Prenatal diagnosis of fetal bowel obstruction with complicated mi associated with cystic fibrosis

(Diagnóstico prenatal de obstrucción intestinal fetal con íleo meconial complicado asociado a fibrosis quística)

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Abstract (english)
Congenital obstruction of the digestive tract is one of the most common surgical neonatal pathologies, affecting 1/1000-1/2000 neonates. The anatomical obstructions can be intrinsic or extrinsic to the bowel, with the main cause being ileal atresia. Prenatal diagnosis is possible via an ultrasound scanning of the fetus, although only possible in late pregnancy and with a varying sensitivity. In comparison to diagnosing postnatally, it improves the prognosis as it allows for better management of cases at fetal medicine units and specialist centres, where there are multidisciplinary team members available. These include obstetricians, neonatologists and paediatric surgeons. Frequently, congenital intestinal obstructions are associated with chromosomal abnormalities, malformations of other organs and genetic diseases such as cystic fibrosis. Fundamentally the diagnosis depends on highlighting the cause, the level of the obstruction and the length of the intestine that is affected, as well as the weight of the neonate and gestational age at birth. We present a case diagnosed prenatally, at 32 weeks gestation, of an intestinal obstruction associated with an ileal volvulus and meconium ileus of a fetus affected by cystic fibrosis.

Keywords (english)
Intestinal obstruction, prenatal, volvulus, ileus, meconium, cystic fibrosis

Resumen (español)
La obstrucción congénita del tubo digestivo es una de las patologías quirúrgicas neonatales más frecuentes. Afecta a 1/1000-2000 neonatos. Las obstrucciones anatómicas pueden ser intrínsecas o extrínsecas, siendo la causa más frecuente la atresia ileal. El diagnóstico prenatal es posible mediante ecografía fetal, aunque suele ser tardío en la gestación y con una sensibilidad variable. Este diagnóstico en comparación con el postnatal mejora el pronóstico ya que permite un manejo adecuado de los casos en unidades de medicina fetal y la programación del parto en un centro terciario donde exista disponibilidad de un equipo multidisciplinar que incluya obstetras, neonatólogos y cirujanos pediátricos. Frecuentemente las obstrucciones congénitas intestinales se asocian a cromosomopatías, malformaciones de otros órganos y enfermedades genéticas como la fibrosis quística. El pronóstico depende fundamentalmente de la causa subyacente, del nivel de la obstrucción y longitud intestinal afectada, del peso y edad gestacional al nacer. Presentamos el caso del diagnóstico prenatal a las 32 semanas de amenorrea de una obstrucción intestinal fetal asociada a un vólvulo ileal e íleo meconial en un feto afecto de fibrosis quística.

Palabras clave (español)
Introduction

Congenital obstruction of the digestive tract is one of the most frequent neonatal surgical pathologies. It affects one out of every 1000-2000 newborn babies. The anatomical obstructions can be either intrinsic or extrinsic to the bowel. The intrinsic obstructions are caused by either an interruption of the flow of the digestive tract, bowel wall pathology, a narrowing of the lumen or because of an extremely viscous meconium. The extrinsic obstructions can be produced by one of the following; annular pancreas, volvulus, internal hernias, flanges or congenital bands, intestinal duplications and retroperitoneal tumours.

The prenatal diagnosis of congenital intestinal obstructions is possible via a fetal ultrasound scan, although this is only possible in later pregnancy and has a poor sensitivity (1-3). The expressivity of an obstruction on prenatal ultrasound depends on its location. If dilatation is greater than 7mm of the average, there is a central distribution and peristalsis is present, it suggests obstruction of the small intestine. If dilatation is greater than 20mm, it shows a peripheral distribution and peristalsis is absent, this usually corresponds to a colon obstruction. Anorectal atresias are difficult to identify (3-6). Additional signs of intestinal obstruction are hyperechogenicity (thickening) of the intestinal walls (greater than 3mm) and calcifications of the peritoneum.

Jejunoileal atresia is the most common cause of fetal-neonatal intestinal obstruction, with an incidence of 1 in every 2500-5000 neonates and with a detection rate in later pregnancy of less than 50%. Jejunoileal atresia has a small link to chromosomal abnormalities and other malformations. 10% of these cases are associated to cystic fibrosis (an even higher percentage in the case of those associated with meconium peritonitis). Generally, there is a good prognosis except when dealing with multiple atresias (apple peel intestinal atresia), meconium peritonitis and volvulus. On the contrary, the obstructions of the large intestine are largely associated to chromosomal abnormalities and other VACTER (Vertebral, Anal, Cardiac, Tracheal, Esophageal, Renal) malformations, for which the prognosis is determined by the associated anomalies.

Out of the genetic diseases that are related to fetal-neonatal bowel obstruction, the most common is cystic fibrosis (7). It is the most frequent autosomal recessive illness in the Caucasian population, with a frequency of one in every 9000-10000 births. It is characterised by the production of high salt content sweat and mucous secretions with abnormal viscosity. Its incidence is variable: it is much less common in Asian and African populations than in European and North American countries, with variations within each country. The exact prevalence in Europe is unknown, however it is estimated that it occurs in 1 in 8000 – 1 in 10000 individuals. It is generally a progressive chronic illness which usually presents during early childhood. More rarely, it is present from birth. Meconium ileus and meconium peritonitis occur in around 7-15% of these cases. Any internal organ can be shown to be affected, even though the principal manifestations are in the respiratory system (chronic bronchitis), the pancreas, (pancreatic insufficiency, cystic fibrosis related diabetes and occasionally pancreatitis) and, even more rarely, the intestine, (faecal obstruction) or the liver (cirrhosis). The most common form of cystic fibrosis is related to the respiratory system, digestive problems, (steatorrhoea and/or constipation) and anomalies of the statural growth. The mortality and morbidity depends on the severity of the broncho-pulmonary involvement.

Cystic fibrosis is characterised by mutations of the CFTR protein gene ((Cystic Fibrosis Transmembrane Conductance Regulator) (Chromosome 7)) which plays a role in the regulation of the hydroelectric transmembranous flow. The absence of the functional membrane protein CFTR at the epithelial cell membrane, causes the production of high salt content sweat (associated with the risk of hypotonic dehydration) and of mucous secretions with abnormal viscosity which causes stasis, obstruction and infection in the bronchi. More than 1,250 mutations have been identified. Some 70% of cases are caused by the F508 allele, while another 30 mutations explain 20% of cases. There is not a clear correlation between the genotype and the phenotype. As well as allelic heterogeneity and the occurrence of multiple mutations of the same gene, a wide range of factors can influence the phenotype, including environmental factors and the genetic modifications during the illness. If cystic fibrosis is suspected, the results of a sweat test (concentration of excessive chloride above 60 mmol/L) can help formalise a diagnosis which is only confirmed by the identification
of a CFTR gene mutation. The neonatal diagnosis is carried out by screening, a process which has been available since the end of 2002. It has enabled the diagnosis of 95% of cases specifically for the DF508 mutation; the prenatal diagnosis is possible in 70% of cases. In some occasions, the diagnosis of cystic fibrosis via blood can be difficult, especially if the specific family mutation is unknown. For all newborns with intestinal obstructive syndrome, a repeated sweat test should be included to quantitatively measure the chloride for the diagnosis of cystic fibrosis.

If an intestinal atresia is suspected, investigations should include the following: morphological ultrasound to rule out other VACTER structural anomalies and flow regression to establish the level of the lesion, echocardiography, karyotype, chorionic villous sampling or amniocentesis to detect cystic fibrosis and screening for congenital infections (most importantly cytomegalovirus and parvovirus B19). Magnetic resonance imaging (MRI) can complement ultrasound scans in the diagnosis of other malformations and of the obstruction level (10-12). It is also necessary to consult a paediatric surgeon. These types of anomalies require a multidisciplinary approach in order to establish a prognosis and plan the perinatal management.

The following is carried out via a biophysical profile; Doppler ultrasound and cardiotocography (CTG) every 2-4 weeks if the amniotic fluid index (AFI) is normal and weekly if polyhydramnios is present. Transvaginal ultrasound is carried out due to the risk of a premature birth if polyhydramnios exists, AFI monitoring, detecting complications and to assess prognosis.

Prenatal diagnoses differ from postnatal ones, not only with regard to lower mortality rates, but also in reducing morbidity and improving prognoses (13). Amongst the strictly intestinal causes of obstruction in the newborn, it is necessary to highlight the seriousness of midgut volvulus and meconium peritonitis (15).

Higher frequency of nosocomial infection is another association of this pathology. This can be related to the intestinal lesion itself, the need for surgery and central venous access, prolonged parenteral feeding, the use of antibiotics and the underdeveloped immunity of newborns, especially if they are born premature.

A favourable prognosis should be expected now, even in premature pregnancies with uncomplicated intestinal obstruction or with simple meconium peritonitis, as the rate of complications is low (16). One of the prognostic factors that can help indicate a successful neonatal surgical outcome is the weight of the newborn (13, 17). An amnioreduction in cases of polyhydramnios can be useful in preventing prematurity. In cases where massive fetal ascites exist, an elevated diaphragm can cause pulmonary hypoplasia, which is associated with postnatal respiratory failure (18) and an elevated risk of developing hydrops. In these cases a paracentesis can lower the morbidity and mortality rates, as well as averting abdominal dystocia at birth. If signs of complicated meconium peritonitis exist (intestinal fluid and large dilatations, a large meconium cyst, massive ascites and fetal deterioration) or there are signs of perforation/ neonatal sepsis, immediate surgery is necessary. It will consist of an intestinal resection of the affected segment and a primary end to end anastomosis (11,19,20).

The birth should take place in a tertiary care hospital, by vaginal delivery and at term if there are no contraindications for this (21).

**Case report**

We present a pregnant mother of 29 years of age with the following history. Current pregnancy: uncomplicated. HIV, syphilis and hepatitis B serology of the first three months are negative, shows rubella immunity. The combined triple screening for aneuploidy (in the first 12 weeks) was low risk. The morphological ultrasound scan at 20 weeks did not present any pathological findings. Obstetric: gravida three, parity two. First pregnancy; spontaneous vaginal delivery (now a healthy girl of 10 years, father a different partner from a previous relationship). Second pregnancy; resulted in termination in the first 12 weeks. Past medical: herniated disc (C5-C6 level), no reference to surgical interventions. Her blood group is 0, Rh positive. Drug: she does not take any regular medications and has no known allergies. Social: smoker of 8-10 cigarettes per day throughout the pregnancy. Family: type 2 diabetic mother, father and brothers fit and well. There are no known family antecedents with cystic fibrosis. No links of consanguinity with her current partner.

The pregnancy continued with a normal evolutionary course until 32+4 weeks, when dilatation and intestinal fluids were detected on ultrasound. There was a maximum intestinal cross diameter of 19.9mm, interior meconium content, increased wall density (1.8mm) and with signs of ascites without abdominal calcifications. The estimated fetal weight is
situated on the 13th percentile and the amniotic fluid index at 24.7. There is a clinical suspicion of intestinal obstruction, which can be made as a prenatal diagnosis. At 33+4 weeks, the valuation in the consultation confirms the findings (of intestinal obstruction) and mild ascites can now be seen too. The rest of the morphological ultrasound, including the neurosonography and echocardiography was normal. The estimated fetal weight was on the 23rd percentile and the maximum vertical column length was 8.5cm. Amniocentesis was offered to test for cystic fibrosis, infections and to do karyotyping, but the patient declined the offer of a test. A further check at 34+6 weeks showed persisting dilatation of the bowel loops, maximum vertical column length at 7cm and an estimated fetal weight of 2,500g. An appointment for an assessment with the Paediatric Surgeon was made for a week’s time.

At 35+4 weeks the patient was admitted because of contractions and the baby was delivered by a caesarean section. This helped maintain fetal wellbeing and was deemed less risky compared to a vaginal delivery. The baby girl was born with a weight of 2.06kg, had an Apgar score of 9 and the pH of the umbilical artery 7.23. Initial respiration started spontaneously, but assistance with intermittent positive pressure ventilation (IPPV) with an inspired oxygen fraction (FiO2) of 30% was required. This had to be increased to 40% due to the compression of the thorax from abdominal distension. The neonate was taken into the neonatal intensive care unit.

The neonate had a very distended abdomen with a violet appearance. The following day an exploratory laparotomy was performed: blood and necrotic tissue was seen in the peritoneal cavity, a blockage was found in the mid gut which was adhering to the abdominal wall. An ileal volvulus was found which consequently devoluted. The proximal ileum was dilated, it had perforated and necrotic tissue was present. The distal ileum was shortened, it showed bleeding and a moudly internal content had formed, suggestive of complicated meconium ileus (volvulus and perforation). A 40cm resection of the medial ileum was performed. The distal ileum was washed out with double-distilled water. N-acetylcysteine therapy was used to extract the mouldy material from the intraluminal meconium. A defunctioning loop ileostomy was performed forming a stoma. Echocardiography was performed and no structural heart disease was detected, but a patent ductus arteriosus with left-right shunting and compression of the inferior vena cava was present. PCR testing did not detect the presence of cytomegalovirus (from a urine sample). Extended screening tests for common neonatal pathologies were all negative. A Grade 1 germinal matrix haemorrhage was detected on cranial ultrasound. CF screening was carried out by testing the blood for immunoreactive trypsin (IRT): IRT 1 151 ng/mL; IRT 2 159 ng/mL. These values were both higher than the normal range, suggestive of CF. The genetic study confirmed the diagnosis with CFTR gene mutations (R1066C/N1303K) detected. The results were provided by a specialist Cystic Fibrosis centre. Both of the parents were tested and both turned out to be carriers (mother N1303K and father R1066C).

The neonate needed total parenteral nutrition (TPN) from birth to prevent a significant decline in status, since increasing enteral nutrition (EN) flow to the stoma gradually is very important and initially there is virtually no absorption. Enteral nutrition (EN) was used to supplement maternal milk after the first five days of life. At 34 days of age it was noted she had poor weight gain and a high output from the ileostomy.
At the age of one year and nine months she was admitted for respiratory exacerbation of her cystic fibrosis. She was methicillin sensitive staphylococcus aureus positive and was treated with IV cloxacillin.

**Discussion**

Distal intestinal obstructive syndrome (DIOS) is one of the most frequent surgical pathologies in neonate. Prenatal diagnosis, though difficult to make and often late, can reduce morbidity and mortality. In this case a prenatal ultrasound scan, at 33 weeks, identified an intestinal obstruction. There were dilated bowel loops measuring 19mm, accompanied by an AFI above the normal limits (with a value of 23), a normal morphological ultrasound and a normal echocardiogram. Testing for congenital infections, cystic fibrosis from amniocentesis and karyotyping were not carried out, because the mother declined to have them.

Intestinal obstruction occurs with a classic triad of symptoms: vomiting, abdominal distension and the absence of meconium excretion. Abdominal distension is more apparent the lower the level of obstruction; large peristaltic waves can be visible on abdominal examination and it can be a cause of respiratory failure.

The two principal aetiologies to be considered in diagnosis, with regard to intestinal obstruction, are intestinal atresia and meconium ileus. At the same time, meconium ileus should be considered as a feature of cystic fibrosis. Intestinal atresia is the most common cause of intestinal obstruction in neonates with an incidence of 1/6,000 births. Ischemic injury can be caused by secondary volvulus, intussusception, strangulated hernia, meconium ileus, omphalocele etc. Given that intestinal content is sterile in the fetus, the aetiologies causing ischemic injury listed above, following perforation or not, will continue until the reabsorption of the ischemic segment (intestinal atresia).

Meconium peritonitis is a factor of a bad prognosis and can lead to an intestinal perforation of the small intestine, peritonitis and abdominal sepsis.

The prognosis of intestinal atresia depends on the underlying cause, the length of the remnant intestine, the level of the obstruction, the presence of meconium peritonitis, associated malformations and especially, the birth weight and prematurity.

In this case meconium ileus was identified through an exploratory laparotomy. The meconium ileus had perforated and was complicated by a...
volvulus. A resection of 40cm of the mid ileum was performed, as well as a wash out of the distal ileum in order to eliminate the impacted intraluminal meconium. A defunctioning loop ileostomy was carried out due to the discordance in joining the proximal and distal ends of the obstruction. The volvulus involved the rotation of the small intestine and the proximal part of the colon around the upper mesenteric artery causing intestinal ischemia (22). The problematic part of the treatment was the discordance in the size of the open intestinal ends and the loss of intestinal length. The solutions to these problems can be: resection of the dilated part of bowel, with a risk of developing short bowel syndrome; grafting of the dilated segment to diminish its size (difficult surgery, with high blood loss and risk of dehisced wounds), colostomy (in the dilated part) and stimulation (in the narrowed part). When the two ends become equal, an end to end anastomosis can be performed. A latero-lateral anastomosis should never be carried out in this instance.

Meconium ileus can cause an intestinal obstruction due to the intraluminal presence of an abnormally thick meconium. It appears in 7% of cases of newborns affected by cystic fibrosis (23), as demonstrated in this case. This case presents an example of a complicated meconium ileus, with a volvulus leading to intestinal necrosis and perforation, as well as peritonitis. Other possible complications of meconium ileus include a pseudocyst (necrotic intestine and meconium liquid), or singular or multiple intestinal atresia.

Surgical treatment is reserved for cases that develop complications, as in the case presented and when medical treatments have not been successful. It consists of an ileostomy to divert intestinal content and lavage with distilled water in order to unblock the distal intestine. In this case the washouts were carried out with double-distilled water and acetylcysteine.

Genetic counselling should be offered to couples with heterozygous mutations of the cystic fibrosis gene (identified by having family antecedents with the illness, after the detection at birth of the heterozygous mutation of the newborn or after the birth of the first baby with cystic fibrosis). Treatment for cystic fibrosis continues to be for symptomatic relief, through bronchial drainage of excessive mucus, antibiotics for respiratory infections, pancreatic analysis and through the administration of vitamins and calorific supplements for digestive and nutritional problems that occur. Treatment should involve the care of a multidisciplinary team with specialist input. These treatments, with a good cost-benefit relationship, significantly improve the prognosis of patients: in the 1960s, the majority of patients died before the age of five, while nowadays the average age of those with cystic fibrosis exceeds 35 years old and the average life expectancy is 40. The main prognostic factor in CF is the severity of lung disease, which in some cases requires lung transplantation.

**Ethics statement**

The study has been approved by a research ethics committee and there are no conflicts of interest to declare.

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**References**


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