INTRODUCTION

Since its first appearance in December 2019, severe acute respiratory syndrome coronavirus 2 has spread worldwide resulting in the current coronavirus disease 2019 (COVID-19) pandemic. As a result, the Belgian government has implemented primary prevention actions and restrictive measures to contain the spread of the virus, such as social distancing, quarantine of suspected cases, and global lockdowns (from March 18 to May 4, 2020, and from November 2, 2020 to April 26, 2021). Moreover, to protect mothers and children, most hospitals changed their policies about prenatal and postnatal care, cancelling non-essential consultations, check-ups and prenatal classes, restricting the presence of the woman’s partner during...
prenatal consultations, and excluding family and visitors from postpartum units. All these measures resulted in mothers’ social isolation, which, associated with health and economic uncertainties, may be the background of psychiatric and affective disorders.1

Over the last year, several studies have documented maternal psycho-emotional distress linked to the COVID-19 pandemic.2-3 A recent meta-analysis about the impact of COVID-19 on maternal and perinatal health identified a significant increase in postpartum depression (PPD) during the pandemic.4 These results confirm the psycho-emotional vulnerability of mothers postpartum during the COVID-19 pandemic.

To our knowledge, no studies have focused specifically on the impact of the COVID-19 pandemic on psychological distress following preterm birth. Overall, during the pandemic, the prevalence of preterm birth (before 37 weeks of gestation) has not significantly changed, but seems to have decreased in high-income countries.4 Under normal conditions, mothers of preterm infants already show a higher risk of depression in the immediate postpartum period.5-7 Hence, we may assume that the pandemic has worsened the risk factors of PPD linked with preterm birth. Indeed, prematurity is a stressful experience, which leads to prolonged hospitalization and parental concerns about their child’s health. After preterm birth, the restrictive measures that were imposed in the Neonatal Intensive Care Units (NICU) and the social isolation after hospital discharge might increase the risk of depressive symptoms. Moreover, PPD is related to several complications impacting both maternal health and infant’s development,6-8 and its consequences on infant’s development will be all the more important because preterm infants are already at risk of neurodevelopmental delay.9 Therefore, it is paramount to analyze the impact of the COVID-19 pandemic on PPD in this specific population in order to implement early targeted interventions. The aim of this study is twofold: to determine the prevalence of depression symptoms following preterm birth during the COVID-19 pandemic and to highlight an eventual association between the pandemic and the risk of PPD.

2 | MATERIALS AND METHODS

2.1 | Design and participants

In Belgium, a standardized follow-up program for extreme and early preterm infants (<32 weeks of gestation) and/or infants with a very low birth weight (<1500 g) is planned at corrected ages 3–6 months, 9–14 months, 22–26 months, and 4.5–5.5 years. In our Follow-up Center, mothers of preterm infants are systematically assessed by a psychologist at the consultation at 3–6 months, and the child is neurologically assessed by a physiotherapist. Consequently, we performed a non-concurrent cross-sectional study including all mothers assessed at the 3–6 months corrected age follow-up consultation, between April 1, 2020 and March 31, 2021 (COVID-19 study group), and between January 1, 2017 and December 31, 2019 (control group). The COVID-19 study period was chosen based on the start of the first Belgian lockdown on March 18, 2020. Mothers assessed between January and March 2020 were not included in this study to limit the potential interference between the two study periods. The exclusion criteria were the inability of mothers to read and/or write French.

2.2 | Demographic and perinatal characteristics

As part of the follow-up program, all data concerning birth conditions, perinatal history, and follow-up evaluation of preterm infants were encoded prospectively and anonymously in the databases of the Newborn College. The clinical information used for this study was collected directly from these databases. Clinical information included both maternal demographic and pregnancy data, as well as delivery mode and perinatal infant history during NICU hospitalization.

2.3 | Edinburgh Postnatal Depression scale

PPD represents the end of a continuum of severity of symptoms. Maternal depressive symptoms were assessed using the French version of the Edinburgh Postnatal Depression Scale (EPDS).10 The EPDS is specifically designed for perinatal depression because it does not include confounding items about somatic depressive symptoms (such as sleep or appetite changes), common in the prepartum and postpartum periods. It is a 10-item self-report questionnaire that can be easily completed in less than 5 min by mothers. Responses to items are scored from 0 to 3, with a maximum score of 30. Scores of 13 or more are usually used to identify women with clinical major depression symptoms. In a recent meta-analysis, the cut-off score of 13 showed a sensitivity of 0.66 and a specificity of 0.95 to detect major depression among pregnant and postpartum women, whereas the cut-off of 10 had a sensitivity of 0.85 and a specificity of 0.84.11 The same results were described in a previous systematic review, confirming the high screening accuracy of the EPDS.12

2.4 | Statistical analysis

The statistical analysis was performed using the statistical package GraphPad Prism, version 9.1.0 (GraphPad, San Diego, CA, USA). For the population’s characteristics analysis, the categorical variables were described in the form of proportions and the continuous variables in the form of means and standard deviations. Comparison of categorical variables was performed using χ² test and Student’s t test was used to compare continuous variables. Significance level was set at P value <0.05.

Considering the different inclusion lengths between the control and the study group (respectively, 3 years versus 1 year), the homogeneity of the control group was examined to exclude any statistical bias. The population’s characteristics of the control
group were compared year by year using χ² test for the categorical variables and one-way analysis of variance test for the continuous variables.

A multivariable logistic regression model was used to examine the relationship between the independent and dependent variables, while adjusting for confounding. Confounding factors included in the multivariable model were chosen as follows: well-known risk factors of PPD and factors significantly associated with the COVID-19 period (prevalence statistically different between the COVID-19 study group and the control group). Odds ratios (OR) adjusted for the confounding factors were calculated by the multivariable model, with their 95% confidence interval (95% CI).

3 | RESULTS

3.1 | Sample description

All of the 34 mothers who were assessed at the 3–6 months follow-up consultation for preterm infants during the COVID-19 period were included in the COVID-19 study group. Out of the 111 mothers assessed by the psychologist during the control period, only 108 were included in the control group (two refusals and one uninterpretable result). The results of the χ² and one-way analysis of variance tests showed a great homogeneity among the control group over the 3-year period, except for the maternal education level and for the prevalence of breastfeeding at discharge, both higher in 2018 and 2019 than in 2017 (see Table S1). The clinical and sociodemographic characteristics of the two groups are described in Table 1. The populations’ characteristics were similar between the two periods, except for a decrease of multiple pregnancies and an increase of pre-eclampsia and Apgar score less than 5 at 5 min in the COVID-19 study group. No preterm infant has tested positive for COVID-19. One infant was isolated from his parents from day 66 to day 80 because his mother was diagnosed with COVID-19. His mother showed no symptoms of depression at the follow-up assessment (EPDS score ≥13). The prevalence of symptoms of major PPD (EPDS score ≥13) was significantly higher in the COVID-19 study group than in the control group (respectively 9/34 [26%] versus 13/108 [12%], P = 0.043).

3.2 | Impact of COVID-19 on depression symptoms

After adjusting for confounding factors, the multivariable logistic regression model showed a significant association between the COVID-19 pandemic period and the risk of major PPD, defined by EPDS score of 13 or more, (adjusted OR 3.60, 95% CI 1.06–12.59, P = 0.040). The confounding factors included in the multivariable logistic regression model were the following: maternal age, education and history of affective disorder, parity, multiple pregnancy, adverse pregnancy outcomes, cesarean section, Apgar score less than 5 at 5 min, and breastfeeding at discharge. No significant interactions between these other variables and the risk of PPD were found (results shown in Table 2).

4 | DISCUSSION

This study found that mothers of early and very preterm infants assessed during the COVID-19 pandemic at the 3–6 months corrected age follow-up consultation for preterm infants, presented a higher risk of PPD compared with a control group of mothers assessed between 2017 and 2019. The findings of this study illustrate a significant increase in depressive symptomatology after preterm birth during the current pandemic.

All over the world, studies about maternal mental health during the COVID-19 pandemic found similar results. The prevalence of PPD founded in the COVID-19 study group (26%) is shared by several other studies that reported a prevalence of postpartum depressive symptoms (EPDS score ≥13) ranging from 28.6% and 44% during the current pandemic. All of these studies indicate that some COVID-19-related variables must have an impact on maternal psycho-emotional distress by exacerbating risk factors of PPD. First, the COVID-19 pandemic has created a climate of fear for people regarding their health and the health of their children, which may lead to anxiety and depressive symptoms. Second, this pandemic is responsible for a significant lack of social support due to social isolation linked to restrictive measures and repeated lockdowns. Two recent studies have confirmed the psychological impact of quarantine measures on maternal psychological health. Indeed, better social support is associated with lower symptoms of maternal depression, as it buffers the effects of stress on anxiety and depression symptoms. Third, this pandemic has deeply impacted the global economy and increasing numbers of women have become unemployed or had to take on childcare responsibilities because of nursery and school closure. This situation can lead to a decrease in families’ income, which was significantly associated with higher scores on the EPDS among postpartum mothers. Nevertheless, some studies showed an improvement in maternal psychological health during the COVID-19 pandemic, which highlights the role of the socio-cultural environment of the mothers. Indeed, some postpartum mothers might have benefited not only from greater family support during quarantine, but also from a closer mother-child attachment due to their relative isolation from the external world.

This study specifically focuses on the mental health of mothers of very and early preterm infants. As preterm birth already increases the risk of depressive postpartum symptoms, it is fundamental to pay special attention to this vulnerable population during the current pandemic. Indeed, this pandemic may worsen the risk factors of PPD initially linked to prematurity, such as adverse pregnancy and neonatal outcome, anxiety about child health, and prolonged separation of the mother-child dyad during neonatal hospitalization. Moreover, it is essential to identify and detect maternal depression after preterm birth, so that prematurity does not lead to a double penalty for infant development. The preterm infant is already...
at risk of neurodevelopmental delay, and PPD might be responsible for an impaired mother-child bonding, which might affect the later cognitive, behavioral, and social-emotional development and physical health of the infant.\textsuperscript{8,23} However, the choice to target a specific population of mothers affected by a preterm birth could reduce the statistical impact of COVID-19 on PPD in this study, as additional problems do not necessarily result in additional distress above a certain threshold of medical co-morbidities.\textsuperscript{7} This "ceiling-effect" might also hide potential impacts of the other traditional risk factors of PPD.

| Characteristics (n = 142) | COVID–19 study group (n = 34) | Control group (n = 108) | P value |
|--------------------------|-------------------------------|-------------------------|--------|
| Maternal age, years      | 30.9 ± 5.1                    | 30.0 ± 5.2              | 0.658  |
| <25                      | 5 (15)                        | 19 (18)                 |        |
| 25–35                    | 23 (67)                       | 68 (63)                 | 0.620  |
| >35                      | 6 (18)                        | 21 (20)                 | 0.816  |
| Civil status             |                               |                         |        |
| Married                  | 8 (23)                        | 28 (26)                 | 0.780  |
| Cohabitating             | 25 (74)                       | 78 (72)                 | 0.883  |
| Single/divorced          | 1 (3)                         | 2 (2)                   | 0.695  |
| High maternal education\textsuperscript{b} | 15 (44) | 61 (56) | 0.209 |
| Occupation\textsuperscript{c} |                              |                         |        |
| Working                  | 28 (82)                       | 73 (68)                 | 0.099  |
| Not working              | 6 (18)                        | 35 (32)                 | 0.099  |
| History of affective disorder\textsuperscript{d} | 2 (6) | 6 (6) | 0.947 |
| Fertility treatment\textsuperscript{e} | 6 (18) | 19 (18) | >0.99 |
| Primiparous              | 24 (71)                       | 70 (65)                 | 0.534  |
| Multiple pregnancy       | 3 (9)                         | 28 (26)                 | 0.036  |
| Gestational diabetes mellitus | 1 (3) | 4 (4) | 0.826 |
| Pre-eclampsia            | 12 (35)                       | 16 (15)                 | 0.009  |
| Delivery mode            |                               |                         |        |
| Vaginal delivery         | 11 (32)                       | 30 (28)                 | 0.607  |
| Cesarean section         | 23 (68)                       | 78 (72)                 | 0.607  |
| Gestational age at birth, weeks | 29.0 ± 2.4 | 29.5 ± 2.7 | 0.926 |
| Birth weight, g          | 1170 ± 344                    | 1232 ± 330              | 0.922  |
| Males/females            | 17/17 (50/50)                 | 51/57 (47/53)           | 0.776  |
| Apgar score <5 at 5 min  | 9 (26)                        | 4 (4)                   | <0.001 |
| Need for invasive ventilation | 11 (32) | 27 (25) | 0.400 |
| Bronchopulmonary dysplasia | 21 (62) | 48 (44) | 0.079 |
| Necrotizing enterocolitis | 2 (6) | 4 (4) | 0.583 |
| IVH grade 3–4 and/or PVL | 1 (3) | 3 (3) | 0.958 |
| Breastfeeding at NICU discharge | 17 (50) | 57 (53) | 0.779 |
| Chronological age at consultation, months | 6.7 ± 0.7 | 6.9 ± 0.9 | 0.901 |
| EPDS score               |                               |                         |        |
| Total EPDS score ≥10     | 15 (44)                       | 39 (36)                 | 0.403  |
| Total EPDS score ≥13     | 9 (26)                        | 13 (12)                 | 0.043  |

Abbreviations: COVID-19, coronavirus disease 2019; EPDS, Edinburgh Postnatal Depression Scale; IVH, intraventricular hemorrhage; NICU, Neonatal Intensive Care Unit; PVL, periventricular leukomalacia.

\textsuperscript{a}Values are given as mean ± standard deviation or as number (percentage).

\textsuperscript{b}High maternal education: university or college.

\textsuperscript{c}Working: employed or self-employed; Not working: unemployed, stay-at-home mother or student.

\textsuperscript{d}Affective disorder: generalized anxiety disorder, depression or bipolar disorder.

\textsuperscript{e}Fertility treatment: ovulation induction, in vitro fertilization or intracytoplasmic sperm injection.
Another specificity of this study has been the choice to recruit mothers through the standardized follow-up consultation for preterm infants, preventing a population selection bias, but excluding mothers of deceased infants. Moreover, this late evaluation at 3–6 months (infant’s corrected age) allows us to decrease potential confounding symptoms of other affective disorders linked to preterm birth and long-term hospitalization, such as simple adjustment disorder with depressed mood and post-traumatic symptoms. In addition, this late evaluation might take more account of the long-lasting social isolation of mothers than psychological assessments made in the first week postpartum, as realized in the studies cited above.3,15,16 Furthermore, this study evaluated mothers during an entire year during the COVID-19 pandemic, so avoiding the seasonal impact on depressive symptoms.

The first limitation of this study is its monocentric retrospective construction. The sample is small and geographically specific, limiting the generalization of the results. However, this should not invalidate the results because the population characteristics of the two groups were quite similar. The only significant differences were a decrease of multiple pregnancies and an increase of pre-eclampsia and Apgar scores less than 5 at 5 min in the COVID-19 study group. Such an increase of adverse perinatal outcomes might be explained by reduced access to medical care during the pandemic.4 Moreover, the risk of statistical bias due to the different inclusion lengths between the control and the study groups (respectively, 3 years versus 1 year) is compensated by the great homogeneity of the control group over the years. The higher prevalence of breastfeeding at discharge, observed from 2018 onwards, can be explained by the improvement of the hospital breastfeeding policy. The second limitation is the use of the self-reported EPDS questionnaire to define PPD, instead of a clinician-administered structured interview. Nevertheless, several studies have proven the effectiveness of the EPDS to identify PPD.12,24 Moreover, the choice of a higher cut-off, such as an EPDS score of 13 or more, increased the specificity of the scale and improved the reliability of this study.

In conclusion, the results of our study indicate that the COVID-19 pandemic and the resulting restrictive measures had increased the risk of PPD among mothers of extreme and early preterm infants. As we know, PPD may interfere with the cognitive, behavioral, and social-emotional development of preterm infants that are already at risk of poor health condition and neurodevelopmental impairment because of their prematurity. This vulnerable population needs to be carefully followed, because the secondary socio-economic impacts of the pandemic are still unknown. Therefore, longitudinal long-term studies will be necessary to further understand the impact of the ongoing COVID-19 pandemic on the emotional distress of mothers.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

TV, EH, and LL conceived the study idea. All authors contributed to the study design. AM and LL performed the data collection. LL
performed the statistical analysis. TV and LL drafted the first version of the manuscript. All authors have discussed the results and revised this manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.