

1 Prenatal treatment of meconium peritonitis with urinary trypsin inhibitor

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1 Abstract

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3 We describe a case of congenital meconium peritonitis (MP) with progressive fetal
4 ascites and polyhydramnios. Fetal ascites largely remained and increased after the
5 paracentesis at 29 weeks' gestation. Therefore, urinary trypsin inhibitor (UTI), a
6 physiological anti-inflammatory substance, was administered into the fetal abdominal
7 cavity at the second paracentesis at 35 week' gestation. Significant amount of fetal
8 ascites remaining after the second paracentesis was completely resolved in 5 days.
9 Vaginal delivery was safely accomplished and the neonate had an excellent outcome
10 without any surgical intervention. The case illustrates that UTI can reduce
11 meconium-induced chemical peritonitis to facilitate the intrauterine remission of MP.

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1 Case report

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3 A 32-year-old pregnant woman (gravida 1, para 1), whose pregnancy course had been
4 uneventful until 24⁺² weeks' gestation, was referred to our hospital at 27⁺² weeks'
5 gestation. Ultrasonography revealed a fetus with massive ascites, collapsed intestine,
6 and peritoneal calcification (Figure 1A). Polyhydramnios (amniotic fluid index=27)
7 was also noted. T2-weighted magnetic resonance image revealed moderate reduction
8 of fetal lung volume due to compression by the ascites (Figure 1B).

9 Polyhydramnios was rapidly aggravated (Figure 2) and maternal appetite was reduced
10 due to severe abdominal distension. Fetal ascites was gradually increased and
11 development of pulmonary hypoplasia was anticipated. At 29⁺² weeks' gestation,
12 1200 ml of amnioreduction was executed without any complication (Figure 2). We
13 also attempted to remove the fetal ascites as much as possible by paracentesis.
14 However, only 70 ml of the ascites could be aspirated for fear of possible fetal injury,
15 since maternal intravenous anesthesia failed to sufficiently restrain the fetal movement.
16 As a result, significant amount of the fetal ascites remained after the paracentesis.
17 High bilirubin concentration (3.6 mg/dl) in the aspirated ascites established the
18 diagnosis of meconium peritonitis (MP).

19 Afterwards, amniotic fluid was rapidly reaccumulated and repetitive amnioreduction
20 was required to control the maternal symptom (Figure 2). On the other hand, increase
21 of fetal ascites was moderate and ultrasonographic fetal lung volume was relatively
22 preserved. Therefore, additional fetal paracentesis had not been considered until the
23 patient expressed her desire to have vaginal delivery. Abdominal dystocia was highly
24 anticipated in case of vaginal delivery. Although removal of the fetal ascites in large
25 amount seemed necessary to obviate the abdominal dystocia, our experience in the prior
26 paracentesis suggested that this was a difficult procedure carrying high risk of fetal
27 injury. Since meconium-induced chemical peritonitis was considered to be a cause of
28 the ascitic accumulation, we expected that control of the peritoneal inflammation could
29 lead to reduction of the fetal ascites. After obtaining informed consent from the
30 parents, 50,000 units of human urinary trypsin inhibitor (UTI), a physiological
31 anti-inflammatory substance, was administered into the fetal peritoneal cavity
32 immediately after removal of 120 ml of the fetal ascites at 35⁺¹ weeks' gestation. The

1 fifth amnioreduction of 1000 ml was also performed. Significant amount of the fetal
2 ascites remaining at 1 day after the paracentesis (Figure 3A) completely disappeared in
3 the following 4 days (Figure 3B) and no reaccumulation occurred thereafter. Notably,
4 the amniotic fluid index, which had tended to increase before this final amnioreduction,
5 remained within the normal range thereafter (Figure 2).

6 Labor was induced at 37⁺² weeks' gestation and a male baby weighing 3360 g was
7 vaginally delivered without any respiratory compromise. Meconium was
8 spontaneously passed 2 hours after the birth. Although contrast studies revealed
9 moderate dilation of the small intestines, oral feeding of the neonate was successfully
10 established without any surgical intervention. At 10 months after birth, the baby
11 tended to be constipated but his development and growth were within normal limits.

12

1 Discussion

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3 MP is a chemical intraabdominal inflammation resulting from intrauterine bowel
4 perforation. Possible causes of bowel perforation include mesenteric vascular
5 insufficiency and bowel obstruction such as meconium ileus, intestinal atresia/stenosis,
6 volvulus, intussusception, duplication, and extrinsic band ¹. Dilated bowel loop and/or
7 polyhydramnios is usually associated with bowel obstruction. Meconium and
8 digestive enzymes spilt from the perforation cause sterile inflammation of the
9 peritoneum that leads to ascitic accumulation. The subsequent adhesion between
10 bowel loop and omentum can circumscribe the ascitic fluid, resulting in the formation
11 of abdominal pseudocyst ². In the present case, progressive polyhydramnios suggested
12 that bowel obstruction was a primary etiology, although we were not able to detect
13 bowel dilation throughout the prenatal course.

14 Closure of the perforation and clearance of the underlying bowel obstruction can lead
15 to spontaneous intrauterine remission, where peritoneal calcification remains as an only
16 detectable ultrasonographic finding and no postnatal surgery is required ³. As shown
17 in Table 1, although high remission rates (nearly 80%) were described in the earlier
18 reports, recent larger studies suggest that majority (76-100%) of the prenatally
19 diagnosed cases are not resolved spontaneously.

20 Massive fetal ascites, even if it exists only for a limited period, could have deleterious
21 effect on the neonatal outcome. Elevation of fetal diaphragm by massive ascites could
22 cause fetal pulmonary hypoplasia that is associated with postnatal ventilatory failure.
23 Moreover, hydrops fetalis could develop as a consequence of diastolic cardiac failure.
24 Kamata et al. demonstrated that MP patients with massive ascites or huge pseudocyst
25 are at greater risk of hydrops development, requirement of resuscitation at birth, and
26 neonatal death ⁴. In these respects, control of the massive ascites or huge pseudocyst
27 may contribute to improved outcome of the affected neonates. At present, however,
28 possible benefit of paracentesis is not fully evaluated. As even massive ascites may be
29 spontaneously absorbed, we consider that such invasive procedure should be limited to
30 prevent fetal pulmonary hypoplasia, cardiac failure, or abdominal dystocia.

31 Meconium contains digestive enzymes such as trypsin that induce aseptic peritonitis.
32 Extensive inflammation could inhibit spontaneous sealing of the perforation and

1 inflammation-induced bowel edema could aggravate the underlying bowel obstruction.
2 In these respects, worsening polyhydramnios and meconium ascites as observed in the
3 present case is likely to reflect the persistence of severe chemical peritonitis. Human
4 UTI, a physiological anti-inflammatory substance, is known to inhibit serine proteases
5 including trypsin and chymotrypsin ⁵. Recently, Olguner et al. demonstrated that UTI
6 prevents meconium-induced intestinal damage in experimental animal model of
7 gastroschisis ⁶. Thus, UTI is a possible agent that could control meconium-induced
8 inflammation. In the present case, injection of UTI into fetal peritoneal cavity at the
9 second paracentesis led to complete disappearance of the fetal ascites and stabilization
10 of the amniotic volume. The neonate had an excellent outcome without any surgical
11 intervention. This suggests that reduction of chemical peritonitis by intraabdominal
12 UTI administration facilitates sealing of the bowel perforation, thus contributes to
13 intrauterine remission of MP. From this experience, we propose the prenatal
14 intraperitoneal UTI injection as a promising treatment approach for MP accompanying
15 massive and recurrent fetal ascites.

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1 Figure legends

2

3 Figure 1. Fetal ultrasonography (A) and T2-weighted magnetic resonance image (B) at 27
4 weeks' gestation.

5 (A) Horizontal section of fetal abdomen shows massive ascites and collapsed intestine with
6 spotty peritoneal calcification (arrows) (B) Fetal lung (broken line) is compressed by
7 massive ascites (asterisk).

8

9 Figure 2. Serial change of amniotic fluid index.

10 Broken line shows the upper limit of normal amniotic fluid index. Timings of
11 amnioreduction and fetal ascitic removal are indicated by open arrows and closed arrows,
12 respectively. Amount of amniotic fluid or fetal ascites removed in each procedure is specified
13 in the arrows. Note that the amniotic fluid index remains within the normal limit after the
14 final amnioreduction when intraabdominal injection of urinary trypsin inhibitor (UTI;
15 arrowhead) is also performed.

16

17 Figure 3. Sagittal ultrasonographic view of the fetal abdomen at 1 day after (A) and at 5 days
18 after (B) the injection of urinary trypsin inhibitor into the fetal abdominal cavity.

19 Note that significant amount of fetal ascites (asterisk) remaining after 1 day (A) completely
20 disappears in the following 4 days (B).

21

1 Table

2

3 Table 1. Outcomes of prenatally diagnosed meconium peritonitis

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Reference no.	Year	No. of cases	Spontaneous remission*	Perinatal death	Etiology of perinatal death	Morbidity in survivors
3	1992	9	7 (78%)	1 (11%)	n.d.	0%
7	1995	9	7 (78%)	1 (11%)	Postoperative complication	0%
8	2003	11	0 (0%)	2 (18%)	Postoperative complication Sepsis/DIC/ICH	0%
9	2003	17	3 (18%)	3 (18%)	PPHN PPHN NEC	n.d.
10	2007	41	10 (24%)	1 (2%)	Postoperative complication	35%

5 * The cases that had good postnatal prognosis without any surgical intervention.

6 n.d.=not described; DIC=disseminated intravascular coagulopathy; ICH=intracerebral hemorrhage;

7 PPHN=persistent pulmonary hypertension of newborn; NEC=necrotizing enterocolitis.

8

Figure 1



Figure 2

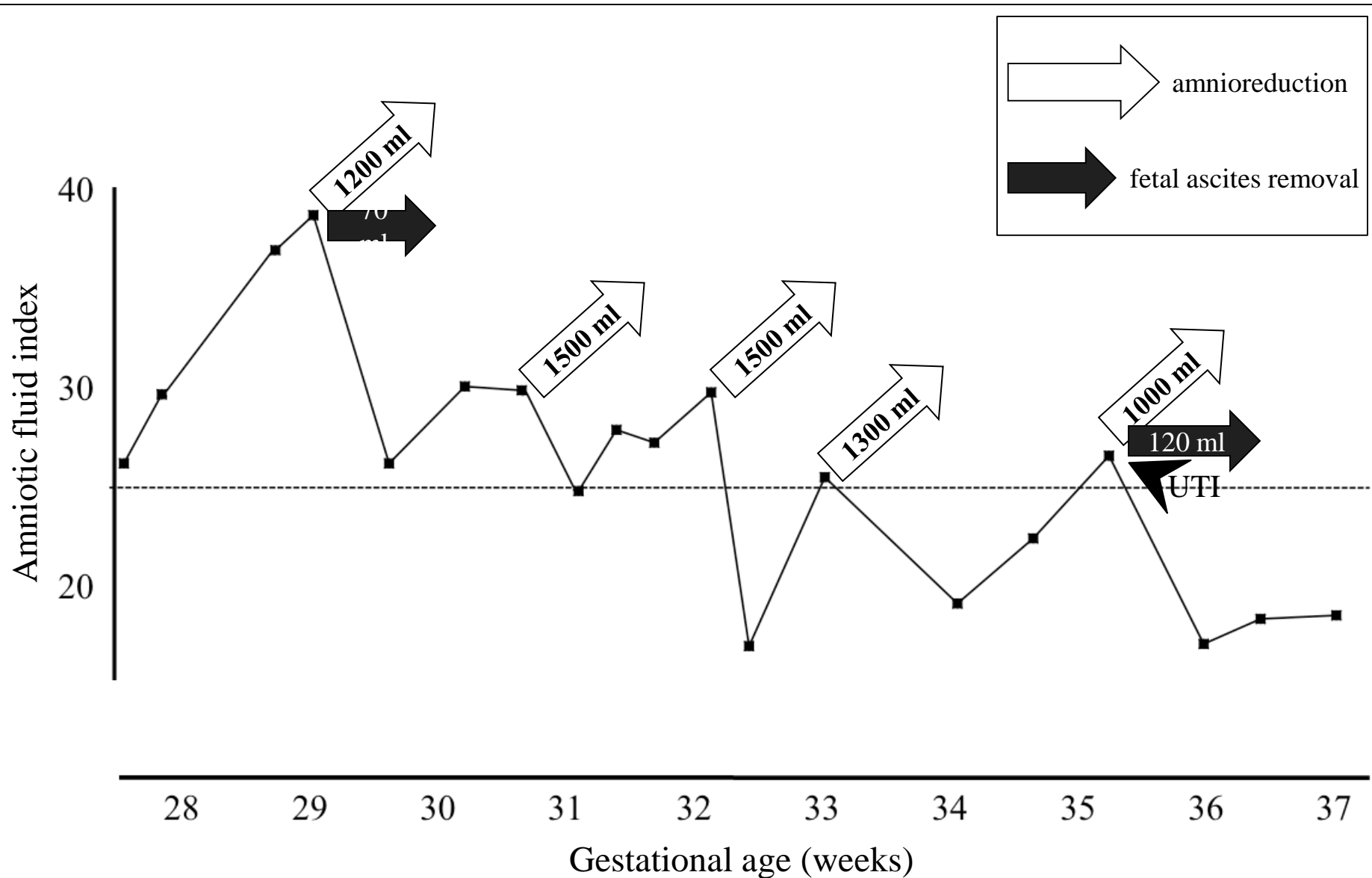


Figure 3

