Original Research

When Two Coincidences are a Clue: A Retrospective Cohort Study Regarding the Incidence of Ruptured Tubal Pregnancies in a Northern Italy Hospital During the COVID-19 Pandemic

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Abstract

Background: Undiagnosed ectopic pregnancies are among the main gynecological emergencies, and hemorrhage from an ectopic pregnancy is still the leading cause of maternal mortality in the first trimester. During the first lockdown period in Italy (March–April 2020) and in March 2021 restrictive measures were issued by the Italian government, but their impact on the incidence of ruptured tubal pregnancies remains unknown. Methods: The purpose of this study was to evaluate the impact of restrictive measures for the COVID-19 outbreak on the incidence of ruptured tubal pregnancies at our referral center for endoscopic gynecologic surgery. In particular, the primary outcome was the comparison of the incidence of ruptured tubal pregnancies between the lockdown phases and the other months of the pandemic. For this retrospective cohort study we considered all women examined for tubal ectopic pregnancy at our emergency unit from 1 January 2019 to 30 April 2021. We divided patients into three groups according to the period they were referred to our center: 10 March 2019–10 March 2020 (Pre-Covid period); 11 March–4 May 2020 and 6 March–30 April 2021 (Lockdown periods); 5 May 2020–5 March 2021 (COVID-19 pandemic period without restrictive policies). We compared data acquired during the lockdown phases with data collected both before the COVID-19 pandemic and during the restriction-free COVID-19 period. Results: 31 of 85 women were diagnosed with a ruptured tubal pregnancy. The proportion of ruptured ectopic pregnancies was higher during the lockdown period than the other two periods combined (62.5% vs 30.4%, $p = 0.016$). Mean gestational age and beta-HCG levels showed the same tendency ($7.31 \pm 1.25$ weeks vs $5.99 \pm 1.28$ weeks, $p < 0.0001$; $7392.56 \pm 4337.50$ mIU/mL vs $4188.36 \pm 3235.95$ mIU/mL, $p = 0.001$). There were no differences between the proportion of ruptured pregnancies during the whole COVID-19 pandemic and the months preceding it (45.7% vs 25.6%, $p = 0.07$). Conclusions: Our study demonstrated that restrictive lockdown policies for the containment of the COVID-19 outbreak are associated with an increased rate of ruptured extraterine tubal pregnancies.

Keywords: COVID-19; early pregnancy; ectopic pregnancy; lockdown; pregnancy outcomes; ruptured ectopic pregnancy; women’s healthcare

1. Introduction

In March 2020, the World Health Organization (WHO) declared viral pneumonia caused by SARS-CoV-2 a global pandemic, and healthcare providers were forced to reorganize their resources to protect patients and staff from the infection and to deal with the acute needs of the healthcare system [1]. Several preventive strategies were implemented worldwide to limit the activities that could be a source of contagion. The Italian government instated a forced lockdown between 11 March and 4 May 2020, issuing several restrictive regulations that strongly limited people’s circulation and closed public venues. Also, all non-urgent medical activities were suspended, including routine outpatient evaluations for chronic conditions and scheduled surgical procedures for benign, non-urgent diseases. Following an initial drop in the incidence of the infection during the summer of 2020, the Italian government adopted a more lenient attitude, only to reinstate restrictive measures between 6 March and 30 April 2021, due to a second wave of the pandemic. Throughout the lockdown periods, our National Health System provided only essential and urgent health services. These included two ultrasound scans during pregnancy, normally offered to all women; one in the first trimester (11–13 weeks), and one in the second trimester (19–21 weeks). The adoption of restrictive measures during the pandemic had deleterious effects on women’s health [2]. The obstetrical population faced distinctive obstacles, especially during early gestation, having to forego many of those scheduled outpatient examinations in the first trimester [3]. Despite benefiting from excellent

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pregnancy care programs, women in Emilia-Romagna are not freely offered an early first-trimester scan. However, most women electively choose to receive ultrasonographic scans in private clinics 2–6 weeks after a positive pregnancy test, to assess the presence, vitality, and location of the pregnancy.

Ectopic pregnancies account for 1–2% of all pregnancies, and the Fallopian tube is the site of implantation in 96% of cases [4]. When undiagnosed, they represent one of the main causes of gynecological emergency, and hemorrhage from an ectopic pregnancy is the leading cause of maternal mortality in the first trimester, determining 4–10% of all pregnancy-related deaths [5].

We had already noticed an increased proportion of ruptured ectopic pregnancies during the first lockdown phase at our Institution, in comparison with the previous period [6]. The responsible factors for this phenomenon may include women’s tendency for social isolation, fear of infection, and the reduced number of early scans [7]. The impact of the restrictive measures has not yet been fully assessed. For this objective, we aimed to compare the incidence of ruptured tubal pregnancies between the lockdown phases, the pre-Covid 19 months, and the other months during the pandemic when less restrictive policies were adopted.

2. Materials and Methods

We conducted a retrospective cohort study at Sant’Orsola-Malpighi University Hospital in Bologna, Italy, including all patients who underwent gynecological examination for tubal ectopic pregnancy at our center from 1 January 2019 to 30 April 2021.

For each patient, data were collected from clinical records on maternal age, parity, previous extrauterine pregnancies, time of amenorrhea, initial serum beta-human Chorionic Gonadotropin (beta-HCG) values, hemoglobin (Hb) value. Moreover, data regarding the therapeutic management of each patient were recorded. Based on their anamnesis, clinical presentation, laboratory results, and ultrasonographic findings, women were either managed conservatively (wait-and-see) with regular scans and lab tests, or administered medical therapy with systemic methotrexate, or subjected to surgical salpingectomy (with a laparoscopic or laparotomic approach), as recommended by international guidelines [8]. All the interventions performed within 6 hours of hospital admission were considered as “emergency surgery”. For those patients who were not eligible for outpatient management and were therefore admitted to our unit, the length of hospitalization—measured in days—was recorded.

We divided patients into three groups according to the period they were referred to our emergency unit: 1: 10 March 2019–10 March 2020 (Pre-Covid period); 11 March–4 May 2020 and 6 March–30 April 2021 (Lockdown period); 5 May 2020–5 March 2021 (COVID-19 pandemic period without restrictive policies). We then compared data acquired during the lockdown phases with data collected both before the COVID-19 pandemic and during the restriction-free COVID-19 period, to determine the impact of restrictive measures on the incidence of ruptured tubal pregnancies. Secondarily, we compared data acquired during the whole COVID-19 pandemic period with data gathered before the global pandemic. Subsequently, we compared the proportion of women who underwent emergency surgical intervention for a ruptured tubal ectopic pregnancy between the study groups.
Fig. 2. Incidence of ruptured tubal pregnancies during the study periods. The figure shows the timeline of the overall tubal pregnancies diagnosed at our hospital.

Given the retrospective design of the study, institutional review board approval was not required, but the local Ethics Committee was duly notified and approved the collection of data for research purposes. Patients also expressed their informed consent to participate in the study, which was conducted following the STROBE guidelines for observational studies.

Continuous data were expressed as the mean ± standard deviation (SD) or as the median (range) and interquartile range. Categorical variables were expressed as absolute numbers and percentages. Univariate comparisons of continuous data were conducted with a 2-sample t-test, the Wilcoxon test for continuous data, the one-way analysis of variance (ANOVA), and a chi-square test or Fisher’s exact test for categorical data. All reported p values were 2-sided, and a p value of less than 0.05 denoted a significant difference. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) software version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

From 1 March 2019 to 30 April 2021, 85 patients underwent gynecological examination for tubal ectopic pregnancy at our institution; 31 of these pregnancies were diagnosed as ruptured and required emergency surgery. Anamnestic and clinical characteristics of all patients are summarized in Table 1. The mean age of patients was 33 ± 6 years and most patients were experiencing their first pregnancy (59, 69.4%). Only 6 women had already had a previous ectopic pregnancy (7.1%), whereas 7 of them (8.2%) had resorted to in vitro fertilization techniques, with no significant differences between the groups.

In our hospital’s case history there was no significant difference regarding the seasonal differences in number of pregnancies and between different months.

Of the 16 analyzed patients during the lockdown periods (March–April 2020 and March–April 2021), 10 had a ruptured extraterine pregnancy at admission requiring emergency surgical intervention. When comparing the three significant periods (Pre-Covid period, Lockdown period, and COVID-19 pandemic period without restrictive policies), the proportion of ruptured ectopic pregnancies was significantly higher during the lockdown period (10/39–25.6%, 10/16–62.5%, and 11/30–36.7% respectively, p = 0.036), as detailed in Figs. 1, 2 and Table 1. The statistical significance was maintained also when we compared the incidence of ruptured ectopic pregnancies between the lockdown period and the other two periods combined (62.5% vs 30.4%, p = 0.016) (Table 2).

In the Lockdown period (4 months in total), 10 ruptured tubal pregnancies occurred with a rate per month of 2.5 ruptured and 1.5 non-ruptured tubal pregnancies. This rate of ruptured tubal pregnancies per month was higher if compared with the same rate during no restrictions in place (Pre-COVID-19 period: rate per month of 1.0 ruptured and 2.9 non-ruptured tubal pregnancies; Not-restrictive policies during the COVID-19 pandemic: rate per month of 0.9 ruptured and 1.6 non-ruptured tubal pregnancies).

Noteworthy to mention, the statistical analysis highlighted that there was no statistical significance comparing the number of ruptured pregnancies during the whole COVID-19 pandemic (with and without restrictive policies), and the pre-Covid period preceding the first outbreak
Table 1. Comparison of anamnestic, demographic, and clinical characteristics of patients.

<table>
<thead>
<tr>
<th></th>
<th>Pre-Covid period</th>
<th>Lockdown period</th>
<th>Non-restrictive policies</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 39)</td>
<td>(n = 16)</td>
<td>(n = 30)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>33 ± 6</td>
<td>34 ± 5</td>
<td>33 ± 6</td>
<td>0.768</td>
</tr>
<tr>
<td>Previous miscarriages</td>
<td>11 (28.2%)</td>
<td>7 (43.7%)</td>
<td>14 (46.7%)</td>
<td>0.207</td>
</tr>
<tr>
<td>Previous preterm pregnancies</td>
<td>1 (2.6%)</td>
<td>1 (6.3%)</td>
<td>4 (13.3%)</td>
<td>0.221</td>
</tr>
<tr>
<td>Previous term pregnancies</td>
<td>11 (28.2%)</td>
<td>7 (43.7%)</td>
<td>8 (26.7%)</td>
<td>0.388</td>
</tr>
<tr>
<td>Previous ectopic pregnancy</td>
<td>3 (7.7%)</td>
<td>2 (12.5%)</td>
<td>1 (3.3%)</td>
<td>0.501</td>
</tr>
<tr>
<td>Current pregnancy achieved by in vitro fertilization</td>
<td>5 (12.8%)</td>
<td>1 (6.3%)</td>
<td>1 (3.3%)</td>
<td>0.346</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>6.0 ± 1.5</td>
<td>7.3 ± 1.3</td>
<td>6.0 ± 1.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Days of amenorrhea</td>
<td>44 ± 10</td>
<td>54 ± 9</td>
<td>44 ± 7</td>
<td>0.001</td>
</tr>
<tr>
<td>Beta-HCG levels (mIU/mL)</td>
<td>4334 ± 3987</td>
<td>7393 ± 4338</td>
<td>3999 ± 1928</td>
<td>0.005</td>
</tr>
<tr>
<td>Hemoglobin levels (g/dL)</td>
<td>12.2 ± 1.4</td>
<td>10.6 ± 1.4</td>
<td>12.4 ± 1.1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Numbers are means (±SD) or counts (percentage proportion).

Table 2. Comparison between data from the lockdown period and the other two timeframes combined.

<table>
<thead>
<tr>
<th></th>
<th>Lockdown period</th>
<th>Pre-Covid period + Non-restrictive policies</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 16)</td>
<td>(n = 69)</td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>7.3 ± 1.3</td>
<td>6.0 ± 1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days of amenorrhea</td>
<td>54 ± 9</td>
<td>44 ± 9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Beta-HCG levels (mIU/mL)</td>
<td>7393 ± 4338</td>
<td>4188 ± 3236</td>
<td>0.001</td>
</tr>
<tr>
<td>Hemoglobin levels (g/dL)</td>
<td>10.6 ± 1.4</td>
<td>12.3 ± 1.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Numbers are means (±SD) or counts (percentage proportion).

Table 3. Comparison between data from the pre-Covid period and the pandemic period (lockdown and non-restrictive policies combined).

<table>
<thead>
<tr>
<th></th>
<th>Pre-Covid period</th>
<th>COVID-19 pandemic</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 36)</td>
<td>(n = 46)</td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>6.0 ± 1.5</td>
<td>6.4 ± 1.3</td>
<td>0.145</td>
</tr>
<tr>
<td>Days of amenorrhea</td>
<td>44 ± 10</td>
<td>47 ± 9</td>
<td>0.133</td>
</tr>
<tr>
<td>Beta-HCG levels (mIU/mL)</td>
<td>4334 ± 3981</td>
<td>5179 ± 3367</td>
<td>0.292</td>
</tr>
<tr>
<td>Hemoglobin levels (g/dL)</td>
<td>12.2 ± 1.4</td>
<td>11.7 ± 1.5</td>
<td>0.157</td>
</tr>
</tbody>
</table>

Numbers are means (±SD) or counts (percentage proportion).

in March 2020 (45.7% vs 25.6%, p = 0.07) (Table 3).

Our analysis also showed that during the lockdown period the mean gestational age and mean beta-HCG levels of patients at hospital admission were significantly higher compared to the other two timeframes combined (7.3 ± 1.3 weeks vs 6.0 ± 1.3 weeks, p < 0.0001; 7393 ± 4338 mIU/mL vs 4188 ± 3236 mIU/mL, p = 0.001). On the contrary, the mean hemoglobin levels were lower when more restrictive policies were in force (10.6 ± 1.4 g/dL vs 12.3 ± 1.3 g/dL, p < 0.0001) (Table 2).

Similar to our findings about the incidence of ruptured pregnancies, there was no significant difference in terms of gestational age, mean beta-HCG levels, and mean hemoglobin levels at admission when comparing the Pre-Covid period with the whole COVID-19 pandemic (with and without restrictive policies) (Table 3).

All ruptured pregnancies were subjected to emergency laparoscopic salpingectomy and no conversion to laparotomy occurred.

4. Discussion

4.1 Principal Findings

The results of this study show that the rate of ectopic pregnancy rupture was significantly higher during the two lockdown phases adopted in Italy to contrast the SARS-CoV-2 epidemic when compared to those months without restrictive policies. On the other hand, the comparison of the total number of ruptured tubal pregnancies that occurred during the entire pandemic period (from March 2020 to April 2021) with those diagnosed at our institution before the outbreak of the COVID-19 infection yielded no significant differences.

4.2 Results

The percentage of women presenting to our emergency department due to the rupture of an ectopic pregnancy located in the Fallopian tube more than doubled during the lockdown phases, confirming what was previously observed by our group during the first lockdown period...
[6]. Our evidence further confirms the existence of a plausible correlation between extrauterine pregnancy rupture and lockdown policies, while excluding a direct association with the viral infection. In agreement with the study of Toma et al. [9], our data suggest that during the lockdown period women may be delaying necessary self-care, due to their concerns about COVID-19 exposure, only seeking medical attention in case of emergency. This tendency is not peculiar to gynecology but has been observed also in other specialties, coming to the attention of healthcare providers worldwide and raising concerns regarding the indirect effects of the pandemic [10].

4.3 Clinical Implications

The relationship between our findings and the current situation is complex and several reasons must be taken into account in order to explain it. First, this increased rate of adverse outcomes might be driven by the work overload of the healthcare systems and their inability to cope with the pandemic, predominantly during lockdown periods, when only essential or emergency health procedures could be guaranteed. Emilia-Romagna, in Northern Italy, can boast an excellent healthcare system, which follows up all pregnant women from early pregnancy to the puerperium and guarantees two scans during pregnancy, one at 11–13 weeks and the other at 19–21 weeks. Nonetheless, the two lockdown periods have greatly impaired women’s chance to get additional scans, in particular early first-trimester ones [7]. In fact, early first trimester scans are not routinely planned in our Region, but many women electively choose to undergo examinations 2–6 weeks after a positive pregnancy test. This effectively places the gestational age anywhere between 6 and 10 weeks at the time of that first antenatal visit, which is crucial to determine the presence, vitality, and location of the pregnancy. This, in turn, reduced the possibility of an early diagnosis of extrauterine pregnancies, which were only detected in case of major symptoms that prompted women to access the obstetrics emergency unit at a later gestational age. This is further supported by our findings, which clearly show that women with ruptured tubal pregnancies accessed the emergency unit at a later gestational age and had higher levels of serum beta-HCG, compared to women with no rupture. As a result, it is not surprising that most cases were managed with surgery, mostly within 8 hours of hospital admission. This change in the management of this condition is in contrast with the experience of Platts et al. [11], who recorded that a significantly lower number of women underwent surgical management during the COVID-19 pandemic, compared to a pre-pandemic cohort. However, they also reported that only 7.4% of English women delayed their hospital referral due to the COVID-19 outbreak, with only 3/162 (1.9%) patients experiencing a ruptured ectopic pregnancy following conservative management.

Another factor that may have influenced our results is women’s reluctance to visit hospital units during the pandemic, due to strong governmental advice, concerns about the risk of acquiring the COVID-19 infection, reduced public transport, and access to childcare [12,13]. Pregnant women have arguably prioritized their protection against the COVID-19 infection over their concerns about their ongoing pregnancies, leading them to forego routine medical assistance. Indeed, it has already been documented that in times of disasters women’s healthcare is adversely affected, and the COVID-19 outbreak was no exception, in particular for pregnant women, who often received inadequate antenatal examinations [3,13–16]. In fact, this trend has also been observed for other pregnancy outcomes during this time of crisis, like increased stillbirth, maternal mortality, and stress [2]. Taking note of this, general awareness about first trimester complications should be raised, and patients should be educated regarding the early symptoms of ectopic pregnancy, as to seek medical attention as soon as possible.

4.4 Research Implications

The COVID-19 pandemic is still ongoing, and although great steps have been made to reduce the virus’s spread, the return to normality is not imminent yet. In light of this, it is possible that new restrictive measures might be reapplied in the future. Thus, we believe that women at risk for ectopic pregnancy should be strongly advised not to neglect early pregnancy assessments and should have early scans during the first trimester, within the strategic response to this global pandemic. Further research should focus on investigating whether the improvement of antenatal care in women with an increased risk of ectopic pregnancy during these times could help reduce the incidence of rupture. Also, it should be interesting to compare the experience of different countries and healthcare systems about this condition, and the effects of different lockdown policies on the incidence of this complication.

4.5 Strengths and Limitations

The main limitations to our study are the small number of patients recruited and its retrospective design. Conversely, our findings offer interesting insights on a worrisome trend that was already observed by our group and further confirmed by other authors [6,9]. Additionally, by further dividing the COVID-19 period based on the presence of restrictive measures, we were able to gain a better interpretation of this trend, identifying the lockdown policies as the main cause of our findings.

5. Conclusions

During the COVID-19 pandemic and, in particular, during the lockdown phases, the rate of ruptured tubal pregnancies has dramatically increased at our institution. On the one hand, our already overloaded health care system was forced to deal with a higher number of emergency cases, with possible life-threatening consequences. Furthermore,
the diagnostic delay observed for this pregnancy complication during this period has inevitably deprived patients of the possibility to benefit from more conservative management, such as a wait-and-see and/or a medical approach with the use of methotrexate. Thus, an increased number of women were subjected to urgent surgical procedures, namely salpingectomy, with non-negligible repercussions on their fertility, wellbeing, and recovery.

Our study demonstrated that restrictive lockdown policies for the containment of the COVID-19 outbreak are associated with an increased rate of ruptured extratubal pregnancies, further highlighting that global maternal outcomes have worsened over the last 18 months. With the specter of new waves and the new rapid rise of infection rates, social distancing measures still represent an essential tool to contain the spread of the disease. However, the indirect effects of COVID-19 on pregnancy outcomes should not be neglected and adequate levels and pathways of antenatal care should be maintained, starting with the first trimester of pregnancy.

Author Contributions

AA, RS and PC designed the research study. MA, FF and EDE performed the research. AY provided help and advice on obstetric part of the paper. CF, AV and RP analyzed the data. MA, FF, EDE and CF wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Given the retrospective design of the study, institutional review board approval was not required, but the local Ethics Committee was duly notified and approved the collection of data for research purposes. Patients also expressed their informed consent to participate in the study, which was conducted following the STROBE guidelines for observational studies.

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Conflict of Interest

The authors declare no conflict of interest. PC is serving as one of the Editorial Board members of this journal. We declare that PC had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to KCW and KW.

References