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REVIEW

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Hyperechogenic fetal bowel: Current evidence-based prenatal diagnosis and management

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Abstract

Echogenic fetal bowel (EB) is a prenatal ultrasound finding (0.2%–1.4% of all pregnancies) defined as bowel of similar or greater echogenicity than surrounding bone. In fact, the ultrasound assessment is strongly subjective with inter-observer variability. The pathophysiology depends on the underlying condition, apparently related with meconium stasis and hypercellularity. It is often an isolated finding, with possible association with other structural anomalies. About the origin, it was observed in fetuses with cystic fibrosis, congenital infections, thalassemia, intraamniotic bleeding, fetal growth restriction. Fetuses with EB are at increased risk of adverse perinatal outcome, such as intrauterine growth restriction, placental dysfunction and perinatal death, highlighting the need for a thorough antenatal management and post-natal follow-up. It seems to be associated with a plenty of conditions, such as a poor fetal outcome, fetal growth restriction and placental dysfunction. Therefore management requires a multidisciplinary approach with different specialties' involvement and the prognosis is influenced by the underlying pathophysiology. In this complex scenario, the present review aims to define the clinical pathway which should be offered to pregnant women in case of finding of fetal EB ultrasound marker, to rule out any suspected pathological cause.

KEYWORDS
cystic fibrosis, echogenic bowel, fetal infection, prenatal screening, prognosis, ultrasonography

1 | INTRODUCTION

Echogenic fetal bowel is a prenatal ultrasound finding, where the echogenicity of the fetal bowel appears increased. This finding can be seen in 0.2%–1.4% of all pregnancies[1,2] examined in the second trimester, at the 18–20 weeks anatomy scan. Echogenic bowel seems to be associated with a plenty of conditions, such as a poor fetal outcome, fetal growth restriction, placental dysfunction and perinatal death in 16%–30% of cases.

It is part of the so-called soft markers of chromosomal abnormality, but can also be associated with other pathologic conditions. At the beginning it was considered as a different appearance of non-pathological condition, thereafter it was observed in fetuses with cystic fibrosis, congenital infections, thalassemia, intraamniotic bleeding,

fetal growth restriction (FGR). Echogenic bowel is often an isolated finding, even if in these fetuses has been found an increased incidence of structural anomalies, such as renal and cardiac anomalies as most frequent.[3–6]

1.1 | Definition

Most authors have defined hyperechogenicity as bowel of similar or greater echogenicity than surrounding bone. It has been described as focal, multifocal or diffuse finding. Single or multiple loops of bowel may be identified, and it may be noted to be solid intraluminal echogenicity or occasional echogenicity of the walls only (tram line).[2]

Echogenic bowel is not an easy find to describe and at the same time it is difficult to measure and quantify. Since the ultrasound assessment of echogenic bowel is strongly subjective, its detection is subject to significant inter-observer variability. The subjective assessment of fetal intestinal echogenicity varies between different sonographers, but can also vary between different evaluations of the same case by the same sonographer. The outcome of the ultrasound evaluation of the fetal intestine does not seem to be influenced by the experience of the sonographer.[4]

1.2 | US and grading system for diagnosis

Furthermore, a role in the diagnosis of hyperechoic intestine seems to be played by the frequency of the ultrasound transducer. Fetal bowel may show increased echogenicity, similar to bone, when a 6.5–8 MHz transducer is used, but appears normal in the same patients when a 5 MHz transducer is used. The higher frequency of the transducer may accentuate the echogenicity of the bowel wall.[7] The diagnosis should always be confirmed using a lower frequency transducer (<5 MHz) with harmonic imaging turned off and set at a lower gain.[8]

A ranking system for the fetal echogenic bowel was first proposed and developed by Slotnick and Abuhamad.[6] It is based on the rank of similarity in echogenicity of the bowel with the surrounding bone, as fetal iliac cresta. Some authors have defined grades of echogenicity with the most severe form (grade 3) bright as bone, while grade 1 or grade 2 are mildly or moderately echogenic, however the prognostic significance is unclear.[4] Echogenicity similar to or greater than bone is a subjective determination and therefore prone to inter-observer and intraobserver variability.

1.3 | Incidence

As previously explained, isolated report of echogenic bowel can be a transient or idiopathic finding in about 0.5% of all fetuses at second trimester scan, but it also can be associated with a number of pathologic conditions, such as cystic fibrosis, aneuploidy, congenital viral infection, gastrointestinal pathology, intraamniotic bleeding, and fetal growth restriction (FGR). Due to the small sample size studies available at the moment and the subjectivity in the ultrasound assessment and diagnosis, the incidence of each possible etiology varies.[8]

1.4 | Pathogenic mechanism and causes of echogenic bowel

The pathophysiology of echogenic bowel has still not fully been established and seems to depend on the underlying condition. There seems to be a double condition at the basis of the hyperechogenicity of fetal intestine: meconium stasis and hypercellular meconium.

The accumulation of meconium or meconium stasis can be linked to different underlying causes, as hypoperistalsis, distal obstruction, meconium ileus, fetal intestinal ischemia or perforation. Decreased levels of microvillar enzymes, as observed in abnormal karyotypes conditions, can lead to hypoperistalsis and reduce the passage of meconium.[3]

TORCH infections (toxoplasmosis, rubella cytomegalovirus, herpes simplex, and HIV) seems to act inducing a direct cytotoxic effect and ischemia of fetal bowel, ending in hypoperistalsis, ileus, intestine perforation.[9]

In fetuses with isolated idiopathic echogenic bowel, the primary mechanism is thought to be the accumulation of meconium.

Regarding the hypercellular meconium, it is associated with conditions that leads to abnormal consistency of the meconium as due to abnormal enzyme secretion, but is also associated with proximal bowel obstructions, intra-amniotic fluid bleeding or intrauterine transfusions.

Cystic fibrosis and its decreased pancreatic enzyme secretion causes a thickened and viscous meconium, with hypoperistalsis. Its abnormal consistency makes the bowel appear as increased in echogenicity, sometimes in association with calcifications and dilations.[1]

The risk for cystic fibrosis ranges from 0% to 13% in the presence of isolated echogenic bowel, but it increases up to 17% when associated with the finding of dilated loops of bowel.[8]

Gastrointestinal tract pathology, as proximal bowel obstruction, can hinder amniotic fluid swallowing, causing a reduction in fluid content of meconium, which leads to the formation of meconium plugs that appear as increased echogenicity.[10]

It has been observed idiopathic echogenic bowel developed after invasive procedures, such as intrauterine fetal transfusions or as a consequence to fetal swallowing of blood from the amniotic cavity, or amniocentesis, with an association with blood-tinged or dark fluid at the time of amniocentesis.[11]

Finally, echogenic bowel as isolated ultrasound finding can be associated with compromised placental perfusion and FGR. The background mechanism seems to be the blood flow redistribution away from the fetal intestine that results in areas of ischemia in the fetal bowel.[5]

To regard differential diagnosis, it is important to keep in mind all the possible causes of hyperechoic intestine, previously mentioned, so

as to direct the patient towards the most appropriate diagnostic pathway.

1.5 | Obstetric management

In cases of suspected underlying pathologies, management of the echogenic bowel requires a multidisciplinary approach with the involvement of the following specialties:

- Maternal-fetal medicine
- Neonatology
- Pediatric surgery
- Clinical genetics
- Radiology
- Pediatric gastroenterology
- Pediatric infectious disease

Detailed ultrasound assessment should be performed in order to look for additional markers of aneuploidies and invasive procedures offered in case of associated markers on ultrasound or abnormal screening test results. Maternal serological assessment for congenital infection and cystic fibrosis should be performed in order to stratify the risk of these anomalies. Finally, longitudinal assessment during pregnancy and after birth is warranted in order to detect FGR and associated anomalies, mainly gastro-intestinal which can be detected only later on in pregnancy or after birth.

For pregnant women who has not previously been screened for aneuploidy, with isolated finding of echogenic bowel, is recommended counseling to evaluate the risk of trisomy 21 and options for noninvasive aneuploidy screening should be discussed.[12] Otherwise, for pregnant women with negative screening test and isolated fetal echogenic bowel, no further evaluation for aneuploidy is required.[8]

Regarding risk of correlation of iperechoic bowel and cystic fibrosis, if not previously studied, parental carrier status should be determined. If it results in both parent carriers, genetic counseling should be taken, due to discuss risks and benefits of invasive testing for fetal genotyping.

Cytomegalovirus (CMV) infection is the most commonly observed, but toxoplasmosis, rubella, herpes, varicella, and parvovirus have been reported too. The incidence of congenital infection in fetuses with echogenic bowel is 2%–4%, but rates up to 10% have been reported.[13]

Titer of Cytomegalovirus immunoglobulins (IgG and IgM) should be dosed, with IgG avidity test when available. Amniocentesis as confirmatory test should be evaluated when test results suggest a primary Cytomegalovirus infection. Amniocentesis with CMV-DNA PCR should be considered after 21 pregnancy weeks and after 6 weeks from infection.[14–18]

Routine tests for other infections, as varicella, herpes, parvovirus, or toxoplasmosis should be considered according to the clinical signs, potential exposure or other risk factors.

In conclusion, since isolated echogenic bowel is associated with FGR, a third-trimester ultrasound examination for reassessment and evaluation of fetal growth should be assessed and recommended for all fetuses with this ultrasound finding.[5] Pediatrics at birth should be informed of the prenatal finding of echogenic bowel so that appropriate neonatal evaluation and diagnostic path can be followed.[8] Figures 1 and 2 show a diagnostic flowchart in the assessment and

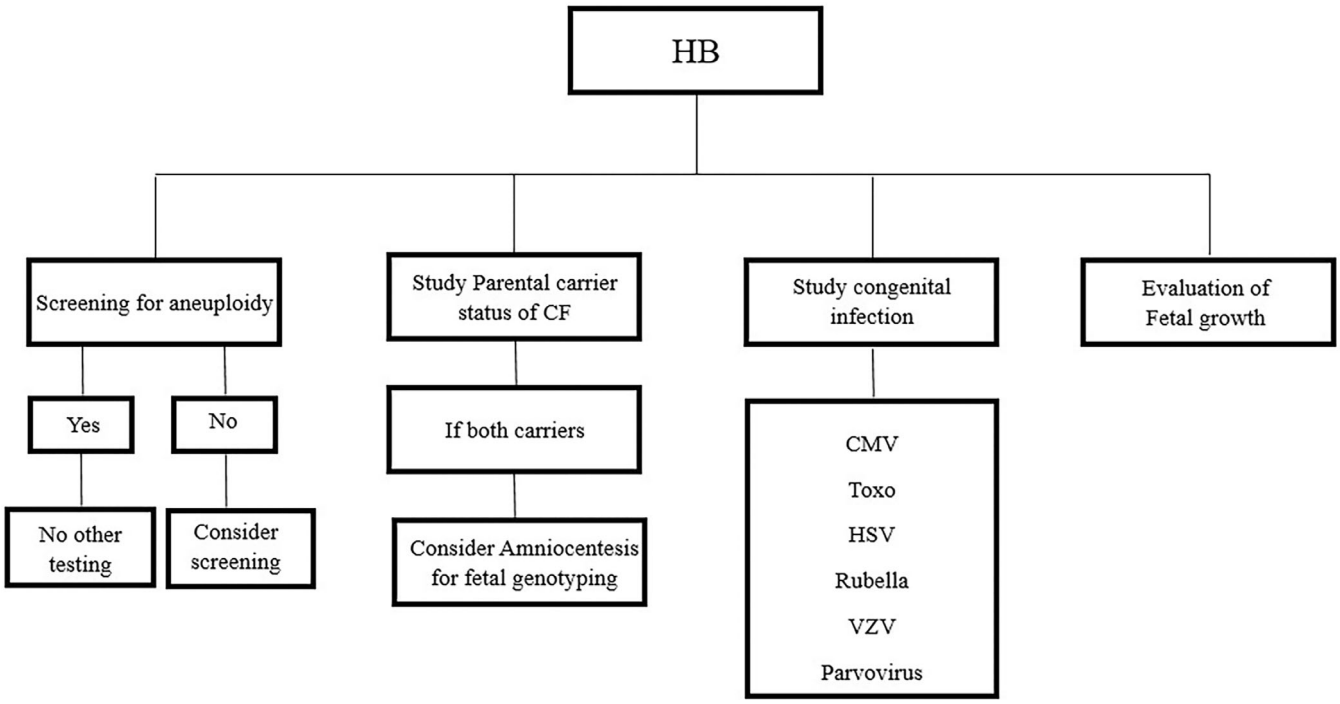

FIGURE 1 Diagnostic flowchart of the fetus with hyperechogenic bowel. CF, cystic fibrosis; CMV, Cytomegalovirus infection; HB, hyperechogenic bowel; HSV, herpes virus; Toxo, toxoplasma infection; VZV, varicella zoster virus.

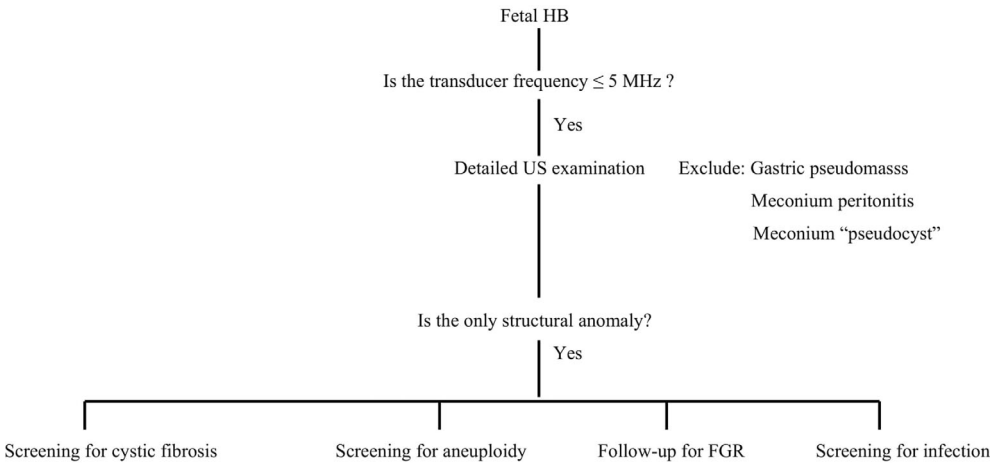

FIGURE 2 Immediate algorithm for prenatal management. FGR, fetal growth restriction; HB, hyperechogenic bowel; US, ultrasound.

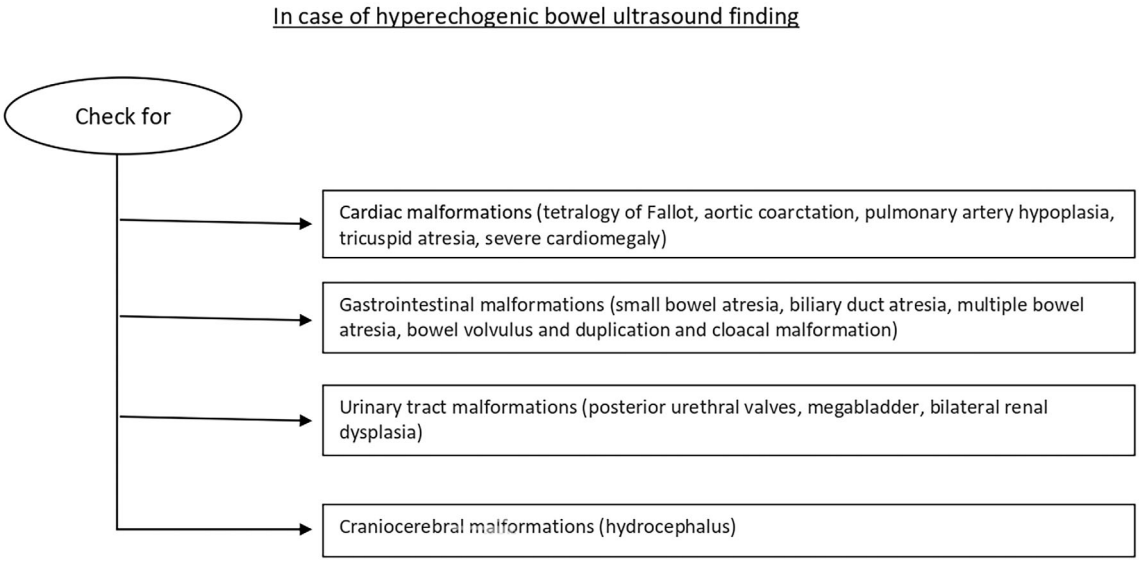

FIGURE 3 Flowchart for a systematic ultrasound scan in fetuses with hyperechogenic bowel.

diagnosis process of hyperechoic bowel. Figure 3 shows a systematic study of the fetal body when hyperechogenic bowel is present to look for associated malformations.

1.6 | Prognosis

The prognosis of echogenic bowel is influenced by the underlying pathophysiology. When isolated, it seems to be associated with normal postnatal outcomes, representing a benign finding. Nevertheless, the finding of echogenic bowel on second-trimester scan, even when isolated, is associated with an increased risk for both fetal growth restriction (FGR) and intrauterine fetal demise. Some studies show a twofold increase in FGR in these patients, both when isolated finding or with associated anomalies, and this risk seems to be independent of karyotypic abnormalities or previous diagnosis of congenital infections.[5]

Different outcomes can take place when fetal echogenic bowel is associated with other ultrasonographic markers of pregnancy complications. For example, when associated with other anomalies such as intrauterine growth restriction, elevated maternal levels of alpha-fetoprotein (AFP) or a worsening in grade of bowel echogenicity during pregnancy, it may be associated with worse outcomes. This condition can be seen after intra-amniotic bleeding and may be a sign of the maternal–placental barrier alteration and dysfunction. Echogenic bowel can be associated with bowel dilatation. This condition is often predictive of bowel obstruction, usually requiring surgery after birth. However surgical outcomes are good. The finding of echogenic foci in the abdomen has little postnatal significance.[19–21]

Finally, regarding the association between hyperechoic intestine and cystic fibrosis or aneuploidy, the degree of echogenicity appears to play a role. Intestinal echogenic grades 2 and 3 (according to Slotnick et al. classification) is associated with a high positive rate of parental carrier testing for cystic fibrosis (CF) and amniocentesis.[6]

1.7 | Association with other malformations

As already mentioned, the finding of echogenic bowel may represent an isolated finding, though several studies underline the possible association with malformations of other body districts. For this reason, the finding of fetal echogenic bowel should always be followed by a careful examination through prenatal ultrasound of other fetal districts.

The most common finding is usually cardiovascular anomalies, followed by urinary tract, craniocerebral and gastrointestinal malformations.[22,23] Cardiac malformation usually found in association with echogenic bowel are: tetralogy of Fallot, aortic coarctation, pulmonary artery hypoplasia, tricuspid atresia, severe cardiomegaly. Among gastrointestinal malformations, small bowel atresia, biliary duct atresia, multiple bowel atresia, bowel volvulus and duplication and cloacal malformation appeared to be the most observed. Urinary tract malformations usually regard posterior urethral valves, megabladder associated with bilateral renal dysplasia. Finally hydrocephalus among craniocerebral malformations.[23] The association between echogenic bowel and other malformation is stronger in patients with diagnosed chromosomal abnormality. Furthermore the combined malformation rate is high in fetuses with echogenic bowel.[22]

2 | GENETIC DISORDERS

2.1 | Chromosomal anomalies

In literature the estimated incidence of karyotype disorders among fetuses with isolated hyperechogenic bowel is about 3%–5% and it could be the only finding in a quarter of cases.[24-26]

Moreover, the incidence rate of chromosomal disorders could rise up in case of association with major abnormalities, while remains almost the same if the ultrasound marker of hyperechogenic bowel is associated with other soft markers.[27]

Among the aneuploidies, hyperechogenic bowel could be related to trisomy 13, trisomy 18, monosomy X, Klinefelter's syndrome, chromosomal mosaicism trisomy, but trisomy 21 is the most common.[28–32]

Literature data about chromosomal microarray analysis (CMA) anomalies are contrasting: Singer et al.[33] did not report an increased risk of anomalies in CMA, compared to the general population. On the contrary, in 2021 Fan et al. carried out a retrospective study collecting 147 pregnant women with fetal hyperechogenic bowel and performing prenatal invasive diagnosis with CMA. Thirteen Copy Number Variations (CNVs) were identified, including four fetuses with aneuploidies and nine fetuses with normal karyotype. Of these nine fetuses, in six cases CMA identified variants of uncertain significance (VOUS), and in the other cases pathological CNVs were diagnosed, related to the development of neurological and mental disorders and Hirschsprung's disease. The use of CMA in addition to karyotype plays an important role in the improvement of genetic prenatal diagnosis, although CMA could often find VOUS, but anyway both VOUS and pathological CNVs could present several manifestations among family members, ranging from completely normal phenotypes to full-blown disease.[34]

In conclusion, the importance of CMA for prenatal diagnosis in fetal hyperechogenic bowel is still debated, and its use it is not mandatory.

3 | NON-CHROMOSOMAL ABNORMALITIES

3.1 | Cystic fibrosis

Cystic fibrosis (CF) is the most common autosomal recessive diseases in Caucasians, since approximately one individual in 30 is a CF carrier, with several regional variations.[35] Overall, CF was reported in 2.5%–13% of cases of fetal hyperechogenic bowel,[11,35] since the ultrasound finding is related to meconium ileus, and the risk of CF increases if fetal gallbladder is not visible. Therefore the parents should be informed about this risk of CF and should be able to choose parental testing for cystic fibrosis carrier status, which allows diagnosing approximately 80%–90% of cystic fibrosis carriers. In case of positive test, amniocentesis could be performed for DNA analysis to assess whether the fetus is affected (1 in 4 risk).[36,37]

In a prospective study by De Becdelievre et al.[38] were collected 694 cases of fetal bowel anomalies, including hyperechogenic bowel, in an 18 years period. CF transmembrane conductance regulator (CFTR) gene analysis was performed, including both frequent and rare mutations. According to their results, an isolated hyperechogenic bowel showed a sensitivity of 26.7% and a specificity of 35.9% in detecting fetuses affected by cystic fibrosis. Such data seem higher than the risk of cystic fibrosis previously reported by Muller et al.[39] due to the more accurate CFTR analysis performed in the second study.

Nevertheless the diagnosis of CF among fetuses presenting fetal bowel anomalies still remains challenging, due to the huge number of CFTR gene mutations, and this is the reason why performing exhaustive CFTR study in all patients is always indicated.[40,41]

4 | OTHERS

4.1 | Zellweger syndrome

A series of case report analyzes the association between hyperechogenic bowel and Zellweger syndrome (ZS), which is a peroxisomal disorders characterized by craniofacial dysmorphism and severe neurological diseases. In fact, ultrasound hyperechogenic bowel finding seems to be related to hypotonia and poor bowel motility, resulting in dehydrated meconium. Prenatal diagnosis of ZS is performed through chorionic villus sampling or amniocentesis, looking for specific enzymes. ZS usually leads to death in few month after birth.[42]

4.2 | IPEX syndrome

Two cases in literature[43] are reported about the diagnosis of Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked

(IPEX) syndrome in fetuses with echogenic bowel. IPEX syndrome is a rare, X- linked recessive syndrome, caused by the dysregulation of immune regulatory T cells (Tregs), which is related to pathogenic alterations in the gene FOXP3 (Xp11.23), implicated in the proper cellular differentiation of Tregs. Ultrasound prenatal findings are fetal hyperechogenic bowel in association with echogenic debris, scalp edema, and hydrops or polyhydramnios with echogenic debris and prominent fluid-filled loops of bowel.

4.3 | Postnatal management

The association of gastrointestinal anomalies and other comorbidities in infants with a diagnosis of fetal echogenic bowel highlights the need to be referred to a center with a higher neonatal intensive care unit with pediatric subspecialties services. Postnatally, a thorough clinical examination of the infant must be performed. Abdominal X-RAY, UGI series, barium, or gastrograffin edema may be required to evaluate for intestinal obstruction.[44]

5 | CONCLUSION

Fetuses with EB are at increased risk of adverse perinatal outcome, highlighting the need for a thorough antenatal management and post-natal follow-up. Detailed ultrasound assessment should be performed in order to look for additional markers of aneuploidies and invasive procedures offered in case of associated markers on ultrasound or abnormal screening test results. Maternal serological assessment for congenital infection and cystic fibrosis should be performed in order to stratify the risk of these anomalies. Finally, longitudinal assessment during pregnancy and after birth is warranted in order to detect FGR and associated anomalies, mainly gastro-intestinal which can be detected only later on in pregnancy or after birth.

AUTHOR CONTRIBUTIONS

Conceptualization: Flaminia Vena. Methodology: Adele Vasta and Elena D'Alberti. Validation: Flaminia Vena, Antonella Giancotti, Valentina D'Ambrosio, and Daniele Di Mascio. Formal analysis, investigation: Flaminia Vena. Resources: Adele Vasta and Elena D'Alberti. Data curation: Adele Vasta, Elena D'Alberti, and Fabrizio Signore. Writing: Flaminia Vena, Martina Bartolone, and Alessandra Mazza. Original draft preparation: Flaminia Vena, Martina Bartolone, and Alessandra Mazza. Writing – review & editing: Martina Bartolone and Alessandra Mazza. Visualization: Adele Vasta and Elena D'Alberti. Supervision: Antonella Giancotti, Valentina D'Ambrosio, Daniele Di Mascio, Antonio Pizzuti, and Fabrizio Signore.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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