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ORIGINAL ARTICLES AND REVIEWS

The first SARS-CoV-2 wave among pregnant women in Italy: results from a prospective population-based study

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Abstract

Introduction. This study aimed to estimate the incidence of SARS-CoV-2 infection among pregnant women during the first pandemic wave in Italy, and to describe COVID-19 disease characteristics and maternal and perinatal outcomes.

Materials and methods. National population-based prospective cohort study collecting information on women with SARS-CoV-2 diagnosis, confirmed within 7 days from hospital admission.

Results. The national SARS-CoV-2 rate was 6.04 per 1,000 births (95% CI 5.62-6.49) among pregnant women and 7.54 (95% CI 7.47-7.61) among women in reproductive age. 72.1% of the cohort developed mild COVID-19 disease without pneumonia nor need for ventilatory support. Severe disease was significantly associated with women's previous comorbidities (OR 2.55; 95% CI 0.98-6.90), obesity (OR 4.76; 95% CI 1.79-12.66) and citizenship from High Migration Pressure Countries (OR 3.43; 95% CI 1.27-9.25).

Conclusions. During the first pandemic wave in Italy, the SARS-CoV-2 rate among pregnant women was lower compared to that detected among women of reproductive age, and risks of severe COVID-19 disease and adverse maternal and perinatal outcomes were rare.

Key words

- cohort studies
- Italy
- pregnancy outcome
- SARS-CoV-2

INTRODUCTION

At the beginning of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic, it was feared that the virus could cause the same dramatic maternal and perinatal outcomes observed during the outbreak of other respiratory viruses, such as SARS-CoV-1, Middle East Respiratory Syndrome (MERS) and H1N1 flu [1].

Research capable of gathering sound information in support of public health recommendations and clinical practice was therefore urgently needed. Several publications of single case reports and case series [2] were meta-analysed in a living systematic review by WHO [3]. International multicentre registries [4-6] recruiting from many different countries, have been established, with frequent data overlapping influencing the quality of successive systematic reviews [7-11]. Because of the lack of population-based studies, the proportion of ascertained cases were unclear due to unknown underlying denominators. Therefore, interpreting the findings from these studies in order to give a confident estimate of the true rate of complications for women infected during pregnancy and for their newborns was challenging.

Few countries, participating in the International Network of Obstetric Survey System (INOSS) [12] including Italy with the Italian Obstetric Surveillance System (ItOSS), launched prospective population-based cohort studies able to reliably estimate the prevalence of SARS-CoV-2 infection, investigate COVID-19 disease characteristics and describe adverse maternal and perinatal outcomes. Preliminary results published by the UK Obstetric Surveillance System (UKOSS) [13], ItOSS [14-16] and Nordic Obstetric Surveillance System (NOSS) – that includes Sweden, Denmark, Finland and Norway – [17], showed an absolute low risk of severe COVID-19 disease and rare adverse maternal

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and perinatal outcomes during the first pandemic wave.

The aim of this paper, which is an extension of a previous published series [14], was to estimate the incidence rate of SARS-CoV-2 infection among pregnant women during the first pandemic wave in Italy, and to describe COVID-19 disease characteristics and maternal and perinatal outcomes.

MATERIALS AND METHODS

This national population-based prospective cohort study collected information on women with confirmed SARS-CoV-2 infection admitted to any Italian hospital during pregnancy and within 42 days from its outcome.

Trained reference clinicians in each of the 315 participating maternity hospitals (*Appendix 1*) entered the requested information in a web-based secure system. The online form investigating women's socio-demographic characteristics, medical and obstetric history, disease management, mode of delivery and maternal and perinatal outcomes was revised and pre-tested by a multidisciplinary group of experts. Complete data reporting was ensured by weekly email reminders and phone contacts with the reference clinicians.

Confirmed SARS-CoV-2 infection was defined as the detection of viral RNA on reverse transcriptase-polymerase chain reaction (RT-PCR) testing of nasopharyngeal swab and/or blood and/or the radiological diagnosis of COVID-19 pneumonia. Neonatal SARS-CoV-2 infection was defined as the detection of viral RNA on RT-PCR testing of a nasopharyngeal swab.

In Italy, until the end of March 2020 only symptomatic pregnant women and those defined as close contacts of a SARS-CoV-2 infected person were tested. In April, the Regions progressively adopted universal screening policies, and from May all pregnant women admitted to hospital were tested, regardless of symptoms or exposure.

The present analysis refers to the first pandemic wave, defined as the period between February 25 and August 31, 2020 and includes hospitalized pregnant women with SARS-CoV-2 diagnosis confirmed within 7 days from hospital admission.

ETHICS AND CONSENT

The Ethics Committee of the Istituto Superiore di Sanità (Italian National Institute of Health) approved the project (Prot. 0010482 CE 01.00, Rome 24/03/2020). The study protocol is available at https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-pregnancy-childbirth-breastfeeding-prospective-study-itoss (Italian).

An informed consent to participate in the study was acquired from any woman at study enrolment.

OUTCOMES

The main outcome measures included in the study are: COVID-19 pneumonia confirmed by chest imaging, mechanical ventilatory support (non-invasive mechanical ventilation, orotracheal intubation, extracorporeal membrane oxygenation – ECMO), intensive care unit (ICU) admission. COVID-19 disease severity was defined as follows:

a. mild disease: absence of COVID-19 pneumonia;
b. moderate disease: confirmed COVID-19 pneumonia requiring at most oxygen therapy;
c. severe disease: confirmed COVID-19 pneumonia requiring mechanical ventilatory support and/or ICU admission.

Secondary outcomes include: maternal mortality (maternal death during pregnancy or within 42 days from any pregnancy outcome), maternal severe morbidity, preterm birth (22-31 and 32-36 gestational weeks), mode of delivery (vaginal, elective caesarean section (CS), urgent/emergency CS due to COVID-19, urgent/emergency CS due to maternal/foetal indications), stillbirth (intrauterine foetal death ≥22 completed weeks of gestation), low birth weight (<2,500g), neonatal intensive care unit (NICU) admission, neonatal mortality (death of a live-born infant <7 days of life) and neonatal severe morbidity.

COVARIATES

Covariates include the following socio-demographic and medical characteristics: women's age (<30, 30-34, ≥35 years), citizenship (Italian, High Migration Pressure Countries – HMPCs, not HMPCs) [18], educational level (low: primary school or lower; medium: high school; high: bachelor's degree or higher), previous comorbidities (at least one of the following: diabetes, asthma requiring medical treatment, hypertension, cardiovascular diseases, lung diseases, HIV/AIDS, other morbidities), obesity (body mass index [BMI]>30 kg/m^2).

STATISTICAL ANALYSIS

Statistical analyses were performed using the Statistical Package STATA/MP version 14.2. Frequency distributions, prevalence and odds ratios (ORs) with their 95% confidence intervals (CI) were used to describe data. Missing data were excluded when their proportion was lower than 5%, otherwise included as a modality in the frequency distributions.

The national SARS-CoV-2 incidence rate with 95% CI was estimated among pregnant women. All the hospitalized and outpatient women, with ongoing pregnancy or who gave birth during the study period, irrespective of time of diagnosis, were included in the numerator. Latest available (2019) data on deliveries from the national Birth Registry were used as denominator [19], applying a 3.6% reduction in accordance with the Italian National Statistics Institute (ISTAT) estimate for births variation between 2019 and 2020 [20]. Deliveries were weighted with an estimate of the time of exposure to the risk of infection during pregnancy. The incidence rate among pregnant women has been compared with the rate among the background population of women of reproductive age (15-49 years), calculated considering the SARS-CoV-2 positive cases notified to the national surveillance system during the exact study period. [21].

Percentage distributions of socio-demographic, medical and obstetric characteristics stratified by severity of COVID-19 disease were calculated.

The association between infection severity and potential risk factors (woman's age, citizenship, educational

level, presence/absence of previous comorbidities, and presence/absence of obesity) was assessed by estimating mutually adjusted ORs and their 95% CI, through a multinomial logistic regression model. Plausible interactions (corresponding to all pairwise interactions between the variables included in the model) were tested using the Likelihood Ratio Test ($p<0.05$). The model was performed on complete cases defined as cases without missing data for any variable of interest (see *Appendix 2* for details about handling of missing data).

Prevalence of mode of delivery and maternal and neonatal outcomes were stratified by infection severity. CS, preterm birth, and neonatal birthweight were compared with data retrieved from the 2019 national Birth Register, and unadjusted risk ratios (RRs) were estimated.

In this observational study, no formal power calculation was performed because the sample size was governed by the disease incidence.

RESULTS

From February 25 to August 31, 2020, the trained clinicians of the 315 Italian participating maternity units (*Appendix 1*) notified 786 women with current or previous confirmed SARS-CoV-2 infection during pregnancy and up to 42 days after childbirth (*Figure 1*). Most of the cases (84.6%) occurred in northern Italy, 10.3% in the Centre and 5.1% in the South. As described in *Figure 1*, this study includes 548 women with ongoing pregnancy or who gave birth, admitted to hospital with a positive SARS-CoV-2 test within 7 days from admission.

The national SARS-CoV-2 incidence rate among pregnant women was 6.04 per 1,000 births (95% CI 5.62-6.49), slightly lower than the rate of 7.54 per 1,000 women (95% CI 7.47-7.61) estimated among the background population of Italian women of reproductive age. The incidence rate among pregnant women ranged between 11.15/1,000 (95% CI 10.31-12.07) in the North, 3.25/1,000 (95% CI 2.59-4.08) in the Centre, and 0.87/1,000 (95% CI 0.63-1.20) in the South of the country. The corresponding figures among women of reproductive age were respectively 12.52/1,000 (95% CI 12.39-12.65), 5.19/1,000 (95% CI 5.07-5.32) and 2.50/1,000 (95% CI 2.43-2.57).

Table 1 describes women's socio-demographic, medical and obstetric characteristics, stratified by COVID-19 disease severity. The vast majority of the cohort (72.1%; n = 395) developed a mild disease, 22.4% (n = 123) a moderate and 5.5% (n = 30) a severe disease. Women's mean age was 31.9 years (SD = 5.54); the percentage of women with foreign citizenship was 28.6%, ranging from 26.1% in the mild disease group to 46.7% in the severe group. Pre-existing comorbidities and obesity concerned respectively 17.8% and 12.1% of the entire cohort and 34.5% and 44.8% of the women with severe disease. Information on educational level was missing for 28.5% of the cases.

At first positive SARS-CoV-2 test, 85.8% of the women were at ≥28 weeks of gestation, 11.8% between 15 and 27 weeks, and 2.4% ≤14 weeks. The vast majority (95.2%) has been diagnosed through a RT-PCR of nasopharyngeal swab specimen, 2.4% respectively through chest imaging and through blood antibodies detection (data not shown). Overall, during the hospital stay, 22.6% (n = 124) of women was with ongoing pregnancy and 77.4% (n = 424) gave birth (*Table 1*). Women with ongoing pregnancy were admitted to hospital mostly for COVID-19 disease (75.0%) while other obstetric reasons or delivery were the main causes for hospitalization of those who gave birth (85.8%) (*Table 1S*, available online as Supplementary material).

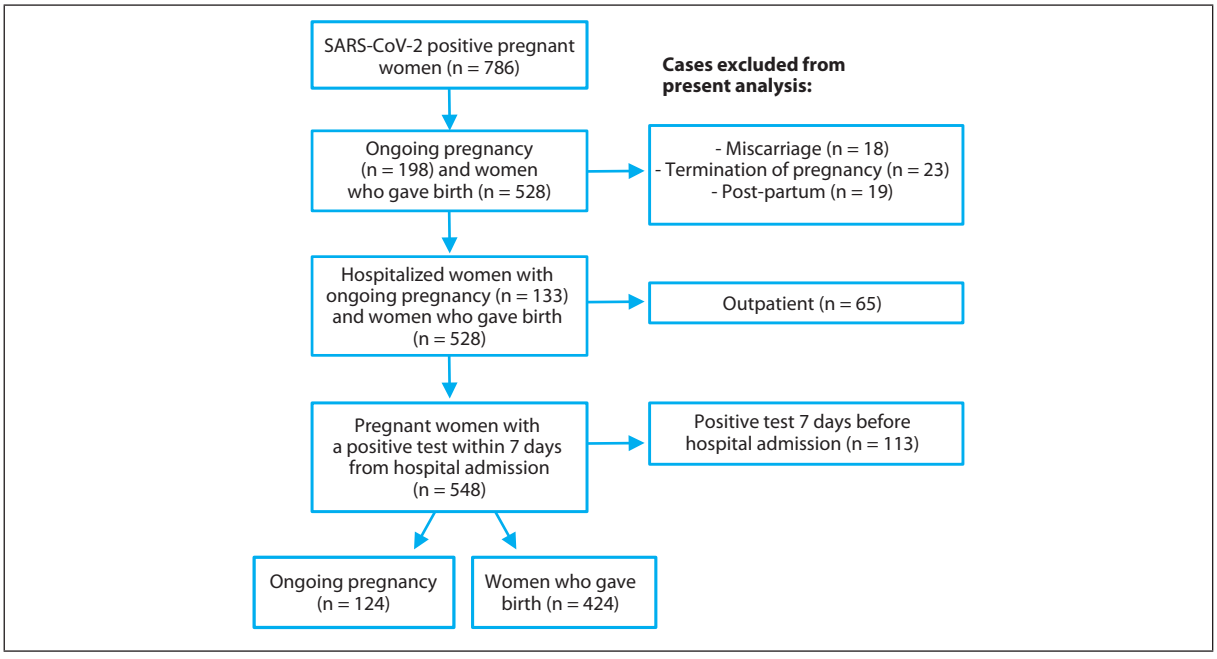

Figure 1
Women enrolled in the ItOSS cohort from February 25 to August 31, 2020.

Table 1
Women's characteristics by COVID-19 disease severity

	Mild[a] (n = 395)		Moderate[b] (n = 123)		Severe[c] (n = 30)		Total (N = 548)	
	n	%	n	%	n	%	N	%
Age, years (7 missing)								
<30	126	32.5	41	33.3	9	30.0	176	32.5
30-34	140	36.1	37	30.1	10	33.3	187	34.6
≥35	122	31.4	45	36.6	11	36.7	178	32.9
Citizenship								
Italian	292	73.9	83	67.5	16	53.3	391	71.4
HMPCs	101	25.6	40	32.5	14	46.7	155	28.3
Not HMPCs	2	0.5	0	0.0	0	0.0	2	0.4
Country of birth								
Italy and western Europe	262	66.3	75	61.0	12	40.0	349	63.7
East Europe	27	6.8	9	7.3	3	10.0	39	7.1
Africa	46	11.6	15	12.2	9	30.0	70	12.8
South/Central America	29	7.3	13	10.6	4	13.3	46	8.4
Asia	31	7.8	11	8.9	2	6.7	44	8.0
Level of education*								
Low	78	19.7	20	16.3	8	26.7	106	19.3
Medium	121	30.6	42	34.1	10	33.3	173	31.6
High	81	20.5	28	22.8	4	13.3	113	20.6
Missing	115	29.1	33	26.8	8	26.7	156	28.5
Previous comorbidities (10 missing)	56	14.5	30	24.6	10	34.5	96	17.8
Pre-gestational diabetes	4	1.0	2	1.6	3	10.3	9	1.7
Autoimmune diseases	7	1.8	5	4.1	0	0.0	12	2.2
Chronic hypertension	3	0.8	3	2.5	5	17.2	11	2.0
BMI >30 kg/m² (10 missing)	36	9.3	16	13.1	13	44.8	65	12.1
Multiparous (2 missing)	215	54.6	79	64.2	16	55.2	310	56.8
Multiple pregnancy (1 missing)	8	2.0	3	2.4	1	3.3	12	2.2
Gestational age at diagnosis, weeks (14 missing)								
≤14	8	2.1	4	3.4	1	3.3	13	2.4
15-27	25	6.5	27	23.1	11	36.7	63	11.8
≥28	354	91.5	86	73.5	18	60.0	458	85.8
Ongoing pregnancy	57	14.4	56	45.5	11	36.7	124	22.6

[a]Absence of COVID-19 pneumonia.
[b]Confirmed COVID-19 pneumonia requiring at most oxygen therapy.
[c]Confirmed COVID-19 pneumonia requiring mechanical ventilatory support and/or ICU admission.
HMPCs: high migration pressure countries.
*Low: primary school or lower; medium: high school; high: bachelor's degree or higher.

Figure 2 describes the weekly trend of the number of positive pregnant women enrolled during the study period, stratified by COVID-19 disease severity. The majority of cases (61.3%), including all severe and most moderate cases, occurred between March and April 2020.

At time of diagnosis, 45.5% of the women was asymptomatic with an increasing trend ranging from 10.8% in March to 74.2% in July - August 2020 (*Figure 3*). Fever (36.3%), cough (33.7%) and tiredness (21.0%) were the most frequently reported symptoms. Dyspnoea was reported by 14.7% of the women, 5.4% among those with mild disease and 76.7% among those with severe COVID-19 disease (*Table 2S*, available online as Supplementary material).

Table 2 shows the ORs of developing moderate and severe disease *vs* mild disease, mutually adjusted for women's age, citizenship, educational level, previous comorbidities and obesity. Women with at least one previous comorbidity were more likely to develop a moderate (OR = 1.87; 95% CI 1.03-3.41) and a severe

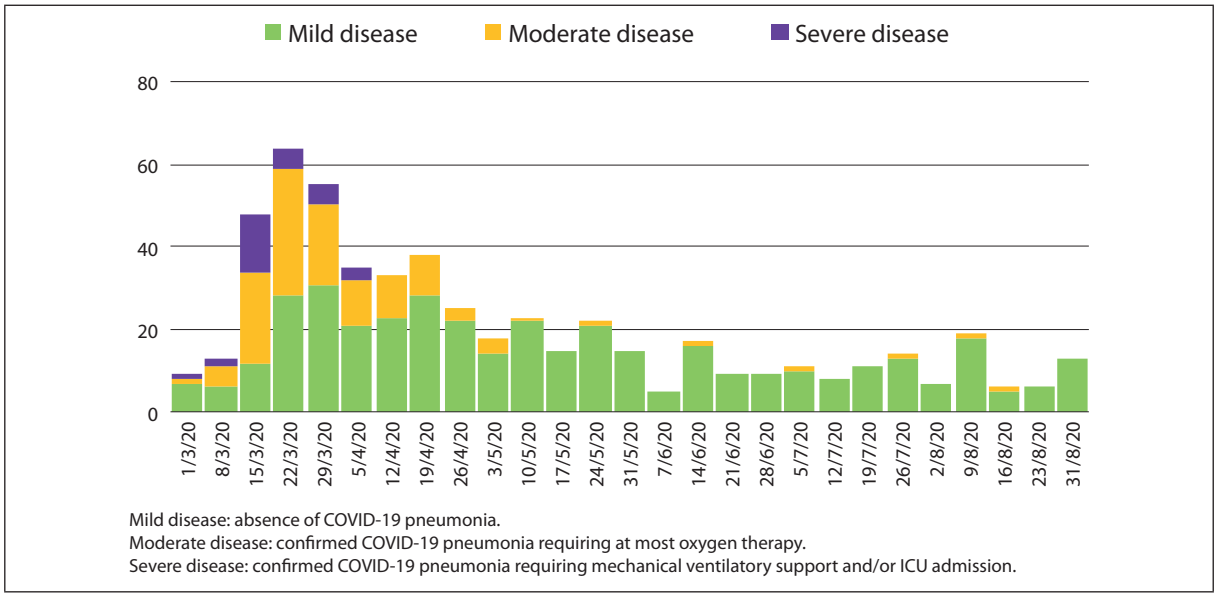

Figure 2
Weekly trend of the number of enrolled women by COVID-19 disease severity, between February 25 and August 31, 2020 (n = 548).

(OR = 2.55; 95% CI 0.98-6.90) COVID-19 disease. The occurrence of severe illness was significantly higher among obese women (OR = 4.76; 95% CI 1.79-12.66) and those with citizenship from HMPCs (OR = 3.43; 95% CI 1.27-9.25). No statistically significant association was found with educational level. None of the tested plausible interactions was statistically significant.

Table 3 describes women's and perinatal outcomes stratified by disease severity. Overall, 29 women (5.3%) received non-invasive ventilatory support, six (1.1%) underwent orotracheal intubation and two (0.4%) received ECMO. Eighteen women (3.3%) were admitted to ICU and 23 (4.2%) developed severe morbidity. No maternal deaths occurred.

Overall, ten of the 438 livebirths (2.3%) developed severe morbidity and 63 (14.7%) were admitted to NICU (*Table 3*). The percentage of neonates with a birthweight <2,500 grams was 13.6%, higher than the 7.1% national proportion in 2019 [19] (RR = 1.91; 95% CI 1.50-2.43). As shown in *Table 3* neonatal morbidity, access to NICU and low birthweight were more common among mothers with more severe conditions. Four stillbirths (0.9% of total births) were recorded and no neonatal deaths occurred. Overall, 4% of the livebirths

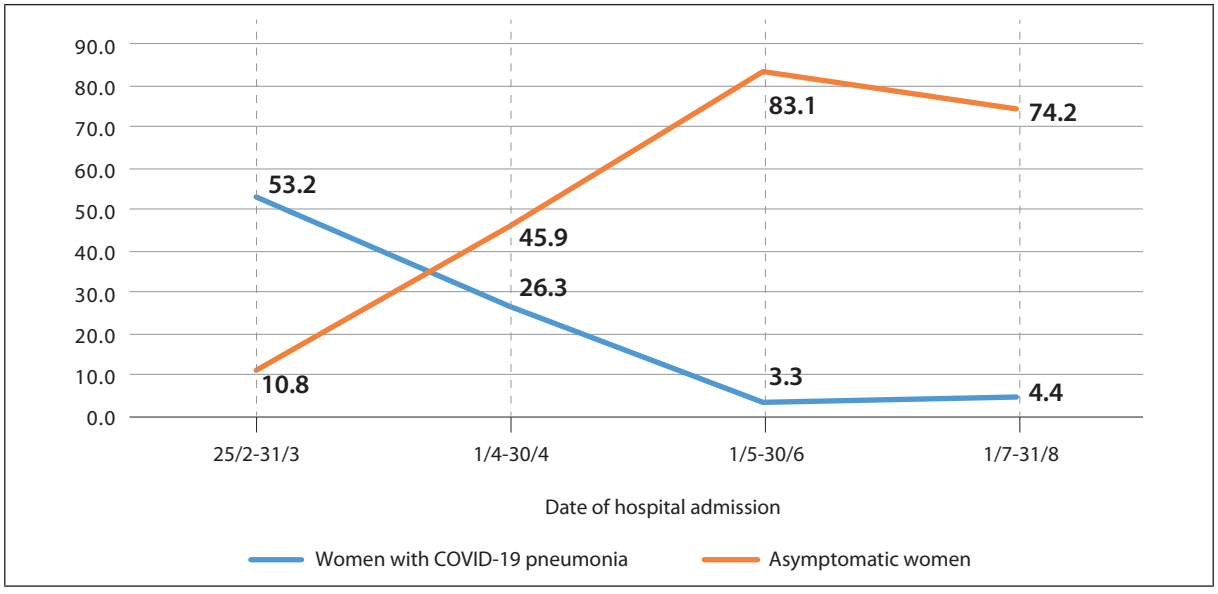

Figure 3
Temporal trend of proportions of women with COVID-19 pneumonia and asymptomatic women.

Table 2
Mutually adjusted odds ratios of moderate and severe disease for the selected variables

Variable	OR (95% CI)	
	Moderate *vs* mild	Severe *vs* mild
Age		
<34	1.00	1.00
≥35	1.20 (0.72-1.99)	1.26 (0.49-3.26)
Citizenship		
Italian + no HMPCs	1.00	1.00
HMPCs	1.47 (0.82-2.62)	3.43 (1.27-9.25)
Level of education[a]		
Low	1.00	1.00
Medium-high	1.65 (0.89-3.06)	1.41 (0.50-3.99)
Previous comorbidities		
No	1.00	1.00
Yes	1.87 (1.03-3.41)	2.55 (0.98-6.90)
Obesity		
No	1.00	1.00
Yes	1.15 (0.55-2.39)	4.76 (1.79-12.66)

Mild disease: absence of COVID-19 pneumonia.
Moderate disease: confirmed COVID-19 pneumonia requiring at most oxygen therapy.
Severe disease: confirmed COVID-19 pneumonia requiring mechanical ventilatory support and/or ICU admission.
HMPCs: high migration pressure countries.
[a]Low: primary school or lower; medium-high: high school or higher.

had a positive SARS-CoV-2 test, 10 within and 7 after 24 hours from birth. Among positive babies, eight were delivered vaginally and nine by CS.

Table 4 shows mode of delivery and gestational age at birth among the 424 SARS-CoV-2 positive women who gave birth. The CS rate was 33.6%, close to the national figure of 31.8% recorded in 2019 [19] (RR = 1.06; 95% CI 0.93-1.21). Urgent and emergency CS were significantly more frequent among mothers with severe COVID-19 disease. CS was performed under general anaesthesia in 7.3% of the cases and in 31.3% of the women with severe COVID-19 illness. The proportion of preterm delivery (13.7%) was higher compared to the 6.7% national average [19] (RR = 2.05; 95% CI 1.60-2.61), especially among mothers with severe disease (63.2%). Iatrogenic indications – defined as elective CS or induction of labour – were responsible for 22.6% of the recorded preterm births.

DISCUSSION

Principal findings

The national incidence rate of SARS-CoV-2 infection in pregnancy during the first pandemic wave in Italy (6.04 per 1,000 births; 95% CI 5.62-6.49) was lower compared to the rate estimated among the background population of women of reproductive age [21] (7.54 per 1,000 women; 95% CI 7.47-7.61).

The vast majority of SARS-CoV-2 positive pregnant women (72.1%) developed a mild disease without COVID-19 pneumonia and no need for ventilatory support, 22.4% a moderate illness with confirmed pneumonia not requiring any mechanical ventilatory support (at most oxygen therapy), and only 5.5% a severe disease requiring mechanical ventilatory support and/or ICU admission. Previous comorbidities, obesity and foreign citizenship from HMPCs were significantly associated to a higher occurrence of severe disease. Overall, the enrolled pregnant women had an absolute low risk of severe maternal (4.2%) and perinatal (2.3%) morbidity.

Strengths and weakness of the study

A strength of the present study is the nationwide prospective population-based cohort design. The offer of routine screening tests at hospital admission from May 2020, provided a complete denominator assuring reliably ascertainment of incident cases and robust estimates of COVID-19 severe disease among positive pregnant women. Stratifying the cohort by COVID-19 disease severity, instead of presence/absence of SARS-CoV-2 symptoms, represents a further strength of the study, allowing a better portray of women's clinical conditions. The accuracy of the collected data has been monitored and assured by the durable network of trained clinicians in each participating maternity unit and by the weekly email reminders and phone contacts, in order to solicit case notification and recovery of essential missing information.

The study limitations include the absence of a control group of pregnant women without SARS-CoV-2 infection and the small number of women diagnosed during the first two trimesters of pregnancy (14.2%), which requires further analysis to investigate possible effects of early infection. The lack of information on the pregnancy status of women notified to the national SARS-CoV-2 surveillance did not allow a crosscheck of the cases detected through the ItOSS study. In addition, in Italy universal testing for hospitalized pregnant women was implemented from May 2020, we might therefore have missed cases occurred during the first two months of the study. Failure to identify these cases leads to a possible underestimation of the phenomenon among pregnant women, and to a greater extent among the background population of women of reproductive age for whom the screening offer was partial and delayed.

Moreover, due to the restrained circulation of the virus in centre and southern Italy during the first pandemic wave, we cannot generalize the findings of this paper to the whole country.

Comparison with other studies

Similarly to the UKOSS cohort [22], women with ongoing pregnancy compared to those who gave birth were hospitalized more often due to COVID-19 disease. As reported by previous studies [10, 13, 17, 22-24], women with previous comorbidities, obese, and foreigners from HMPCs showed a significantly higher occurrence of more severe forms of COVID-19 disease. A pattern of disadvantaged social conditions affecting ethnic minorities [25, 26] may be linked to worse clinical conditions observed in migrant women.

Table 3
Women's and perinatal outcomes

Women's outcome	Mild[a] (n = 395)		Moderate[b] (n = 123)		Severe[c] (n = 30)		Total (N = 548)	
	n	%	n	%	n	%	N	%
Respiratory support								
Oxygen therapy	8	2.0	51	41.5	30	100.0	89	16.2
Non-invasive ventilatory support	0	0.0	0	0.0	29	96.7	29	5.3
Orotracheal intubation	0	0.0	0	0.0	6	20.0	6	1.1
ECMO	0	0.0	0	0.0	2	6.7	2	0.4
ICU admission	0	0.0	0	0.0	18	60.0	18	3.3
Severe maternal morbidity*	5	1.3	7	5.7	11	36.7	23	4.2
Maternal death	0	0.0	0	0.0	0	0.0	0	0.0
Perinatal outcome	**(n = 343)**		**(n = 69)**		**(n = 20)**		**(n = 432)**	
Stillbirth	3	0.9	1	1.4	0	0.0	4	0.9
Livebirth	340	99.1	68	98.6	20	100.0	428	99.1
Severe neonatal morbidity**	3	0.9	5	7.4	2	10.0	10	2.3
NICU admission	41	12.1	12	17.6	10	50.0	63	14.7
Neonatal death	0	0.0	0	0.0	0	0.0	0	0.0
Birthweight <2500 grams (3 missing)	38	11.3	10	14.7	10	50.0	58	13.6
5-min Apgar score								
<7	1	0.3	0	0.0	1	5.0	2	0.5
≥7	311	91.5	63	92.6	15	75.0	389	90.9
Missing	28	8.2	5	7.4	4	20.0	37	8.6
Neonatal positive SARS-CoV-2 test:								
<24 hours from delivery	7	2.1	3	4.4	0	0.0	10	2.3
≥24 hours from delivery	4	1.2	1	1.5	2	10.0	7	1.6

[a]Absence of COVID-19 pneumonia.
[b]Confirmed COVID-19 pneumonia requiring at most oxygen therapy.
[c] Confirmed COVID-19 pneumonia requiring mechanical ventilatory support and/or ICU admission.
*Shock, acute respiratory stress syndrome, kidney failure, other.
**Acute respiratory distress syndrome, interstitial pneumonia, intraventricular haemorrhage, necrotizing enterocolitis, neonatal encephalopathy, sepsis, other.
ECMO - extracorporeal membrane oxygenation; ICU - intensive care unit; NICU - neonatal intensive care unit.

Table 4
Mode of delivery and gestational age at birth by COVID-19 disease severity

Outcome	Mild[a] (n = 338)		Moderate[b] (n = 67)		Severe[c] (n = 19)		Total (N = 424)	
	n	%	n	%	n	%	N	%
Mode of delivery (2 missing)								
Vaginal	237	70.1	41	62.1	2	11.1	280	66.4
Elective CS	55	16.3	10	15.2	0	0.0	65	15.4
Urgent/emergency CS due to maternal/foetal indication	43	12.7	10	15.2	6	33.3	59	14.0
Urgent/emergency CS due to COVID-19	3	0.9	5	7.6	10	55.6	18	4.3
Gestational age at birth*, weeks (16 missing)								
≤31	4	1.2	3	4.5	5	26.3	12	2.9
32-36	26	7.9	11	16.4	7	36.8	44	10.8
≥37	299	90.9	46	68.7	7	36.8	352	86.3
Missing	9	-	7	10.4	0	-	16	-

[a]Absence of COVID-19 pneumonia.
[b]Confirmed COVID-19 pneumonia requiring at most oxygen therapy..
[c]Confirmed COVID-19 pneumonia requiring mechanical ventilatory support and/or ICU admission.
CS: caesarean section.
*Missing data were not ignored among the Moderate group because higher than 5%.

Although Italy holds one of the highest CS rates in the world [27], during the pandemic it was close to the 2019 national rate [19] (33.6% *vs* 31.8%), and significantly lower compared to the figure reported in two systematic reviews [10, 28] and by other European countries [13, 17, 22] that usually record lower rates than Italy. The prompt and wide dissemination among Italian obstetricians of the evidence of lack of indication to CS in case of SARS-CoV-2 infection [29, 30] probably helped in limiting it to women in critical conditions, which in fact underwent urgent/emergency CS due to COVID-19 in 55.6% of the cases.

Preterm delivery has been an issue of concern during the pandemic. To date, most studies confirm a higher risk of preterm birth among SARS-CoV-2 positive women, especially in case of severe disease [10, 22, 24]. We detected a two-fold rate (13.7%) compared to the 2019 national figure (6.7%), with significant differences between women affected by severe COVID-19 disease (63.2%) and those with mild disease (9.1%). Moreover, the estimated preterm birth rate could be underestimated due to the missed identification of SARS-CoV-2 positive women not hospitalized before the due date, responsible for a possible deflated denominator. Excluding the proportion of cases with iatrogenic indications (22.6% of preterm births), spontaneous preterm birth rate was equal to 10.6%, mostly due to late preterm births. Although newborns were more likely to be admitted to NICU, no increase in stillbirths and neonatal deaths compared to previous national data was observed, in accordance with the UKOSS data. Given the possibility of a deflated denominator due to the missed identification of SARS-CoV-2 positive women during the first two months of the study, also the reported estimate of low birthweight should be interpreted with caution.

As for maternal outcomes, 153 women (27.9%) was affected by COVID-19 pneumonia but only 23 (4.2%) developed severe morbidity. The prevalence of pneumonia (27.9%; 95% CI 24.3-31.8) was lower compared to that reported by Northern Europe (57.1%) [17], in line with the Spanish data (30.8%) [31], and higher compared to Allotey's systematic review (17.5%) [10] and UKOSS data (15%) [22].

Consistently with other studies [17, 22], poor neonatal outcomes were rare, no neonatal deaths occurred and four stillbirths (0.9%) were notified. During the first pandemic wave, 17 neonates (4.0%; 95% CI 2.5-6.3) had a SARS-CoV-2 positive test at birth. Data from UKOSS and US showed similar percentages, respectively 2% [22] and 2.5% [32]. Our findings cannot confirm or deny the hypothesis of a transplacental virus transmission [33], but reassure on the good outcomes of these positive babies [34].

CONCLUSIONS

The Italian ob-gyn health professionals have shown to be able to manage the emergency context, despite initial fear and uncertainty. Differently from international retrospective non population-based studies [2,4-6], and similarly to the prospective population-based results of the European INOSS cohorts [13,17,22], in Italy the SARS-CoV-2 incidence rate among women was comparable to the one detected among the background population of women of reproductive age [21], and the vast majority of pregnant women and newborns had mild disease and good outcomes. Except for the higher risk of preterm birth, that concerned mainly women with severe COVID-19 disease, the results of this study should reassure women, health professionals and decision makers about the impact of the SARS-CoV-2 infection in pregnancy during the first pandemic wave.

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Conflict of interest statement

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Individual contribution to the manuscript

Serena Donati: conceptualization, methodology, formal analysis, writing original draft, project administration, supervision; Edoardo Corsi: software, investigation, data curation, writing-review and editing, project administration; Alice Maraschini: methodology, formal analysis; Michele Antonio Salvatore: methodology, software, formal analysis, writing-review and editing; Federica Baltaro: investigation, data curation; Rosaria Boldrini: cooperation in formal analysis; Silvia Bonassisa: investigation, data curation; Roberto Brunelli: investigation, data curation; Angelo Cagnacci: investigation, data curation; Paola Casucci: investigation, data curation, supervision; Ilaria Cataneo: investigation, data curation; Irene Cetin: investigation, data curation, supervision; Elena De Ambrosi: investigation, data curation; Martina Del Manso: cooperation in formal analysis; Massimo Fabiani: cooperation in formal analysis; Stefania Fieni: investigation, data curation; Massimo Piergiuseppe Franchi: investigation, data curation, supervision; Enrico Iurlaro: investigation, data curation; Livio Leo: investigation, data curation, supervision; Marco Liberati: investigation, data curation, supervision; Lucia Li Sacchi: investigation, data curation; Stefania Livio: investigation, data curation; Mariavittoria Locci: investigation, data curation, supervision; Luca Marozio: investigation, data curation; Claudio Martini: investigation, data curation, supervision; Gianpaolo Maso: investigation, data curation; Federico Mecacci: investigation, data curation, supervision; Alessandra Meloni: investigation, data curation, supervision; Anna Domenica Mignuoli: investigation, data curation, supervision; Sascia Moresi: investigation, data curation; Luisa Patanè: investigation, data curation; Francesca

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Liguria Region

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Sicily Region

Vincenzo Aidala, *Castiglione Prestianni - Bronte;* Luigi Alio, Giuseppina Orlando *ARNAS Civico di Cristina Benfratelli - Palermo;* Maria Grazia Arena, Santo Recupero *S. Marco (ex V. Emanuele S. Bambino) - Catania* e *Osp. Generale - Lentini;* Salvatore Bevilacqua, Fabrizio Quartararo *Casa di cura Candela SPA - Palermo;* Rocco Billone *Civico Partinico* e *Dei Bianchi - Corleone;* Giuseppe Bonanno, *Maria Paternò Arezzo - Ragusa;* Antonio Bucolo, *Umberto I - Siracusa;* Claudio Campione, *Casa di cura prof. Falcidia - Catania;* Giuseppe Canzone, *S. Cimino - Termini Imerese;* Angelo Caradonna, *V. Emanuele II - Castelvetrano;* Sebastiano Caudullo e Cosimo Raffone, *AO Papardo - Messina;* Giovanni Cavallo, *PO Maggiore - Modica;* Antonio Cianci, Michele Fichera *V. Emanuele Rodolico - Catania;* Salvatore Corsello, Sergio Di Salvo *Casa di cura Villa Serena - Palermo;* Gaspare Cucinella, Maria Elena Mugavero *Villa Sofia - Cervello-Palermo;* Rosario D'Anna, *AOU G. Martino - Taormina,* Maria Rosa D'anna, *Buccheri La Ferla - Palermo;* Maria Di Costa, *Basilotta - Catania;* Giuseppe Ettore, *ARNAS Garibaldi Nesima - Catania;* Giovanni Falzone, Marta Fauzia *Umberto I - Nicosia;* Roberto Fazio, *G. Fogliani - Milazzo* e *Lipari;* Matteo Giardina *Ospedale Paolo Borsellino di Marsala*; Michele Gulizzi e Francesco La Mantia, *G. F. Ingrassia - Palermo;* Laura Giambanco, *S. Antonio Abate - Erice* e *B. Nagar-Pantelleria;* Salvatore Incandela, *S. Giovanni di Dio - Agrigento* e *Giovanni Paolo II - Sciacca;* Lilli Maria Klein *S. Vincenzo - Enna* e *Barone Romeo - Patti;* Michele La Greca, Venera Mille, *M. SS. Addolorata - Biancavilla;* Luigi Li Calsi *S. Giacomo d'Altopasso - Licata;* Emilio Lo Meo, Paolo Scrollo *Cannizzaro - Catania;* Vincenzo Miceli, *S. Raffaele Giglio - Cefalù;* Maria Pia Militello, *S. Marta e S. Venera - Acireale;* Alfio Mirenna, *Istituto clinico Vidimura (ex Casa di cura Gretter e Lucina) - Catania;* Pietro Musso, *Abele Ajello - Mazara del Vallo;* Michele Palmieri, *V. Emanuele-Gela;* Concetta Remigia Pettinato, Angelo Tarascio *Gravina - Caltagirone - Caltagirone;* Vincenzo Scattarreggia *Barone Lombardo - Canicattì;* Antonio Schifano *R. Guzzardi - Vittoria;* Calogero Selvaggio *S. Elia - Caltanissetta;* Luigi Triolo *Casa di cure Triolo Zancla SPA-Palermo;* Renato Venezia *P. Giaccone - Palermo*

Sardinia Region

Speranza Piredda *Civile Alghero;* Giangavino Peppi *Giovanni Paolo II - Olbia;* Giovanna Pittorra *S. Fracesco - Nuoro;* Gianfranco Depau *Nostra Signora della Mercede - Lanusei;* Gianfranco Puggioni *S. Martino - Oristano;* Loredana Pagliara *Nostra Signora di Bonaria - San Gavino;* Giulietta Ibba *CTO - Iglesias;* Caterina Tronci, *SS Trinità - Cagliari;* Giampiero Capobianco, *AOU Sassari;* Alessandra Meloni *Duilio Casula Monserrato AOU - Cagliari;* Francesca Palla *S. Michele AO Brotzu - Cagliari*

APPENDIX 2. MISSING DATA

Among the variables included in the model, the percentage of missing values was zero for disease severity and citizenship, 1.3% for woman's age, 1.8% for presence/absence of previous comorbidities, 1.8% for presence/absence of obesity, 28.5% for woman's educational level (*Table 1*). Overall, 29.4% of cases had missing data on at least one variable of interest.

The percentage of missing values was negligible for all variables considered except for educational level. The choice of listwise deletion to handle missing data in the model was justified by the condition that missingness for educational level was not significantly associated to the outcome (COVID-19 disease severity). This condition ensures that listwise deletion does not introduce any bias in the coefficients estimates [1, 2] regardless of whether the missing data mechanism was at random (MAR), as assumed in our case, or not at random (MNAR).

Model interactions were tested through Likelihood Ratio Test to verify that no interaction terms were omitted and no bias was introduced.

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