



Impact of COVID-19 on pregnancy and fetal outcomes in women with Multiple Sclerosis

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Complete List of Authors:	<p> Aprea, Maria Grazia; University of Florence, NEUROFARBA Department Schiavetti, Irene; University of Genova, Biostatistics Unit, Department of Health Sciences (DISSAL) Portaccio, Emilio; University of Florence, Neurology Ballerini, Clara; University of Florence, Neurological and Psychiatric Sciences Bonavita, Simona; University of Campania "Luigi Vanvitelli", I Division of Neurology, Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences; University of Campania "Luigi Vanvitelli" and Institute of Diagnosis and Care "Hermitage-Capodimonte", MRI Center "SUN-FISM" Buscarinu, Maria Chiara; Università degli Studi di Roma La Sapienza Facoltà di Medicina e Psicologia, NESMOS, Neurosciences, Mental Health, and Sensory Organs Calabrese, Massimiliano ; University of Verona Department of Neuroscience Biomedicine and Movement, Multiple Sclerosis Center Cavalla, Paola; A.O.U. Città della Salute e della Scienza, Dipartimento di Neuroscienze Cellerino , Maria ; University of Genoa, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, and Mother-Child health Cordioli, Cinzia; Spedali Civili di Brescia, Presidio di Montichiari, Multiple Sclerosis Centre Dattola, Vincenzo; MS Center, Bianchi Melacrino Morelli Great Metropolitan Hospital, MS Center, Bianchi Melacrino Morelli Great Metropolitan Hospital, Reggio Calabria De Biase, Stefano; Neurology Unit, Ospedale dell'Angelo, Venezia Mestre, Italy, Neurology Unit, Ospedale dell'Angelo, Venezia Mestre, Italy De Meo, Ermelinda; Department of NEUROFARBA, University of Florence, Florence, Italy, University of Florence Fantozzi, Roberta; NEUROMED, MS Centre Gallo, Antonio; University of Campania "Luigi Vanvitelli", I Division of </p>

	<p>Neurology, Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences; University of Campania "Luigi Vanvitelli" and Institute of Diagnosis and Care "Hermitage-Capodimonte", MRI Center "SUN-FISM" Iasevoli, Luigi; Fondazione Santa Lucia Istituto di Ricovero e Cura a Carattere Scientifico, Multiple Sclerosis Karabudak, Rana; Hacettepe University Faculty of Medicine, Department of Neurology-Neuroimmunology Unit Landi, Doriana; Fondazione PTV Policlinico Tor Vergata, Multiple Sclerosis Clinical and Research Unit Loreface, Lorena; Ospedale Binaghi, Cagliari, Italy, Centro Sclerosi Multipla Moiola, Lucia; IRCCS Ospedale San Raffaele, Multiple Sclerosis Center and Neurology Department, Ragonese, Paolo; University of Palermo, Department of Experimental Biomedicine and Clinical Neurosciences Ruscica, Francesca; Fondazione Istituto G. Giglio, Cefalù (Italy), U.O.C. Neurologia e Centro SM - Sen, Sedat; Ondokuz Mayıs University, Neurology Sinisi, Leonardo; San Paolo Hospital, ASL NA1, MS Center Signoriello, Elisabetta; Second University of Naples, Multiple Sclerosis Center, Department of Clinical and Experimental Medicine Toscano, Simona; University of Catania, G.F. Ingrassia, Section of Neurosciences Verrengia, Elena Pinuccia; ASST Ovest Milanese, Legnano Hospital Siva, Aksel; Istanbul University Cerrahpasa School of Medicine, Neurology Masciulli, Camilla; University of Florence, Department of NEUROFARBA Sormani, Maria Pia; University of Genoa, Dep of Health Sciences; IRCCS, Ospedale Policlinico San Martino, Amato, Maria Pia; University of Florence, NEUROFARBA</p>
Keywords:	Multiple sclerosis, Fetal outcomes, Maternal outcomes, pregnancy, COVID-19, SARS-CoV-2 infection
Abstract:	<p>Background In the general population, maternal COVID-19 is associated with worse maternal and fetal outcomes. Two previous studies have assessed COVID-19 clinical outcomes in pregnant women with Multiple Sclerosis (MS), but there is no data about maternal and fetal outcomes. Objectives In this multicenter study we aimed to assess maternal and fetal outcomes in pregnant women with MS and COVID-19 infection. Methods We recruited pregnant patients with MS who contracted COVID-19 and were followed-up in Italian and Turkish Centers, during 2020-2022. A control group was extracted from a previous Italian cohort. Associations between group (COVID-19 or healthy patients) and clinical outcomes (maternal complications, fetal malformations and spontaneous abortion) were investigated with a weighted logistic regression where propensity score-based inverse probability of treatment weighting (IPTW) approach was applied for adjusting for difference in baseline confounders. Results In the multivariable analysis, COVID-19 during pregnancy was associated with a higher risk of maternal complications (OR: 2.12; 95%CI: 1.32 – 3.48; p = 0.002), while it was not associated with higher risk of spontaneous abortion and fetal malformations. Conclusion Our data indicate that COVID-19 during pregnancy increases the risk of maternal complications, while it seems to have no significant impact on fetal outcomes.</p>

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Impact of COVID-19 on pregnancy and fetal outcomes in women with Multiple Sclerosis

M. G. Aprea^{1#}, I. Schiavetti^{2#}, E. Portaccio¹, C. Ballerini¹, S. Bonavita³, M. Buscarinu⁴, M. Calabrese⁵, P. Cavalla⁶, M. Cellerino⁷, C. Cordioli⁸, V. Dattola⁹, S. De Biase¹⁰, E. De Meo¹, R. Fantozzi¹¹, A. Gallo¹², L. Iasevoli¹³, R. Karabudak¹⁴, D. Landi¹⁵, L. Lorefice¹⁶, L. Moiola¹⁷, P. Ragonese¹⁸, F. Ruscica¹⁹, S. Sen²⁰, L. Sinisi²¹, E. Signoriello³, S. Toscano^{22,23}, E. Verrengia²⁴, A. Siva²⁵, C. Masciulli¹, M. Sormani^{2,26#*}, M. Amato^{1,27#}

1 Department of NEUROFARBA, University of Florence, Florence, Italy; 2 Department of Health Sciences, Section of Biostatistics, University of Genova, Italy; 3 Department of Neurology, II Division, University of Campania Luigi Vanvitelli, Naples; 4 Department of Neurology, Sant'Andrea Hospital, Rome; 5 The Multiple Sclerosis Centre, Dept. of Neurosciences Biomedicine and Movement, University Hospital of Verona, Verona; 6 MS Center, Department of Neuroscience, City of Health and Science University Hospital of Turin, Turin; 7 Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy; 8 Multiple Sclerosis Center, ASST Spedali Civili di Brescia, Montichiari Hospital, Brescia; 9 MS Center, Bianchi Melacrino Morelli Great Metropolitan Hospital, Reggio Calabria; 10 Neurology Unit, Ospedale dell'Angelo, Venezia Mestre, Italy; 11 Department of Neurology, IRCCS Neuromed, Pozzilli (IS); 12 MS Center, I Division of Neurology, Department of Advanced Medical and Surgical Sciences; 13 MS Center, Santa Lucia Foundation IRCCS, Rome; 14 Faculty of Medicine, Hacettepe University, Ankara; 15 MS Center, Tor Vergata University, Rome; 16 Multiple Sclerosis Centre, Binaghi Hospital, ASL Cagliari, University of Cagliari, Cagliari, Italy; 17 Department of Neurology and Multiple Sclerosis Center, ASST Papa Giovanni XXIII, Bergamo; 18 BIND Department, University of Palermo, Palermo; 19 MS Center, Institute Foundation G. Giglio, Cefalù; 20 Ondokuz Mayıs University School of Medicine Samsun, Turkey; 21 MS Center, S. Paolo Hospital, Naples; 22 Multiple Sclerosis Unit, University Hospital G. Rodolico, Catania, Italy; 23 Department of Biomedical and biotechnological sciences, University of Catania, Catania, Italy; 24 Multiple Sclerosis Centre, ASST OVEST MI, Legnano Hospital, Italy; 25 Faculty of Medicine, Cerrahpasa University, Istanbul; 26 IRCCS Ospedale Policlinico San Martino, Genova, Italy; 27 IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy.

Contributed equally.

* Corresponding author.

DISCLOSURES

S. Sen has received honoraria or consultancy fees for participating to advisory boards, giving educational lectures and/or travel and registration coverage for attending scientific congresses or symposia from F. Hoffmann-La Roche Ltd, Sanofi-Genzyme, Merck-Serono, Novartis, Teva, Biogen Idec/Gen Pharma. **R. Karabudak** has received honoraria for giving educational lectures, consultancy fees for participating advisory boards, and travel grants for attending scientific congresses or symposia from Roche, Sanofi-Genzyme, Merck-Serono, Novartis, Teva, Biogen Idec/Gen Pharma of Turkey, Abdi İbrahim İlac, Deva and ARIS. **A. Siva** has received honoraria or consultancy fees for participating to advisory boards, giving educational lectures and/or travel and registration coverage for attending scientific congresses or symposia from F. Hoffmann-La Roche Ltd, Sanofi-Genzyme, Merck-Serono, Novartis, Teva, Biogen Idec/Gen Pharma of Turkey and Abdi İbrahim İlac. **E. Portaccio** received compensation for travel grants, participation in

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2
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45 **Corresponding author:**

46 Professor Maria Pia Sormani

47 mariapia.sormani@unige.it
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Impact of COVID-19 on pregnancy and fetal outcomes in women with Multiple Sclerosis

Abstract

Background In the general population, maternal COVID-19 is associated with worse maternal and fetal outcomes. Two previous studies have assessed COVID-19 clinical outcomes in pregnant women with Multiple Sclerosis (MS), but there is no data about maternal and fetal outcomes.

Objectives In this multicenter study we aimed to assess maternal and fetal outcomes in pregnant women with MS and COVID-19 infection.

Methods We recruited pregnant patients with MS who contracted COVID-19 and were followed-up in Italian and Turkish Centers, during 2020-2022. A control group was extracted from a previous Italian cohort. Associations between group (COVID-19 or healthy patients) and clinical outcomes (maternal complications, fetal malformations and spontaneous abortion) were investigated with a weighted logistic regression where propensity score-based inverse probability of treatment weighting (IPTW) approach was applied for adjusting for difference in baseline confounders.

Results In the multivariable analysis, COVID-19 during pregnancy was associated with a higher risk of maternal complications (OR: 2.12; 95%CI: 1.32 – 3.48; $p = 0.002$), while it was not associated with higher risk of spontaneous abortion and fetal malformations.

Conclusion Our data indicate that COVID-19 during pregnancy increases the risk of maternal complications, while it seems to have no significant impact on fetal outcomes.

Introduction

Since the beginning of COVID-19 pandemic, many questions arose regarding the effects of the infection on categories of vulnerable individuals, such as people with Multiple Sclerosis (MS)¹, pregnant persons, fetuses and neonates. Although the World Health Organization (WHO)-led Emergency Committee has declared an end to COVID-19 as a public health emergency, the disease still represents a global threat. Almost 7 million deaths have been reported to WHO² and, since the virus is still circulating, evidence on maternal and fetal risks associated with COVID19 in MS pregnant patients is highly relevant to guide physicians and patients in family planning.

Moreover, management of pregnant women with MS requires relevant considerations because of the physiological, immunologic, and mechanical changes during gestation that makes pregnant women more susceptible to infections in general³, and seem to predispose to COVID-19^{4,5}. On top of this, consideration must be given to the impact of immunomodulatory therapy⁶ and the interaction between COVID-19 and pregnancy¹.

Data in the general population have shown a generally increased risk for several adverse maternal and fetal outcomes in infected women, in particular: maternal death, pre-eclampsia, and cesarean

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3 delivery for the mother^{7,8}, and severe neonatal mortality and morbidity index (including respiratory
4 distress and admission to neonatal intensive care unit -NICU) for the fetus/newborn⁸.

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6 On April 2022, an international multicenter initiative involving Italian and Turkish MS centers was
7 launched, aimed to gather information on COVID-19 course and maternal and fetal outcomes in
8 pregnant MS women infected with SARS-CoV-2. In a previous analysis on COVID-19 course during
9 pregnancy in MS women, no significant increase of infection severity emerged⁹. In the present paper,
10 we assessed pregnancy-related maternal and fetal outcomes, taking into account the main clinical and
11 demographic confounders.
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14 **Material and methods**

15 *Study design and participants*

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18 This international, retrospective cohort study included pregnant MS patients who contracted SARS-
19 CoV-2 infection after conception followed up in 48 Italian and 13 Turkish centers that agreed to
20 participate in the project. All the patients were administered a structured interview which gathered
21 detailed information on pregnancy course and outcomes, as well as on possible confounders,
22 including disease modifying treatments. When needed, data were validated with the medical records.
23 The start of pregnancy (date of conception, defined as 14 days after the last menstrual period) was
24 considered the baseline. Collected data were sent to the coordinator centers at University of Firenze
25 and University of Genova via an encrypted Research Electronic Data Capture (REDCap) data
26 management platform, subsequently entered into a computerized database and cross-checked.
27 Inclusion criteria for the pregnancy group were: age between 18 and 50 years, diagnosis of MS
28 according to McDonald criteria¹⁰⁻¹³, pregnancy and a laboratory-confirmed SARS-COV-2 infection
29 diagnosed after conception in the period 2020-2022. A confirmed case was defined as a patient with
30 a positive test (reverse transcriptase polymerase chain reaction on nasal and pharyngeal swabs) for
31 SARS-CoV-2 or a positive serological test obtained at any point during the observation period.
32 Maternal complications were assessed and categorized in 7 categories: disorders of placenta,
33 infectious complications (other than COVID19), puerperal hemorrhage, urinary tract disorders,
34 mastitis, postpartum depression, others (including, among others, pre-eclampsia, threatened abortion,
35 metrorrhagia, ectopic pregnancy and gestational diabetes). A control group of MS pregnant patients,
36 matched for demographic characteristics, was extracted from a historical Italian cohort, recruited
37 between 2009 and 2015.^{14,15}
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42 *Outcomes*

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44 The primary outcomes were: (1) spontaneous abortion, defined as the loss of pregnancy prior to 20
45 weeks of gestation; (2) fetal malformations defined and classified according to the European
46 Surveillance of Congenital Anomalies (EUROCAT)¹⁶; (3) any maternal complications other than
47 COVID19.
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49 The secondary outcomes were related to neonatal information, including preterm births and birth
50 weight.
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58 *Statistical analysis*

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60 Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v 24.0.
Continuous variables were reported as mean \pm standard deviation (SD), while categorical as number

with percentage. The relationship between demographic and clinical baseline characteristics and the three outcomes was analyzed using univariate logistic analysis. The effect of COVID-19 on the three outcomes was investigated with a weighted logistic regression where propensity score–based inverse probability of treatment weighting (IPTW) approach was applied for adjusting for difference in baseline confounders. The propensity score weight was computed using a logistic regression where group (COVID-19 or control patients) was set as the dependent outcome variable and age and disease duration at pregnancy, disease modifying treatment, EDSS at pregnancy, MS phenotype, relapses in the previous year, previous spontaneous abortion, and alcohol and smoking habits during pregnancy were included as the independent explanatory covariates.

Results

Sixty-one (61) pregnant MS patients from Italian (n = 48) and Turkish (n = 13) centers fulfilled the inclusion criteria for the pregnancy group. A control group of 428 women was extracted from a historical Italian cohort and matched for the main clinical and demographic characteristics with the IPTW method.

Table 1 presents the characteristics of the entire sample (N = 489) before and after IPTW method implementation.

The frequency and distribution of each of the three outcomes are documented in **Table 2**.

Spontaneous abortion was observed in 30 (7%) patients in the control group and 3 (4.9%) patients from the COVID-19 group. Fetal malformations were observed in 12 (3%) patients in the control group and 3 (5.2%) patients in the COVID-19 group (**Table 2**). The three malformations observed in the COVID-19 group were: craniomegaly; congenital heart defect and intracardiac golf ball. Two cases occurred with Covid-19 spreading in the first trimester, and in one case the infection occurred in the second trimester. For neither of these two outcomes, a role of COVID-19 as a risk factor has been identified (**Table 3**). Adverse maternal outcomes (**Table 4**) were observed in 53 (12.4%) patients in the control group and 12 (19.7%) in the COVID-19 group. In both groups, the most frequent complications were those under the category of “others”, precisely 60.4% in the control group, 58.3% in the COVID-19 group. The second most frequent complication for the COVID-19 group was infection other than COVID-19 (41.7%), while for the control group disorders of placenta (13.2%). The presence of COVID-19 during pregnancy was associated with higher risk of maternal complications (OR: 1.92; 95%CI: 1.18 – 3.16; p = 0.009) (**Table 3**). The complete list of maternal complications collected under the category of “others” is reported in supplementary material (**Table S1**). Among the twelve maternal complications that occurred in women with Covid-19, there were 5 cases with COVID-19 reported in the first trimester, 6 cases reported in the second trimester, and 1 case (infection complication) reported in the third trimester.

As part of additional analysis, we compared birth weights and the incidence of preterm births between two groups. A lower frequency of preterm births was observed in patients with COVID-19 compared to the control group (OR: 0.33; 95% CI: 0.16 – 0.63; p < 0.001), while no significant difference in birth weight was found (p = 0.67).

Discussion

The main findings of this multicenter, international study on 61 MS pregnant women with COVID-19 include: (1) SARS-CoV-2 infection did not confer higher risk of fetal malformations nor spontaneous abortions; (2) COVID-19 was associated with higher risk of maternal complications.

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3 Regarding fetal outcomes, our data seem to be in contrast with the obstetric literature, since we
4 found no correlation between maternal COVID-19 and adverse fetal or neonatal outcomes. Instead,
5 in the general population the infection appears to be associated with higher risk for severe neonatal
6 mortality and morbidity¹⁷⁻²¹, including respiratory distress (OR 1.66), low birth weight (OR 1.69),
7 stillbirth (OR 1.46) and NICU admission (OR 2.12)⁸.

8 To explain this difference, as speculated in other studies assessing COVID19 outcomes in pregnant
9 patients with MS^{9,22}, we can hypothesize a role of the more intensive specialized care received by
10 MS pregnant patients, considered and treated as “high risk” pregnancies. Moreover, our study’s
11 collection of data covered the period 2020-2022, while the majority of the studies on the general
12 population had a collection period in early 2020^{8,21}; therefore, in our sample, most recent strategies
13 of prevention and newly available treatments for SARS-CoV2 infection could explain better fetal
14 outcomes.
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16 Furthermore, our data showed a significant lower rate of preterm birth in women with COVID-19, a
17 finding in line with data from the general population, as confirmed by a recent meta-analysis
18 conducted on the risk of preterm birth during COVID-19 pandemic.²³
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21 As concerning maternal outcomes, instead, our findings are in line with data from the general
22 population on the interaction between COVID-19 and pregnancy, where it has been well described
23 an increased risk of several adverse maternal outcomes^{8,17,24}. In particular, one recent meta-analysis⁸
24 showed increased risk for maternal death (OR 7.05, up to 22.52 in one of the included studies) and
25 pre-eclampsia (OR 1.39) in COVID19 infected pregnant women. In a multinational cohort study
26 included in the meta-analysis²⁵, pregnant women with COVID-19 were at higher risk for mortality
27 (OR 22.3), ICU admission (OR 5.04), infections requiring antibiotic treatment (OR 3.38). In our
28 study, 5 patients in the COVID-19 group developed gestational diabetes. Data in the general
29 population have shown a similar association²⁶ and suggest a possible link between gestational
30 diabetes rates and the disruptions to daily routine, the reduction of exercise options and the stressful
31 condition due to COVID-19²⁷. Moreover, in vitro evidence demonstrated the susceptibility of β
32 cells to SARS-CoV-2 and resulting diabetes mellitus²⁸, and other studies have shown that pancreatic
33 islet cells express the angiotensin-converting enzyme 2 (ACE2) receptor, the receptor used by
34 SARS-CoV-2 for attachment and invasion into cells^{29,30}. In addition, it has to be considered that
35 diabetes mellitus, similarly to overweight or obesity, is a well-known risk factor for COVID-19
36 diagnosis in pregnancy³¹.
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41 Some limitations need to be taken into account. First, the relatively small sample size, which, in
42 addition, prevented us from analyzing the impact of different DMTs on the outcomes. Moreover, it
43 would have been of interest to assess the impact of COVID-19 during pregnancy on MS clinical
44 course, but unfortunately the limited sample size prevented us from obtaining consistent and
45 statistically significant results on relapse rate and Magnetic resonance imaging (MRI) changes. In
46 addition, we did not assessed severity of COVID-19. In the general population, worse maternal and
47 fetal outcomes were associated with moderate or severe COVID-19 disease⁷, therefore a
48 stratification of patients based on the severity of COVID-19 could have led to different results.
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51 Despite the abovementioned limitations, this is the first study assessing the impact of COVID-19 on
52 maternal and fetal outcomes in pregnant patients with MS and provides useful insights on
53 management strategies in pregnant MS women.

54 Our findings highlight the importance of informing and educating MS patients to prevent COVID-
55 19 through vaccination, especially in MS women contemplating a pregnancy plan. Since the virus is
56 still circulating^{32,33}, future studies are needed to better understand the interaction between COVID-
57 19, MS and pregnancy and identify further potential strategies to improve both maternal and fetal
58 outcomes.
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Table 1 - Characteristics of the study sample before and after application of the IPTW method (N = 489)

		MS pregnancies without COVID-19 (N = 428)	MS pregnancies with COVID-19 (N = 61)	P before IPTW	P after IPTW
Age at pregnancy, years – mean ± sd		31.8 ± 4.77	31.7 ± 4.12	0.89	0.20
Disease duration at pregnancy – mean ± sd		7.9 ± 5.15	7.2 ± 5.46	0.35	0.66
Disease modifying treatment – n(%)	No treatment	259 (60.5%)	20 (32.8%)	<0.001	0.51
	Treated	169 (39.5%)	41 (67.2%)		
EDSS at pregnancy	≤ 3.5	399 (93.2%)	59 (96.7%)	0.31	0.51
	> 3.5	29 (6.8%)	2 (3.3%)		
MS phenotype– n(%)	Relapsing remitting	415 (97.0%)	60 (98.4%)	0.55	0.06
	Progressive forms	13 (3.0%)	1 (1.6%)		
Relapses in the previous year– n(%)	No	335 (78.3%)	44 (72.1%)	0.28	0.31
	Yes	93 (21.7%)	17 (27.9%)		
Previous spontaneous abortion– n(%)	No	385 (90.0%)	56 (91.8%)	0.65	0.15
	Yes	43 (10.0%)	5 (8.2%)		
Alcohol consumption during pregnancy– n(%)	No	421 (98.4%)	58 (95.1%)	0.11	0.84
	Yes	7 (1.6%)	3 (4.9%)		
Smoking habits during pregnancy– n(%)	No	391 (91.4%)	56 (91.8%)	0.91	0.21
	Yes	37 (8.6%)	5 (8.2%)		

* IPTW = Inverse Probability Treatment Weighting

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Table 2 – Frequency of study outcomes

		Total	Control	Covid-19	p
Maternal complications – n(%)	No	424 (86.7%)	375 (87.6%)	49 (80.3%)	0.12
	Yes	65 (13.3%)	53 (12.4%)	12 (19.7%)	
Fetal malformations – n(%)	No	441 (96.7%)	386 (97.0%)	55 (94.8%)	0.39
	Yes	15 (3.3%)	12 (3.0%)	3 (5.2%)	
Spontaneous abortion– n(%)	No	456 (93.3%)	398 (93.0%)	58 (95.1%)	0.54
	Yes	33 (6.7%)	30 (7.0%)	3 (4.9%)	

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Table 3 - Effect of Covid-19 on the three outcomes (Propensity score weighted model)

	Maternal complications	Spontaneous abortion	Fetal malformations
Covid-19 vs control	1.92 (1.18 – 3.16); 0.009*	0.46 (0.19 – 1.05); 0.08	1.21 (0.45 – 3.42); 0.70

*Results are expressed as OR (95%CI) and p value * Statistically significant*

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Table 4 - Maternal complications

	Total (N = 65)	Control (N = 53)	Covid-19 (N = 12)	p
Disorders of placenta – n(%)	7 (10.8%)	7 (13.2%)	0 (0.0%)	0.33
Infectious complications – n(%)	7 (10.8%)	2 (3.8%)	5 (41.7%)	0.002
Puerperal hemorrhage – n(%)	5 (7.7%)	5 (9.4%)	0 (0.0%)	0.57
Urinary tract disorders – n(%)	5 (7.7%)	5 (9.4%)	0 (0.0%)	0.57
Mastitis – n(%)	1 (1.5%)	1 (1.9%)	0 (0.0%)	0.99
Postpartum depression – n(%)	1 (1.5%)	1 (1.9%)	0 (0.0%)	0.99
Others – n(%)	39 (60.0%)	32 (60.4%)	7 (58.3%)	0.99

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Table S1: Other maternal complications (N = 39)

	Control (n = 32)	Covid (n = 7)
Abortion threat	8 (25.0%)	0 (0.0%)
Gestosis	3 (9.4%)	0 (0.0%)
Gestational diabetes	2 (6.3%)	5 (71.4%)
Gestational diabetes and abortion threat	2 (6.3%)	0 (0.0%)
Metrorrhagia	2 (6.3%)	0 (0.0%)
Adhesions	1 (3.1%)	0 (0.0%)
Cerclage	1 (3.1%)	0 (0.0%)
Childbirth threat	1 (3.1%)	0 (0.0%)
Cholestasis	1 (3.1%)	0 (0.0%)
Clots	1 (3.1%)	0 (0.0%)
Cord wrapping	1 (3.1%)	0 (0.0%)
Gestosis, hypertension,arteriovenous malformations, haemiplasia	1 (3.1%)	0 (0.0%)
Headache	1 (3.1%)	0 (0.0%)
Hypertension	1 (3.1%)	0 (0.0%)
Meningism	1 (3.1%)	0 (0.0%)
Pelvic floor burst injury	1 (3.1%)	0 (0.0%)
Pharmacologically treated iron defic	1 (3.1%)	0 (0.0%)
Preeclampsia	1 (3.1%)	1 (14.3%)
Sixth-month contractions	1 (3.1%)	0 (0.0%)
Uterine atony	1 (3.1%)	0 (0.0%)
Dysthyroidism	0 (0.0%)	1 (14.3%)