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Stillbirth occurrence during COVID-19 pandemic: a population-based prospective study

Abstract

Objectives: Data collected worldwide on stillbirth (SB) rates during the Covid-19 pandemic are contradictory. Variations may be due to methodological differences or population characteristics. The aim of the study is to assess the changes in SB rate, risk factors, causes of death and quality of antenatal care during the pandemic compared to the control periods.

Methods: This prospective study is based on the information collected by the Emilia-Romagna Surveillance system database. We conducted a descriptive analysis of SB rate, risk factors, causes of death and quality of cares, comparing data of the pandemic (March 2020–June 2021) with the 16 months before.

Results: During the pandemic, the SB rate was 3.45/1,000 births, a value in line with the rates of previous control periods. Neonatal weight >90th centile was the only risk factor for SB that significantly changed during the pandemic (2.2% vs. 8.0%; p-value: 0.024). No significant differences were found in the distribution of the causes of death groups. Concerning quality of antenatal cares, cases evaluated with suboptimal care (5.2%) did not change significantly compared to the control period (12.0%), as well as the cases with less than recommended obstetric (12.6% vs. 14%) and ultrasound evaluations (0% vs. 2.7%).

Conclusions: During the COVID-19 pandemic, no significant differences in SB rates were found in an area that maintained an adequate level of antenatal care. Thus, eventual associations between SB rate and the COVID-19 infection are explained by an indirect impact of the virus, rather than its direct effect.

Keywords: antenatal care; COVID-19; pandemic; public health; risk factors; stillbirth.

Introduction

Once the pandemic was declared, obstetricians tried to evaluate its possible impact on mother and foetus dyad. Preterm birth and stillbirth (SB) were soon reported as increased in a meta-analysis published as early as September 2020. [1]. However, the Authors warned against such conclusion since the paucity of reported events.

Data accumulated and later studies reported either increased [2–5] or unchanged [6–11] risk of SB during the pandemic. Uncertainty was partly solved in two more recent meta-analyses. Indeed, Yang et al. focused on differences existing between data obtained in single centre vs. regional/national data which seem more robust [12]. Chmielewska et al. observed that SB seems significantly increased only in low-middle income countries [13].

Nevertheless, it should be highlighted that many of the available studies were retrospective, hence there is an high risk of reporting bias. Moreover, none of them has evaluated at the same time the quality of the available antenatal cares.

The aim of our study is to report SB changes in a region of almost five million residents, where a Surveillance system of intrauterine death is active since several years, collecting and discussing cases [14].

Materials and methods

This is an area-based, prospective study that uses information collected by the Surveillance System, active since 2014 in Emilia-
Romagna, Italy. An “ad hoc” Commission designed the SB clinical diary as well as the diagnostic work-up. The diagnosis of SB was based on the World Health Organization recommendation: foetal death occurring at 22 weeks of gestation or greater, or birthweight of 500 g or more if the gestational age was unknown [15]. Gestational age was estimated based on the last menstrual period or on the first ultrasound examination if the last menstrual period was unknown or unreliable. Maternal information, details regarding pregnancy and delivery and the list of tests performed at diagnosis of SB were collected [16]. Each case reported by every birth centre of the region was audited in a multidisciplinary meeting to evaluate the causes of SB and the quality of care, according to ReCoDe classification [17] and Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) grade [18], respectively. Cares were graded as: Grade 0 – no suboptimal care, Grade 1 – a different management would have made no difference to the outcome, Grade 2 – a different management might have made a difference to the outcome, Grade 3 – a different management would reasonably have been expected to make a difference to the outcome. The number of births per years was obtained by Birth certificates (CeDAP) annually published [19]. The gestational weight gain and the neonatal anthropometry were evaluated by using the Institute of Medicine (IOM) recommendation [20] and the Italian Neonatal Study (INes) charts [21], respectively.

For this study, we compared SB rate of the pandemic period (March 2020–June 2021) with the one of the previous 16 months periods (November 2014 to February 2020). The data about risk factors for SB, causes of death and quality of care during the pandemic were compared with the ones of the SB occurred in the immediate previous 16 months. The ethical approval for this study was obtained from the local Institutional Review Board (35265 – 24/11/21). Information was stored anonymously in a secure database. Informed consent for diagnostic work-up was not required, because diagnostic investigations are mandatory by law in case of SB in Italy (D.M. 7/2016 and D.P.C. 170/99). Patient and foetus privacy was ensured during all the phases of data collection and analysis.

**Ethics approval**

The ethical approval for this study was obtained from the local Institutional Review Board (35265 – 24/11/21). Information was stored anonymously in a secure database. Informed consent for diagnostic work-up was not required, because diagnostic investigations are mandatory by law in case of SB in Italy (D.M. 7/2016 and D.P.C. 170/99). Patient and foetus privacy was ensured during all the phases of data collection and analysis.

**Theory/calculation**

A descriptive analysis of data was performed. Categorical variables are expressed as frequencies and percentages. Significant differences between the groups were assessed through the Chi-square test for these variables. p-value <0.05 was considered statistically significant.

**Results**

There were 135 SB out of 39,175 births from March 2020 to June 2021 (3.45 per 1,000 births), a value that was not different compared to the previous control periods (Table 1). Moreover, the description of SB rate changes in relation to the spread of the infection throughout the first three waves (March–June 2020, October 2020 – February 2021 and March – June 2021) is reported in Figure 1.

Information of SB occurring during the pandemic were compared with those of the 150 SB cases that have occurred in the immediate previous 16 months.

Risk factors for SB are reported in Table 2. Neonatal weight >90th centile was significantly less represented during the pandemic (p=0.024), while no differences were found among the remnant risk factors for SB.

According to ReCoDe classification, the distribution of causes of death did not change in the pandemic vs. the control period (Foetus: 25.2% vs. 27.3%, Cord: 12.6% vs. 13.3%, Placenta 36.3% vs. 29.3%, Amniotic fluid 0.7% vs. 0%, Uterus 0% vs. 0%, Mother 2.2% vs. 1.3%, Intrapartum 1.5% vs. 2.7%, Trauma 0% vs. 0%, Unclassified 21.5% vs. 26.0%; p=0.714). Moreover, causes of death related to proven infections were also calculated apart, by extracting data from different groups (Foetus, Placenta, Amniotic fluid). Overall, there were no statistically significant differences about proven infections between the pandemic (15/135, 11.1%) and the control period (9/150, 6.0%).

During the pandemic, there were two women testing positive for SARS-CoV-2, one of which was admitted to ICU for severe pneumonia. Both cases were detected during the second wave (Oct 2020–Feb 2021). Audit established that these deaths were not directly correlated to SARS-CoV-2 infection (the primary cause identified was placental abruption and placental insufficiency, respectively). No case (0/135, 0%) has been attributed to maternal COVID-19 infection.

**Table 1: SB rate during pandemic (Mar 20 – June 21) and in a series of previous 16 months periods (Nov 14 – Feb 20).**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>SB</td>
<td>150</td>
<td>144</td>
<td>148</td>
<td>150</td>
<td>135</td>
</tr>
<tr>
<td>Births</td>
<td>47,515</td>
<td>45,365</td>
<td>44,726</td>
<td>42,245</td>
<td>39,175</td>
</tr>
<tr>
<td>Rate (per 1,000 births)</td>
<td>3.16</td>
<td>3.17</td>
<td>3.31</td>
<td>3.55</td>
<td>3.45</td>
</tr>
</tbody>
</table>

SB, stillbirth.
According to audit, quality of care was evaluated as suboptimal (grade 2 or 3) in 7/135 cases (5.2%) during the pandemic, a rate not significantly different from the control period (18/150, 12.0%) (Figure 2). Moreover, during the pandemic the number of women receiving <4 antenatal care visits and <2 ultrasound examinations did not significantly differ from the control period (Table 3).

**Discussion**

The first case of SARS CoV-2 infection in Italy was recorded in Codogno, Lombardia (a neighbour region to Emilia Romagna), in February 2020. In March 2020 mitigation measures were taken by the Italian government to prevent the spread of infection in the general population. Meanwhile, COVID-19 was declared a pandemic by the World Health Organization. During the study period, three peaks of COVID-19 infection were observed in Italy (March – June 2020, Oct 2020 – Feb 2021, March – June 2021). In these periods, when SARS-CoV-2 wild type was predominant over Alpha variant, the Italian late (>28 weeks) SB rate in 2020 (2.65 per 1,000 births) was similar to the one of 2018 (2.59 per 1,000) [22, 23].

The present study shows that the rate of SB occurrence during the pandemic in Emilia-Romagna was similar to the...
one recorded in the same time period of previous years. These findings agree with the German data which reported a pre-pandemic rate of 4.24 per 1,000 births between January and July 2019 compared with 4.15 per 1,000 births in the respective months during the COVID-19 pandemic [9]. In Spain, Arnaez et al. confirms no increased SB rate either [11]. Sweden data by Pasternak et al. even showed a reduction from a pre-pandemic SB rate of 3.3 per 1,000 births to 2.7 per 1,000 births during the lockdown (April to May 2020) [10]. Several European and non-European studies reach similar conclusion [6–8, 24–30]. On the contrary, increase trends of SB rate during the pandemic were reported in England, Italy, Israel and Austria [2–5, 31].

It is difficult to identify which factors might have contributed to the above discrepancies. The period analysed in most of the studies under scrutiny were short, allowing a small sample size [32]. Most importantly, those data were collected through retrospective analyses, with a high risk of potentially missing data [12]. It is important to underline that our study is based on information stored by an area-based Surveillance system, while the major part of the studies in literature reports findings collected in single centres. Apart from those considerations, another possible interpretation of the stable SB trend was offered by Chmielewska et al. who reviewed 12 studies reporting an increase of SB in low- and middle-income countries and a decrease in high-income countries. The Authors suggest that the contradictory results may be explained by inefficiencies in the health systems and/or a failure to adequately address health requests during the pandemic in low-resource settings. [13].

The impact of routine obstetrical care upon perinatal outcomes was well established, namely in high-risk pregnancies. An adequate antenatal surveillance (defined as almost four antenatal visits and two ultrasound examinations [33]) was demonstrated effective to avoid potentially preventable SB, also in high-income countries [32, 34–36]. An important finding of our study is the constant quality of pregnancy care offered during the pandemic period. Indeed, despite limitations imposed by the Italian government to contrast the SARS-CoV-2 spread, the reorganization of regional antenatal services provided the minimum antenatal care visits as well as ultrasound exams in our population. Accordingly, there were no change in SB cases where Audit evaluated pregnancy care as suboptimal. Moreover, the distribution of causes of death (the main one remains the placenta dysfunction [37]) did not change during the pandemic, indirectly

<table>
<thead>
<tr>
<th>Table 3: Evaluation of quality and perinatal care during the pandemic as compared to the control period.</th>
<th>Previous period (n=150)</th>
<th>SARS-CoV-2 pandemic period (n=135)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suboptimal care (CESDI grade 2–3)</td>
<td>18</td>
<td>12.0</td>
<td>7</td>
</tr>
<tr>
<td>&lt;4 obstetric visits</td>
<td>21</td>
<td>14.0</td>
<td>17</td>
</tr>
<tr>
<td>&lt;2 ultrasound evaluations</td>
<td>4</td>
<td>2.7</td>
<td>0</td>
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Figure 2: Quality of care evaluated at audit.
confirming of the above statements. Furthermore, the low prevalence of sub-optimal care in our study compared to data published by other countries [38, 39], supports the importance of a universal and public health care system during pregnancy, as is provided in Emilia-Romagna [35].

**Strengths and limitation of the study**

The major strengths of our study are the high quality of its validated data derived from the regional Surveillance System database, its prospective design and the analysed period which is much longer than other studies. Data are relative to the first three pandemic waves, which were characterized by SARS-CoV-2 Wild-type and Alpha variant. To our knowledge, in literature there are only retrospective studies: the greater part of them covering only the first lockdown. In addition, the design of the present study reduced potential seasonal variations that could affect overall SB rates, by comparing five separate periods.

The limitation of the study is the lack of transferability of the findings since the Surveillance System of Emilia-Romagna region is not extended to other areas of Italy.

**Conclusions**

In conclusion, in a region where adequate levels of antenatal care were offered, no changes in the SB rate occurred, nor there have been changes in the risk factors and in the causes of death. Eventual associations between SB rate and the COVID-19 infection would therefore be explained by an indirect impact of the virus, rather than its direct effect.

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**Author contributions:** FF conceived the study. CS, FM, VF and FF managed the data collection. CS, DM and EP managed the analysis of the data. Drafting of the manuscript was led by CS, FM with input from FF, who gave the final approval of the version to be published. All authors have read and approved the final manuscript.

**Competing interests:** Authors state no conflict of interest.

**Informed consent:** Informed consent for diagnostic work-up was not required because in Italy diagnostic investigation is mandatory by law in case of SB (D.M. 7/2014 and D.P.C. 170/99). Patient and fetus privacy was ensured during the phase of data collection and analysis.

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