver function tests and bile secretion in several species, including man (21–26). Administration of synthetic estrogen to women with a past history of ICP usually induces clinical and laboratory signs of cholestasis similar to those previously experienced during pregnancy (27–29).

However, the clinical and epidemiological characteristics of ICP cannot be attributed solely to female sex hormones. Some cases appear uncomfortably forced into a parallelism with the "temporal profile" of female sex hormones during pregnancy: those in which pruritus and

laboratory alterations start during the first months of pregnancy when the serum levels of female sex hormones are not maximally elevated; those in which jaundice and pruritus disappear a few days before delivery when hormone levels are still high, and those in which pruritus persists 1 or 2 weeks after delivery, and jaundice is prolonged for another 4 to 8 weeks. The analogy between ICP and gestagen-induced jaundice also has limitations; their clinical, biochemical, and histologic characteristics are not identical. Gestagen-induced jaundice generally starts abruptly, jaundice frequently reaches higher levels than in ICP, and liver histology reveals small inflammatory infiltrates scattered in periportal areas (30). Several women with a past history of ICP have used gestagens for years without developing overt liver damage; the converse observation has also been made. In addition, the number of women affected by ICP and/or gestagen-induced jaundice, is very small when compared to the millions of women bearing uncomplicated pregnancies or using gestagens who do not develop intrahepatic cholestasis.

SOME METABOLIC CHANGES DURING NORMAL PREGNANCY AND ICP

Estrogens and Progesterone

Studies comparing estrogen metabolism in normal pregnancy and in ICP have been mainly reported by Adlercreutz et al. In 1967, they demonstrated that total urinary estrone, estriol, and estradiol excretions in women with or without ICP were similar and suggested that estrogen synthesis remains normal during ICP (5). Urinary excretion of estrogen metabolites conjugated with sulfates was increased in ICP with a proportional reduction in glucuronide conjugates. This effect may be secondary to cholestasis and to changes in the enterohepatic circulation of estrogen metabolites (20, 31).

In ICP, the excretion of estriol into bile was reduced to 3% in comparison with results observed in normal pregnancy (32), and the biliary excretion of 12 different estrogenic compounds was uniformly diminished (33). In urine, the relative and absolute excretions of estriol-3-glucuronide was reduced; the reduction was proportionally greater in women with CJP than in PG (31). Estriol-3-glucuronide is formed in the intestine after reconjugation of estriol and its derivatives as catalyzed by enzymes provided by gut bacteria. This single quantitative difference in steroid hormone metabolism between CJP and PG may reflect the impaired excretion of substrate (estrogens) into bile and reduce enterohepatic circulation of hormonal metabolites which are conjugated in the intestinal lumen (31). In plasma from women with ICP, the finding of steroids which do not appear in normal pregnancy may reflect an increased concentration of total neutral steroids (20). There is no evidence that any of these compounds selectively alter canalicular membranes or other hepatocyte subcellular structures in man.

Over-production of estrogens may reduce bile flow in normal pregnancy. Adlercreutz et al. (5) postulated that "predisposed" women may have normal synthesis of estrogens but that estrogen metabolism in the liver is altered resulting in reduced biliary volume and excretion of these compounds during pregnancy. Estrogens, bile salts, and other "cholephiles" could theoretically accumulate in hepatocytes, and compete for conjugation and subsequent excretion into bile. This competition could result in increased sulfated steroids in comparison with glucuronide conjugates in blood and urine (20). Samsioe et al. (13) agree that the key alteration in steroid hormone metabolism during ICP is reduced inactivation rather than increased production of estrogens; they propose a different hypothesis: in the early stage of the disease, an increase in biliary excretion of estrogens requires more estrogens to be handled in the intestine; "irregular" estrogen metabolites appear through partial reabsorption of estrogens acted on by intestinal bacteria, and some estrogenic metabolites may cause intrahepatic cholestasis in "predisposed" subjects. However, there is no evidence that any "specific" estrogenic steroid or "irregular" estrogen metabolite produces the cholestatic syndrome in these women.

Similar observations have been obtained with regards to progesterone and related steroids. Urinary excretion of total progesterone compounds was similar in two cases of PG and in normal pregnancies suggesting that progesterone synthesis is not abnormally increased during ICP (34). Excretion of total progesterone metabolites into bile is diminished during ICP as judged by their concentrations in gallbladder bile and feces (34, 35). Serum concentrations of C_{19} and C_{21} neutral steroids were elevated in ICP-affected women with a main increase in mono and disulfated conjugates, which probably are progesterone metabolites (36). Laatikainen and Karjalainen (35) described decreased excretion of glucuronid conjugates in urine and bile with simultaneous increase in urinary excretion of disulfate conjugates. The wide range in values may be attributed to intestinal bacteria and changes in the enterohepatic circulation of steroid metabolites. Laatikainen and Karjalainen (35) propose that changes in progesterone conjugation and metabolism are not causal but are secondary to cholestasis. However, the altered profile of progesterone metabolites in maternal blood may have deleterious effects on the metabolism of progesterone in the uterus and fetal-placental unit and thereby cause premature delivery.

Bile Acids

In normal pregnancy, the serum concentration of total bile acids during fasting is similar to that in healthy man and nonpregnant women. The proportion of primary bile acids is modified in blood and gallbladder bile with an increase in cholic acid and a decrease in chenodeoxy and deoxycholic acids (37). During ICP, the serum concentration of total bile acids may increase 100-fold, and returns to normal within 1 week after delivery (37). The increase in cholic acid in blood and gallbladder bile, in comparison to chenodeoxy and deoxycholic acids, is significantly greater during ICP than in normal pregnancy (37–39). In two ICP cases, Laatikainen et al. (39) showed that cholic acid represented 50% of total bile acids in gallbladder bile; chenodeoxycholic acid was greatly diminished. The proportion of sulfated bile acids with respect to total bile acids was reduced in normal pregnancy at term (0.4 to 1.2%) and was further diminished in ICP (0.3 to 0.5%).

During ICP, serum bile acids rise more frequently and

earlier than do bilirubin and alkaline phosphatases and amino transferases activities. In two multiparous women reported by Laatikainen and Ikonen (38), and in two cases we studied, a sudden increase in fasting serum total bile acids occurred a few days before the onset of pruritus. Serial measurements of fasting serum total bile acids reveal large fluctuations during ICP and occasionally give normal values (38). Although serum bile acid levels tend to be higher in CJP than in PG, there is substantial overlap between both groups of patients (Reyes et al., unpublished observations). Glasinovic et al. (unpublished observations) reported that the postprandial increase in serum total bile acids appears to be greater in ICP-affected women than in normal pregnancies.

Cholesterol, Triglycerides, and Phospholipids

Samsioe et al. (40) demonstrated that the serum levels of cholesterol, triglycerides, and "calculated lecithin" are significantly higher during normal pregnancy (31 to 37 weeks of gestation) than in healthy nonpregnant women. They also detected differences in serum lecithin-fatty acid composition, with a relative increase in palmitic acid and decrease in linoleic and arachidonic acids. The cause and significance of these metabolic changes during normal pregnancy are unknown. In ICP-affected women, serum levels of cholesterol, phospholipids, and triglycerides are higher than in normal pregnancy (41). Serum pre-β-lipoproteins (*VLD* lipoproteins) and low-density lipoproteins are increased with a simultaneous decrease in the high-density fraction. Lipoprotein-X appears in serum of ICP-affected women, as it does in other intra- and extrahepatic cholestatic syndromes. According to Johnson (42), the increase in serum triglycerides during ICP cannot be attributed to cholestasis because other cholestatic conditions show no increase in this parameter. During pregnancy, women with ICP had a distinctive serum lecithin fatty acid composition with a high palmitic and oleic acid content (43). When studied in the nonpregnant state (8 to 21 months after delivery), they showed a lower content of palmitic acid in serum lecithin than did controls without a past history of ICP (44). This change was exaggerated in women with previous ICP and abnormal cholecystograms. Samsioe et al. (44) propose that women who are prone to develop ICP may have a primary defect in the synthesis of lecithin in the liver, mainly in its fatty acid composition, favoring cholesterol precipitation in bile and, therefore, a high incidence of cholelithiasis. In our experience, the increase in serum cholesterol and triglyceride concentrations during ICP follows the same pattern as does other laboratory changes: values tend to be higher in CJP than in PG.

Pregnancy induces major changes in the metabolism of bile acids and other biliary lipids, as illustrated by shifts in the proportion of cholic:chenodeoxycholic acids in bile and blood, the proportion of sulfated:total bile acids, serum levels of cholesterol, triglycerides, and lecithin, and fatty acid composition of lecithin (the main phosphatide in the serum of normal pregnant women). During ICP, these changes are exaggerated and correlate positively with the severity of the disease. These observations can be added to others which support the dogma that "pregnancy is cholestatic" (45). There is no evidence that these changes are causal or specific in ICP; however, they may play a role in the high prevalence of gallstone disease in ICP-affected women.

Hormone studies in women with ICP have attempted to characterize biochemically the disease, and to discover a specific and causative metabolic abnormality. Unfortunately, the latter goal remains elusive. A review of the available information discloses the following limitations: (i) hormone measurements have been made when the disease is fully developed or 2 weeks after pruritus appeared in a pregnant woman, and only a few studies have been performed in high-risk pregnancies before the onset of cholestatic symptoms (34). (ii) The diagnostic specificity and pathogenetic implications of any hormonal difference thus far detected during ICP cannot be established until comparison is made with other cholestatic syndromes in women, preferentially during pregnancy. (iii) Almost every hormone study is based on a single determination in ICP-affected women. The fluctuations with time in other biochemical parameters of cholestasis during ICP make it reasonable to suspect that similar variability occurs in hormonal parameters. (iv) The number of individuals studied and the measurements performed are few. Results obtained in one or two cases may be illustrative and stimulate future research, but cannot sustain definitive generalizations. (v) The number of normal pregnant women used as controls is small in several studies, although they show a wide dispersion in some important hormonal parameters. Studies employing contemporary technology should be performed in a greater number of normal pregnancies, using serial measurements to delineate dispersion and fluctuation of hormonal parameters.

MATERNAL AND FETAL PROGNOSIS

"ICP is entirely benign for both mother and child" (10). This concept has been challenged by clinical experience. For the mother, the intensity of pruritus often becomes a distressing experience resulting in severe anxiety or depression. Steatorrhea secondary to intestinal malabsorption may affect the nutritional status of both mother and child (Reyes et al., unpublished observations).

The influence of ICP on fetal prognosis has been debated. Based on the careful study of six personal cases plus a review of the literature before 1967, Haemmerli and Wyss (10) concluded that "the occurrence of premature deliveries appears to be a feature of the individual women and not of the disease itself." Several authors disagree because, in their experience, stillbirths and premature deliveries are more frequent in ICP-affected pregnancies than in uncomplicated gestations (4, 6, 8, 12, 38, 46-50). Mery et al. (50) reviewed 87 cases from the Department of Obstetrics in our hospital between 1964 and 1969: 53.5% had premature deliveries and 9.2% had stillbirths; both figures were 5 times higher than those detected among the total number of deliveries during the same period. Premature deliveries were more frequent in CJP than in PG; no correlation was observed between prematurity and the magnitude of hyperbilirubinemia in the mother, but a positive correlation was found between prematurity and the onset of pruritus during pregnancy.

Similar results were obtained in other clinical studies in Chile, leading to a strict obstetrical surveillance of every pregnant woman affected by ICP. A subsequent report by Iglesias et al. (51) included 91 consecutive cases of ICP attended in our hospital after 1969; 63% of whom had cesarean sections due to early detection of fetal distress. Most operations were performed after the 36th week of pregnancy. Only 13% of the newborns had signs of prematurity, and stillbirths were reduced to 3.3%. These observations suggest that ICP is not entirely benign for the mother and that it may endanger fetal outcome.

Examination of placenta often reveals nonspecific abnormalities (edematous villi, degenerative changes, infarcts) which may contribute to fetal hypoxia and defective nutrition of the fetal-placental unit (38). Laatikainen et al. (52) showed that changes in maternal serum levels of estrogens and progesterone, some of their precursors and metabolites, and in serum bile acids were reflected in fetal blood samples obtained from the umbilical cord after delivery. Signs of fetal distress were frequently detected in coincidence with high concentrations of bile acids in umbilical cord and maternal blood samples taken before delivery. They propose that ICP may permit unknown substances to cross the placenta and alter steroid metabolism in the fetus. These metabolic changes may affect placental function and the course of pregnancy.

INSIGHTS FROM EPIDEMIOLOGY

The prevalence of ICP in different countries is an intriguing aspect of the disease. The reports of Svanborg (1) and Thorling (2) revealed that the disease is frequent among Swedish women. Several subsequent publications identified cases of ICP in Europe, North and South America, and Australia. We are not aware of reports in Asiatic women (i.e., Chinese, Japanese, Koreans), Polynesians, African negroes, or black Americans. In most countries, ICP appears to be rare, with an estimated prevalence of one case for every 1,000 to 10,000 deliveries. This fact may explain a lack of awareness of the disease in countries where pregnant women face other more frequent problems. In contrast, a 10- to 20-fold greater prevalence has been registered in Sweden, other Scandinavian countries, Poland, and Chile. The prevalence of the disease in Chile (about 10 cases in every 100 deliveries) is the highest in the world and is substantially greater than in neighboring countries (53). Among other hepatobiliary diseases, only cholesterol, gallstones, and alcoholic cirrhosis have a high prevalence in Chile; viral hepatitis is uncommon during pregnancy. Acute fatty liver of pregnancy, benign recurrent cholestasis, and inborn defects in bilirubin metabolism (with or without cholestasis) are as rare in Chile as in other countries. Cholestatic hepatitis induced by gestagens is more frequent than in other populations but is relatively uncommon (30). The cause of this epidemiologic phenomenon awaits definitive explanation. Data collected in recent years suggest an interaction between an ethnic (genetic?) predisposition and unknown nongenetic factors.

The prevalence of ICP in Chile is similar in cities whose geography, environment, and climate are grossly different (Figure 2). Two surveys which were performed with an 8-year interval showed similar prevalence rates (14, 53). In contrast, interesting dissimilarities appeared when the prevalence of ICP was analyzed with respect to ethnic characteristics of the population: ICP was significantly more frequent in women with overt Araucanian-Indian descent (27.6%) than in Caucasoid women (15.1%) (53). The Araucanian Indians were the predominant aborigine groups inhabiting the central and southern parts of Chile when the Spaniards arrived four centuries ago. At present, a small number of their descendants live in rural isolates in southern Chile. The majority of the Chilean population is Caucasoid but a small proportion of individuals with overt Araucanian Indian descent is found even in urban centers. The low prevalence of the disease in Spain and Latin American countries where different (nonAraucanian) aborigine groups contribute to the ethnic admixture, raises the hypothesis that an ethnic predisposition to ICP is present in Araucanian Indians. Surveys in Bolivia and northern Chile reveal that the prevalence of ICP is also relatively high (13.8%) in another group of South American Indians, the Aimaras,

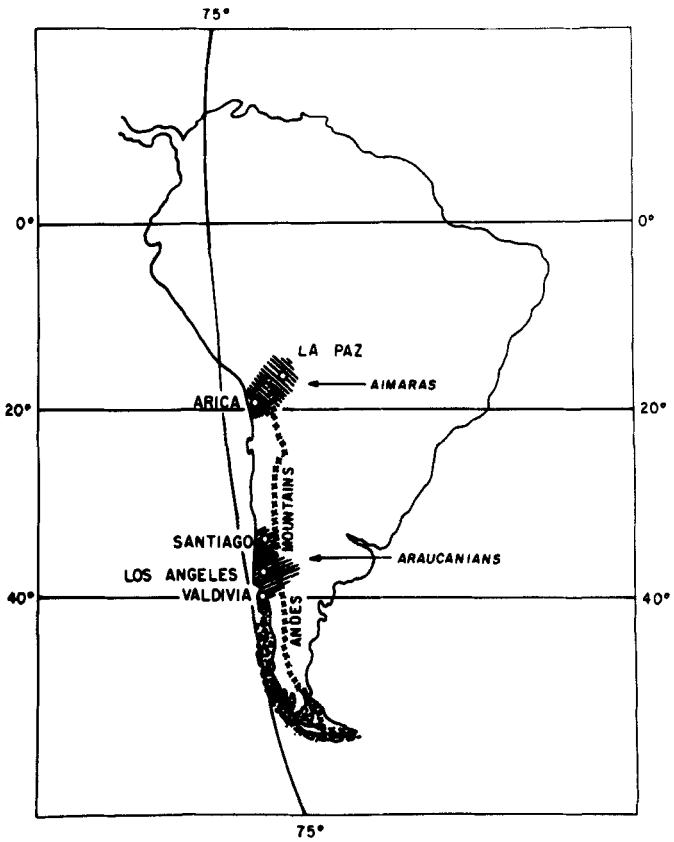

FIG. 2. Geographic site of cities where the prevalence of ICP has been studied in Chile and Bolivia. The *dotted line* shows Chilean boundaries. Arica is a seaport with a desert coastal climate and is geographically separated from other Chilean cities by the Atacama Desert. Santiago, Los Angeles, and Valdivia are located in Chile's main agricultural zone, where about 70% of the Chilean population lives. The climate is moderate in Santiago and rainy in Valdivia. La Paz is located in the Bolivian high Andean plateau (altitude 3,600 m). The zones where Aimara and Araucanian Indians were originally located are shown by *dashed lines*.

regardless of whether they live in the high Andean plateau or at sea level (53, 54) (Table 1). Populations studied in La Paz, Bolivia and in Chile live in extremely different geographic environments and share few common cultural characteristics. These observations suggest a role for genetic factors in the ethnic predisposition for ICP.

TABLE 1. PREVALENCE OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY[a] IN DIFFERENT COUNTRIES AND IN ETHNIC GROUPS

Countries, ethnic groups, and reference sources	Cholestatic jaundice of pregnancy (%)	Pruritus gravidarum (%)
U.S.A. (59)	<0.01	?[b]
Canada (48)	0.036	?
Australia (4)	0.13	0.11
France (46, 61)	0.024	0.2
Switzerland (10)	0.035	?
Poland (60)	1.16	?
Sweden (2, 8, 12, 16, 17)	1.20	1.6-3.0
Bolivia (54)	?	9.2
Caucasoids	?	7.8
Aimara Indians	?	13.8
Quechua Indians	?	4.3
Indian-mixed ("mestizos")	?	7.3
Chile (14, 53)	2.4	13.2
Caucasoids	2.5	12.6
Aimara Indians	?	11.8
Araucanian Indian-mixed	5.5	22.1

[a] Estimated as the proportion of affected cases in relationship to the total number of deliveries attended in general hospitals. Numbers in parentheses indicate reference sources.

[b] ?, unknown prevalence.

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The possibility that a genetic predisposition influences the pathogenesis of ICP was anticipated by Svanborg (1) and Thorling (2) when they reviewed the history of the disease in relatives of affected women. When cholestatic jaundice due to oral contraceptives was recognized as a new entity, it became evident that a large proportion of these cases had previously experienced ICP. Some women also developed ICP after an episode of gestagen-induced hepatitis. Their mothers and sisters often gave a past history of one or both diseases. In a well-designed retrospective study, Dalén and Westerholm (55) demonstrated that a past history of ICP was more frequent in 129 Swedish women who had had gestagen-induced jaundice than in paired controls who had used gestagens for similar periods of time without evidencing liver damage. A past history of ICP was more frequent in the patients' mothers than in the mothers in the control group. A past history of ICP and gestagen-induced hepatitis was also more frequent in the patients' sisters than in the sisters in the control group. In addition, the prevalence of gallstone disease was significantly higher in patients and their sisters than in respective control groups.

Several pedigree studies have shown the occurrence of ICP in two generations of blood relatives (56). This observation usually coincided with a high frequency of gestagen-induced jaundice in the younger generation and a high incidence of cholelithiasis in every generation studied. We have collected cases of ICP, gestagen-induced jaundice, and gallstone disease in families of Araucanian Indian descent, and in families of immigrants of different ethnic origin (Figures 3 and 4). The affected mothers developed ICP in their countries of origin, and their daughters had ICP or gestagen-induced hepatitis

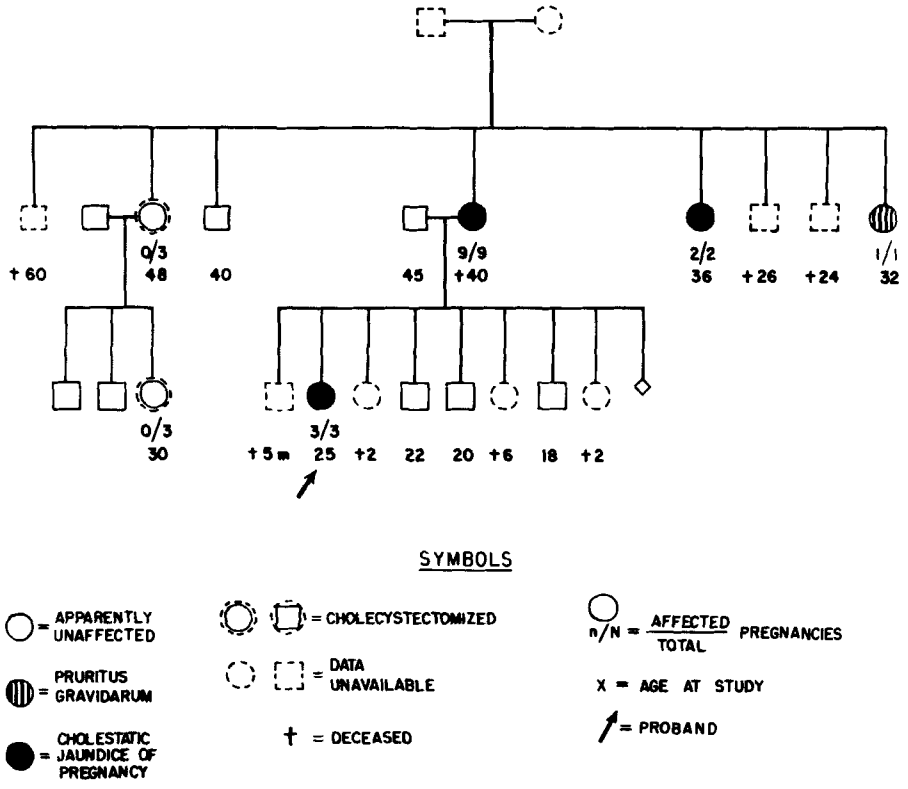

Fig. 3. Pedigree of a Caucasoid Chilean family showing occurrence of ICP in two generations. In 4 of 6 gestant women studied, each pregnancy was affected by ICP.

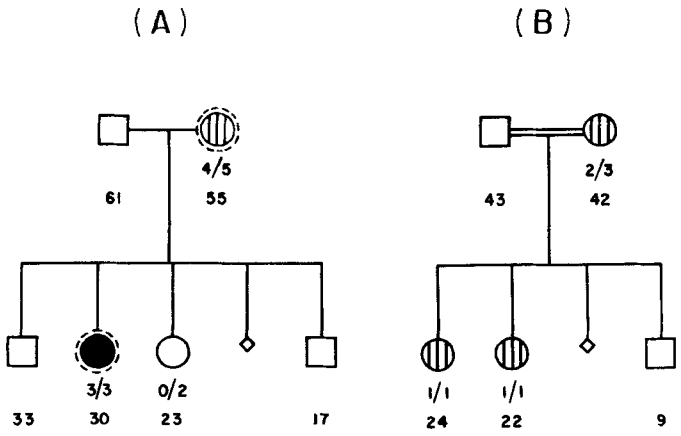

FIG. 4. Pedigrees of two immigrant families, with ICP-affected cases in two generations. Symbols are the same as in Fig. 2. In Family (A), the parents are Ashkenazim Jews who migrated from Rumania to Uzbekistan (U.S.S.R.) and then to Chile. The mother had PG in her first pregnancy (while living in Uzbekistan) and in the last three (while living in Chile); after her second pregnancy, she was cholecystectomized due to gallstones. The elder daughter was cholecystectomized due to gallstones at age 15; she then had CJP while living in Chile (pregnancies 1 and 2) or in the United States (third pregnancy). She also had gestagen-induced jaundice after the first pregnancy while traveling in England. The second daughter lives in Israel and had two uneventful pregnancies. In Family (B), the parents are first-degree cousins who were born in Lebanon from Arabian-Palestinian ancestry. They migrated to Chile where the mother and her two daughters have had PG.

while living in Chile or abroad. We are not aware of pedigree studies including twin sisters. The familial aggregation of ICP-affected cases supports the hypothesis that genetic factors are involved in the pathogenesis of the disease, but the mechanisms are unclear.

None of the "genetic markers" thus far studied in patients with ICP appear directly related to the disease. A large proportion of the Chilean population has O blood group and "shovel-shaped" teeth, but ICP is not restricted to women having these traits. The distribution of classic blood groups is different in Swedish women and they have a low frequency of "shovel-shaped" teeth. Besides North and South American Indians, "shovel-shaped" teeth are highly prevalent in Mongolian populations which are the putative source of this morphologic characteristic which is inherited as a dominant autosomic trait. Some histocompatibility antigens of the HLA system have a different distribution in Caucasoid Chilean women than in Araucanian-mixed women, but a past history of ICP cannot be directly related to A, B, or C series HLA antigens thus far studied (Reyes et al., in preparation).

A main limiting factor in the study of genetic transmission in ICP is its ambiguous phenotype. The disease requires at least one pregnancy to be detected but one or more pregnancies may appear unaffected until ICP becomes obvious. The severity of the disease may be different during consecutive pregnancies and it may remain unnoticed in surveys relying on a past history. Finally, we lack a specific test to identify carriers of the presumptive genetic trait which predisposes to ICP.

In women with a past history of ICP, Kreek et al. (25, 57) observed that administration of ethinyl estradiol at a dose of 1 mg per day was quickly followed by abnormal sulfobromophthalein (BSP) retention, transient nausea, jaundice, and pruritus which resemble symptoms previously experienced during pregnancy. This observation opened the field to develop a test to detect an abnormal subclinical response to estrogens in adults of either sex. The administration of a low dose of ethinyl estradiol (0.1 mg per day) during 6 days did induce pruritus or hyperbilirubinemia but was followed by reduction in the rate of BSP disappearance from blood which was significantly greater in multiparous women with a past history of ICP than in multiparous women with normal pregnancies (58). This phenomenon was detected several months or years after the last ICP-affected pregnancy indicating that an exaggerated response to estrogens may be a constitutional characteristic in some individuals. The same exaggerated response to a low dose of ethinyl estradiol was detected more frequently in nulligestant women and in men from a family with a history of ICP than in their respective control groups, suggesting that the constitutional predisposition to ICP may be present in women before a first pregnancy and in men.

To be manifested, the disease apparently requires interaction of this putative constitutional predisposition with other factors. One factor (i.e., pregnancy) is obvious; the others remain unknown. If the predisposition is inherited and transmitted by individuals of either sex, we could explain why transmission of the defect in several families appears to be from the father of the propositus.

TRENDS OF FUTURE RESEARCH

The unsolved questions raised by epidemiological, clinical, and biochemical characteristics of ICP stimulate many lines of research. Those which currently appear as more relevant and potentially productive will be stressed.

1. Hormonal and biochemical abnormalities should be studied before the onset of pruritus in pregnant multiparous women who manifested ICP in previous pregnancies and in primigravidas with a familial history of ICP. These studies may elucidate a test for early diagnosis of the disease, evaluate the cause-effect relationship of metabolic abnormalities in ICP, and better define the phenotype.
2. The beneficial clinical effects sometimes obtained with cholestyramine and nonabsorbable antacids on pruritus and biochemical abnormalities in ICP may be ascribed to direct effects on intestinal reabsorption and enterohepatic circulation of steroid hormones, bile acids, and their metabolites, and on unidentified substance(s) which may be responsible for pruritus in these women. Adlercreutz et al. (62) demonstrated that bacterial flora in the gut lumen are important in the metabolism of estrogens and in its intestinal reabsorption and enterohepatic circulation. They also illustrated the effects of antibiotics in these physiologic steps. Eriksson et al. (34) observed clinical improvement in two women with PG during oral administration of sulfathiazole; in these cases, a primary effect of sulfathiazole on intestinal microflora may have altered the production and

absorption of deleterious substances by the intestine.

Further research is needed to understand the modifications of steroid hormones, bile acids, and other biliary lipids after biliary excretion into the gut and during enterohepatic circulation. These studies may unveil chemical substances which "trigger" the disease in women who are genetically prone to develop it, and may discover what determines its expressivity and the reasons for clinical and biochemical fluctuations.

3. What is the meaning of epidemiological associations between ICP and other diseases?

In women with recurrent ICP, postpartum and long-term follow-up studies reveal no clinically meaningful abnormality in liver function or structure which indicate chronic progressive liver disease. Samsioe (13) and others demonstrated rapid normalization of several liver function tests after delivery. Kreek et al. (27, 57), Ylöstalo (63), and others (58) have shown that ICP-affected women studied years after their last pregnancy have normal basal plasma BSP disappearance tests. Several cases of ICP, originally reported by Thorling (2), were restudied by Furhoff and Hellström (64, 65) about 15 years later and no significant hepatic abnormality was attributed to their previous ICP. However, other studies establish a close association between ICP and other hepatobiliary diseases. The connection between ICP and gestagen-induced jaundice is an obvious stimulus for further studies on the effects of estrogens and progesterone on liver function and dysfunction. The prevalence of gallstones seems to be 2 or 3 times greater in women with ICP than in the general population of women with a similar age and parity. It is suspected that symptomatic gallstones appear at younger ages in women with ICP (12, 20, 66, 67).

Cholesterol cholelithiasis is a multifactorial disease in which pregnancy and estrogens are influential. Braverman et al. (68) showed that pregnancy increases gallbladder volume during fasting and residual volume after contraction, and reduces the rate of gallbladder emptying. Recently, Ylöstalo et al. (69) reported in five women with ICP that the fasting volume of the gallbladder was significantly greater than in normal pregnant women. Both observations help to understand some mechanisms of gallstone formation in pregnant women and the higher prevalence of cholelithiasis in ICP-affected women.

Both ICP and cholelithiasis are prevalent in Sweden and Chile. This epidemiological association, added to current knowledge on pathophysiological mechanisms involved in both diseases, suggests that they may share common causes. However, although an extremely high prevalence of cholesterol gallstones is characteristic of Pima and Chippewa Indians in the United States, there are no reports indicating the presence of ICP in these ethnic groups. Valdivieso et al. (70) and Nervi et al. (71) showed that bile composition and formation in Chilean women with cholesterol gallstones have several differences as compared with abnormalities reported in North American and European populations. It is important to identify abnormalities in bile formation and composition shared by women with ICP and gallstones to elucidate the reason for their simultaneous occurrence in some countries and ethnic groups.

In several reports (8, 50, 60, 64), the incidence of urinary tract infections ranges between 17 and 30% in ICP-affected women and is significantly higher than in the general population of pregnant women. Symptoms of ICP often increase in coincidence with symptomatic urinary tract infection and tend to be more intense than in pregnancies in the absence of urinary tract infection. These clinical observations should stimulate a study of the role of circulating endotoxins in expressivity of cholestasis in pregnant women who are prone to develop it.

A familial connection between ICP and recurrent benign intrahepatic cholestasis (72) is an exceptional finding which also deserves further studies.

Any progress in understanding mechanisms of bile formation and secretion and in the pathogenesis of intrahepatic cholestasis will help to answer many of these questions. Meanwhile, ICP constitutes the best model of a "pure" intrahepatic cholestasis and challenges basic and clinical investigators to discover the etiology and pathogenesis of a disease which seems to be restricted to the human species.

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