Archives of Gynecology and Obstetrics
https://doi.org/10.1007/s00404-021-06276-4

CORRESPONDENCE

Invasive prenatal diagnosis during COVID-19 pandemic

Luigi Carbone[1] · Antonio Raffone[1] · Laura Sarno[1] · Antonio Travaglino[2] · Gabriele Saccone[1] · Olimpia Gabrielli[1] · Sonia Migliorini[1] · Angelo Sirico[1] · Rita Genesio[3] · Giuseppe Castaldo[3] · Alessandra Capponi[4] · Fulvio Zullo[1] · Giuseppe Rizzo[4] · Giuseppe Maria Maruotti[1]

Received: 3 September 2020 / Accepted: 1 October 2021

Keywords COVID-19 · NIPT · Prenatal diagnosis · Invasive procedure · Amniocentesis

Sirs,

COronaVIrus Disease 2019 (COVID-19) has been declared by the World Health Organization (WHO) as pandemic on the 11th of March 2020. However, the first reported cases in Italy dated on the 30th of January 2020, when a Chinese couple was diagnosed as affected by SARS-COV-2 (Severe Acute Respiratory Syndrome COronaVirus-2) in Rome. Since then, the infection rapidly spread through Italy, and the Italian Prime Minister issued a decree for a strict lockdown of all non-necessary activities since the 8th of March 2020 [1]. Hospitals reorganized their units to provide care for COVID-19 patients. Moreover, elective and non-life saving procedures were reduced to save hospital beds, and to reduce crowding in hospitals and further spread of the disease.

Pregnant women have been considered soon as an at-risk category for the additional risks of transmitting infection to the fetus, with unknown consequences both for fetal and pregnancy outcomes. Little evidence exist so far on maternal–fetal transmission [2].

Many national and international societies issued their recommendations on how to manage pregnancy during this unprecedented outbreak, encouraging telehealth unless face-to-face appointments are needed, and addressing the best practice for antepartum, intrapartum and postpartum care [3, 4]. Although vaccines against SARS-COV-2 infection have been started to be administered to the general population, actually, pregnant women show contrasting feelings regarding the chance to get the vaccine [5, 6]. In reference to invasive procedures, Deprest et al. [7], on Behalf of the International Fetal Medicine and Surgery Society, analyzed potential modifications to obstetric management and fetal procedures during the pandemic. In addition, Deprest et al. [8] addressed the issue of prenatal invasive interventions during the COVID-19 pandemic. On one side, the authors express concerns for patients going to hospitals, and therefore, increasing the risk of COVID-19 infection. On the other side, they acknowledge that invasive procedures should not be declined just for the fear of vertical transmission. Moreover, they advise to avoid transplacental access (due to possible damage to maternal–fetal barrier) or to postpone procedures in COVID-19-positive or -suspected cases.

We performed a multicentre observational retrospective cohort study for comparing invasive procedures for prenatal diagnosis performed during the trimester March–May 2020 to those performed during the same trimester of the year 2019. The aim of our study was to assess if COVID-19 pandemic had caused a significant decrease in the number of invasive procedures for prenatal diagnosis, such as chorionic villous sampling (CVS) and amniocentesis.

We searched medical records and electronic clinical databases for all patients undergone CVS or amniocentesis at the Obstetrics and Gynecology Unit of the Department of

Giuseppe Rizzo and Giuseppe Maria Maruotti share the last authorship.

✉ Antonio Raffone
anton.raffone@gmail.com

1 Gynecology and Obstetrics Unit, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, Federico II University of Naples, Via Sergio Pansini no. 5, 80131 Naples, Italy

2 Anatomic Pathology Unit, Department of Advanced Biomedical Sciences, School of Medicine, University of Naples Federico II, Naples, Italy

3 Department of Molecular Medicine and Medical Biotechnology, Federico II University of Naples, Naples, Italy

4 Division of Maternal Fetal Medicine, Ospedale Cristo Re, University of Rome Tor Vergata, Rome, Italy

Published online: 07 October 2021

Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, Federico II University, Naples, Italy, and at the Division of Maternal Fetal Medicine, Ospedale Cristo Re, University of Rome Tor Vergata, Rome, Italy, during the trimester March–May of the years 2019 and 2020.

The number of CVS and amniocentesis was recorded for each month of the above-mentioned trimesters, and the mean ± standard deviation (SD) of each monthly invasive procedure for prenatal diagnosis (CVS and amniocentesis), CVS alone, and amniocentesis alone was calculated. To adjust for the contribution of non-invasive prenatal testing (NIPT) on the possible reduction in invasive procedures, we calculated the mean ± SD of monthly deliveries, and of invasive procedures for prenatal diagnosis only recommended for investigation of ultrasound abnormalities. Mean ± SD of monthly invasive procedures and deliveries of the year 2020 was compared with that of the year 2019, using the unpaired T test with α error set to 0.05 and 95% confidence intervals (95% CI). Furthermore, to allow for this trend of reduced uptake of invasive prenatal testing due to increased NIPT availability and economic sustainability, we recorded also the invasive procedures carried out in the trimesters immediately preceding the two above-mentioned periods (from December 2018 to February 2019 and from December 2019 to February 2020).

Mean ± SD of each monthly invasive prenatal procedure was 78.7 ± 3.5 for the year 2019 and 57 ± 10.4 for the year 2020. Mean ± SD of monthly CVS alone was 30 ± 1.7 for the year 2019, and 23.7 ± 7.8 for the year 2020. Mean ± SD of monthly amniocentesis alone was 48.7 ± 2.3 for the year 2019, and 33.3 ± 4.2 for the year 2020. Mean ± SD of monthly deliveries was 170.5 ± 9.8 for the year 2019, and 183.8 ± 13.5 for the year 2020. Mean ± SD of monthly invasive procedures for prenatal diagnosis only recommended for investigation of ultrasound abnormalities was 7.7 ± 3.8 for the year 2019 and 6.3 ± 2.9 for the year 2020 (Table 1). Accordingly, data from the two preceding trimesters are shown in Table 1.

Difference in each monthly invasive prenatal procedure was − 21.7 (95% CI: − 23.1 to − 20.3; $p < 0.0001$) between the year 2020 and 2019, and − 6.3 (95% CI: − 8.2 to − 4.4; $p < 0.0001$) by comparing the two preceding trimesters (Table 2).

Difference in monthly CVS alone was − 6.3 (95% CI: − 8 to − 4.6; $p < 0.0001$) between the year 2020 and 2019, and − 5.7 (95% CI: − 7.5 to − 3.9; $p < 0.0001$) by comparing the two preceding trimesters. Difference in monthly amniocentesis alone was − 15.4 (95% CI: − 16.2 to − 14.6; $p < 0.0001$) between the year 2020 and 2019, and − 0.7 (95% CI: − 2 to 0.6; $p = 0.2747$) by comparing the two preceding trimesters (Table 2).

Furthermore, difference in monthly deliveries was 26.7 (95% CI: 25.8 to 27.6; $p < 0.0001$) between the year 2020 and 2019, and 3.3 (95% CI: 2.15 to 4.5; $p < 0.0001$) by comparing the two preceding trimesters (Table 2).

Difference in monthly invasive prenatal procedures only recommended for investigation of ultrasound abnormalities was − 5.4 (95% CI: − 6.2 to − 4.6; $p = 0.0091$) between the year 2020 and 2019, and − 6 (95% CI: − 42.8 to 30.8; $p = 0.7268$) by comparing the two preceding trimesters (Table 2).

We found a significant decrease in each outcome (all monthly invasive prenatal procedures, monthly CVS alone, and amniocentesis alone) comparing the trimester March–May of the year 2020 with that of the year 2019.

Regarding adjustment for the number of deliveries, we found a significant increase in monthly deliveries. Controlling for the number of deliveries at our hospitals, we found that people were still coming for delivery at the same rate and even more.

Looking to overall indications for prenatal invasive procedures at Federico II University, we observed the greater reduction for age and for first trimester pathologic combined test (Supplementary table 1).

At Cristo Re hospital, a decline was noted for all the common indications as first trimester pathologic combined test, malformation or cystic hygroma and also NIPT-indicated amniocentesis (Supplementary table 2).

In addition, we focused on ultrasound-indicated procedures, since an eventual reduction of these ones would not be attributable to the increased uptake of NIPT, and found that they were significantly reduced comparing the trimester March–May of the year 2020 with that of the year 2019.

When assessing the preceding trimesters to take into account the impact of NIPT uptake, we observed statistically significant differences in all monthly invasive prenatal procedures and monthly CVS alone, but not for monthly amniocentesis alone and monthly invasive prenatal procedures only recommended for investigation of ultrasound abnormalities. Indeed, the rate of ultrasound abnormalities does not change over time, and the finding of not statistically significant differences between the preceding trimesters strengthen the idea of a sudden reason for the following drop, which could be ascribed to the fear of contagion due to the pandemic. Differently from CVS, amniocentesis depends more on ultrasound abnormalities, which become more evident in the second trimester, and therefore, although a reduction is noted, the non-significant difference is probably due to the same reasons as above. In addition, all the above-mentioned statistically significant differences between the two preceding trimesters were lower than those found between the March–May trimester. Such finding would also strengthen the fear of contagion rather than NIPT impact as the underlying reason for the drop in invasive procedures for prenatal diagnosis during the lockdown period. In fact, NIPT has reached

Table 1 Invasive procedures for prenatal diagnosis

ITEM	2018–2019										2019–2020									
	Dec	Jan	Feb	*T*	Mean ± SD	Mar	Apr	May	*T*	Mean ± SD	Dec	Jan	Feb	*T*	Mean ± SD	Mar	Apr	May	*T*	Mean ± SD
CVS				87	29 ± 5.7				90	30 ± 1.7				70	23.3 ± 5.5				71	23.7 ± 7.8
Federico II	7	3	12			9	7	6			1	2	7			3	5	5		
Cristo Re	18	22	25			20	22	26			17	21	22			12	25	21		
Amniocentesis				128	42.7 ± 3.7				146	48.7 ± 2.3				126	42 ± 6.2				100	33.3 ± 4.2
Federico II	14	22	13			22	21	18			11	20	17			16	15	16		
Cristo Re	24	25	30			28	25	32			24	27	27			14	17	22		
Total	63	72	80	215	71.6 ± 8.5	79	75	82	236	78.7 ± 3.5	53	70	73	196	65.3 ± 10.8	45	62	64	171	57 ± 10.4
Deliveries				1052	350.7 ± 7				1023	341 ± 11.9				1062	354 ± 17.7				1103	367.7 ± 9
Federico II	173	169	178			156	186	178			166	183	179			177	194	208		
Cristo Re	177	175	180			171	170	162			169	174	191			178	180	166		
Total	350	344	358			327	356	340			335	357	370			355	374	374		
CVS only recommended for investigation of ultrasound abnormalities				40	13.3 ± 6.6				37	6.2 ± 3.3				33	11 ± 3.6				38	6.3 ± 3.6
Federico II	3	1	9			4	3	2			0	1	5			3	3	3		
Cristo Re	7	8	12			8	9	11			8	9	10			7	12	10		
Amniocentesis only recommended for investigation of ultrasound abnormalities				53	17.7 ± 1.2				55	9.2 ± 3.6				54	18 ± 4.3				38	6.3 ± 2
Federico II	6	7	3			8	5	5			3	8	9			5	4	5		
Cristo Re	11	12	14			12	10	15			10	12	12			7	7	10		
Total	27	28	38	93	31 ± 6.1	32	27	33	92	30.7 ± 2.6	21	30	36	87	29 ± 7.5	22	26	28	76	25.3 ± 2.5

Data are presented as absolute numbers and mean ± standard deviation (SD). CVS, chorionic villous sampling; Dec, December; Jan, January; Feb, February; Mar, March; Apr, April; T, total (intended as sum of the two centers in the trimester and year considered)

Table 2 Difference in each monthly invasive prenatal procedure

ITEM	2020–2019			Preceding trimesters (December–February)		
	Difference	95% CI	*p*	Difference	95% CI	*p*
Chorionic villous sampling	− 6.3	− 8 to − 4.6	**< 0.0001**	− 5.7	− 7.5 to − 3.9	**< 0.0001**
Amniocentesis	− 15.4	− 16.2 to − 14.6	**< 0.0001**	− 0.7	− 2 to 0.6	0.2747
Total	− 21.7	− 23.1 to − 20.3	**< 0.0001**	− 6.3	− 8.2 to − 4.4	**< 0.0001**
Deliveries	26.7	25.8 to 27.6	**< 0.0001**	3.3	2.15 to 4.5	**< 0.0001**
Prenatal invasive procedures only recommended for investigation of ultrasound abnormalities	− 5.4	− 6.2 to − 4.6	**< 0.0001**	− 6	− 42.8 to 30.8	0.7268

Bold value indicates statistic signicance

a high detection rate for trisomy 21, 18 and 13, being as high as 99, 98 and 99%, respectively [9, 10]. However, it is also recommended to not use NIPT for the evaluation of the etiology of ultrasound anomalies since sensitivity and negative predictive value are low if compared to karyotyping or microarray analysis [12].

To the best of our knowledge, our data are the first to show a reduction of invasive procedures uptake during the COVID-19 lockdown, and is not yet possible to evaluate the consequences of such choice on maternal–fetal outcomes.

Anxiety has been showed to rise in pregnant women during the COVID-19 pandemic [12] and could be one of the main reasons to explain the drop in the number of invasive procedures. After a year, however, COVID-19 is still quite prevalent in the country and the pandemic persists. Therefore, it is of striking importance to adequately counsel pregnant women to not lose sight of the need to assess fetal status during pregnancy because of psychological distress and fear of hospitals or meeting healthcare providers. Severe genetic conditions require appropriate screening and eventually invasive procedures for the diagnosis. Management of such conditions is considered time-sensitive. As a matter of fact, they should be discovered as early as possible to seek for special antenatal and postnatal care. Early diagnosis and specific management of severe genetic conditions aim to reduce the strong impact both on the unborn and on parents' life. To conclude, we warn healthcare providers to stress on the importance of the invasive prenatal diagnosis, whenever indicated.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00404-021-06276-4.

Author contributions LC: conception, carrying out, analyzing, and writing up. AR: planning, analyzing, and writing up. LS: conception, planning, and carrying out, AT: planning, analyzing, and writing up. GS: planning, carrying out, and writing up. OG: planning, analyzing, and carrying out, SM: carrying out, analyzing, and writing up. AS: carrying out, analyzing, and writing up. RG: conception, carrying out, analyzing, and writing up. GC: conception, planning, and supervision. AC: conception, planning, and supervision. FZ: conception, planning, and supervision. GR: conception, planning, and supervision. GMM: conception, planning, and supervision.

Funding No financial support was received for this study.

Declarations

Conflict of interest The authors report no conflict of interest.

Informed consent All the patients provided their written consent.

Ethical approval Given the study design (retrospective analysis of anonymous data), the authors considered ethical approval not necessary.

References

1. (2020) https://it.wikipedia.org/wiki/Pandemia_di_COVID-19_del_2020_in_Italia. Accessed 7 Jun 2020
2. Ferrazzi E, Frigerio L, Savasi V et al (2020) Vaginal delivery in SARS-CoV-2 infected pregnant women in Northern Italy: a retrospective analysis. BJOG. https://doi.org/10.1111/1471-0528.16278
3. Narang K, Ibirogba ER, Elrefaei A et al (2020) SARS-CoV-2 in pregnancy: a comprehensive summary of current guidelines. J Clin Med 9(5):E1521. https://doi.org/10.3390/jcm9051521
4. Carbone L, Esposito R, Raffone A et al (2020) Proposal for radiologic diagnosis and follow-up of COVID-19 in pregnant women. J Matern Fetal Neonatal Med 16:1–2. https://doi.org/10.1080/14767058.2020.1793325
5. Carbone L, Mappa I, Sirico A et al (2021) Pregnant women perspectives on SARS-COV-2 vaccine: condensation: most of Italian pregnant women would not agree to get the SARS-COV-2 vaccine, irrespective of having features of high risk themselves, or being high-risk pregnancies. Am J Obstet Gynecol MFM 23:100352. https://doi.org/10.1016/j.ajogmf.2021.100352
6. Mappa I, Luviso M, Distefano FA et al (2021) Women perception of SARS-COV-2 vaccination during pregnancy and subsequent maternal anxiety: a prospective observational study. J Matern Fetal Neonatal Med. https://doi.org/10.1080/14767058.2021.1910672 ((**Inpress**))
7. Deprest J, Choolani M, Chervenak F et al (2020) Fetal diagnosis and therapy during the COVID-19 pandemic: guidance on Behalf of the International Fetal Medicine and Surgery Society

[published online ahead of print, 2020 May 6]. Fetal Diagn Ther 2020:1–10. https://doi.org/10.1159/000508254
8. Deprest J, Van Ranst M, Lannoo L et al (2020) SARS-CoV2 (COVID-19) infection: is fetal surgery in times of national disasters reasonable? Prenat Diagn 2020:1–4. https://doi.org/10.1002/pd.5702
9. Gil MM, Accurti V, Santacruz B et al (2017) Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol 20(3):302–314. https://doi.org/10.1002/uog.17484
10. Carbone L, Cariati F, Sarno L et al (2020) Non-invasive prenatal testing: current perspectives and future challenges. Genes (Basel) 12(1):15. https://doi.org/10.3390/genes12010015
11. Beulen L, Faas BHW, Feenstra I et al (2017) Clinical utility of non-invasive prenatal testing in pregnancies with ultrasound anomalies. Ultrasound Obstet Gynecol 49(6):721–728. https://doi.org/10.1002/uog.17228
12. Durankuş F, Aksu E (2020) Effects of the COVID-19 pandemic on anxiety and depressive symptoms in pregnant women: a preliminary study [published online ahead of print, 2020 May 18]. J Matern Fetal Neonatal Med 2020:1–7. https://doi.org/10.1080/14767058.2020.1763946