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Association of Hyperechoic Fetal Bowel with Covid-19 Infec-tion in Pregnancy: A Prospective Cohort Study

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Abstract

Objective : The goal of the study is to assess the potential correlation between maternal Sars-cov-2 infection , detected three months before the second trimester anomaly scan, and fetal iperecogenicity in order to determine whether or not this could be considered a predictive factor for maternal-fetal complications.

Subjects and Methods: The study included 48 pregnant women who did not have any clear maternal or fetal problems. These individuals had an anomaly scan in the second trimester, as well as amniocentesis and fetal cariotyping, and then RT-PCR testing on their placental tissue after birth to rule out transplacental transmission.

Results: There have been no reports of fetal abnormalities via amniocentesis or fetal cariotyping. The patients experienced a high rate of spontaneous births (83%). Fetal development problems (2%) and premature delivery (4%) were uncommon, although pla-cental swabs revealed a possibility of viral transmission across the placenta itself.

Conclusions: To the best of our knowledge, this is the first observational study to show that detecting isolated intestinal hyperechogenicity during an abnormality scan in fetuses of women infected with Sars-Cov-2 in the previous three months does not appear to be a predictor of poor maternal-fetal outcomes, but may be linked to transplacental virus transmission.

Keywords: Hyperechoic Fetal Bowel, Sars-Cov-2, Anomaly Scan, Transplacental Trasmission

Introduction

Severe acute respiratory syndrome Coronavirus-2 (Sars-Cov-2) is a member of Human Coronaviruses (HCoV), a heterogeneous group of viruses able to infect humans with airborne transmission [1]. Covid-19 pneumonia was first reported in December 2019 in Wuhan, a province of China [2]. On 30th of January 2020, the World Health Organiza-tion (WHO) declared Covid epidemic to be a public health emergency of international relevance. Due to the physio-logical immunosuppression occurring in pregnancy, a higher risk of viral infection could occurr [3,4]. After Covid-19 infection, while pregnant women are less frequently affected by respiratory symptoms and fever, they are more like-ly to be admitted to intensive care (11%) or need invasive ventilation, with a maternal mortality rate of approxi-mately 0.8% [5-7]. Some risk factors appear to increase morbidity in pregnancy, such as obesity (BMI > 35 kg/m2), asthma and cardiovascular disease [8]. Covid-19 infection was associated with a higher rate of preterm delivery, pre-eclampsia, caesarean section and perinatal mortality [9]. Furthermore, the risk of vertical transmission to fetus is possible since the Angiotensin-Converting Enzyme 2 (ACE2) receptor – the main viral entry door to the cells of hu-man body – is widely expressed in placental syncytiotrophoblast [10]. This idea has been reinforced by the observed higher incidence of symptoms of decidual arteriopathy in pregnant women with SARS-CoV-2 infection, indicating a possible link between infection and altered placental function. The potential mechanisms responsible for the in-creased risk of fetal death in pregnancy may be primarily explained by a secondary effect of the virus resulting from placental hypoperfusion caused by the mother's compromised hemodynamic status, as viremia in patients with SARS-CoV-2 infection is uncommon, making direct virus damage to the placenta unlikely. An alternate possibility might be that the virus induces an increase in proinflammatory mediators. SARS-CoV-2 infection triggers a strong inflammatory response,

resulting in the production of a high number of proinflammatory cytokines, characterized as a "cytokine storm." The host immune response to the SARS-CoV-2 virus is overactive, resulting in an exaggerated inflammatory response. In this case, inflammation may cause plaque destruction and, as a result, histopathologic abnormalities associated with inflammation. Furthermore, the proinflammatory impact of the infection may be driven by a down-regulation of the renin-angiotensin system (RAS) caused by the virus attaching to the ACE2 recep-tor. Consequently, the decreasing level of the Renin-Angiotensin System (RAS) induced by the binding of the virus to the ACE2 receptors is involved in balancing the uteroplacental blood flow through the alternating pathways of vasodilation and vasoconstriction, resulting in a more plausible condition of placental ischemia.

Hyperechogenicity of the fetal bowel, first described in 1985, belongs to the so-called "soft markers", a term which collects together ultrasound findings in order to use them for the screening and care of pregnant women [11-14]. It has been defined as bowel able to gain similar or greater echogenicity than adjacent bone (iliac crest). The detection of this ultrasound feature covers 0-6 to 1-4% of all second trimester fetuses, given by the brightness of the meconium which is stored inside the intestinal lumen from about 16 weeks gestation. Usually, this singular aspect is transient and disappears without any long-term consequence. However, the persistency of the intestinal hyperchogenicity was proved to be possibly linked to a higher incidence of pathologic outcomes. Placental dysfunction has been asso-ciated with intrauterine gut ischemia and the following bowel hyperechogenicity [15-17].

In a recent research, the presence of three or more soft markers was connected to significant fetal abnormalities or early IUGR, with a death risk of almost 80% [17]. The majority of patients with isolated FEB had a positive outcome, with just 6.7% having underlying illness.

Hyperechogenic bowel may occur as a result of hypoperistalsis and/or reduced fluid content in the meconium, kary-otype abnormalities, mechanical proximal bowel blockage, or Cystic Fibrosis. Furthermore, placental disruption, one of the primary pathophysiological mechanisms of star cov2 infection during pregnancy, has been linked to intrauter-ine gut ischaemia, bowel hyperechogenicity, and poor newborn function. The following are the causes of echogenic bowel: Fetal aneuploidy, including Trisomy 21 (less frequently Trisomy 18 or 13), Turner's syndrome, and triploidy where the reason of echogenic bowel might be reduced intestinal motility along with increased water absorption from the meconium; small bowel blockage proximally, particularly duodenal atresia, might cause hyperechogenic bowel by reducing meconium fluid content ; Oligohydramnios ; Hirschsprung's disease (which occurs more fre-quently in Down syndrome pregnancies); Bowel atresia where echogenic bowel is hypothesized to be caused by a reduction in the amniotic fluid content of the meconium; IUGR; Cystic Fibrosis and congenital infections (CMV, Toxoplasmosi, Parvovirus).

Considering that covid-19 was found associated with placenta-related pregnancy complications, we hypothesized that the hyperechogenicity of the fetal bowel could be linked to a Sars-Cov-2 infection of the mother in the previous three months from the anomaly scan we performed.

Materials and Methods

Our prospective cohort study comprised 96 pregnant women from January 2022 to January 2023. The study was au-thorized by the Institutional Review Boards (IRB) (protocol number CD-32/2022). Every woman provided written approval after being informed. Good Clinical Practice Guidelines were followed throughout the research's execution. The clinical investigation was carried out as a multicentric prospective study at Sandro Pertini Hospital (Rome) and Maternal and Infant department of San Camillo De Lellis Hospital (Rieti).

We enrolled 48 pregnant women with documented Sars-Cov-2 infection in the previous three months from the anomaly scan coupled with a control group of the same number of women who had a normal pregnancy and no Sars-Cov-2 infection at the time of enrollment.

Gestational age was calculated from the date of the last menstrual period and confirmed at the first trimester scan. All pregnancies were uncomplicated, without any maternal or fetal anomalies. Abnormal karyotype or positive screening for Down Syndrome (ie. combined test, free cell DNA) were excluded. A detailed familial history was ac-quired in order to rule out the risk for cystic fibrosis. Every pregnant woman with Sars-Cov-2 infection underwent a placental swab which was taken in order to investigate and clarify a possible transplacental transmission that might highlight the pathogenic power provided by virus particles passing through the placental membranes

Real-time polymerase chain reaction (RT-PCR) testing was performed on 48 placental tissues. PowerChek PCR real-time kit (South Korea) with two target genes (E gene and Rd Rp gene) and was used to test all samples. Positive samples had risen as cycle 22–32.

During the anomaly scan, we excluded pregnancies with procedures dealing with medically assisted procreation, being affected from other infectious diseases and the evidence of intestinal hyperechogenicity in the first trimester of pregnancy.

Each ultrasound examination was performed by experienced and qualified sonographers (V. S., P. C., F. B.). All women were evaluated by the same examiner using a Voluson E8 system device (GE Healthcare, Zipf, Austria) with a RAB 4-8-D transabdominal probe (2 to 8 mHz). The ultrasound study was performed in order to evaluate every anatomical district according to the Italian Society of Obstetric and Gynecological Ultrasound (SIEOG).

In order to minimize observers' variability of hyperechoic bowel, we used the scale proposed by Slotnick et al [18]: grade
0 = normal
Grade 1 = increased echogenicity, but less echogenic than bone
Grade 2 = echogenicity equal to bone
Grade 3 = echogenicity greater than bone
When hyperechogenic bowel was suspected, we set gain lower in order to mini-mize false positive diagnosis of hyperechogenic bowel.

When hyperechogenic bowel was suspected, we set gain lower in order to minimize false positive diagnosis of hy-perechogenic bowel. Every woman with ultrasound confirmed hyperechogenic bowel and increased wall thickness together with enlarged bowel lumen underwent amniocentesis for the screening of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene and fetal karyotyping. Quantitative Polymerase Chain Reaction (qPCR) were available after 48 hours to rule out major trisomies. Giving the geographical distribution of our study population – Italian population – we performed the screening upon thirty mutations through PCR technologies.

These procedures were performed only under a valid medical indication (Prudent Use in Pregnancy) and using the lowest possible ultrasound exposure to gain the necessary diagnostic information following the ALARA principle ("As Low as Reasonably Achievable").

A written informed consent was obtained from every woman. Using Fisher's exact test, we determined the statistical significance of each event based on its incidence. For each comparison, an odds ratio (OR) and 95% confidence inter-val (CI) were generated. To evaluate whether data were sampled from a Gaussian distribution, normality tests (D'Agostino and Pearson tests) were used. To compare continuous parametric and non-parametric variables (data that do not fall into a normal distribution), the t-test and Mann–Whitney U test were employed, respectively. The Spearman rank coefficient was used to calculate correlations between numerical parameters. All analyses were car-ried out with the Statistical Package for the Social Sciences (SPSS) 22.0 for Mac (SSPS, Chicago, IL, USA).

Results

During the study period, a total of 48 women women with documented Sars-Cov-2 infection in the previous three months from the second trimester screening scan, presenting Fetal Echogenic Bowel (FEB), were analyzed in com-parison to the control group of the same number of women in which no Sars-Cov2 infection was observed and no fetal echogenic bowel was detected. Baseline characteristics of the study populations are reported in Table I and Ta-ble II. Among the study populations, neither abnormal karyotype nor mutation of CFTR gene were found by amnio-centesis.

The first group had a mean mother age of 26.34 ± 8.21, a BMI of 24.18 ± 5.12, and no prior pregnancies. The average weight change during pregnancy was 11.88±5.45, and the average gestational age at birth was 40 weeks. In the other group, the average mother's age was 25.31 ± 7.11, her average BMI was 22.18 ± 5.22, and she had no prior pregnancy history. 39 weeks was the mean gestational age at delivery, and the mean weight change during pregnancy was 9.28±4.25. Regarding maternal-fetal outcomes of the population with Sars-cov-2 infection, vaginal delivery without complications was the mostly represented (83%), while just one case of obstetric anal tear of 3rd/4th degree and two cases of instrumental delivery were observed. Cesarean sections accounted for just 16% of all births. The same per-centage was represented by labor inductions, which lasted 9.34 hours (stage 1) and 1.44 hours (stage 2). The patients typically underwent epidural anesthesia (91%), and the average birth weight was 3447 grams, with a mean hospital stay of 2 days. In the control group, the most common type of birth was vaginal delivery (87%) with a high percentage (40%) of intact perineum. No incidence of obstetric anal tear of the third or fourth degree and two occur-rences of instrumental delivery were recorded. Less than nine percent of deliveries were cesarean sections. Stage 1 and Stage 2 labor inductions lasted 8.32 and 1.27 hours, respectively. Eighty-seven percent of the patients underwent epidural anesthesia. The average birth weight of the patients was 3567 grams, and their usual hospital stay was two days. After the deliveries, as shown in table III, 48 placental tissues of the women with Sars-Cov-2 infection were tested using real-time polymerase chain reaction (RT-PCR). All samples were tested using a PowerChek PCR real-time kit (South Korea) with two target genes (E gene and Rd Rp gene). Five samples from the initial PowerChek RT-PCR kit were positive for a single gene (10.4%), and one sample was positive for both genes (2%).

FETAL ECHOGENIC BOWEL

Table1: Clinical and demographic characteristics in 48 patients with Sars-Cov-2 infection and FEB

Variables	n
Age, y (mean ± SD)	26.34 ± 8.21
BMI (mean ± SD)	24.18 ± 5.12
Parity (median)	0 (0-2)
Smoke (%)	4 (8.3)
Weight changes in pregnancy (kg), (mean ± SD)	11.88±5.45
Gestational age at FEB	21 (20-23)
Abnormal NIPT (%)	0 (0)
Amniocentesis alterations (%)	0 (0)
Gestational age at delivery (weeks), (range)	40 (37-40)
Type of Delivery Vaginal Delivery (%) Cesarean Section (%)	 40 (83.3) 8 (16.6)
Induction of labor (%) Instrumental delivery (%) Obstetric anal tear 3 rd - 4 th degree (%) Episiotomy (%) Intact perineum (%) Epidural anesthesia in vaginal delivery (%) Length of 1 stage of labor in hh:mm (mean ± SD) Length of 2 stage of labor in hh:mm (mean ± SD)	8 (16.6) 2 (4.2) 1 (2.1) 5 (10.4) 14 (29.2) 44 (91.6) 9:34 (3:52-22:53) 1:44 (0:37-2:61)
Birth weight (g), (mean ± SD)	3447.53±487.21
Length of stay in hospital, days (median)	2 (2-3)
Aneuploidy (%) Genetic abnormalities (%) Malformative syndrom (%) Congenital infection (%) Cystic fibrosis (%) Intestinal abnormalities (%) Small bowel atresia (%) Meconium peritonitis(%) FGR (%) Preterm Delivery (%)	0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 1 (2.1) 2 (4.2)

Table2: Clinical and demographic characteristics in 48 patients with healthy pregnancies and no Sars-Cov-2 infection (control group)

Variables	n
Age, y (mean ± SD)	25.31 ± 7.11
BMI (mean ± SD)	22.18 ± 5.22
Parity (median)	0 (0-2)
Smoke (%)	2 (4.16)
Weight changes in pregnancy (kg), (mean ± SD)	9.28±4.25
Abnormal NIPT (%)	0 (0)
Gestational age at delivery (weeks), (range)	39 (38-40)
Type of Delivery Vaginal Delivery (%) Cesarean Section (%)	 42 (87.5) 4 (8.3)
Induction of labor (%) Instrumental delivery (%) Obstetric anal tear 3 rd - 4 th degree (%) Episiotomy (%) Intact perineum (%) Epidural anesthesia in vaginal delivery (%) Length of 1 stage of labor in hh:mm (mean ± SD) Length of 2 stage of labor in hh:mm (mean ± SD)	6 (12.5) 2 (4.16) 0 (0) 4 (8.3) 20 (41.6) 42 (87.5) 8:32 (3:36-20:29) 1:27 (0:48-2:13)

Birth weight (g), (mean ± SD)	3567.23±385.41
Length of stay in hospital, days (median)	2 (2-3)
Aneuploidy (%) Genetic abnormalities (%) Malformative syndrom (%) Congenital infection (%) Cystic fibrosis (%) Intestinal abnormalities (%) Small bowel atresia (%) Meconium peritonitis(%) FGR (%) Preterm Delivery (%)	0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0)

Abbreviation: SD: Standard Deviation; BMI: Body Mass Index

All patients referred had a control ultrasound scanning examination by two expert sonographers in order to define the grade and confirm the presence of hyperechogenicity. When the experts did not confirm the presence of FEB, the patients were excluded from the study. Fetal bowel was considered echogenic according to Slotnick's definition with grade 1 (more echogenic than liver but less than the bone), grade 2 (echogenicity similar with the adjacent bone) and grade 3 (echogenicity greater than adjacent bone). All grades of FEB were included.
Slotnick RN, Abuhamad AZ. Prognostic implications of fetal echogenic bowel. Lancet 1996;347:85–7.

Table 3: SARS-CoV-2 RT-PCR of placental tissue of the 48 patients with Sars-Cov-2 infection

Variables	n
Patient 1	Negative
Patient 2	Negative
Patient 3	Negative
Patient 4	Negative
Patient 5	E Positive
Patient 6	Negative
Patient 7	Negative
Patient 8	Negative
Patient 9	Negative
Patient 10	Negative
Patient 11	E Positive
Patient 12	Negative
Patient 13	Negative
Patient 14	Negative
Patient 15	Negative
Patient 16	Negative
Patient 17	Negative
Patient 18	Negative
Patient 19	Negative
Patient 20	E Positive
Patient 21	Negative
Patient 22	Negative
Patient 23	Negative
Patient 24	Negative
Patient 25	Negative
Patient 26	E Positive
Patient 27	Negative
Patient 28	Negative
Patient 29	Negative
Patient 30	Negative
Patient 31	Negative
Patient 32	Negative
Patient 33	E Positive
Patient 34	Negative
Patient 35	Negative
Patient 36	Negative
Patient 37	Negative
Patient 38	Negative
Patient 39	E Positive/Rd Rp Positive
Patient 40	Negative
Patient 41	Negative
Patient 42	Negative
Patient 43	Negative
Patient 44	Negative
Patient 45	Negative
Patient 46	Negative
Patient 47	Negative
Patient 48	Negative

Discussion

Several large population studies from North America showed that second trimester fetuses with hyperechogenic bowel reported no abnormalities after birth [19-22]. However, Nyberg et al. found isolated hyperechogenic bowel in 7% of second trimester fetuses with Down's syndrome [23]. Similarly, Scioscia et al. detected chromosomal abnor-malities in 27% of newborns with hyperechoic bowel while Bromley et al. identified fetal aneuploidy in 16% of the cases [20,24]. Moreover, hyperechoic bowel was frequently associated with Cystic Fibrosis: indeed, Dicke and Crane's review [19] reported four of 30 fetuses with hyperechoic bowel and positive Cystic Fibrosis testing; while Nyberg et al. were not able to detect any case of Cystic Fibrosis.

Fetal growth restriction and intrauterine fetal death were also observed in fetuses with isolated hyperechogenic bowel. In fact, Nyberg et al. reported fetal death in 6% of the analyzed cases, while Dicke and Crane reported a peri-natal death rate of 17% [16,19]. Furthermore, mechanical intestinal obstruction, intestinal atresia, volvulus and con-genital Cytomegalovirus (CMV) infection were also associated with fetal echogenic bowel [25-28].

In 1993, Nyberg et al. found a 6.5-fold higher risk of poor outcomes in 95 babies with echogenic bowel compared to 110 control fetuses [15]. When only solitary cases of echogenic bowel were included, the relative risk reduced to 4.9 but remained statistically significant. The previous research we cited have revealed a link between EB and other poor pregnancy outcomes. Gestational age at birth has been reported to be considerably lower and there is an ele-vated risk of SGA and intrauterine fetal death in pregnancies when EB is present. The mechanism behind the link between EB and these unfavorable pregnancy outcomes is unknown, however it may include vascular disturbance, resulting in intestinal hypoperfusion and ischaemia. Stillbirth, premature birth, and SGA have several causes. When combined with bowel dilatation, fetal echogenic bowel could be suggestive of meconium ileus or gut ischemia: in these cases, because of the hemodynamic redistribution, the subsequent gut vascular

damage is considered the main cause [29].

Sars Cov2 infection during pregnancy can occur in utero, but there is uncertain evidence about the occurrence and timing of vertical transmission in infected mothers, with a reported overall low percentage of vertical transmission rate (1-2%) [30]. The potential development of higher risk of fetal death in pregnancy could be due to either hy-poperfusion induced by the compromised hemodynamic status of the mother or increasing levels of proinflammato-ry cytokines induced by the virus itself [31].

SARS-CoV-2's cellular entrance is mediated by the spike protein. The interaction of the S protein to the cell surface receptor angiotensin-converting enzyme 2 (ACE2) reveals a cleavage site on the S protein. The transmembrane pro-tease serine 2 recognizes this cleavage site and proteolytically cleaves the S protein, causing fusion and endocytosis. Sarscov2 virus prefers to infect the outer layer of multinucleated cells that cover the chorionic villi and come into touch with maternal blood in the intravillus space. This is demonstrated by the presence of high levels of SARS-CoV-2 and the invasion of intervillous macrophages (intervillositis), which includes fibrin deposits and mononuclear cell infiltration of the intervillous space [32-34].

To our knowledge, this is the first paper describing Covid infection, in the previous three months from the first clinical evaluation, being associated with hyperechogenic bowel lately in the second trimester of pregnancy and with a possible transplacental transmission of the virus itself.

Despite fetal echogenic bowel has been often associated with chromosomal anomalies (Trisomy 21), congenital malformations (Oligohydramnios, Hirschsprung's disease and Bowel Atresia) or Cystic Fibrosis, the conditions were ruled out in our cohorts by amniocentesis for the screening of CFTR gene and fetal karyotyping.

Furthermore, we speculate that the relationship between Covid-19 and its effects on our study population was not associated with higher risks of perinatal death, preterm deliveries or growth retardation or other adverse maternal-fetal outcomes (in our series, only one case of fetal growth restriction was recorded).

In order to strengthen our hypothesis, the role of the different molecular variants of the Sars-Cov-2 virus and their possible influence on the first trimester of pregnancy still need to be deeply studied. Overall, we acknowledge that our study was largely limited by the small number of women collected, selective timing of ultrasound scan (second trimester screening), enrollment of only healthy pregnancy (except for Covid-19 infection in the three months be-fore the ultrasound scan), and lack of stratification for Covid-19 infection severity. Considering these limitations, further studies with larger samples of population are needed.

As previously reported from several studies about this topic, hyperechogenic bowel is usually associated with hypoperistalsis, decreased fluid content of the meconium, chromosomal abnormalities, Cystic Fibrosis, IUGR (IntraUterine Growth Restriction) or viral infections.

To the best of our knowledge, this is the first observational study to show that finding isolated intestinal hyperecho-genicity during an anomaly scan in fetuses of women infected with Sars-Cov-2 in the previous three months may indicate transplacental transmission but does not appear to be a prognostic factor for adverse maternal-fetal out-comes.

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