

PROFESSOR GIUSEPPE RIZZO (Orcid ID : 0000-0002-5525-4353)

DR ALEXANDER MAKATSARIYA (Orcid ID : 0000-0001-7415-4633)

Article type : Original Research Article

Effect of SARS-CoV-2 infection during the second half of pregnancy on fetal growth and hemodynamics: a prospective study

Giuseppe Rizzo^{1,2}, Ilenia Mappa¹, Pavjola Maqina¹, Victoria Bitsadze^{1,2}, Jamilya Khizroeva^{1,2}, Alexander Makatsarya², Francesco D'Antonio³

1: Division of Maternal Fetal Medicine, Ospedale Cristo Re, Università di Roma Tor Vergata, Rome, Italy

2: Department of Obstetrics and Gynecology, The First I.M. Sechenov Moscow State Medical University, Moscow, Russia

3: Department of Obstetrics and Gynecology, Università di Chieti, Chieti, Italy

Corresponding author

Giuseppe Rizzo

Università di Roma Tor Vergata, Division of Maternal Fetal Medicine, Ospedale Cristo Re, 00167 Rome, Italy

email: giuseppe.rizzo@uniroma2.it

<https://orcid.org/0000-0002-5525-4353>

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/AOGS.14130](https://doi.org/10.1111/AOGS.14130)

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Conflicts of interest:

None

ABSTRACT

Introduction: Our objective was to compare the fetal growth velocity and fetal haemodynamic in pregnancies complicated and in those not complicated by SARS-CoV-2 infection.

Material and methods. Prospective case-control study of consecutive pregnancies complicated by SARS-CoV-2 infection during the second half of pregnancy matched with unaffected women. Z-scores of head circumference, abdominal circumference, femur length and estimated fetal weight were compared between the 2 groups. Fetal growth was assessed analysing the growth velocity of head circumference, abdominal circumference, femur length and estimated fetal weight between the second and third trimester scan. Similarly, changes in the pulsatility index of uterine, umbilical, middle cerebral arteries and their ratios were compared between the two study groups.

Results: Forty-nine consecutive pregnancies complicated and 98 not complicated by SARS-CoV-2 infection were included. General baseline and pregnancy characteristics were similar between pregnant women with compared to those without SARS-CoV-2 infection. There was no difference in either head circumference, abdominal circumference, femur length and estimated fetal weight z-scores between pregnancies complicated and those not complicated by SARS-CoV-2 infection both at the second and third trimester scan. Likewise, there was no difference in the growth velocity of all these body parameters between the two study groups. Finally, there was no difference in the pulsatility index of both maternal and fetal Doppler's through gestation between the two groups.

Conclusions: Pregnancies complicated by SARS-CoV-2 infection are not at higher risk of developing fetal growth restriction due to impaired placental function. The findings from this study do not support a policy of increased fetal surveillance in these women.

Key words

SARS-CoV-2-infection, COVID-19, fetal growth, growth velocity, uterine artery Doppler, fetal Dopplers

Abbreviations

SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2
PI pulsatility index

UA umbilical artery

MCA middle cerebral artery

Key message

In pregnancies complicated by SARS-CoV-2 infection, fetal growth and growth velocity between the second and third trimester of pregnancy were similar compared to pregnancies not exposed to the virus not supporting a policy of increased fetal surveillance in these women.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection has been representing a major issue of Public Health since the beginning of 2020, with new cases of infection, hospitalization, admission to Intensive Care Unit and deaths increasing on a daily basis worldwide (1). The impact of SARS-CoV-2 infection on pregnancy is a major concern for obstetrical care providers (2,3,4,5). Since the beginning of the pandemic, pregnancy has been claimed to represent an independent risk factors for severe disease. Several systematic reviews and large observational cohorts have reported a higher risk of severe respiratory symptoms, need for mechanical ventilation and admission to Intensive Care Unit in pregnant women with SARS-CoV-2 infection compared to non-pregnant population women(6,7,8).

The viral agent responsible of SARS-CoV-2 infection, COVID-19, enters the host cells by interacting with the angiotensin-converting-enzyme receptor, whose levels are increased in the pregnant uterus and placenta making the latter a potential target for the infection (9,10). This assumption has been subsequently strengthened by the reported increased prevalence of signs of decidual arteriopathy in pregnant women with SARS-CoV-2 infection, suggesting a potential connection between infection and impaired placental function. (11,12,13). On this basis, we hypothesized that placental changes due to SARS-COV-2 infection may lead to impaired fetal growth in these pregnancies and alter fetal haemodynamic.

The primary aim of this study was to compare the fetal growth velocity in pregnancies complicated and in those not complicated by SARS-CoV-2 infection. The secondary aim was to elucidate whether SARS-CoV-2 infection can alter in maternal and fetal Dopplers.

MATERIAL AND METHODS

Study population

This is a prospective case-control study including consecutive singleton pregnancies complicated by SARS-CoV-2 infection earlier in gestation and receiving antenatal care at the Division of Maternal Fetal Medicine, Università di Roma Tor Vergata, Italy between 35 and 38 weeks of gestation from September 2020 to November 2020. Further inclusion criteria were 1) gestational age confirmed by crown- rump length at the 11-14 weeks scan, 2) second trimester

ultrasound assessment including uterine Doppler done in our unit 3) delivery in our unit.

Pregnancies complicated by fetal structural or chromosomal anomalies, maternal smoking or medical complications potentially affecting fetal growth (i.e. diabetes, chronic hypertension and autoimmune diseases) were excluded from the analysis. This cohort was compared to a control group of pregnancies unexposed to SARS-CoV-2 managed in our centre in the same time interval. The control group had the same exclusion criteria of the study group and was matched with the latter as regard as the main maternal and pregnancy characteristics with a 1:2 ratio.

SARS-CoV-2 infection was confirmed by the presence of positive real-time polymerase-chain reaction (RT-PCR) result obtained by nasopharyngeal swab specimens during pregnancy. All women with confirmed SARS-CoV-2 infection experienced mild symptoms (fever, cough, sore throat, loss of smell and taste, diarrhoea) and none required hospitalization.

Ultrasound assessment

Ultrasound assessment was performed at the time of second trimester scan and later on at 36 weeks of gestation. Third trimester scan is offered to all women in order to confirm fetal well-being, ascertain fetal growth and rule out impaired placental function and fetal growth restriction. Head circumference, abdominal circumference and femur length were measured transabdominally according to International Society of Ultrasound in Obstetrics and Gynecology guidelines (14). Estimated fetal weight was calculated with Hadlock-4 formula (15).

Doppler velocity waveforms were obtained from the following vessels: uterine, umbilical (UA) and middle cerebral arteries (MCA) according to previously reported techniques (16) Briefly both uterine arteries were recorded at the apparent cross-over with the external iliac artery and the mean pulsatility index (PI) calculated as the average between left and right side. UA was recorded from a free-floating cord loop and the MCA in an axial section of the fetal head at its origin from the circle of Willis. Cerebroplacental ratio and umbilical cerebral ratio were computed respectively dividing MCA-PI by UA-PI and UA-PI by MCA-PI. All Doppler parameters were obtained according to the recommendations provided by the International Society of Ultrasound in Obstetrics and Gynecology (17), with an angle of insonation $<30^\circ$, in the absence of maternal and fetal movements and using an automated trace of at least three consecutive waveforms. Uterine artery velocity waveforms were recorded at both ultrasonographic recordings while UA and MCA-PI were evaluated only during the third trimester scan.

Data Analysis

Since biometric variables, estimated fetal weight and Doppler indices change with gestational age, data were expressed as the number of standard deviations (z-score) by which they diverge from the expected mean difference obtained from previously constructed reference limits. (16,18,19)

A sample size analysis was performed to evaluate the sample size necessary. Given a significance of 0.05 and power of 0.80 a sample size of 47 in the study group and 94 in the control group is necessary to demonstrate differences of 0.5 z-scores in the variables considered.

Growth velocity was calculated as the difference in the Z-scores between the measurements recorded at the time of second trimester scan and at 35-38 week of gestation, divided by the time interval (expressed in days) between the two scans and multiplied by 100. (20,21). A similar approach was used for quantifying the Doppler changes in the PI of uterine arteries.

Categorical variables were presented as numbers (n) and percentages (%) and analysed using Chi-square test, while continuous variables as median and interquartile range and analysed using Mann-Whitney U test.

Data were analysed using SPSS version 23.0 (IBM Corp.; Armonk, NY, USA) and MedCalc Statistical softwares version 14.8.(MedCalc Software bvba, Ostend, Belgium). A two-tailed p-values lower than 0.05 were considered statistically significant.

Ethical approval

The study was approved by Institutional Review Board of our institution (#Ost4-2020 on 30 July 2020) and all included women gave their written informed consent to participate.

RESULTS

Forty-nine consecutive pregnancies complicated and 98 not complicated by SARS-CoV-2 infection and managed at our centre were included in the analysis. Median gestational age at COVID-19 infection was 30.6 weeks (interquartile range 28.9-32.3) and all women were asymptomatic with negative RT-PCR swabs at the time of the 36 weeks scan. General characteristics of cases and controls are reported in Table 1. There was no difference as regard as

the main maternal and pregnancy characteristics, including maternal age, body mass index, parity, gestational age at ultrasound and at birth.

There was no difference in either head circumference, abdominal circumference, femur length and estimated fetal weight z-score between pregnancies complicated and those not complicated by SARS-CoV-2 infection both at the second and third trimester scan (Table 2). Likewise, there was no difference in the growth velocity of head circumference (cases 0.14 vs control 0.02; $p=0.477$), abdominal circumference (cases 0.12 vs control 0.01; $p=0.871$), femur length (cases 0.23 vs control 0.16; $p=0.423$) and estimated fetal weight (cases 0.54 vs control 0.02; $p=0.166$) between the two study groups (Figure 2).

Finally, there was no difference in the PI of both maternal and fetal Doppler's through gestation between the 2 groups (Table 2).

DISCUSSION

The findings from this study show that in pregnancies complicated by SARS-CoV-2 infection during the second half of pregnancy fetal growth and growth velocity between the second and third trimester of pregnancy were similar compared to pregnancies not exposed to the virus. Likewise, there was no differences in both maternal and fetal Dopplers between the two study groups. These data suggest that SARS-CoV-2 infection in pregnancy is unlikely to increase the risk of fetal growth restriction and that these pregnancies do not require additional scans to detect growth disorders.

To the best of our knowledge, this is the first study investigating the effects of SARS-CoV-2 infection on fetal growth. Prospective design, relatively large sample size, longitudinal assessment of fetal growth and Dopplers in the second and third trimester of pregnancy represent the main strengths of this study. Furthermore, the two study populations were balanced as regard the main maternal and pregnancy variables potentially affecting fetal growth. The major limitation of the present study relies in the inclusion of only mildly symptomatic cases. Severe SARS-CoV-2 infection has been associated with higher risk of vasculopathy and it may be entirely possible that the lack of association between SARS-CoV-2 infection and fetal growth disorders may be due to the fact that we included only pregnant women in the mild spectrum of the disease. However, about 92-95% of pregnant women with SARS-CoV-2 infection does not experience the severe spectrum of the disease thus making the results for this study applicable to the large majority of

the infections in pregnancy. Further we limited our observation to women that contracted the infection during the second half of pregnancy and we cannot exclude that the outcome could be different, if the infection had occurred earlier in pregnancy.

Despite the ongoing body of evidence rapidly accumulating on the course of the SARS-CoV-2 infection in pregnancy, several questions, including the potential effect of the virus on the fetus and placenta, remain unanswered. Among them, vertical transmission of SARS-CoV-2 infection is still a matter of debate. Mother to fetus transmission was reported as negligible at the beginning of the pandemic (2,3). Conversely, more recent and large cohorts have reported a higher risk of vertical transmission. (22,23,24,25). A recent systematic review of 39 cohort or case series studies including 936 new-borns from mothers affected by COVID-19 showed that the pooled proportion of vertical transmission was 3.2%, with 27 neonates tested positive for SARS-CoV-2 infection by nasopharyngeal swab (26). A subgroup analysis based on the study location showed a similar rate of vertical transmission when comparing studies from China with those from outside China (2.0% vs 2.7%) (26). Despite this, the actual risk of vertical transmission and its potential consequences on the fetus are currently largely unknown.

SARS-CoV-2 has been isolated exclusively from the placenta but not from the new-borns in recent report, thus questioning the actual (27). Features of fetal and maternal vascular malperfusion characterized by decidual arteriopathy with atherosclerosis, fibrinoid necrosis and mural hypertrophy of decidual arterioles have been described in placentas from pregnant women with SARS-CoV-2 infection (11,12,13).

Since in this study placental pathology was not analyzed we cannot address this question. Moreover, outside SARS-CoV-2 infection, every condition leading to maternal vascular hypoperfusion is potentially associated with higher risk of impaired placental function, growth restriction and stillbirth (28). Although we do not perform findings from this study do not support this theory and show that pregnancies complicated by SARS-CoV-2 infection are not at higher risk of fetal growth restriction, thus not requiring additional scans through pregnancy to rule out these disorders.

A likely explanation for the lack of association between SARS-CoV-2 infection and fetal growth restriction may rely in the inclusion of women with mild symptoms, which may represent only the milder spectrum of the disease. In this scenario, we cannot completely rule out that women experiencing the more severe forms of the disease may be at higher risk of fetal growth restriction. Furthermore, the time at maternal infection may change the risk of developing

placental lesions. Finally, we did not consider whether SARS-CoV-2 infection represent an additional risk factor in women.

One of the more debated issues when managing pregnancies complicated by SARS-CoV-2 infection is whether a more intensive fetal monitoring should be applied to these women. The findings from the present study do not support a policy of additional ultrasound scan to assess fetal well-being in view of the lack of association between infection and impaired fetal growth. Furthermore, the risk of stillbirth in women with SARS-CoV-2 infection has been reported to be not significantly different from that of the baseline pregnant population not affected by the infection. Therefore, women with SARS-CoV-2 infection should be reassured about the low risk of adverse fetal outcome. This is also important as pregnant women with SARS-CoV-2 infection experience increased levels of anxiety due to their specific concerns about the potential negative effect of the infection on their new-born (29,30)

CONCLUSION

Pregnancies complicated by SARS-CoV-2 infection during the second half of pregnancy are not at higher risk of developing fetal growth restriction. The findings from this study do not support a policy of increased fetal surveillance in these women.

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LEGEND TO FIGURE

Figure 1 Box-whisker plots of growth velocity (GV) of head circumference (HC), abdominal circumference (AC), femur length (FL) and estimated fetal weight (EFW) in SARS-CoV-2 affected mothers (dotted line) and in control fetuses (solid line).

Table 1. General characteristics of study population stratified according to the exposure to SARS-CoV-2.

Characteristics	Pregnancies complicated by SARS-CoV-2 infection (N= 49)	Pregnancies not complicated by SARS-CoV-2 infection (N= 98)	p-value
Maternal age (years)	30.4 (29.6-32.1)	30.5 (29.25-32.2)	0.712
Maternal height (cm)	160 (158-165)	160 (158-166)	0.829
BMI (kg/m ²)	26.9 (24.3-29.1)	26.2 (24.1-29.2)	0.345
Ethnicity (No %)			0.784
Caucasian	47 (95.9%)	93 (84.647%)	
other	2 (4.1%)	5 (5,1%)	
Parity (No %)			1
Nulliparous	35 (71.4%)	70 (71.4%)	0.797
Assisted conception (No %)	3 (6.1%)	5 (5.1%)	0.846
Gestational age at first US examination (weeks)	20.1 (19.3-22.2)	20.2 (19.5-22.1)	0.912
Gestational age at second US examination (weeks)	36.4 (35.4-36.9)	36.4 (35.9-36.7)	
Gestational age at COVID-19 infection	30.2 (26.2 34.1)		
Gestational age at delivery (weeks)	39.9 (38.0-40.9)	40.2 (38.1-40.7)	0.224
Birthweight (g)	3322 (2830-3590)	3424(3030-3780)	0.377
Head circumference at birth (mm)	353 (344-369)	355 (342-370)	0.254
Male No (%)	24(49.0%)	50(51.0.6%)	0.816

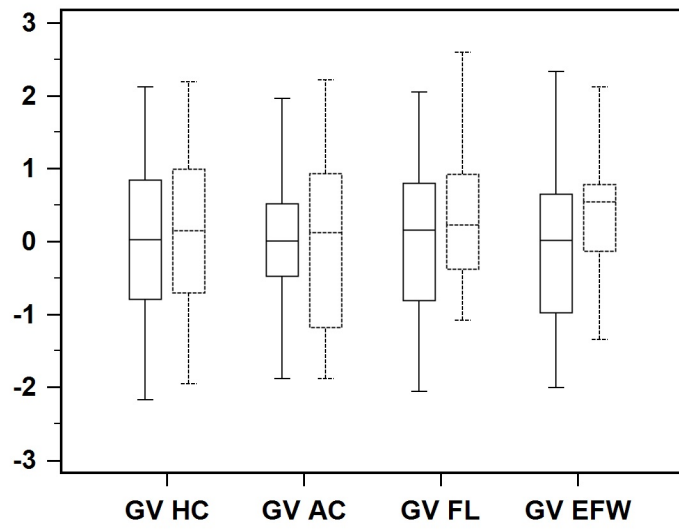
Data are expressed as median and interquartile range or No and %.

Table 2. Comparison of biometric and Doppler indices between the two groups obtained at the time of the two ultrasonographic examination. Data are expressed as z values.

Characteristics	Pregnancies complicated by SARS-CoV-2 infection (N= 49)	Pregnancies not complicated by SARS-CoV-2 infection (N= 98)	p-value
Second trimester scan			
HC z value	-0.07 (-0.63 - 0.56)	0.18 (-0.34 - 0.76)	0.229
AC z value	-0,04 (-0.54 - 0.9)	0.01 (-0.48 - 0.89)	0.526
FL z value	0.36 (-0.15 - 0.95)	0,23 (-0.48 - 0.70)	0.163
EFW z Value	0.19 (-0.65 - 0.68)	0.25 (-0.24 - 0.69)	0.168
Mean uterine artery PI z value	0.06 (-0.40 - 0.60)	0.14 (-0.37 - 0.62)	0.183
35-38 weeks scan			
HC mm	326 (320 - 336)	328 (322 - 339)	0.104
HC z value	-0.16 (-0.97 - 0.48)	0.18 (-0.40 - 0.89)	0.133
AC mm	322 (312 - 351)	323 (314 - 347)	0.526
AC z value	0.01 (-0.58 - 0.82)	0.06 (-0.53 - 0.70)	0.957
FL mm	69 (66 - 70)	68 (67 - 71)	0.745
FL z value	0.27 (-0.97 - 0.87)	0.21 (-0.70 - 0.91)	0.942
EFW g	2812 (2640 - 2980)	2829 (2640 - 2930)	0.672
EFW z Value	0.14 (-0.76 - 0.78)	0.02 (-0.76 - 0.52)	0.235
Mean uterine artery PI z value	0.04 (-0.65 - 0.74)	0.06 (-0.52 - 0.62)	0.309
UA PI z value	-0.09 (-0.58 - 0.75)	0.01 (- 0.61 - 0.73)	0.354
MCA PI z value	0.20 (- 65 - 0.85)	0.11 (-0.62 - 0.84)	0.444
CPR z value	-0.19 (-0.52 - 0.71)	0.04 (-0.44 - 0.69)	0.240
UCR z value	-0.11 (-0.44 - 0.61)	0.07 (- 0.39 - 0.67)	0.300

Data are expressed as median and interquartile range.

HC, head circumference; AC, abdominal circumference; FL, femur length; EFW, estimated fetal weight; PI, pulsatility index; UA, umbilical artery; MCA, middle cerebral artery; CPR, cerebroplacental ratio; UCR, umbilical cerebral ratio.



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