

## MATERNAL SERUM BILE ACID LEVELS AND FETAL DISTRESS IN CHOLESTASIS OF PREGNANCY

TIMO LAATIKAINEN and ANNIKA TULENHEIMO

*Departments I and II of Obstetrics and Gynecology, Helsinki University Central Hospital, Helsinki (Finland)*

(Received March 22nd, 1983)

(Accepted September 11th, 1983)

### Abstract

*Laatikainen T, Tulenheimo A (Departments I and II of Obstetrics and Gynecology, Helsinki University Central Hospital, Helsinki, Finland). Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy.*

*Int J Gynaecol Obstet 22: 91–94, 1984*

*Cardiotocography (CTG) and serum total bile acid level were used in the perinatal surveillance of 117 pregnancies with intrahepatic cholestasis. Signs of fetal distress occurred more commonly in cholestasis pregnancies with high maternal bile acid levels. Despite careful monitoring one intrauterine fetal loss occurred without any warning signs in CTG. In this case the serum bile acid level was only moderately elevated. CTG seems to be suitable for detection of fetal distress in cholestasis pregnancies. Those with high maternal bile acid level should be subjected to a more intensive follow-up. Some fetal risk, however, seems to remain despite of the use of these methods.*

---

**Keywords:** Pregnancy; Intrahepatic cholestasis; Cardiotocography; Serum total bile acid level; Perinatal surveillance; Fetal distress; Fetal risk.

### Introduction

Increased risk for fetal well-being has been

reported to be associated with pregnancies complicated by maternal intrahepatic cholestasis [2,5,8,11]. The mechanism leading to fetal distress in these pregnancies is not known. Retarded fetal growth related to chronic placental insufficiency such as, e.g. in toxemia, was not found in cholestasis pregnancies [8]. It has been suggested that disturbed maternal liver function might affect fetal well-being [9,10]. In these pregnancies bile acid levels are also elevated in the fetal circulation [6]. Previously we have found that maternal cholestasis causes large changes in fetal steroid metabolism [10]. These findings show that metabolic changes in cholestasis of pregnancy are also reflected in the fetal compartment.

We have considered these pregnancies a risk group for a more intensive surveillance of the fetal well-being. Biochemical markers of the fetoplacental function, estriol and human placental lactogen (HPL), did not prove effective in prediction of fetal distress [3,8]. The main method which we have used to obtain information on the fetal condition is the ante- and intrapartal monitoring of fetal heart rate (FHR) by CTG. Serum bile acid levels have proved to be sensitive indicators of disturbed liver function in pregnant women [4,9]. They reflect the severity of intrahepatic cholestasis. We have applied a rather simple enzymatic method for the determination of serum total bile acid levels and correlated them with the occurrence of the signs of fetal distress.

## Patients and methods

### Patients

All patients with cholestasis of pregnancy, a total of 117 women who gave birth in the years 1980–1981 at this hospital, were included. They were referred from the maternity care units because of pruritus and elevated serum values of ASAT and ALAT, which were routinely used as a screening test to detect disturbed liver function. Intrahepatic cholestasis was confirmed by excluding the possibility of other liver diseases and by confirming the disappearance of pruritus and normalization of liver function after delivery [5].

Pruritus appeared at a mean gestational age of  $32 \pm 4$  weeks and at the mean gestational age of  $33 \pm 5$  weeks the patients were admitted to the hospital outpatient clinic. The non-stress test was taken weekly until the patients were taken to the hospital at 35–37 weeks. Then the fetal heart rate was monitored daily until delivery.

### Methods

Serum total  $3\alpha$ -hydroxy bile acids were determined as described by Bruusgaard et al. [1] with some modifications. One-milliliter samples of serum were diluted to 10 ml with 0.1 M NaOH. Bile acids were extracted with 1 g of Amberlite XAD-7 [7] for 60 min using a rotating mixer. The supernatant was decanted and the Amberlite phase was washed with 2 ml of 0.004 M NaOH. Bile acids were extracted twice from the Amberlite with 6 ml of methanol. The combined phases of methanol were evaporated, and total  $3\alpha$ -hydroxy bile acids were determined by using a purified  $3\alpha$ -hydroxy steroid dehydrogenase preparation (Sterognost- $3\alpha$ , Nyegaard & Co A/S, Oslo, Norway). NAHD generated from the reaction was measured by fluorometry at 346 nm.

Normal values of total  $3\alpha$ -hydroxy bile acids in uncomplicated pregnancy were obtained by analyzing serum samples from 60 healthy women at 14–42 weeks of preg-

nancy. Mean value ( $\pm$ S.E.) was  $1.96 \pm 1.56$   $\mu$ mol/l, and normal limits 0–5  $\mu$ mol/l.

The method was controlled by analyzing 20 serum samples using a gas chromatographic method [7]. The total  $3\alpha$ -hydroxy bile acid value was 32% larger than the total amount of cholic, chenodeoxycholic and deoxycholic acid obtained by the gas chromatographic method. There was a correlation between the values obtained by the two different methods ( $r = 0.88$ ,  $P < 0.001$ ).

## Results

The 117 patients were divided into three groups according to the serum total bile acid level during the last week before delivery (Table I). Fifty seven of these patients had had at least one previous pregnancy and in 56% of them cholestasis had been present. The occurrence of twin pregnancies was 14% in the whole group, and an especially large proportion of twins, 32% was present in Group C with severe cholestasis.

There were four spontaneous deliveries before the 34th week, and 3 of them were twin pregnancies. One baby in Group B and the other in Group C were small-for-date weighing below the 10th percentile. Mothers of these babies also had toxemia.

**Table I.** Clinical characteristics and serum total bile acid levels in patients with cholestasis of pregnancy.

	Group A (%)	Group B (%)	Group C (%)
Serum bile acid level ( $\mu$ mol/l)	<10	10–40	>40
No. of patients	59	37	21
Age (years $\pm$ S.E.)	$30.7 \pm 0.6$	$29.7 \pm 0.8$	$29.9 \pm 0.9$
Previous pregnancies			
0	28	19	13
1	21	10	5
2 or more	10	8	3
Cholestasis in previous pregnancies	21 (67)	10 (59)	1 (13)
Singleton pregnancy	57	29	15
Twin pregnancy	2 (3.5)	7 (15)	7 (32)

**Table II.** Signs of fetal distress in the groups of mild (A), moderate (B) and severe (C) cholestasis.

	Group A		Group B		Group C	
	S <sup>a</sup>	G	S	G	S	G
No. of pregnancies	57	2	29	7	15	7
Intrauterine fetal loss	—	—	1	—	—	—
Pathological antepartum FHR	3	—	4	1	7	2
Pathological intrapartum FHR	2	—	1	1	1	—
Caesarean section because						
of fetal asphyxia	4	—	4	—	4	2
Green amniotic fluid	2	1	5	—	7	4
Apgar score <6	3	1	1	3	3	1
Intrauterine growth						
retardation	—	—	1	—	1	—
Pregnancies with fetal distress <sup>b</sup>	6	—	5	2	6	3

<sup>a</sup> S, singleton pregnancy; G, twins.

<sup>b</sup> Pregnancies with two or more signs of fetal distress.

Antepartum monitoring revealed pathological findings in 14 of the 117 pregnancies leading to induction of labor because of fetal indications. Reduced FHR variability and/or late decelerations were found more often in Group C with severe cholestasis than in Group A with mild cholestasis. Green amniotic fluid was found in half of the patients in Group C but in only two of 59 patients with mild cholestasis. Total serum bile acid level correlated significantly with the occurrence of the signs of fetal distress but no such correlation was found with the values of serum aminotransferases, ASAT and ALAT (Table III).

One intrauterine fetal loss occurred in Group B. The patient was admitted to the hospital at 38 weeks. The non-stress test of

FHR was performed daily for a week until a sudden intrauterine fetal death occurred at 39 weeks without any preceding warning signs in CTG of FHR. Maternal serum total bile acid level, 15  $\mu\text{mol/l}$ , was only moderately elevated. The labor begun spontaneously and a dead male baby weighing 3490 g was born. Autopsy revealed small petechiae in the lungs and kidneys, and larger hemorrhagic areas in the adrenals. This finding was related to acute asphyxia. No other apparent abnormality than maternal cholestasis was found.

## Discussion

The present results of perinatal care of the cholestasis pregnancies were better than reported earlier at this hospital: 20 years ago Ikonen [5] found perinatal mortality of 24% and 10 years later it was 6.4% [8]. The 0.75% in the present series indicates that fetal loss in cholestasis of pregnancy now seems to be rare. This is due to more effective perinatal care of these pregnancies. The other factor is that severe cholestasis cases with icterus are rare at the present time. So only one case with icterus was found in the present series although the incidence of cholestasis pregnancies of the total amount of deliveries at this hospital (1.1%) was the same as 10 years ago [8].

Measurement of total serum 3 $\alpha$ -hydroxy bile acid concentration using an enzymatic method is practical for clinical laboratories, although the method is less sensitive than the radioimmunoassay [4] and does not give any information on the individual bile acids. Our results suggest that total bile acid level is more

**Table III.** Liver function tests and occurrence of the signs of fetal distress in cholestasis pregnancies.

	ASAT (IU/l)			ALAT (IU/l)			Bile acids ( $\mu\text{mol/l}$ )		
	<100	100–200	>200	<150	150–200	>350	<10	10–39	>40
No. of mothers	62	33	22	51	43	23	59	36	22
Distress	10	7	5	9	8	5	6 <sup>a</sup>	7 <sup>a</sup>	9 <sup>a</sup>

<sup>a</sup>  $P < 0.05$ ;  $\chi^2$ -test.

valuable in prediction of fetal distress in cholestasis pregnancies than the aminotransferase values. Mothers with high bile acid levels should be subjected to a more intensive monitoring of fetal condition. It seems, however, that fetal risks cannot be completely excluded even in mild or moderate degree of cholestasis.

The non-stress test of CTG of the FHR was extensively used here in the perinatal surveillance of cholestasis pregnancies. Recently, the monitoring of the short-term variability of the FHR was reported to reflect fetal condition even more closely [13] but this was not routinely used in the present patients. Despite careful monitoring by CTG we had one intrauterine fetal loss near term, because no preceding warning signs could be detected. Autopsy of the dead fetus revealed signs suggesting the presence of acute asphyxia. No other apparent abnormality than maternal cholestasis was found. Maternal bile acid level was moderately elevated and did not arise any suspicion of great fetal risk. Most of unexpected intrauterine fetal losses in cholestasis pregnancies have occurred near term [2,5,8,11,12]. Induction of labor 1–2 weeks before term also in cases without any signs of fetal distress may reduce the risk of such a complication.

## References

- 1 Bruusgaard A, Pedersen LR, Sørensen H: Determination of total 3 $\alpha$ -hydroxy bile acids in serum. *Clin Chem* 93: 1, 1979.
- 2 Friedlaender P, Osler M: Icterus and pregnancy. *Am J Obstet Gynecol* 97: 894, 1967.
- 3 Garoff L: Prediction of fetal outcome by urinary estriol, maternal serum placental lactogen, and alpha-fetoprotein in diabetes and hepatitis of pregnancy. *Obstet Gynecol* 48: 659, 1976.
- 4 Heikkinen J, Mäentausta O, Ylöstalo P, Jänne O: Changes in serum bile acid concentrations during normal pregnancy, in patients with intrahepatic cholestasis of pregnancy and in pregnant women with itching. *Br J Obstet Gynaecol* 88: 240, 1981.
- 5 Ikonen E: Jaundice in late pregnancy. *Acta Obstet Gynecol Scand* 43: Suppl 5, 1964.
- 6 Laatikainen T: Fetal bile acid levels in pregnancies complicated by maternal intrahepatic cholestasis. *Am J Obstet Gynecol* 122: 852, 1975.
- 7 Laatikainen T, Hesso A: Determination of serum bile acids by glass capillary gas-liquid chromatography. *Clin Chim Acta* 64: 63, 1975.
- 8 Laatikainen T, Ikonen E: Fetal prognosis in obstetric hepatitis. *Ann Chir Gynaecol Fenn* 64: 155, 1975.
- 9 Laatikainen T, Ikonen E: Serum bile acids in cholestasis of pregnancy. *Obstet Gynaecol* 50: 313, 1977.
- 10 Laatikainen TJ, Peltonen JI, Nylander PL: Effect of maternal intrahepatic cholestasis on fetal steroid metabolism. *J Clin Invest* 53: 1709, 1974.
- 11 Reid R, Ivey KI, Rencoret RH, Storey B: Fetal complications of obstetric cholestasis. *Br Med J* 1: 870, 1976.
- 12 Rencoret R, Aste H: Jaundice during pregnancy. *Med J Aust* 1: 167, 1973.
- 13 Ämmälä P, Kariniemi V: Short-term variability of fetal heart rate in cholestasis of pregnancy. *Am J Obstet Gynecol* 141: 217, 1981.

## Address for reprints:

**Timo Laatikainen, M.D.**  
**Departments of Obstetrics and Gynecology**  
**University Central Hospital**  
**Haartmaninkatu 2**  
**SF-00290 Helsinki 29**  
**Finland**