Intestinal Atresia Following Intraamniotic Use of Dyes

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Summary
Since 1990 avoidance of methylene blue as a dye in diagnostic amniocentesis is recommended. This is a result of the observation that a high incidence of jejunoileal atresia appeared in twin pregnancies following intraamniotic injection of methylene blue.

We report four further cases of jejunoileal atresia in twins after intraamniotic injection of dyes since 1991. We describe the clinical course, discuss possible teratogenic mechanisms and emphasize again that synthetic dyes should not be used in second trimester amniocentesis.

Key words
Intestinal atresia - Intraamniotic use of dyes - Methylene blue - Diagnostic amniocentesis

Résumé
Depuis 1990, on évite l'utilisation du bleu de méthylène pour l'amniocentèse diagnostique. En effet on a observé que l'atresie intestinale s'est présentée en grande nombre après injection intra-amniotique de bleu de méthylène dans les grossesses gémellaires.

Depuis 1991, nous avons 4 cas d'atresie intestinale chez des jumeaux après injection intra-amniotique de substance colorante. L'évolution de ces cas et la tératogénèse observée sont discutées. De nouveau, nous avertissons que l'utilisation de substance colorante synthétique pour l'amniocentèse pendant le 2ème trimestre peut être très toxique pour l'intestin.

Mots-clés
Atresie intestinale - Injection intra-amniotique de substance colorante - Bleu de méthylène - Amniocentèse diagnostique

Zusammenfassung


Schlüsselwörter
Dünnarmatresie - Intraamniale Anwendung von Farbstoffen - Methyleneblau - Diagnostische Amniozentese

Introduction
Clinical and experimental observations strongly suggest that small bowel atresia - in contrast to duodenal and rectal atresia - is an intrauterine acquired disease. Lanugo hairs and bile pigments are always found distal to the atretic segment, serving as evidence that the bowel passage was open before formation of atresia. Well known is the appearance of small bowel atresia after intrauterine volvulus, intussusception, internal hernia, omphalocele and gastrochisis. The relative low incidence of associated extraintestinal anomalies similarly indicates an acquired and not inherited disease.

Until now, no teratogenic substance was known to produce intestinal atresia. Nicolini and Monni for the first time suspected that the intraamniatal injection of methylene blue could cause jejunoileal atresia (6). Methylene blue and other dyes are instilled during diagnostic amniocentesis in twin gestations to ensure that amniotic fluid is sampled from both cavities.

At the Department of Pediatric Surgery, Medizinische Hochschule Hannover, 31 children were operated on for small bowel atresia from 1977 until 1994. Six children were out of a set of twins. The latest four cases since 1991 were twin gestations in which prenatal amniocentesis with intraamniotic injection of dyes was performed.
### Case reports

The clinical data of the cases are summarized in Table 1.

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<td>5th DOL</td>
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<tr>
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<td>ileus and sepsis</td>
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</table>

AC = amniocentesis; WOG = weeks of gestation; DOL = day of life; WOL = week of life; sp/se = spontaneous/cesarean section; TPN = total parenteral nutrition.

#### Case 1

L. K., male, born Dec. 9, 1991

Mother 35 years old, IVG/JVP Indication for amniocentesis: age of the mother. Amniocentesis in the 15th WOG with intranamniotic injection of 1–3 ml of methylene blue 1%. Result of amniocentesis for both children normal. Two weeks prenatally diagnosed of intestinal obstruction by ultrasound. Birth in the 30th WOG spontaneously, birth weight 2300 g. Sex of the other twin: male. Operation on the first DOL. Intraoperative one single atresia in the upper and another membrane atresia in the middle part of jejun. Resection of 10 cm bowel in total, end-to-end-anastomosis with modellage. Total parenteral nutrition on 12 days. Postoperative course complicated with ileus and sepsis in the second WOL.

#### Case 2

D. G., male, born Dec. 16, 1993

Mother 38 years old, III/G/JVP Indication for amniocentesis: age of the mother. Amniocentesis in the 16th WOG with intranamniotic injection of 1–3 ml on indigo carmine. Result of amniocentesis for both children normal. Birth in the 28th WOG spontaneously, birth weight 1120 g. Sex of the other twin: female. Diagnosis of small bowel obstruction at the 5th DOL. Operation on the sixth DOL. Intraoperative one atresia in the upper and three further atreic segments in the middle part of jejun. Resection of 24 cm bowel in total, 3 end-to-end-anastomoses with modellage of the first. Total parenteral nutrition for 17 days. Postoperative course complicated with sepsis in the sixth WOL and severe cholestasis.

#### Case 3

F. T., female, born Jan. 18, 1994

Mother 33 years old, I.G/JVP Indication for amniocentesis: pathologic result in the "triple test". Amniocentesis in the 17th WOG with intranamniotic injection of 1–3 ml of methylene blue 1%. Result of amniocentesis for both children normal. In the 22nd WOG prenatal diagnosis of intestinal obstruction by ultrasound. Birth in the 34th WOG per cesarean section because of misposition of the healthy twin, birth weight 2300 g. Sex of the other twin: female. Operation on the first DOL. Intraoperative one single membrane atresia in the middle part of jejun. Resection of 20 cm bowel in total, end-to-end-anastomosis with modellage. Total parenteral nutrition of 15 days. Postoperative course complicated with ileus and sepsis in the sixth WOL.

#### Case 4

F. B., male, born Febr. 12, 1994

Mother 37 years old, I.G/JVP Indication for amniocentesis: age of the mother. Amniocentesis in the 16th WOG with intranamniotic injection of 1–3 ml of methylene blue 1%. Result of amniocentesis for both children normal. In the 28th WOG prenatal diagnosis of intestinal obstruction by ultrasound. Birth in the 34th WOG per cesarean section because of misposition of the patient, birth weight 1950 g. Sex of the other twin: male. Operation on the second DOL. Intraoperative four atresias in the upper and middle part of jejunum. Resection of 10 cm bowel in total, end-to-end-anastomosis with modellage. Total parenteral nutrition for 12 days. Postoperative course complicated with ileus and sepsis in the third WOL.

### Discussion

Children with congenital small bowel atresia show a considerable amount of complications. They are often born preterm, leading to problems of prematurity like respiratory distress, sepsis and NEC. The most significant causes of surgical complications are anastomotic leak and postoperative ileus. As consequence of total parenteral nutrition toxic liver disease with cholestasis may occur.

The four reported children were born between the 29th and 36th week of gestation. Birth weights were 1120 to 2300 g. No associated anomalies appeared. Three children had multiple atresias in the upper and middle jejunum, whereas one child had a single anastomous atresia in the middle jejunum. The dilated proximal part of the jejunum was resected resulting in removal of altogether 10 to 24 cm of small bowel. End-to-end-anastomosis was carried out with tapering of the enlarged proximal end. Careful oral feeding begun after 12 to 17 days of initial total parenteral nutrition. All children had a complicated postoperative course with sepsis. Reoperation for postoperative ileus was performed in two children and severe cholestasis occurred in one child. The courses of the unaffected twins were completely uneventful.

The indication for amniocentesis was advanced maternal age (≥ 35 years) in three cases and a pathologic result in the "triple test" in one case. In all cases possible harmful effects of the amniocentesis to the fetuses were discussed with the mother. Amniocentesis was performed in the 15th to 17th week of pregnancy.
gestation. The results were normal for all children. To be certain that the two samples of amniotic fluid were taken from both separate cavities, dyes were injected into the amniotic sac punctured first. Due to misposition of the fetuses this was not possible by ultrasound alone. In three cases methylene blue and in one case indigo carmine was used to stain the amniotic fluid. By means of the position of the fetuses and additionally by means of the sex in the case of the discordant twins the fetus having received the dye could be identified as the one with jejunoileal atresia.

Until recently, jejunoileal atresia in twins was at best subject to case reports. In 1990 an unexpected high incidence of jejunal atresia in twins was recorded (5). Nicolini and Monni were the first to suspect methylene blue as the causative agent (6). Further retrospective studies were able to corroborate this suspicion: Those twin pregnancies in which prenatal diagnostic amniocentesis with intraamniial injection of methylene blue was performed, showed a manifold increased rate of small bowel atresia compared to normal twin pregnancies (7, 10). Atresia also occurred after the use of indigo carmine as a dye. However, Cragan et al failed to show a statistically significant increase of atresia after the use of indigo carmine (2).

Methylene blue is a common tool to stain various fluids in medicine. For obstetric purposes it was first used in the third trimester to diagnose ruptured membranes. As side effects neonatal hemolytic anemia, methemoglobinemia and hyperbilirubinemia occurred (9). Because of the implications in producing fetal intestinal atresia, it has been recommended since 1990 that methylene blue should not be used for second trimester amniocentesis.

The teratogenesis of small bowel atresia after the injection of methylene blue is still unclear. It is not known whether the dye is locally toxic after oral ingestion of the stained amniotic fluid by the fetus nor whether it is resorbed and disturbs the normal bowel development indirectly. Furthermore it is unknown whether the concentration or amount of dye or the time of injection has any influence on the appearance of atresia.

Impaired mesenteric vascular blood flow seems to be very important in the pathogenesis of jejunoileal atresia. In experimental studies atresia occurred after intrauterine ligation of mesenteric vessels (4). In-vitro investigations showed an increased release and redistribution of adrenergic transmitters around mesenteric arterial vessels in dogs after incubating small bowel with methylene blue (8). The resulting vasoconstriction could lead to an impaired blood flow in the fetal mesenteric vessels with necrosis and later atresia of the dependent bowel segment. Fetal methemoglobinemia and hemolysis due to methylene blue could lead to a redistribution of fetal circulation with decreased blood flow to the mesenteric vessels. This again would result in acute intestinal hypoxia, necrosis and possibly atresia. Indigo carmine, also known as a vasoconstrictor (3), might produce similar fetal abnormalities. This could explain cases of atresia after the use of indigo carmine.

As long as the pathogenesis of jejunoileal atresia is speculative and possible teratogenic substances are not identified, synthetic dyes should no longer be used in second trimester amniocentesis. Recently, a membrane-free hemolysate of maternal blood as a dye marker was proposed as an alternative (1).

References


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