

Development of Signs and Symptoms of Congenital Choledochal Dilatation: Its Relation to Pregnancy with Special Reference to Experimental Study in Guinea Pigs

YOZO AOKI, KOSUKE SHIMADA, HIROAKI KAWASHIMA
and MASA HARU KATSUMI

Department of Gastroenterological Surgery, Wakayama Medical College, Wakayama City,
(Director: Prof. MASA HARU KATSUMI)
Received for Publication, Oct. 25, 1983.

Introduction

Many theories have been proposed regarding the etiology of the congenital choledochal dilatation. Among them, extrinsic or acquired factors have been defended by some surgeons.

In this paper, the experimental study on the relationship of development of this disease to pregnancy and two cases of congenital choledochal dilatation developed on pregnancy are reported.

Part I. Experimental Study

The following experiments were made to elucidate the effect of pregnancy on the bile excretion dynamics of the gallbladder.

Materials and Methods

(1) Female Hartley strain guinea pigs weighing 400 to 500 g were used. The animals at the 30th and 50 to 60th day of pregnancy were employed as a pregnant model. Non-pregnant female guinea pigs were served as control. Each group consisted of 2 guinea pigs.

(2) After fasting overnight, the jugular vein was exposed, the blood was drawn for the measurement of estrogen and progesterone levels, and 2 mCi of technetium-99 m-N-(2,6-dimethylacetanilide)-iminodiacetic acid (^{99m}Tc -E-HIDA) was injected, and then the wound was closed under ether anesthesia.

(3) The animals were positioned under pinhole collimator of a LFOV scintillation camera (Searle) in the supine position under conscious state. Data from the gamma camera were stored in at 5 min intervals for 1 hr and processed by the analyser. Thereafter, 0.26 g/kg b.w. of yolk preparation was administered orally, and the scanning was continued for more 1 hr. These images were played back and the scans from each animal were inspected and the gallbladder area

Key words: congenital choledochal dilatation, pregnancy, hepatobiliary scintigraphy, estrogen, progesterone,

索引語: 先天性胆道拡張症, 妊娠, 肝・胆道シンチグラフィ, エストロゲン, プロゲステロン.

Present address: Yozo Aoki, M.D., Department of Gastroenterological Surgery, Wakayama Medical College, Wakayama City, Wakayama 640, Japan.

of interest was marked out on each. Then the radioactivity in the area was counted and the activity counts against time, i.e., the time-activity curve (T-A curve) was obtained.

Results

(1) Estrogen and progesterone levels in serum

The results obtained are shown in Table 1. Estrone (E_1), estradiol (E_2) and progesterone in serum were extremely elevated in both gestational subgroups though there was no relation between estriol (E_3) and pregnancy.

(2) Hepatobiliary scintigram and its T-A curve

Figure 1 shows the hepatobiliary scintigrams of pregnant and non-pregnant animals 50 min after the injection of ^{99m}Tc -E-HIDA. In both subgroups on the 30th and 50 to 60th day of gestation, the gallbladder markedly enlarged compared to control.

T-A curve of the gallbladder area appeared to support this phenomenon as shown in Figure 2. In both gestational subgroups, the ^{99m}Tc activity continued to rise at a rapid rate and reached its maximum within 60 min. The maximum activities were about twofold of that of the non-pregnant group. The administration of yolk preparation prompted the bile excretion from the gallbladder.

Part II. Clinical Cases

Case 1.

The patient, 27 year old multipara, was admitted under suspicion of congenital choledochal dilatation because she had experienced right hypochondrial pain at and after the 30th week gestation of her first and second pregnancies. At the same time, she had been pointed out by a physician a mass in the right upper quadrant. These signs and symptoms disappeared after each delivery. Various examinations yielded a diagnosis of congenital choledochal dilatation (Alonso-Lej I type).

She underwent a cholecystectomy and Roux-Y cystojejunostomy. The dilated common bile duct contained a calcium bilirubinate gallstone.

Follow-up of the patient 6 years later shows normal liver functions.

Table 1. Estrogen and progesterone in serum of experimental animals.

			Control group	Gestation group	
				30th day of gestation	50-60th day of gestation
Estrone (E_1)	(pg/ml)	(1)	55	195	151
		(2)	98	172	114
Estradiol (E_2)	(pg/ml)	(1)	<10	49	23
		(2)	12	63	56
Estriol (E_3)	(pg/ml)	(1)	<2	<2	<2
		(2)	<2	<2	<2
Progesterone	(ng/ml)	(1)	1.5	376.1	108.3
		(2)	9.2	329.1	109.6

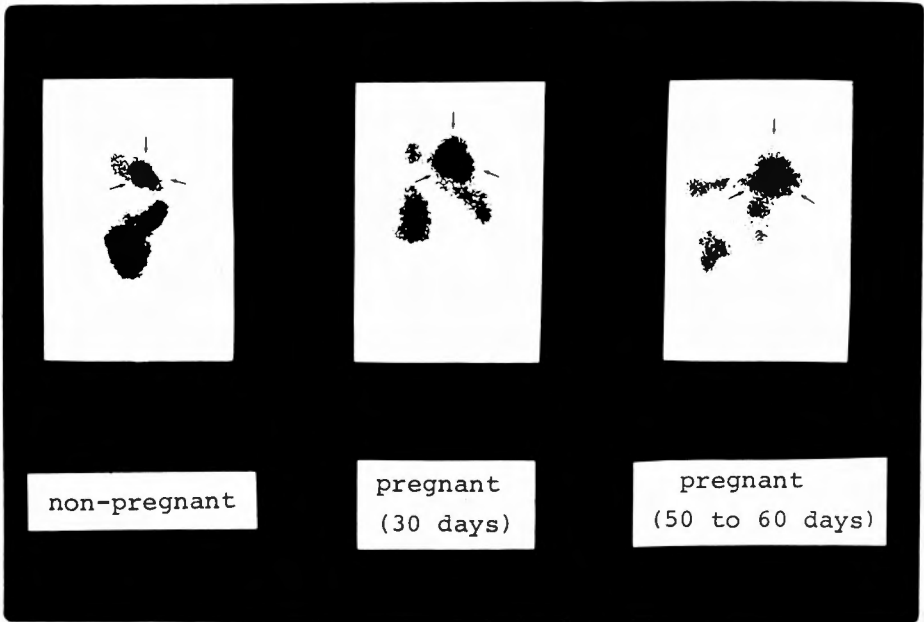


Fig. 1. Hepatobiliary scintigrams of pregnant and non-pregnant animals. Arrows in each scintigram showing the gallbladder area.

Case 2.

The patient, 39 year old multipara, was admitted with a chief complaint of intermittent colicky right hypochondrial pain and pyrexia. These symptoms developed at the 16th week of her every 3 gestations and continued till the end of each gestation. The diagnosis of congenital choledochal

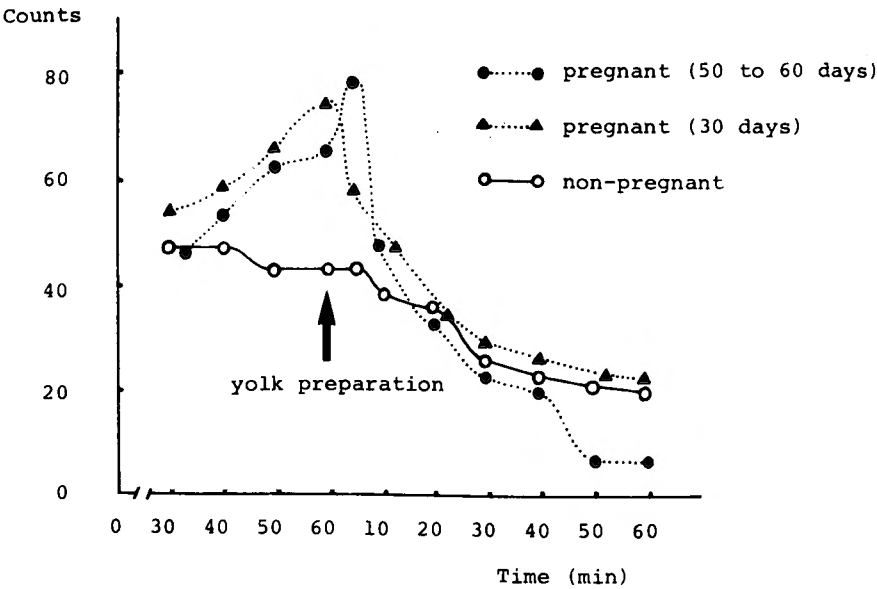


Fig. 2. Time-activity curve of the gallbladder area in pregnant and non-pregnant animals.

dilatation was made and the patient underwent a resection of the dilated common bile duct and Roux-Y hepaticojejunostomy. The dilated common bile duct contained a calcium bilirubinate gallstone.

Three-year-follow-up has revealed she has been doing well.

Discussion

In the last 11 years from 1972 to 1982, fifteen cases of congenital choledochal dilatation complicated with pregnancy have been reported in Japan^{6,7,9,10,12,15,17,19,20,21}. As listed in Table 2, mean patient age was 26.2 years ranging from 23 to 33. Among these patients, six had formerly experienced similar signs and/or symptoms in their childhood or previous pregnant periods. Relationship between the developmental period of the clinical pictures and pregnant stages was very interesting. Some cases of them developed their signs and symptoms in the early

Table 2. A review of cases in Japanese literature.

Case No.	Age (yrs.)	Wks. of gestation on onset	Signs and symptoms*	Operation*	Prognosis of gestation	Remarks
1 ¹⁵	23	28	J, M	Cystojejunostomy	not described	
2 ¹⁵	23	28	J, M	Cystectomy, HJ	not described	
3 ¹⁹	26	24	J, M, P	Cystectomy, HJ	Artificial abortion	
4 ⁹	not described	32	P, V	Cystojejunostomy	Cesarean section	
5 ⁶	27	not described	J, M, P	not described	Cesarean section	Epigastric pain in former times
6 ¹⁰	23	28	J, M, P	Cystojejunostomy	Premature delivery	
7 ¹²	26	32	J, P	Cystojejunostomy	Cesarean section	Treated with a diagnosis of cholecystopathy at her age of 16 yrs.
8 ¹⁷	33	24	J, M, P	Cystectomy, CD	Artificial abortion	Some time epigastric pain since her childhood
9 ⁷	25	20	J, M, P	Cystectomy, HJ	Artificial abortion	Primipara, P and J at her age of 16 yrs. and diagnosed of cholecystitis
10 ²⁰	24	40	J, P, V	Cystoduodenostomy	Cesarean section	Multipara
11 ²⁰	24	36	J, P, V	Cystectomy, HJ	Cesarean section	Primipara
12 ²⁰	26	24	P, V	Cystectomy, HJ	Normal delivery	Primipara
13 ²¹	27	28	J, P, V	Cystojejunostomy	Cesarean section	
14**	27	32	P	Cystojejunostomy	Normal delivery	Multipara, similar symptoms in pervious pregnancy
15**	33	12	P	Cystectomy, HJ	Normal delivery	Multipara, similar symptoms in previous pregnancies

* Abbreviations are: J, jaundice; M, abdominal mass; P, pain; V, vomiting; HJ, hepaticojejunostomy; CD, choledochoduodenostomy.

** Our cases

gestational stage in which their uteri were still small and they never pressed on the biliary system.

Many theories have been proposed regarding the etiology of the congenital choledochal dilatation^{1,2,13,22}. ALONSO-LEJ et al.¹⁾ stated that this disease is caused by two factors—weakness of the wall of the common bile duct in a specific segment and obstruction distal to it. They also described that one group defended extrinsic or acquired factors (pregnancy, abdominal trauma etc.) and the other congenital origin: obstructive factor localized at the junction of the choledochus with the duodenum, and a factor originating in the common bile duct proper. Many authors tend to support the second theory, however, some cases developed the signs and symptoms in an early gestational stage and this fact supports the possibility that compression to the dilated common bile duct by enlarged pregnant uterus is not always necessary in the development of the disease.

IMAMOGLU et al.⁸⁾ reported that fifty young women were subjected to intravenous cholangiographic studies 4 to 10 hrs after delivery and that 56 per cent of the subjects showed delayed emptying of the gallbladder. Based on these clinical data, they succeeded to produce gallstones by prolonged administration of progesterone and estradiol in rabbits, and concluded that the increased incidence of gallstones in women following pregnancy perhaps was owing to changes in gallbladder functions secondary to elevated titers of the placental hormones.

Our experimental (Table 1, Figures 1 and 2) and clinical studies clearly demonstrate these facts. Case 1 in our series showed clinical symptoms at and after the 30th week gestation. These symptoms were suspected to be partly due to a compression to the biliary tract by pregnant uterus. Clinical signs and symptoms in Case 2 developed at the 16th week gestation when the uterus was still small. In this case, increased serum progesterone and estrogen might play one of the causative factors in the development of clinical symptoms^{3,4,5,11,14,16,18}.

Hence, it is possible that pregnancy especially in an early gestational stage, adding to the pre-existence of congenital choledochal dilatation with anomalous choledochal junction, may lead to stagnation of bile in the extrahepatic biliary system and reflux of the pancreatic juice to the biliary system, thus predispose to cholangitis and provoke clinical signs and symptoms in selected cases.

Summary

From two experiences of congenital choledochal dilatation developed in pregnancy, experimental and clinical studies on the relationship of the sign and symptom of this pathological condition to pregnancy were investigated.

Pregnant guinea pigs revealed a dilated gallbladder and delayed emptying of the gallbladder on hepatobiliary scintigraphy regardless of their gestational stage. These phenomena were suspected to make the ground to lead to cholangitis under the pre-existence of congenital dilatation of the common bile duct.

References

- 1) Alonso-Lej F, Rever WB Jr, et al: Congenital choledochal cyst, with a report of 2, and an analysis of 94, cases. *International Abstracts of Surgery* **108**: 1-30, 1959.
- 2) Babbitt DP, Starshak RJ, et al: Choledochal cyst: A concept of etiology. *Am J Roentgenol* **119**: 57-62, 1973.
- 3) Braverman DZ, Johnson ML, et al: Effects of pregnancy and contraceptive steroids on gallbladder function. *New Engl J Med* **302**: 362-364, 1980.
- 4) Everson GT, McKinley C, et al: Gallbladder function in the human female: Effect of the ovulatory cycle, pregnancy, and contraceptive steroids. *Gastroenterology* **82**: 711-719, 1982.
- 5) Fisher RS, Roberts GS, et al: Inhibition of lower esophageal sphincter circular muscle by female sex hormones. *Am J Physiol* **234**: E243-E247, 1978.
- 6) Fujimoto M, Miyata K, et al: A case of huge choledochal dilatation developed in pregnancy. *J Jpn Surg Soc* **81**: 178, 1980. (in Japanese)
- 7) Ihara Y, Murata T, et al: A case of pregnancy complicated with severe jaundice due to congenital choledochal dilatation. *Acta Obst Gynec Jpn* **30**: 605-608, 1978. (in Japanese)
- 8) Imamoglu K, Wangenstein SL, et al: Production of gallstones by prolonged administration of progesterone and estradiol in rabbits. *Surg Forum* **10**: 246-249, 1960.
- 9) Ishida F, Matsumoto K, et al: A case of congenital choledochal dilatation developed with right hypochondrial pain in the 8th month gestational stage. *J Jpn Surg Soc* **79**: 518, 1978. (in Japanese)
- 10) Kawai F, Karaki K, et al: Choledochal cyst with special reference to large cyst developed in late gestational stage. *J Jpn Pract Surg Soc* **40**: 737-738, 1979. (in Japanese)
- 11) Kern E Jr, Everson GT, et al: Biliary lipids, bile acids, and gallbladder function in the human female. Effects of pregnancy and the ovulatory cycle. *J Clin Invest* **68**: 1229-1242, 1981.
- 12) Kimura T, Doba S, et al: A case of congenital dilatation of the common bile duct undergoing acute necrotizing inflammation during pregnancy. *Aomori Ken Byo Shi* **18**: 283-291, 1973. (in Japanese)
- 13) Komi N, Kashiwagi Y, et al: The etiology of congenital dilatation of the biliary duct. *Jpn J Pediatr Surg* **9**: 1101-1108, 1977. (in Japanese with English abstract)
- 14) Kumar D: In vitro inhibitory effect of progesterone on extrauterine human smooth muscle. *Am J Obst Gynecol* **84**: 1300-1304, 1962.
- 15) Muto Y, Uchimura M, et al: Two cases of choledochal dilatation developed in pregnancy. *J Jpn Pract Surg Soc* **39**: 250, 1978. (in Japanese)
- 16) Ryan JP, Pellicchia D: Effect of progesterone pretreatment on guinea pig gallbladder motility in vitro. *Gastroenterology* **83**: 81-83, 1982.
- 17) Sakai T, Miyazaki M, et al: A case of congenital choledochal cyst developed in pregnancy. *Shika-gakuho* **75**: 1094-1095, 1975. (in Japanese)
- 18) Takahashi T, Yamamura T, et al: Effects of progesterone on contractile responses of the guinea-pig gallbladder. *Jpn J Gastroenterol* **80**: 1754-1759, 1983. (in Japanese with English abstract)
- 19) Tanimura H, Nagase M, et al: Congenital choledochal cyst developed with obstructive jaundice in pregnancy. *J Jpn Surg Soc* **79**: 240, 1978. (in Japanese)
- 20) Tsujinaka T, Kawasaki T, et al: Congenital choledochal cyst in pregnancy—Etiologic consideration of our 3 cases and analysis of 28 cases in Japanese literature of past 10 years. *Jpn J Gastroent Surg* **14**: 1708-1712, 1981. (in Japanese)
- 21) Tsunekawa H, Suga S, et al: A case of huge congenital choledochal dilatation developed in pregnancy. In *Congenital Intrahepatic Bile Duct Dilatation* edited by Oto M. Tokyo, Igaku-Tosho-Syuppan Inc 1980, p. 63-69.
- 22) Yotuyanagi S: Contributions to the etiology and pathology of idiopathic cystic dilatation of the common bile-duct with report of three cases; A new aetiological theory based on supposed unequal epithelial proliferation at the stage of the physiological epithelial occlusion of the primitive choledochus. *Gann* **30**: 601-652, 1936.

和文抄録

先天性胆道拡張症における症状発現と妊娠との関係

和歌山県立医科大学消化器外科

青木 洋三, 嶋田 浩介, 川嶋 寛昭, 勝見 正治

我々の教室で妊娠を契機に発症した先天性胆道拡張症を2例経験した。第1例は過去2回の分娩歴がある症例で、何れの妊娠時にも8カ月目(30週)に右上腹部痛をもって発症した。第2例は過去3回の分娩歴がある症例で、何れの妊娠時にも3~4カ月目(16週)に右上腹部痛と発熱をもって発症し、以後分娩時までこれらの症状が間歇的に出現した。

妊娠ホルモットを用いて肝・胆道シンチグラフィーを行い、胆嚢での胆汁排泄動態を解析すると、胆嚢の拡張と胆汁のうっ滞が妊娠日数に関係なく認められ、また同時に血中エストロゲン、プロゲステロン値を測定すると何れも高値を示した。

従来から本症における臨床症状の発現機構に関しては、拡張した胆管の存在に加え、何らかの後天的因子が加わって発症するものと考えられてきた。後者の1つに妊娠子宮による胆道の機械的圧迫、あるいは妊娠に伴うホルモン動態の変化による胆汁の流出障害、胆汁の濃縮などが挙げられている。我々が今回経験した2症例はその発症時期に明らかな相異があり、妊娠期における本症の発症には妊娠子宮による胆道の物理的圧迫の他、妊娠に伴う母体の液性変化、すなわち増量するエストロゲン、プロゲステロンの関与が実験的にも推定された。