LIVER DYSFUNCTION AND JAUNDICE IN PREGNANCY

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I. Normal Pregnancy

A. Liver Size

The liver in human pregnancy appears to be approximately the same size as in non-pregnant women. Moreover, no increase in size ensues during the course of pregnancy. These findings in man contrast with those in experimental animals in whom significant increases in liver weight are observed during gestation. Excluding 10 cases of acute yellow atrophy, 90 livers weighed an average of 1770 grams in the experience of Sheehan (Sheehan, H.L., Amer. J. Obstet. Gynecol. 81:427, 1961). Average liver weight was 1725 grams in 16 women dying after a brief illness in pregnancy at Parkland Memorial Hospital; 1708 gram average in the first 4 months; 1732 gram average in the last trimester and at term (Combes, B., Shibata, H., Adams, R.H., Mitchel, B.D. and Trammell, V., J. Clin. Invest. 42:1431, 1963).

B. Liver Histology

Changes in histology in normal pregnancy are subtle and for practical purposes the liver appears normal (Ingerslev, M., and Teilum, G., Acta Obstet. Gynecol. Scand. 25:352, 1945; Nixon, W.C.W., Egeli, E.S., Laqueur, W., and Yahya, O., J. Obstet. Gynaecol. Brit. Emp. 54:642, 1947; Dietel, H., Z. Geburtsh. Gynaekol. 128:127, 1947; Antia, F.P., Bharadwaj, T.P., Watsa, M.C., and Master, J., Lancet 2:776, 1958). No ultrastructural changes were observed by electron microscopy (Aldercreutz, H., Svanborg, A., and Anberg, A., Amer. J. Med. 42:335, 1967).

C. Liver Blood Flow

Data in normal pregnancy are limited to 15 women studied by Munnell and Taylor (Munnell, E.W., and Taylor, H.C., Jr., J. Clin. Invest. 26:952, 1947) utilizing hepatic vein catheterization and the BSP clearance and extraction method of Bradley et al. (Bradley, S.E., Ingelfinger, F.J., Bradley, G.P., and Curry, J.J., J. Clin. Invest. 24:890, 1945) (see Table I).

TABLE I

Estimated Hepatic Blood Flow in Normal Pregnancy[a]

Clinical status	Number of subjects	Estimated hepatic blood flow [Mean (range)]	
		ml/min/1.73 m²	% Total blood volume
Nonpregnant women	15	1548 (1177–1900)	35 (28.2–42.8)
Pregnancy trimester			
1st	4	1803 (1273–2465)	32.8 (24.7–44.2)
2nd	3	1600 (1423–1878)	32.8 (29.4–38.1)
3rd	8	1414 (1075–1854)	24.8 (17.1–34.7)

Adapted from Munnell, E.W., and Taylor, H.C., Jr., J.Clin.Invest. 26:952, 1947

Hepatic blood flow averaged 1548 ml/ min/1.73 m^2 in 15 nonpregnant women in the reproductive age range. During pregnancy, hepatic blood flow averaged 1803, 1600, and 1414 ml/ min/1.73 m^2 in the 1st, 2nd and 3rd trimesters, respectively. Because of the small number of subjects, it is impossible to state whether there are significant differences in blood flow from one trimester to another. Nevertheless, no striking changes from values in nonpregnant women were noted.

Blood volume and cardiac output rise in pregnancy. Data on these parameters are summarized by Hytten and Leitch (Hytten, F.E. and Leitch, I., "The Physiology of Human Pregnancy." Blackwell, Oxford, 1964). In the last trimester, total blood volume and cardiac output increase approximately 30 to 40%, while hepatic blood flow does not change significantly. Thus a smaller proportion of the total blood volume and cardiac output reaches the liver each minute throughout much of pregnancy. Despite these changes, blood flow per unit hepatic mass (see data for liver weights in pregnancy) appears to vary little in normal pregnancy.

D. Laboratory Tests

The following represent brief summaries of numerous reports. Comprehensive bibliography can be found in Combes, B. and Adams, R.H. Chapter 6 Disorders of the liver in pregnancy in Pathophysiology of Gestation Disorders, Vol 1, Ed. Assali, N., Academic Press, Inc. 1972.

1. Serum Bilirubin

Values for total serum bilirubin remain within the range found in nonpregnant subjects, and no significant change in bilirubin concentration occurs during the course of normal pregnancy. Occasionally, bilirubin values up to 2 mg% are reported, but it is not clear whether these elevated values are related to normal pregnancy or to some preexistent or coincident condition.

Increased bilirubin retention in blood after intravenous administration of bilirubin has been observed, particularly in the second half of pregnancy. Soffer (Soffer, L.J., Bull. Johns Hopkins Hosp. 52:365, 1933) and Sullivan et al (Sullivan, C.F., Tew, W.P., and Watson, E.M., J. Obstet. Gynaecol. Brit. Emp. 41:347, 1934), each found increased retention in only 1 of 11 patients in the first trimester and first half of pregnancy, respectively. By contrast, abnormal retention was noted in 9 of 10 (Soffer) and 15 of 47 women (Sullivan et al.) in the latter part of pregnancy. Soffer (Soffer, L.J., Bull. Johns Hopkins Hosp. 52:365, 1933) performed tests in both the first and second halves of pregnancy in 10 women and observed significant increases in bilirubin retention in late pregnancy in 7 of them.

2. Serum Transaminases

Serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) remain within the normal range throughout pregnancy. Occasional slight increases in serum transaminase activity are detected during labor.

3. Thymol Turbidity and Cephalin Flocculation Tests

The majority of results for these two tests in uncomplicated pregnancy are within the normal range. A variable number of patients in some series, usually less than 10%, have abnormal values. In most instances, when abnormal values have been found, it is not clear whether they developed during pregnancy, or were present prior to gestation.

Although rarely used at present for diagnostic purposes, the tests are of some value in liver disorders in pregnancy since they are usually abnormally elevated in viral hepatitis, but usually in the normal range in the liver dysfunction of hyperemesis gravidarum and cholestasis of pregnancy.

4. Serum Alkaline Phosphatase

Serum alkaline phosphatase activity increases during pregnancy, particularly in the latter half. Peak levels of activity are reached at term, then fall after delivery, reaching normal values within a few weeks postpartum.

Alkaline phosphatase activity in normal human sera is derived from bone, the hepatobiliary system and the intestinal tract, with skeletal phosphatase probably accounting for 40-75% of the total activity. In pregnancy, there is now abundant evidence that the increment in serum alkaline phosphatase is of placental origin.

Interpretation of abnormally high increases in serum alkaline phosphatase activity during pregnancy will obviously be complicated because of the many tissue sources that can contribute to serum activity. Persistent alkaline phosphatase activity after heating serum is accounted for by placental phosphatase. Abnormally high and low values for this moiety have been described in a variety of disorders of and in pregnancy. Heat-labile alkaline phosphatase activity reflects bone, hepatobiliary, and intestinal alkaline phosphatase. Unraveling the tissue source in the pregnant woman will be difficult unless other diagnostic tests indicate disorders of these organs. Thus alkaline phosphatase determinations are of limited value in diagnosis of hepatic disease in pregnancy.

In the nonpregnant patient, estimation of leucine aminopeptidase, 5'-nucleotidase, and gamma glutamyl transpeptidase activity in serum is of value in appraising whether an elevated value of serum alkaline phosphatase is due to a disorder of liver or bone. Thus the activity of these enzymes in serum is elevated in most liver disorders in which serum alkaline phosphatase is elevated. By contrast, activity of leucine aminopeptidase, 5'-nucleotidase, and gamma glutamyl transpeptidase is not increased in patients with various disorders of bone. For reasons cited below these determinations are of little value in the pregnant woman.

5. Leucine Aminopeptidase

Activity is increased severalfold in the last trimester of pregnancy and during labor, then falls reaching normal values within 4-5 weeks postpartum. The syncytiotrophoblast of the maturing placenta is the probable source of the enzymic activity in maternal serum derived from the placenta.

6. 5'-Nucleotidase

Conflicting data have been reported. No change (1 study) and increases in serum activity (2 studies) have been found in the last trimester. It is not clear whether these experiences differ because of methodologic difference.

7. Gamma Glutamyl Transpeptidase (GGT)

Serum GGT activity does not change in pregnancy.

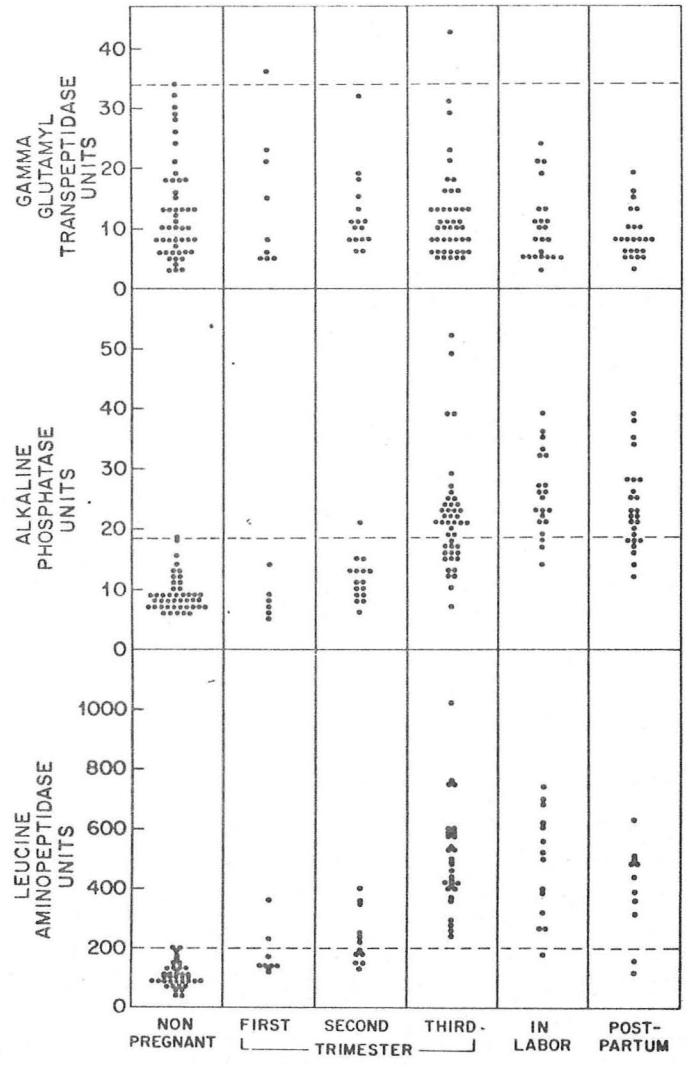

Fig 1. Activities in serum of gamma glutamyl transpeptidase, alkaline phosphatase, and leucine aminopeptidase in normal nonpregnant women, and in various stages of pregnancy. The broken lines indicate the highest value obtained for each enzyme in normal controls.

from Walker, F.B.,Iv., et al., Obstet. Gynecol, 43:745, 1974

However, estrogen and/or progestational compounds affect liver such that less GGT is released into blood with acute hepatocellular injury. In addition, hyperbilirubinemia is associated with depressed GGT activity, and bilirubin added to serum in vitro interferes with measured activity of the enzyme (Combes, B., Shore, G.M., Cunningham, F.G., Walker, F.B., IV, Shorey, J.W. and Ware, A., Gastroenterology 72:271,1977). These factors, particularly the former, limit the differential diagnostic usefulness of the GGT enzyme test in liver diseases in pregnancy.

II. Classification of Liver Dysfunction in Pregnancy

Three broad types can be distinguished. (1) The hepatic disorder is related to pregnancy or is seen predominantly in the setting of pregnancy. Included is the dysfunction found in patients with hyperemesis gravidarum, preeclampsia, and eclampsia, and the conditions of acute fatty metamorphosis of pregnancy and intrahepatic cholestasis of pregnancy. (2) The hepatic disturbance is acute and incidental to pregnancy, occurring frequently in nonpregnant subjects too. The most common of these disorders is viral hepatitis. Other examples include the hepatic dysfunction induced by drugs and toxins, that associated with severe systemic infection, and that accompanying stones in the biliary tract. (3) The hepatic disorder was present prior to gestation and persists after pregnancy is completed. Its manifestations may be exaggerated by pregnancy, or it may first be recognized during pregnancy. Included are such disorders as chronic active hepatitis, various cirrhoses, various forms of congenital hyperbilirubinemia, and the congenital hemolytic anemias.

III. Liver Dysfunction Related to Pregnancy

A. Hyperemesis Gravidarum

Alterations in hepatic function occur frequently in pregnant women with vomiting severe enough to require hospitalization (Adams, R.H., Gordon, J., and Combes, B., Obstet. Gynecol. 31:659, 1968). Thus interference with nutrition is an important factor in the development of hepatic dysfunction. (See Table II)

Increased retention of BSP in plasma in the 45-min clinical BSP test was the commonest abnormality detected in 46 women hospitalized for hyperemesis. BSP retention greater than 10% at 45 min was found in 60% of them (Adams, R.H., Gordon, J., and Combes, B., Obstet. Gynecol. 31:659, 1968). When hepatic BSP removal mechanisms were examined by a prolonged infusion method, impairment of transport of BSP from liver cells into bile was the major abnormality detected (Combes, B., Adams, R.H., Gordon, J., Trammell, V., and Shibata, H., Obstet. Gynecol. 31:665, 1968).

Increased values for SGOT were detected in approximately one-fourth of the patients (Adams, R.H., Gordon, J., and Combes, B., Obstet. Gynecol. 31:659, 1968).

TABLE 2 RESULTS OF LIVER FUNCTION TESTS IN PATIENTS WITH HYPEREMESIS GRAVIDARUM

Test		No. of patients				
			Complications clinic		Hospitalized	
Upper limit of normal in non-pregnant patients	Ranges shown	Normal pregnancy	1st trim.	2nd trim.	1st trim.	2nd trim.
BSP	5 or <	19	17	21	7	4
(% retention,	5.1–10	6	5	9	7	1
45 min.)	10.1–15	0	1	2	4	1
5	15.1–20	0	1	0	5	2
	>20	0	1	0	9	6
Bilirubin	1.2 or <	25	24	35	21	9
(mg./100 ml.)	1.3–2.5	0	1	0	7	3
1.2	2.6–4.0	0	0	0	5	0
Thymol turbidity	5 or <	25	25	36	32	11
(U.)	5.1–10	0	0	0	1	1
5						
Cephalin flocculation	0–2+	24	25	36	28	11
2+ at 48 hr.	3+, 4+	1	0	0	3	1
SGOT	40 or <	25	25	36	22	10
(Karmen U.)	41–100	0	0	0	6	1
40	101–200	0	0	0	0	3
Alkaline phosphatase	5 or <	21	22	30	25	6
(Bodansky U.)	5.1–10	4	3	6	7	5
5	10.1–15	0	0	0	0	1

from Adams, R.H., et al., Obstet. Gynecol. 31:660, 1968

The elevation was usually slight with most values less than 100 Karmen units. Three patients had maximal values of 115, 144, and 193 units. Since this report, the highest value seen by the present authors was 400 units, in a liver biopsy confirmed case. Thymol turbidity and cephalin flocculation tests are rarely abnormal (Adams, R.H., Gordon, J., and Combes, B., Obstet. Gynecol. 31:659, 1968; Thorling, L., Acta Med. Scand., Suppl 302:1, 1955).

Histology of the liver was normal in 5 of 6 patients undergoing percutaneous liver biopsy in this unit (Adams, R.H., Gordon, J., and Combes, B., Obstet. Gynecol. 31: 659, 1968; Combes, B., and Adams, R.H., unpublished observations); centrilobular

fatty metamorphosis was noted in the sixth. Normal histology was observed in 1 patient by Ingerslev and Teilum (Ingerslev, M., and Teilum, G., Acta Obstet. Gynec. Scand. 25:339, 1945, and in 2 patients by Nixon et al. (Nixon, W.C.W., Egeli, E.S., Laqueur, W., and Yahya, O., J. Obstet. Gynaecol. Brit. Emp. 54:642, 1947). except that parenchymal cells were shrunken in the former report and were poor in glycogen in 1 patient in the latter report.

Sheehan (Sheehan, H.L., J. Obstet. Gynaecol. Brit. Emp. 46:685, 1939), in 1939, reported on 19 patients dying from hyperemesis and more recently presented an additional 5 cases (Sheehan, H.L., Amer. J. Obstet. Gynecol. 81:427, 1961). Jaundice was occasionally present and was slight. In the combined series at autopsy the liver was small with an average weight of 1245 gm (range 910-1680 gm). Fatty metamorphosis was present in 12, with a large or a few medium-sized fat vacuoles present in affected parenchymal cells. The change was centrilobular in 8 cases, periportal in 2, and panlobular in 2 cases. Fat was absent in the remaining 12 cases. Some excess pigment not further characterized was present either in parenchymal or Kupffer cells at the center of the lobules in many of the cases.

Despite evidence of hepatic dysfunction, the liver abnormalities in patients with hyperemesis are not severe. They can be expected to improve rapidly as nutritional status improves. Deaths noted in the past (Sheehan, H.L., J. Obstet. Gynaecol. Brit. Emp. 46:685, 1939) appear to be largely the consequence of Wernicke's encephalopathy, volume depletion and acid-base disturbances. These should be preventable by adequate fluid and vitamin replacement. Currently, a more frequent clinical consideration involves differential diagnosis from viral hepatitis. This should not provide too difficult a problem, however, since results of liver tests will usually be normal in patients with hyperemesis not severe enough to require hospitalization. Moreover, even when hepatic dysfunction is present, the relatively slight elevations in SGOT and normal results for thymol turbidity and cephalin flocculation should distinguish patients with hyperemesis from viral hepatitis. Finally, although only a limited experience with histological material from liver is available, normal histology with or without modest fatty metamorphosis should easily differentiate hyperemesis from viral hepatitis.

Most patients with hyperemesis are seen in the first trimester of pregnancy. Occasionally, severe vomiting occurs in the second half of gestation, and then is usually related to some underlying disease. In those circumstances in which no other primary disturbance is present, hepatic alterations are similar to those observed in patients with the more usual temporal onset of hyperemesis (Adams, R.H., Gordon, J., and Combes, B., Obstet. Gynecol. 31:659, 1968; Sheehan, H.L., J. Obstet. Gynaecol. Brit. Emp. 46:685, 1939), except that in autopsy material, the liver tends to be normal in size (Sheehan, H.L., Amer. J. Obstet. Gynecol. 81:427, 1961).

B. Preeclampsia and Eclampsia

The liver is characteristically involved at autopsy in patients dying with the acute toxemic states referred to as preeclampsia and eclampsia (Popper, H., and Schaffner, F., "Liver: Structure and Function." McGraw Hill, New York, 1957; Sheehan, H.L., Toxaemias Pregnancy, Ciba Found. Symp. 1950 pp. 16-22, 1950). Focal areas of necrosis of parenchymal cells and of hemorrhage with deposition of fibrin are found in the periportal areas. The hemorrhagic areas may be more diffuse and involve whole lobules or several lobules. Inflammatory cells are usually absent unless the patient lives long enough. Then a moderate filtration of polymorphonuclear leukocytes and later of mononuclear cells ensues. The lesions may be plentiful or sparse in number but are found in almost all patients who die with toxemia (Sheehan, H.L., Toxaemias Pregnancy, Ciba Found. Symp. 1950 pp. 16-22, 1950).

The results with liver biopsies obtained from living patients are quite different. (See Table III on the following page)

Thus the incidence of toxemic changes in liver is much lower in biopsy than in autopsy material, and in biopsies, these changes are seen more frequently in patients with eclampsia. Sampling may account for some of these findings since the amount of tissue obtained with a needle is relatively small. Sheehan indicated that even in autopsy material lesions may be so few that several slides must be examined to find a single example (Sheehan, H.L., Toxaemias Pregnancy, Ciba Found. Symp. 1950 pp. 16-22, 1950). In additiona, as Sheehan indicated, the lesions are related to mortality of eclampsia since they are found in nearly all who die of toxemia but in only about a quarter who recover from this condition and then die of other causes in the postpartum period.

Hyperbilirubinemia is rare in toxemia (Antia, F.P., Bharadwaj, T.P., Watsa, M.C., and Master, J., Lancet 2:776, 1958; Maqueo, M., Ayala, L.C. and Cervantes, L., Obstet. Gynaecol. Brit. Commonw. 70:693, 1963; Ylostalo, P., Acta Obstet. Gynecol. Scand. 49, Suppl. 4:1-53, 1970). Only 3 of 134 patients (89 preeclamptics, 45 eclamptics) in our hospital series had a serum bilirubin in excess of 1.2 mg/100 ml, and these were 1.3, 1.3, and 2.3 mg/100 ml, respectively (Combes, B., Adams, R.H., unpublished observations). Jaundice was present in 10 of 90 fatal cases of eclampsia reported by Sheehan (Sheehan, H.L., Amer. J. Obstet. Gynecol. 81:427, 1961), and was attributed to hemolysis, since hemoglobinemia and hemoglobinuria were present during life and hemoglobin casts were present in the renal tubules at autopsy. Thymol turbidity and cephalin flocculation tests are usually normal (Christhilf, S.M., and Bonsnes, R.W., Amer. J. Obstet. Gynecol. 59:1100, 1950; Combes, B., Adams, R.H., unpublished observations; Dieckmann, W.J., and Pottinger, R.E., Amer. J. Obstet. Gynecol. 68:1581,1954; Ylostalo, P., Acta Obstet. Gynecol. Scand 49, Suppl. 4:1-53, 1970). Results of other conventional liver tests are frequently abnormal but it is not certain that this is the consequence of hepatocellular disease. A number of authors have reported an increase in serum alkaline phosphatase activity above the elevated values found in normal pregnancy (Antia, F.P., Bharadwaj, T.P., Watsa, M.C., and Master, J., Lancet 2:776, 1958; Combes, B., Adams, R.H., unpublished observations; Mukherjee, C., J. Indian Med. Ass. 21:43, 1951; Ylostalo, P., Acta Obstet. Gynecol. Scand 49, Suppl. 4:1-53, 1970), whereas others have found no differences in normal and toxemic

TABLE III

LIVER BIOPSIES IN TOXEMIA OF PREGNANCY

	Ingerslev and Teilum[a] (126)	Antia et al.[b] (10)	Maqueo et al.[c] (174)	Adams and Combes[d]	Total
Preeclampsia					
Normal	6	16	35	6	63
Abnormal	0	0	7	0	7
					70
Eclampsia					
Normal	2	10	3	12	27
Abnormal	3	4	5	0	12
					39

[a] Ingerslev, M., and Teilum, G., Acta Obstet. Gynecol. Scand. 25, 361 (1945)

[b] Antia, F. P. et al., Lancet 2, 776 (1958)

[c] Maqueo, M., Obstet. Gynecol. 23, 222 (1964)

[d] Adams, R. H., Combes, B., unpublished observations

pregnancies (Aoba, A., Harui, Y., and Yamaguchi, R., Tokoku J. Exp. Med. 91:301, 1967; Dass, A., and Bhagwanani, S., Obstet. Gynaecol. Brit. Commonw 71:727, 1964). Increased alkaline phosphatase activity in toxemia as in normal pregnancy is heat-stable and thus is presumably derived from the placenta. Disproportionately high values in toxemia (Curzen, P., and Morris, I., J. Obstet. Gynaecol. Brit. Commonw. 73:640, 1966; Hunter, R.J., Pinkerton, J.H.M., and Johnston, H., OBstet. Gynecol. 36:536, 1970) suggest a placental abnormality leading to increased release of alkaline phosphatase into the circulation. Serum transaminase activity is elevated modestly in a variable proportion of patients (Borglin, N.E., J. Clin. Endocrinol. Metab. 18:872, 1958; Crisp, W.E., Miesfeld, R.L., and Frajola, W.J., Obstet. Gynecol. 13:487, 1959; Dass, A., and Bhagwanani, S., Obstet. Gynaecol. Brit. Commonw. 71:727, 1964; Maqueo, M., Ayala, L.C., and Cervantes, L., Obstet. Gynecol. 23:222, 1964; Theisen, R., Jackson, C.R., Morrissey, J., and Peckham, B., Obstet. Gynecol 17:183, 1961; Ylostalo, P., Acta Obstet. Gynecol. Scand 49: Suppl. 4:1-53, 1970). In general, higher values are observed in eclampsia than in preeclampsia The tissue source(s) of the elevated transaminase activity in serum in toxemics is not certain. Although there is a tendency to consider release from liver as the cause of the elevated transaminases it should be remembered that transaminases are found in many tissues, including the placenta (DaCunha, D.P., and Azevedo, M.D., C. R. Soc. Biol. 155:207, 1961) and these may be the source of serum enzyme, too. Not surprisingly, the placenta contains a large number of enzymes, including those found in most of the common metabolic pathways (Hagerman, D. D., Fed. Proc., Fed. Amer. Soc. Exp. Biol. 23:785, 1964).

In recent years, it has become apparent that a few patients with severe preeclampsia (may or may not be superimposed on chronic hypertension) or eclampsia develop acute liver disease complicated by disseminated intravascular coagulation (DIC). Fibrin deposits are recognized in liver as well as in kidney. (McKay, D.G., Obstet. Gynecol. Surv. 27:399, 1962; Arias, F. and Mancilla-Jimenez, R., N. Engl. J. Med. 295:578, 1976). There is hematologic evidence of DIC including variable degrees of thrombocytopenia, prolongation of the thrombin time, elevated levels of fibrin degradation products in serum, and hypofibrinogenemia. Microangiopathic hemolysis with deformities of circulating red cells and evidence of acute hemolysis including reticulocytosis, nucleated red cells in the peripheral blood and in florid cases, gross hemoglobinemia and hemoglobinuria may be present (McKay, D.G., Obstet. Gynec. Surv. 27:399, 1962; Beecham, J.B., Watson, W.J., and Clapp, J.F.III., Obstet. Gynecol. 43:476, 1974; Killam, A.P., Dillard, S.H., Jr., Patton, R.C., and Penderson, P.R., Amer. J. Obstet. Gynecol. 123:823-1975). The trauma to red cells that leads to their deformity and destruction has commonly been attributed to fibrin strands that formed intravascularly.

Data from 5 cases reported by Killam et al. in 1975 are contained in the following three tables. (see Tables IV, V, and VI).

Table IV. Clinical information

	Case 1	*Case 2*	*Case 3*	*Case 4*	*Case 5*
Parity	2	0	0	3	1
Malaise	Minimal	Moderate	Minimal	Minimal	Minimal
Nausea & vomiting	Minimal	Moderate	Moderate	Moderate	Minimal
Epigastric pain	Severe	Severe	Severe	Moderate	Moderate
Dark urine	Marked	Moderate	Minimal	None	None
Ecchymoses	None	Moderate	None	None	None
Hypertension history	None	Yes	None	Yes	Yes
Scleral icterus	Moderate	Minimal	None	None	Minimal
Tender hepatomegaly	Minimal	Marked	Marked	Minimal	Marked
Fever	Moderate (101°)	Moderate (101°)	Moderate (101°)	Moderate (102°)	Moderate (102°)
Edema	None	None	None	None	None
Blood pressure:					
Prior to illness	110-134/70-80	110-150/70-84	120/70-80	112/70	122-130/70-90
Highest antepartum	190/120	160/108	180/129	190/136	226/156
Postpartum	110/80	128/80	116/70	140/90	130/100

Table V. General studies

	Case 1	*Case 2*	*Case 3*	*Case 4*	*Case 5*
High bilirubin:					
Total	5.9	2.4	1.8	1.7	2.9
Direct	2.7	0.7	0.3	0.5	1.5
High SGOT	1,350	810	500	900	340
High SGPT	—	350	119	—	49
High LDH	1,335	577	506	870	1,386
LDH isoenzyme fractionation*	Isoenzymes 1 + 2	Isoenzymes 1 + 2	Isoenzymes 1 + 2	Isoenzymes 1 + 2	—
Alkaline phosphatase (norm. 25-100 U.)	200	234	235	143	178
Hepatitis associated antigen	Negative	Negative	Negative	Negative	Negative
Proteinuria (maximum)	3+	3+	3+	3+	3+
Blood urea nitrogen	5-10	6-17	9-12	14-15	14-18
Creatinine	0.8-0.9	0.6-1.1	0.8	1.0	0.8-0.9
Uric acid	6.0-8.0	6.3-9.3	6.9-8.6	6.4-6.6	7.6
Serum electrolytes	Normal	Normal	Normal	Normal	Normal

*Isoenzyme fractions 1 and 2 are the anodal fractions.

from Killam, A.P., et al., Amer. J. Obstet. Gynecol. 123:823, 1975

Table VI. Hematologic studies

	Case 1	*Case 2*	*Case 3*	*Case 4*	*Case 5*
Hematocrit (%):					
Admission	40	40	37	38.7	40.0
Low	26	24	26	37.2	27.9
WBC (per mm.³):					
Admission	7,000	7,500	8,900	8,000	12,800
High	9,000	16,500	10,300	11,200	18,400
Platelet count (per mm.³):					
Lowest	40,000	26,000	46,000	53,000	40,000
Discharge	180,000	470,000	640,000	210,000	370,000
Peripheral smear (Burr cells, schistocytes, helmet cells)	Marked	Moderate	Moderate	Minimal	Minimal
Reticulocyte count (maximum)	5.0	8.9	8.9	—	3.6
Prothrombin time (sec.):					
Patient	15.5	15.1	13.0	12.5	11.9
Control	12.2	13.3	13.4	11.9	12.4
Partial thromboplastin time (sec.):					
Patient	43.5	36.0	32.8	40.0	80.0
Control	29.6	33.5	30.7	32.5	40.2
Thrombin time, maximum (sec.):					
Patient	17.2	15.5	21.0	14.6	17.5
Control	13.0	11.5	12.7	12.0	10.9
Fibrinogen (normal 115-380 cong.%);					
Lowest	442	547	575	375	504
Highest	1,004	575	862	510	1,160
Fibrin split products, maximum (normal 10 ng./ml. or less)	20	20	20	40	160
Factor studies (low %):					
5	100%	Not	115%	90%	128%
8	65%	avail-	160%	108%	128%
10	62%	able	115%	98%	129%

from Killam, A.P., et al., Amer. J. Obstet. Gynecol. 123:823, 1975

Although coagulation changes occur in eclamptic patients, they occur in a minority and it is clear that DIC is not essential to the development of eclampsia (Pritchard, J.A., Cunningham, F.G. and Mason, R.A., Am. J. Obstet. Gynecol. 124:855, 1976; Cunningham, F.G., and Pritchard, J.A., Seminars in Perinatology 2:29, 1978).

Table VII

Measurements of coagulation factors that imply disseminated intravascular coagulation

	Healthy intrapartum primigravidas	*Most abnormal value for each case of eclampsia*
Platelets*		
Mean, (cu. mm.)	278,000	202,000
−2 standard deviations	150,000	—
<150,000	0/20	28/95
<100,000	0/20	16/95
< 50,000	0/20	3/95
Serum fibrin degradation products†:		
8 μg/ml or less	17/20	57/65
16 μg/ml	3/20	6/65
>16 μg/ml	0/20	2/65
Plasma fibrinogen*		
Mean, mg./100 ml.	415	412
−2 standard deviations	285	—
<285 mg./100 ml.	0/20	7/92
Fibrin monomer		
Positive	1/20	1/20
Plasma thrombin time†		
Mean, (sec.)	8.9	11.3
>2.0 sec. slower than healthy pregnant	—	19/38

*Lowest value identified for each case of eclampsia.

†Highest value identified for each case of eclampsia.

Pritchard, J.A., et al., Amer. J. Obstet. Gynecol. 124:855, 1976

In toxemia, it is postulated that vasospasm induced by as yet unknown factors leads to vascular endothelial damage. Platelet adherence and fibrin disposition occur at the sites of endothelial disruption. Such changes contribute to microangiopathic hemolysis and to ischemic necrosis of liver tissue. A combination of hemolytic and hepatocellular jaundice may be apparent.

In some instances, the process is accompanied by diffuse oozing of blood from the liver and spontaneous rupture of this organ (Villegas, H., Azuela, J.C., and Maqueo, T. Int. J. Gynaecol. Obstet. 8:836, 1970; Bis, K.A. and Waxman, B., Obstet. Gyneocol. Surv. 31:763, 1976). Rarely, diffuse infarction of the liver may ensue.

Hepatic necrosis accounted for 10 of the 67 toxemic deaths occurring in Los Angeles County in the period 1957-72 (Hibbard, L.T., Obstet. Gynecol. 42:263, 1973). In Mexico City, between 1960-1968, 29 autopsies in toxemic patients (41 died) revealed severe liver disease in 21, and a ruptured liver in 6 (Villegas, H., Azuela, J.C. and Maqueo, T. Int. J. Gynaecol. Obstet 8:836, 1970).

Hepatic complications ensue most often in severe toxemia.

Table VIII Intensity of Pregnancy-Induced Hypertension

Abnormality	Mild	Severe
Convulsions	Absent	Present
Diastolic blood pressure	< 100	> 110
Proteinuria	Minimal	Overt and persistent
Headache	Absent	Persistent
Visual disturbances	Absent	Persistent
Upper abdominal pain	Absent	Persistent
Oliguria	Absent	Persistent
Azotemia	Absent	Present
Thrombocytopenia	Absent	Present
Hyperbilirubinemia	Absent	Present
Hepatocellular damage	Absent	Present
Fetal growth retardation	Absent	Obvious

from Pritchard, J.A., Seminars in Perinotology 2:83, 1978

The only specific treatment for preeclampsia and eclampsia is termination of the pregnancy. A successful management program for this group of disorders is outlined in detail in the paper of Pritchard, J.A., Seminars in Perinatology 2:83, 1978.

C. Acute Fatty Metamorphosis of Pregnancy

A special form of small-droplet fatty change observed in the liver histologically is the feature that characterizes the hepatic pathology of a virulent form of liver disease encountered predominantly in the third, but also in the second trimester of pregnancy and occasionally in the early postpartun period (Stander, H.J., and Cadden, J.F., Amer. J. Obstet. Gynecol. 28:61, 1934; Sheehan, H.L., J. Obstet. Gynaecol. Brit. Emp. 47:49, 1940; Ober, W.B., and LeCompte, P.M., Amer. J. Med. 19: 743, 1955; Moore, H.C., J. Obstet. Gynaecol. Brit. Emp. 63:189, 1956; Kahil, M.E., Fred, H.L., Brown, H., and Davis, J.S., Arch. Intern. Med. 113:63, 1964; Whalley, P.J., Adams, R.H., and Combes, B., J. Amer. Med. Ass. 189:357, 1964; Kunelis, C.T., Peters, J.L., and Edmondson, H.A., Amer. J. Med. 38:359, 1965; Breen, K.J., Perkins, K.W., Mistilis, S.P., and Shearman, R., Gut 11:822, 1970). Clinically, the illness resembles fulminant viral hepatitis. Anorexia, nausea, vomiting, abdominal discomfort or frank pain, weakness, and malaise are the features that predominate initially. Within 1-3 weeks, jaundice appears and deepens. Premature delivery is common and fetal mortality is very high. Depression of mentation, restlessness with progression to stupor, and coma bracket the period of delivery. Maternal mortality is also very high with hematemesis, coma, and shock comprising the usual terminal events. Occasionally the patient dies undelivered.

Hyperbilirubinemia, both conjugated and unconjugated, is usually moderate with values less than 10 mg% in the majority. However, higher values up to 30 mg% have been found in approximately 20% of the patients. Marked prolongation of the prothrombin time is common, with less than 50% of normal activity found in about 70-75% of the patients. Hypoglycemia has been documented on occasion (Green, K.J., Perkins, K.W., Mistilis, S.P., and Shearman, R., Gut 11:822, 1970). Elevated SGOT is usual, although peak values greater than 400 units (and as high as 1000) are recorded in only approximately 40% of the patients. Thymol turbidity is normal in 80 to 90%. The results of these latter two tests differ from those observed in viral hepatitis where higher values for SGOT and abnormal values for thymol turbidity are expected in the majority of patients. Other prominent laboratory features include elevation of serum amylase the consequence of pancreatitis, elevation of blood urea nitrogen and serum creatinine, depression of serum bicarbonate a manifestation of metabolic acidosis, and striking leukocytosis. The laboratory features are those of hepatic and renal insufficiency and pancreatitis. Disseminated intravascular coagulation has been described in recently reported cases (Pride, G.L., Cleary, R.E., and Hamburger, R.J. Am. J. Obstet. Gynecol 115:585, 1973; Holzbach, R.T., Obstet. Gynecol. 43:740, 1974; Cano, R.I., Delman, M.R., Pitchumoni, C.S., Lev, R., and Rosenthal, W.S., J. Amer. Med. Ass. 231:159, 1975).

Macroscopically, the liver appears yellow with weights varying from 900 to over 2000 gm. The prominent histological finding is the presence of multiple small droplets of fat in parenchymal cells giving them a fine foamy appearance. Nuclei remain centrally located in the swollen cells. The fatty change is usually most prominent in the central and midzonal parts of the liver lobule. Peripheral cells near the portal tract may be spared or involved in the fatty process. Although individual cell necrosis is usually not evident, the presence of cellular debris and pigment within Kupffer cells suggests that necrosis has occurred, and prominent centrilobular necrosis has been described in two reports (Czernobilsky, B., and Bergnes, M.A., Obstet. Gynecol. 26:792, 1965; Joske, R.A., McCully, D.J., and Mastaglia, F.L., Gut 9:489, 1968). Portal tracts tend to be normal. Cellular infiltrate of the lobules and portal tracts is usually sparse and consists predominantly of mononuclear cells. The pathological findings are clearly different from those observed in fulminant viral hepatitis.

Significant lesions have also been noted in other organs. Fatty vacuolization of renal tubules (Kunelis, C.T., Peters, J.L., and Edmondson, H.A., Amer. J. Med. 38:359, 1965; Ober, W.B., and LeCompte, P.M., Amer. J. Med. 19:743, 1955; Schultz, J.C., Adamson, J.S., Jr., Workman, W.W., and Norman, T.D., N. Engl. J. Med. 269:999, 1963) and sharply demarcated areas of cortical necrosis (Kunelis, C.T., Peters, J.L., and Edmondson, H.A., Amer. J. Med. 38:359, 1965) have been described in the kidney. Pancreatitis is commonly reported (Kunelis, C.T., Peters, J.L., and Edmondson, H.A., Amer. J. Med. 38:359, 1965; Ober, W.B., and LeCompte, P.M., Amer. J. Med. 19:743, 1955; Schultz, J.C., Adamson, J.S., Jr., Workman, W.W., and Norman, T.D., N. Engl. J. Med. 269:999, 1963; Van Itallie, T.B., and Hashim, S.A., Med. Clin. N. Amer. 47:629, 1963). Ischemic changes with cortical atrophy have been noted in the brain (Kunelis, C.T., Peters, J.L., and Edmondson, H.A., Amer. J. Med. 38:359, 1965), and protein-losing enteropathy has been documented (Hatfield, A.K., Stein, J.H., Greenberger, N.J., Abernethy, R.W. and Ferris, T.F., Dig. Dis. 17:167, 1972).

Although instances of acute fatty metamorphosis were reported as early as 1934, and prior to introduction of antibiotics in clinical medicine, the majority of cases from 1963-1970 appear to be the consequence of tetracycline toxicity occurring in pregnant women being treated for pyelonephritis. The doses of tetracycline given to many patients were clearly much larger than recommended (Kunelis, C.T., Peters, J.L., and Edmondson, H.A., Amer. J. Med. 38:359, 1965; Schoenfield, L.J., and Foulk, W.T., J. Clin. Invest. 43:1419, 1964). On other occasions, tetracycline toxicity ensued despite administration of generally acceptable doses of the antibiotic. Nevertheless, in both instances, current information suggests that unusually high levels of tetracycline were attained in blood and tissues and were responsible for the abnormalities observed in this clinical syndrome.

The studies of Whalley et al. demonstrated that tetracycline is disposed of comparably in normal pregnant and nonpregnant women (Whalley, P.J., Martin, F.G., Adams, R.H., and Combes, B., Obstet. Gynecol. 28:103, 1966). Disappearance rate from blood was also normal in the majority of tests conducted in pregnant women with pyelonephritis (Whalley, P.J., Martin, F.G., Adams, R.H., and Combes, B., Obstet. Gynecol. 36:821, 1970). In a small number of patients, however, the half-life in blood was prolonged, and in all of these, creatinine clearance, a measure of GFR, was depressed to less than 60 ml/min. GFR was low either because of preexisting intrinsic renal disease or because of pyelonephritis per se. When GFR is reduced significantly, removal of antibiotic from the circulation will be delayed and even normally recommended doses of tetracycline will result in unusually high blood and thus tissue levels of the antibiotic. Indeed this has been documented in a number of instances (Breitenbucher, R.B., and Crowley, L.V., Minn. Med. 53:949, 1970; Dowling, H.F., and Lepper, M.H., J. Amer. Med. Ass. 188:235, 1964; Whalley, P.J., Adams, R.H., and Combes, B., J. Amer. Med. Ass. 189:357, 1964; Whalley, P.J., Martin, F.G., Adams, R.H., and Combes, B., Obstet. Gynecol. 36:821, 1970). Higher blood and tissue levels will obviously result from administration of unusually large doses of antibiotic to patients with impaired renal function. Thus depressed GFR undoubtedly contributes in a major way to the pathogenesis of the syndrome. Finally, toxic levels of antibiotic can be obtained if abnormally high doses are administered to patients with normal renal function. The issue of tissue sensitivity to tetracycline in pregnancy is unresolved.

As mentioned earlier, not all cases of acute fatty metamorphosis of the liver in pregnancy are related to tetracycline. Clearly, instances were recognized prior to use of antibiotics. Sheehan's description of obstetric acute yellow atrophy in 1940 (Sheehan, H.L., J. Obstet. Gynaecol. Brit. Emp. 47:49, 1940) is strikingly similar to recent reports. Although the etiology of nontetracycline-treated disease is unknown, the similarity in clinical and pathological findings suggests that similar biochemical pathways are disturbed in both conditions.

Differentiation during life of acute fatty metamorphosis (in the absence of a history of ingestion of tetracycline), from severe viral hepatitis (when Australia antigen is absent in blood) requires a liver biopsy. This may be impossible to obtain if clotting studies are markedly abnormal. The theoretical advantage of having a tissue diagnosis involves the possibility that early induction of labor or caesarian section will be of benefit in ameliorating the maternal disease. This remains unproven, however. The limited experience with acute fatty metamorphosis of pregnancy

(Breen, K.J., Perkins, K.W., Mistilis, S.P., and Shearman, R., Gut 11:822, 1970; Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444:1-111, 1966) is reminiscent of that acquired with viral hepatitis, a disorder in which early termination of pregnancy is not considered to be indicated.

There now exist reports of five women who survived an episode of idiopathic acute fatty metamorphosis, became pregnant again, underwent an uncomplicated pregnancy without evidence of liver disease and delivered healthy babies (Breen, K.J., Perkins, K.W., Schenker, S., Dunkerley, R.C., and Moore, H.C., Obstet. Gynecol 40:813, 1972; MacKenna, J., Pupkin, M., Crenshaw C., Jr., McLeod, M. and Parker, R.T., Amer. J. Obstet. Gynecol. 127:400, 1977). This suggests the disorder is not a recurrent condition.

D. Intrahepatic Cholestasis of Pregnancy

The term intrahepatic cholestasis of pregnancy encompasses two cholestatic syndromes now recognized as variants of a common disorder. Pruritus is the initial and most prominent symptom. It may be confined to the extremities, or be generalized, and is most distressing in the evening. In the absence of hyperbilirubinemia, this condition is referred to as pruritus gravidarum (Arfwedson, H., Obstet. Gynecol. 7:274, 1956; Kasdon, S.C., Amer. J. Obstet. Gynecol. 65:320, 1953). Jaundice supervenes in many instances, almost always preceded by pruritus of 1-2 weeks duration, but hyperbilirubinemia has appeared as long as 22 weeks after the onset of pruritus. This type of jaundice with prominent obstructive features has been referred to as jaundice in late pregnancy (Ikonen, E., Acta Obstet. Gynecol. Scand. 43, Suppl. 5, 1-130, 1964; Thorling, L., Acta Med. Scand., Suppl. 302:1, 1955), idiopathic hepatopathy of pregnancy (Ljunggren, G., Nord. Med. 55:373, 1956), intrahepatic cholestasis of pregnancy (Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444:1-111, 1966), obstetric cholestasis (Kater, R.M.H., and Mistilis, S.P., Med. J. Aust. 1:638, 1967), and because of its tendency to recur in subsequent pregnancies, as recurrent jaundice of pregnancy (Svanborg, A., and Ohlsson, S., Amer. J. Med. 27:40, 1959), recurrent intrahepatic cholestasis of pregnancy (Haemmerli, U.P., Acta Med. Scand 179, Suppl. 444:1-111, 1966), and recurrent intrahepatic cholestatic jaundice of pregnancy (Sherlock, S., Brit. Med. Bull. 24:39, 1968).

Symptoms begin during the last 4 months of pregnancy in the majority of cases. The range of onset is broad, however, and has been observed between the 7th and 39th weeks of gestation. Pruritus alone, or pruritus and jaundice persist through delivery, then both disappear relatively rapidly. Pruritus abates before jaundice subsides completely. Jaundice is usually gone within 1-2 weeks, but may persist somewhat longer. Liver and spleen are usually not palpable, although occasionally mild, nontender hepatomegaly is present.

The results of laboratory tests are those of incomplete obstructive jaundice. Hyperbilirubinemia is primarily direct-reacting, with values for total bilirubin usually less than 7 mg/100 ml. Higher values are found occasionally. Bilirubin and urobilinogen are detected in the urine. Alkaline phosphatase activity in serum is moderately to markedly elevated, but in some instances falls within the range of values found in normal pregnancy. Thymol turbidity and cephalin flocculation are normal. Serum transaminases, SGOT, and SGPT, are increased (infrequently are normal), with maximal values almost always less than 250 units, although higher values with SGOT up to 920 and SGPT of 875 units have been reported (Ikonen, E., Acta Obstet. Gynecol. Scand. 43, Suppl. 5:1-130, 1964; King, M.J., and Kerrins, J.F., N. Engl. J. Med. 268: 1180, 1963). Serum cholesterol, although elevated when compared to values in non-pregnant women, is within the range found in normal pregnancy (Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444:1-111, 1966; Svanborg, A., and Vikrot, O., Acta Med. Scand. 181:83, 1967). The results of tests in women with pruritus gravidarum, by definition hyperbilirubinemia is absent, are comparable or less abnormal than those in jaundiced patients (Kater, R.M.H., Harrison, D.D., and Mistilis, S.P., Gastroenterology 53: 941, 1967; Kater, R.M.H., and Mistilis, S.P., Med. J. Aust. 1:638, 1967; Kreek, M.J., Weser, E., Sleisenger, M.H., and Jeffries, G.H., N. Engl. J. Med. 277:1391, 1967; Lutz, E.E., and Margolis, A.J., Obstet. Gynecol. 33:64, 1969; Sjövall, K., and Sjövall, J., Clin. Chim. Acta 13:207, 1966). Results of most tests return to normal within 2-3 weeks, although elevation of serum alkaline phosphatase may persist for up to 2 months after delivery (Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444: 1-111, 1966).

The histological picture in liver biopsies is that of intrahepatic cholestasis (Aldercreutz, H., Svanborg, A., and Anberg, A., Amer. J. Med. 42:335, 1967; Brown, D.F., Porta, E.A., and Reder, J., Arch. Intern. Med. 111:592, 1963; Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444:1-111, 1966; Ikonen, E., Acta Obstet. Gynecol. Scand. 43, Suppl. 5:1-130, 1964; Kater, R.M.H., and Mistilis, S.P., Med. J. Aust. 1:638, 1967; Smith, E.E., and Rutenburg, A.M., Nature (London) 197:800, 1963; Thorling, L., Acta Med. Scand., Suppl 302:1 1955). Overall architecture of the liver lobules is intact. Bile plugs are found in some canaliculi in the centrilobular region even in non-jaundiced patients (Kater, R.M.H., and Mistilis, S.P., Med. J. Aust. 1:638, 1967). Occasionally, bile pigment is present only in centrilobular parenchymal cells and not in canaliculi. Portal tracts are usually normal but may contain a mild infiltrate of mononuclear cells.

Maternal outlook is excellent. The patient usually feels well aside from pruritus which may be severe, but which will dissipate rapidly after delivery. Pruritus as in other forms of liver dysfunction is probably due to retention of bile acids (Schoenfield, L.J., in "Bile Salt Metabolism" (L. Schiff, J. B. Carey, Jr., and J. M. Dietschy, eds.), pp. 257-263. Thomas, Springfield, Illinois, 1969; Sjövall, K., and Sjövall, J., Clin. Chim. Acta 13:207, 1966; Van Itallie, T.B., and Hashim, S.A., Med. Clin. N. Amer. 47:629, 1963). Increased bile acids in serum of pregnant women with pruritus are accounted for almost completely by major increases in conjugated cholic and chenodeoxycholic acids. Deoxycholic acid concentration is close to normal. The ratio of the bile acids to each other is similar to that found in patients with obstructive hepatobiliary disease. Serum bile acids returned toward normal in the week after delivery (Sjövall, K., and Sjövall, J., Clin. Chim. Acta 13:207, 1966; Laatikainen, T. and Ikonen, E. Obstet. Gynecol. 50:313, 1977; Laatikainen T., Ann. Clin. Res. 10:307, 1978). Pruritus can be treated effectively in many but not all women with cholestyramine, a polystyrene anion exchange resin (Brown, D.F., Porta, E.A., and Reder, J.,

Arch. Intern. Med. 111:592, 1963; Fast, B.B., and Raulston, T.M., Amer. J. Obstet. Gynecol. 88:314, 1964; Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444:1-111, 1966; Kreek, M. J., in "Metabolic Effects of Gonadal Hormones and Contraceptive Steroids" (H. A. Salhaneck, D. M. Kipnis, and R. L. VandeWiele, eds.), pp. 40-58. Plenum Press, New York, 1969; Lutz, E.E., and Margolis, A. J., Obstet. Gynecol. 33:64, 1969; Laatikainen, T., Amer. J. Obstet. Gynecol. 132:501, 1978). Cholestyramine strongly binds bile salts in the lumen of the intestine, prevents their reabsorption thus leading to increased fecal excretion and decreased serum concentration (Carey, J. M., Jr., J. Lab. Clin. Med. 56:696, 1960; Carey, J.B.,Jr., and Williams, G., J. Amer. Med. Ass. 176:432, 1961; Thompson, W.G., Can. Med. Ass. J. 104:305, 1971). Cholestyramine also binds other steroid compounds including estrogens (Kreek, M.J., and Sleisenger, M.H., Scand. J. Gastroenterol. 5, Suppl. 7:123, 1970; Sjövall, K., and Sjövall, J., Clin. Chim. Acta 13:207, 1966). Whether this contributes to the antipruritic effect of the resin is unknown at present. Hypoprothrombinemia can occur in patients with intrahepatic cholestasis because of malabsorption of vitamin K. Cholestyramine may accentuate this tendency (Thompson, W.G., Can. Med. Ass. J. 104:305, 1971). Hypoprothrombinemia should be prevented by periodic administration of vitamin K parenterally.

There is a tendency to premature delivery in some women, but two-thirds have repeated term pregnancies (Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444:1-111, 1966; Johnson, P., Samsioe, G., and Gustafson, A., Acta Obstet. Gynecol. Scand. 54:771, 1975; Laatikainen, T., and Ikonen, E., Ann. Chir. Gynecol Fenn. 64:155, 1975; Reid, R., Ivey, K. J., Rhencoret, R.H. and Storey, B., Brit. Med. J. 1:870, 1976). Fetal risk is reported as increased. Fetal deaths during pregnancy or labor was found in cases where cord plasma bile acid levels were high (Laatikainen, T., Amer. J. Obstet. Gynecol. 122:852, 1975).

Once pregnancy is over, hepatic function returns to normal and remains normal thereafter, unless the patient becomes pregnant again or takes oral contraceptive steroids. In each instance, the cholestatic syndrome tends to recur. The course in successive pregnancies may be quite variable. For example, jaundice does not necessarily occur in each pregnancy of every woman. The intensity of jaundice may vary from one pregnancy to the next. In some instances, the disorder is more intense with successive gestations, whereas in others, the manifestations are similar or even less intense with successive pregnancies.

Many reports deal with women with previous histories of cholestasis of pregnancy who developed jaundice during ingestion of oral contraceptive steroids (Drill, V.A., Amer. J. Obstet. Gynecol. 119:165, 1947). The largest experience is that of Orellana-Alcade and Dominguez (Orellana-Alcade, J.M., and Dominquez, J.P., Lancet 2:1278, 1966). Fifty of their patients developed jaundice attributed to oral contraceptive agents. Of the 42 who had been pregnant previously, 10 had experienced pruritus alone, and 17 pruritus and jaundice late in pregnancy. Appraisal of the above reports indicates that pruritus and jaundice tend to appear soon after oral contraceptive steroids are begun. Approximately 50 per cent of complications occur in the first contraceptive cycle, and 90 per cent by the sixth cycle. Nevertheless, symptoms do not invariably occur on oral contraceptives and the risk of pruritus and jaundice during the use of hormone contraceptives may be exaggerated (Rannevik, G., Jeppsson, S. and Kullander, S., J. Obstet. Gynecol. Brit. Commonw. 79:1128, 1972; Furhoff, A., Acta Med. Scand. 196: 403, 1974). Thus women with cholestasis of pregnancy have a definite risk of developing cholestasis when exposed to oral contraceptive agents.

A number of observations suggest that intrahepatic cholestasis of pregnancy is induced by steroid hormones elaborated so plentifully in pregnancy, particularly in the last trimester. (1) The onset of pruritus and jaundice occurs primarily in the last 4 months of gestation, the period in which production rates and blood levels at least of estrogens and progesterone are at their highest. (2) The clinical, laboratory, and histological findings improve rapidly after delivery coincident with a decrease in hormone levels. (3) Features of cholestasis reappear only when the patient is re-exposed to steroid hormones, either in a subsequent pregnancy or in the form of oral contraceptive agents or estrogens. (4) A number of steroid compounds are known to produce a cholestatic disorder with features very similar to that seen in pregnancy.

Limitation of the disorder to a relatively small number of women is due to one of the following possible etiological factors (1) There is overproduction of normal hormones of pregnancy. Adlercreutz et al. (Aldercreutz, H., Svanborg, A., and Anbert, A., Amer. J. Med. 42:341, 1967) found that urinary excretion of estrone, estradiol-17β and estriol was normal in 7 patients with cholestatic jaundice of pregnancy. Similar findings were obtained by Mistilis (Mistilis, S.P., Australas. Ann. Med. 17: 248, 1968) in 6 patients, and by Adams and Combes (unpublished observations) in 2 patients. Excretion of progesterone metabolites was also normal in the latter two cases (Steroid analysis in these two cases was performed by Dr. P. MacDonald and Dr. P. Siiteri). Overproduction of hormones seems unlikely therefore. (2) An abnormal hormone is elaborated in pregnancy. Insufficient data are available to assess this possibility. Significant changes in estrogen and progesterone metabolism have been found (Aldercreutz, H., Svanborg, A., and Anberg, A., Amer. J. Med. 42:341, 1967; Sjövall, J. and Sjövall, K., Ann Clin. Res. 2:231, 1970; Eriksson, H., Gustafsson, J.-A, Sjövall, J. and Sjövall, K. Steroids Lipids Res. 3;30, 1972; Tikkanen, M.J., and Adlercreutz, H., Amer. J. Med. 54:600, 1973; Laatikainen, T. and Karjalainen, O., J. Steroid Biochem. 4:641, 1973; Adlercreutz, H., Tikkanen, M.J., Wichmann, K., Svanborg, A, and Anberg, A., J. Clin. End. Med. 38:51, 1974). These are felt to be secondary to the cholestatic state, however, rather than a primary defect causing the liver disorder. (3) The biliary secretary mechanism is unusually sensitive to steroid hormones. This possibility is strongly supported by (a) reports of patients with a background of cholestasis of pregnancy who developed jaundice when taking oral contraceptive compounds (vide supra); and (b) the findings of Kreek and associates who demonstrated the induction of cholestatic symptoms and laboratory findings in women previously known to have had pruritus, or pruritus and jaundice in pregnancy by ethinyl estradiol in daily doses of 0.5-1.5 mg (Kreek, M.J., Sleisenger, M.H., and Jeffries, G.H., Amer. J. Med. 43:795, 1967; Kreek, M.J., Weser, E., Sleisenger, M.H., and Jeffries, G.H., N. Engl. J. Med. 277:1391, 1967). Sensitivity to estrogen compounds seems likely. It is not yet clear whether this also pertains to progestins. Data obtained with progestin administration alone will be difficult to interpret since it is known that some progestins are metabolized to estrogens (Breuer, H., Int. J. Fert. 9:181, 1964; Paulsen, C.A., Metab. Clin. Exp. 14:313, 1965).

The reason for the predisposition to intrahepatic cholestasis in some women is not yet known. The possibility of an inherited predisposition is suggested by at least two pieces of information. First, the majority of cases of this disorder have been reported from Scandinavian countries and from Chile, although it is now well known that the

condition is worldwide in distribution. Second a number of reports describe affected patients with other closely related family members who have experienced pruritus with or without jaundice in pregnancy (Cahill, K.M., Surg. Gynecol. Obstet 114:545, 1962; Fast, B.B., and Raulston, T.M., Amer. J. Obstet. Gynecol. 88:314, 1964; Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444:1-111, 1966; Holzbach, R.T., and Sanders, J.H., J. Amer. Med. Ass. 193:202, 1965; Larsson-Cohn, U., Lancet 1:679, 1967; Svanborg, A., and Ohlsson, S., Amer. J. Med. 27:40, 1959; Thorling, L., Acta Med. Scand., Suppl 302:1, 1955). Additional data will be required, however, before an inherited factor can be accepted.

IV. Liver Dysfunction Intercurrent in Pregnancy

A. Viral Hepatitis during Pregnancy

Viral hepatitis is the commonest cause of jaundice in pregnancy (Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444:1-111, 1966). Most reports dealing with this illness were published prior to the identification of hepatitis B surface antigen (Blumberg, B.S., Alter, H.J., and Visnich, S., J. Amer. Med. Ass. 191:541, 1965; Blumberg, B.S., Gerstley, B.J.S., Hungerford, D.A., London, W.T., and Sutnick, A.J., Ann. Intern. Med. 66:924, 1967; London, W.T., Sutnick, A.J., and Blumberg, B.S., Ann. Intern. Med. 70:55, 1969), a particulate antigen found in serum of a high proportion of patients with hepatitis.

Pregnant women are no more susceptible to hepatitis than the population at large (Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444, 1-111, 1966). The incidence of hepatitis is reported to increase during the course of pregnancy with the highest incidence observed in the last trimester (Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444:1-111, 1966). This is probably a reflection of (1) difficulties in recognition of the disease early in pregnancy when nausea and vomiting are frequent complaints and attributed to pregnancy, and (2) the tendency for patients with hepatitis early in pregnancy to be cared for by medical rather than obstetric departments. It is likely that the incidence of the disease is similar in all trimesters of pregnancy (Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444:1-111, 1966).

Divergent opinions exist about the maternal and fetal outcome of pregnancies complicated by viral hepatitis. In general this reflects (1) the geographical location from which reports emanate; (2) that most reports are retrospective analyses of hospital admissions, usually to an obstetrical service (these may have been unintentionally biased by inclusion of severely ill patients whose disorders are more easily recognized); and (3) lack of a control population of nonpregnant women in the reproductive age range with hepatitis admitted to hospital with comparable severe disease. When these factors are taken into account, it appears that hepatitis is not a more fulminant disease in the pregnant woman seen in North American and in Europe (Adams, R.H., and Combes, B., J. Amer. Med. Ass 192:195, 1965; Haemmerli, U.P., Acta Med. Scand 179, Suppl. 444:1-111, 1966; McCollum, R.W., Amer. J. Med. 32:647, 1962).

By contrast, maternal mortality is high in the majority of reports emanating from the Mediterranean area and Asia (Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444: 1-111, 1966). Malnutrition, and poor hygienic conditions creating situations that may result in massive infection with virus, are probably the major factors accounting for the severity of hepatitis in these areas.

The clinical course and laboratory features of hepatitis in pregnancy are comparable to that seen in nonpregnant patients (Adams, R.H., and Combes, B., J. Amer. Med. Ass. 192:195, 1965; Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444: 1-111, 1966). Although relatively few data are available, chronic sequellae of acute hepatitis seem to be no more common when the illness begins during pregnancy (Adams, R.H., and Combes, B., J. Amer. Med. Ass. 192:195, 1965; Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444:1-111, 1966; Hieber, J.P., Dalton, D., Shorey, J., and Combes, B. J. Ped. 91:545, 1977).

TABLE IX

VIRAL HEPATITIS AND PREGNANCY

MATERNAL OUTCOME

	1959-1964[a]	1970-1974[b]	Total
Uneventful Recovery	28	49	77
Fulminant Hepatitis	1	0	1
Chronic Hepatitis	1	1	2
Inadequate Follow-up	4	0	4

[a] Adams, R., and Combes, B., J. Amer. Med. Ass. 192:195, 1965

[b] Hieber, J. P. et al., J. Ped. 91:545, 1977

A tendency toward abortion and premature delivery is reported to occur with hepatitis, but this is not impressive in patients seen in North America and in Europe (Adams, R.H., and Combes, B., J. Amer. Med. Ass. 192:195, 1965; Haemmerli, U.P., Acta Med. Scand. 179, Suppl. 444:1-111, 1966; Hieber, J.P., Dalton, D., Shorey, J., and Combes, B., J. Ped. 91:545, 1977). Nevertheless, the risk appears to be small unless the mother has fulminant hepatic necrosis. Spontaneous abortion does not appear to ameliorate the maternal disease and it is generally agreed that therapeutic abortion is not indicated when hepatitis occurs in pregnancy.

TABLE X

VIRAL HEPATITIS AND PREGNANCY

FETAL OUTCOME

	Abortions	Stillbirths	Prematurity	Congenital Malformations
1959-1964[a]	6.3%	3.1%	10.3%	0
1970-1974[b]	2.0%	2.0%	27.6%	0
Weighted Average	3.7%	2.5%	21.1%	0

[a] Adams, R., and Combes, B., J. Amer. Med. Ass. 192:195, 1965

[b] Hieber, J. P. et al., J. Ped. 91:545, 1977

Transmission of hepatitis B to the newborn, so-called vertical transmission, occurs but with variable frequency. When the mother has acute viral hepatitis in pregnancy, transmission is found mainly when hepatitis occurs in the 3rd trimester and early post-partum period.

TABLE XI

TRANSMISSION OF HEPATITIS B TO THE NEWBORN
ONSET OF MATERNAL HEPATITIS

	1st or 2nd trimester		3rd trimester or early post partum	
	No. Mothers	No. Babies HB_sAg (+)	No. Mothers	No. Babies HB_sAg (+)
Merrill et al.[a]	1	0	4	4
Cossart et al.[b]	1	0	4	2
Schweitzer et al.[c]	10	1	21	16
Dallas[d]	4	0	8	2
	16	1	37	24

[a] Merrill, D. A. et al., New Engl. J. Med. 287:1280, 1972
[b] Cossart, Y. E. et al., Am. J. Dis. Child. 123:376, 1972
[c] Schweitzer, J. L. et al., Am. J. Med. 55:762, 1973
[d] Hieber, J. P. et al., J. Ped. 91:545, 1977

When the mother is an asymptomatic carrier of HB_sAg, variable rates of transmission have been recorded. Transmission is more frequent in Asian than in European and North American Groups.

TABLE XII

TRANSMISSION OF HEPATITIS B TO THE INFANT
FROM ASYMPTOMATIC CARRIER MOTHERS

Authors	No. Mothers	No. HB_sAg (+) Infants
Skinhoj et al.	28	0
Schweitzer et al.	21	1
Aziz et al.	18	1
Papaevangelou et al.	12	1
Kew et al.	8	1
Derso et al.	122	17
Dupuy et al.	12	7 transient 1 chronic
Stevens et al.	158	63
Okada et al.	23	12
Lee et al.	37	26

Skinhoj, P. J. et al., Am. J. Des. Child. 123:380, 1972
Schweitzer, J. L. et al., Am. J. Med. 55:762, 1973
Aziz, M. A. et al., J. Inf. Dis. 127:110, 1973
Papaevangelou, G. et al., Lancet 2:476, 1974
Kew, M.C. et al., S. Afr. Med. J. 49:1471, 1975
Derso, A. et al., Br. Med. J. 1:949, 1978
Dupuy, J. M. et al., J. Pediatr. 92:200, 1978
Stevens, C. et al., New Engl. J. Med. 292:771, 1975
Okada, K. et al., J. Pediatr. 87:360, 1975
Lee, A. K. Y. et al., J. Inf. Dis. 138:668, 1978

In this latter group transmission is found mainly with high titers of HB_sAg and with HB_eAg positivity in the mother.

TABLE XIII

INFLUENCE OF *e*STATUS ON TRANSMISSION OF HEPATITIS B
TO THE INFANT
FROM ASYMPTOMATIC CARRIER MOTHERS

*e*Status of Mother	No.	Child HB_sAg (+)
*e*Ag (+)	20	19 (95%)
Anti-*e* (+)	57	4 (7%)
*e*Ag (-), Anti-*e* (-)	44	8 (18%)

Schweitzer, J. L. et al., New Engl. J. Med. 293:938, 1975
Skinhoj, P. et al., Br. Med. J. 1:10, 1976
Okada, K. et al., New Engl. J. Med. 294:746, 1976
Derso, A. et al., Br. Med. J. I:949, 1978

Routes of transmission to the fetus include transplacental, delivery and post-delivery mechanisms. Once the fetus is infected, there is a strong tendency for the fetus to remain a chronic HB_sAg carrier. Long term effects of carrier status in the fetus are still not clear.

Gamma globulin prophylaxis of the newborn, utilizing immune serum globulin, ISG, (low titer antibody), and hepatitis B immune globulin, HBIG, (high titer antibody) have yielded conflicting data as to protection of the child.

Kohler, P.F., Dubois, R.S., Merrill, D.A. and Bowes, W.A., N. Engl. J. Med. 291:1378, 1974

Varma, R.R., J. Amer. Med. Ass. 236:2302, 1976

Tong, M.J., McPeak, C.M., Thursby, M.W., Schweitzer, I.L., Henneman, C.E., and Ledger, W.J., Gastroenterology 76:535, 1979

Beasley, R.P., and Stevens, C.E., in "Viral Hepatitis" (G.N. Vyas, S.N. Cohen and R.Schmid, eds.) Chapter 30, pp 330-345. The Franklin Institute Press, Philadelphia, 1978

Reesink, H.W., Reerink-Brongers, E.E., Lafeber-Schut, B.J.T., Kalshoven-Benschop, J. and Brummelhuis, H.G.J., Lancet 2:436, 1979

Iwarson, S., Norkrans, G., Hermodsson, S. and Nordenfelt, E., Scand. J. Infect. Dis. 11:167, 1979

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