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Brief Report

Ursodeoxycholic Acid for the Prevention of Relapse of Pregnancy-Related Acute Gallstones Pancreatitis

Alberto Maringhini ^{1,*}, Rosalia Patti ², Marco Maringhini ³
and Jacopo Maringhini ⁴

¹ Pancreatic Unit La Maddalena Hospital. Via San Lorenzo 312D, 90146 Palermo, Italy

² Pancreatic Unit, ARNAS Civico, Palermo

³ Internal Medicine, ARNAS Civico, Palermo

⁴ University of Palermo, School of Medicine

* Correspondence: alber.ghini55@gmail.com

Abstract

INTRODUCTION: Acute gallstones pancreatitis has an increased incidence after pregnancy. Gallstones may spontaneously disappear after delivery; cholecystectomy during pregnancy is challenging whereas ursodeoxycholic acid is safe during the last 6 months of pregnancy and effective in dissolving small gallstones. Based on these considerations, prevention of recurrent acute pancreatitis during and after pregnancy is unclear. **METHODS:** Between 2002 and 2015, we treated women with acute pancreatitis related to small gallstones (< 1 cm in diameter) during pregnancy or within the first post-partum year, who refused surgery, using ursodeoxycholic acid until stones dissolution. Patients were followed for 79.5 + 9.35 months (mean + SD) with serial clinical and ultrasonographic control. **RESULTS:** ursodeoxycholic acid was effective in dissolving small stones in 13/14 women in 7.77 + 3.14 months (mean + SD). Only 2 patients experienced recurrent acute pancreatitis (at 1 and 88 months after the first episode). **DISCUSSION:** ursodeoxycholic acid may be used during pregnancy to postpone surgery. After delivery, medical treatment should be reserved only for women, refusing cholecystectomy with serial ultrasonographic control to exclude gallstones recurrence.

Keywords: gallstones; biliary sludge; acute pancreatitis; pregnancy; cholecystectomy; ursodeoxycholic acid; breastfeeding

1. Introduction

In a recent population-based cohort study of Sicilian women of childbearing age the incidence of Acute Pancreatitis during pregnancy was similar to that in non-pregnant women, but during the first 6 months after delivery it increased by more than 400%, then slowly declined over 2 years returning to baseline. (1). This increased incidence was mainly observed in patient with gallstones and incidence was more evident in younger women (1). These results confirm a population-based case-control study from Olmstead County, Minnesota, USA (2).

Biliary sludge and stones are a well-known cause of acute pancreatitis (3, 4). Women with gallstones have a 12 to 25 times greater risk for development of acute pancreatitis in comparison to general population (5), and cholecystectomy reduce the risk of recurrent acute pancreatitis of 6- to 12-fold respect to the female general population (5).

During pregnancy, the incidence of new sludge and stones is 31% and 2%, respectively (6), explaining the markedly increased rate of acute pancreatitis after delivery. In the first-year post-partum biliary sludge and stones spontaneously disappear in 68.3% and 30% of cases, predominantly

in older new mothers, which explains why the increased incidence of acute pancreatitis affects mainly younger women (6,7).

The natural history of gallstones-related acute pancreatitis during and after pregnancy remains poorly defined. Cholecystectomy can be performed during pregnancy - preferably in the second trimester and in tertiary Hospital with specific expertise (8) - but in most hospitals worldwide it remains a challenge.

Ursodeoxycholic acid (Urso) is safe in the last semester of pregnancy (8, 9) and effective in dissolving sludge and small gallstones (9, 10). Since acute pancreatitis during and after pregnancy is rare, randomized controlled trials are not feasible. We therefor conducted a prospective study of women with small gallstones related acute pancreatitis during pregnancy or within the first post-partum year who refused surgery, and they were treated with Urso.

2. Methods

Between 2002 and 2017 we enrolled all consecutive women admitted in our hospital who had small gallstones (<10 mm) and acute pancreatitis occurring in the last semester of pregnancy or within the first post-partum year. Acute pancreatitis diagnosis was made according to the 2013 Consensus Conference criteria (11) when at least two of the following criteria were present:

- 1. acute onset of persistent and severe epigastric pain radiating to the back.
- 2. serum lipase or amylase activity > 3 x upper limit of normal
- 3. characteristic imaging findings on contrast enhanced CT, MR or transabdominal ultrasonography (US).

Gallstones were diagnosed by US when a discrete echogenic structure (> 3 mm), mobile with fasting patient positional change and casting an acoustic shadow, was present – thus excluding sludge balls.

Patients with gallstones > 1.0 cm were excluded due to the low likelihood of dissolution with Urso.

Surgery was proposed to all women: only those who refused were enrolled. Written informed consent was obtained, and the study was approved by the Institutional ethics Committee.

Urso (10 mg/kg/day) was started after acute pancreatitis recovery in patients with a patent cystic duct on US. After delivery, non-contrast CT scan excluded stone calcification. Follow-up included clinical examination and gallbladder US (every 3 months during year 1, every 6 months during year 2, then annually). Urso was discontinued 3 months after complete stone disappearance. Patients were followed up for at least 6 years

3. Results

Fourteen women were recruited: 5 during last semester of pregnancy and 9 post-partum (Table 1). Mean age + SD was 25.93 + 6.46 years. Seven additional women were excluded: five underwent cholecystectomy after delivery and 2 had gallstones > 1.0 cm.

Table 1. Clinical and ultrasonographic population data.

Pat	Age	Stones Number/ Diameter, mm*	AP in Pregnancy (month)	AP in Post partum (month)	AP/stones new episode	Stones disappearance Months after therapy	Follow-up Months
1	27	1 / 4	5		0 / 0	4	72
2	24	1 / 7	7		0 / 0	6	84
3	19	2 / 6	6		0 / 0	9	72
4	20	1 / 7	7		0 / 0	9	88
5	23	3 / 8	7		84/84**	6	72
6	39	1 / 9		2	0 / 0	9	72

7	21	1 / 4	4	0 / 0	9	72
8	18	2 / 9	2	0 / 0	12	72
9	26	1 / 8	7	0 / 0	5	84
10	29	1 / 4	3	0 / 0	3	98
11	33	1 / 9	5	0 / 0	12	92
12	25	2/7	11	1/1§	0	1
13	23	1 / 3	2	0 / 0	5	72
14	36	1 / 9	9	0 / 0	12	76

Follow up 78.9 + 16.6 (mean + 2SD) months (patients n = 13), *Largest stone size, ** relapse of stones and new AP 18 months later last follow-up visit. § relapse of AP without GS dissolution.

All deliveries and newborn were complication-free, no child malformations were observed. All acute pancreatitis were mild except one (patient n. 5) with pancreatic effusion at 7 months of pregnancy. She was lost to follow-up after 66 months with empty gallbladder but later (after 18 months) was readmitted with recurrent acute pancreatitis and gallstones (n = 3, largest 6 mm) then she underwent cholecystectomy without complications. Another patient developed recurrent acute pancreatitis one month after discharge before dissolution could occur and she was operated on uneventfully.

In the remaining 13 women gallstones dissolution was obtained after a mean + SD of 7.77 + 3.14 months.

In 12 women Urso achieved complete stone dissolution with no recurrence over a mean + SD follow up of 79.5 + 9.35 months.

4. Discussion

This study confirms that Urso is effective in dissolving small gallstones and preventing recurrent acute pancreatitis in most cases (12/14 women over 79.5 + 9.35 months follow-up). Failures occurred in one patient with early recurrence (insufficient time for dissolution) and one with late recurrence after apparent stone clearance. We report a consecutive series of patients with acute pancreatitis during pregnancy or in the first-year post-partum. Seven women were excluded, five because had cholecystectomy in post-partum after acute pancreatitis, two because had gallstones larger than 1.0 cm.

All deliveries and newborn were complication-free, we did not observe any fetal malformation and there was no mortality in mothers due to acute pancreatitis. Only one woman had local complication of acute pancreatitis. In our knowledge this is the first prospective study on medical treatment of gallstones for prevention of recurrent acute pancreatitis during pregnancy or in the first year after delivery: Urso appeared to perform better than in general population, likely because most of gallstones in pregnancy related acute pancreatitis are not only small but also recent. Furthermore, the pathophysiology of bile during and after pregnancy helps efficacy of Urso.

The main limitation of the study is the low sample size – inevitable given the rarity of disease - and the single centre design. We had excluded 5 women who were operated on according with international guideline. Results apply only to women in the last semester of pregnancy or in the first post-partum year, with small stones (< 10 mm), patent cystic duct and no calcified gallstones.

A relationship between gallstones and acute pancreatitis has been recognized since the beginning of 20th century, when Opie described a patient who had acute pancreatitis associated with gallstones impacted in the ampulla of Vater (12); later Acosta and Ledesma (4), Kelly and Swaney (13, 14) have shown that 85 - 90% of patients suspected of having biliary pancreatitis pass gallstones in stools in the first few days after the onset of pain. In a review of the literature, Goebell and Hotz noted that 20% of 1,450 patients suspected of having biliary pancreatitis had gallstones in the common biliary duct and 72% had stones in the gallbladder (15). Microscopic evidence of biliary sludge in duodenum juice has been found in 36% of idiopathic pancreatitis (3),

In a population cohort study conducted in Olmsted County the maximal and minimal relative risk in women with gallstones in whom acute pancreatitis developed were 25 (95% CI 18-35) and 12 times (95% CI 7-19) respectively compared with what would be expected in the general population. In this study cholecystectomy reduced the relative risk for acute pancreatitis 6-to 12- fold (5), with only two patients with relapse: one with alcoholic pancreatitis, the other with jejunal perforation due to Zollinger-Ellison syndrome. Cholecystectomy can be performed during P - preferably in the second trimester and in tertiary hospitals with specific experience (6) – but it is challenging in many canterers; thus, medical treatment may simplify the management of gallstones-related acute pancreatitis during pregnancy.

Despite concern about high long-term recurrence rates (30-50% within 5 years) (16) and the widespread availability of laparoscopic cholecystectomy, Urso may still be valuable in selected women after pregnancy, especially given the high rate of spontaneous gallstone disappearance in post-partum period (6, 7).

Biliary sludge and GS remain the leading causes of pregnancy related acute pancreatitis (1, 2). In a population cohort study the acute pancreatitis incidence during pregnancy was 21.6/100,000 persons-year not different from 20.0/100,000 persons-years in childbearing non pregnant women. In the post-partum period acute pancreatitis increased to 96.4 in the first semester, decreasing to 26.1/100,000 only in the third year after delivery with Rate Ratio significant from 4.36 (95% CI 3.63-5.3) through 1.48 (95% CI 1.15-1.86) in the second year. Acute pancreatitis was related to gallstones in 38% during pregnancy, in 70% in post-partum and in 49% in non-pregnant women. In this cohort acute pancreatitis incidence increased with age in non-pregnant, decreased with age in post-partum (1).

During pregnancy the incidence of new sludge and stones was 31% and 2% (6), but, in the first year after delivery, they spontaneously disappear in 68.3% and 30% of cases (6, 7). During pregnancy obesity was a risk factor for new sludge; the presence of sludge was a risk factor for new gallstones (6). After delivery age < 30 years and a small diameter (< 8 mm) of gallstones were predictors of spontaneous disappearance (6, 7).

This phenomenon, new stones during pregnancy, spontaneous disappearance in the first year after delivery, mainly small stones (< 1 cm) in oldest new mothers (> 30 years old)) confirms old epidemiological studies demonstrating parity is a risk factor only for women with pregnancies in youngest age (16, 17). This evidence also suggests that most of disappeared stones does not relapse without any treatment.

The precipitation of biliary sludge and stones during pregnancy is due to increased bile cholesterol saturation for high serum estrogen levels and reduced gallbladder motility for high serum progesterone levels. After delivery the collapse of progesterone levels restores gallbladder motility with ejection of biliary sludge/stones trough bile duct with acute pancreatitis (18, 19). The increase incidence of acute pancreatitis only after delivery supports a role for gallbladder motility in the pathogenesis of acute pancreatitis.

In older and in breastfeeding new mothers' longer amenorrhea and anovulatory cycles cause lower estrogen levels with likely lower bile cholesterol saturation, more spontaneous stones dissolution and less acute pancreatitis (20, 21).

In conclusion, our findings support Urso therapy after gallstones-related acute pancreatitis during pregnancy to postpone surgery in the post-partum period. After delivery we recommend at least 3 months of breastfeeding (21). Since relapse cannot be excluded after discontinuation of therapy, laparoscopic cholecystectomy remains the treatment of choice post-partum. Urso may be considered for women who refuse surgery, with annual ultrasonographic monitoring

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Abbreviations

Ursodeoxycholic Acid: (Urso). Transabdominal Ultrasonography (US), Computed Tomography (CT), Magnetic Resonance (MR)

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