Risk of COVID-19 in Pregnancy Re-Visited: A Scientific Brief

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Abstract

Current government health policy for coronavirus disease-2019 (COVID-19) during pregnancy has been established from a retrospective analysis of electronically reported data showing that symptomatic pregnant women are at an increased risk of severe disease including admittance to intensive care units, invasive ventilation, and death. Recent comparative, dual cohort studies shed new light on this previous analysis by the United States Centers for Disease Control, indicating that outcomes from this analysis should be interpreted with caution. Recent studies show that data fail to support the claim that pregnant women are at increased risk for developing severe COVID-19 outcomes.

Keywords

COVID-19; SARS-CoV-2; pregnancy; severe outcome; risk analysis

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Introduction

The novel coronavirus disease that was first identified in 2019 (COVID-19) is caused on a subset of people infected with the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Since the onset of the declared COVID-19 pandemic, a number of studies have retrospectively and prospectively investigated the severity of COVID-19 in pregnant women using data from multiple types of medical databases. Currently, government health policy has been established from a retrospective analysis of electronically reported data submitted to the United States Centers for Disease Control (CDC) using standard case report forms, or from the National Notifiable Diseases Surveillance System (NNDSS), showing that symptomatic pregnant women are at in-creased risk of severe disease compared with non-pregnant women[1]. Since then, however, three additional comparative, dual cohort studies have been released that shed new light on the CDC analysis[2,3].

What do COVID-19 registries tell us of the risk of severe disease in pregnant women?

The NNDSS has been utilized to aggregate and track cases of COVID-19 nationally. This information, along with data from the Response Pregnancy and Infant Linked Outcomes Team (CDC analysis) was used to perform the largest and most well-recognized assessment of COVID-19 risk among pregnant women. This retrospective registry analysis published by Zambrano et al. in November 2020 analyzed 23,434 pregnant and 386,028 non-pregnant women 15 to 44 years of age with symptomatic COVID-19 recorded in the NNDSS from January 22 to October 3, 2020[1]. Differences in intensive care unit (ICU) admissions, invasive ventilation and death between pregnant and non-pregnant women were assessed. When outcomes were adjusted for cardiovascular and chronic lung disease, age, and diabetes, adjusted risk ratios (aRR) for serious events were significantly higher for symptomatic pregnant women compared with symptomatic non-pregnant women, including ICU admittance (aRR = 3.0 (95%CI, 2.6–3.49); 1.05% vs. 0.39%), invasive ventilation (aRR = 2.9 (95%CI, 2.2–3.8); 0.29% vs. 0.11%) and death (aRR = 1.7 (95%CI, 1.2–2.4); 0.15% vs. 0.12%). The analysis showed that older women (aged 35 to 44 years) were at a particular risk of severe outcomes, with a nearly four-fold increased risk of invasive ventilation and two-fold increased risk of death compared with non-pregnant women. Authors concluded that although the absolute risk of severe disease was low for symptomatic pregnant women, the risk was significantly higher than for symptomatic non-pregnant women.

Similar outcomes were seen in a second large retrospective analysis using data from the COVID-19 National Data Registry of Mexico published by Martinez-Portilla et al. in February 2021[4]. This study included 5,183 pregnant and 175,905 non-pregnant women aged 15 to 45 years with symptomatic COVID-19. The primary outcome was death, with rates of pneumonia, intubation, and ICU admission as secondary outcomes. A propensity score-matched analysis was conducted to control for underlying conditions (chronic obstructive pulmonary disease, asthma, smoking, hypertension, cardiovascular disease, obesity, diabetes, chronic renal disease, immunosuppression, age, language, nationality, and level of health insurance). Unadjusted outcomes did not show

increased risk of death for symptomatic pregnant versus symptomatic non-pregnant women (1.5% vs. 1.5%, OR = 1.01, 95% CI 0.80 to 1.26, P=0.935), although ICU admittance was higher (13.0% vs. 6.9%, OR = 2.03 95% CI 1.69 to 2.44, P<0.001) and invasive ventilation was significantly lower in the pregnant cohort (8.1% vs. 9.9%, OR = 0.80, 95% CI 0.64 to 0.99, P=0.044). Matched analysis, however, showed a significantly high-er mortality rate in pregnant versus non-pregnant women (1.5% vs. 0.8%, OR=1.84; 95%CI 1.26 to 2.69, P=0.001) and ICU admissions (13.0% vs. 7.4%, OR=1.86, 95% CI 1.41 to 2.45, P<0.001). Authors concluded that pregnancy was a risk factor for death and ICU admission in symptomatic SARS-CoV-2-infected women of reproductive age after adjusting for differences in baseline risk factors.

Although helpful for identifying potential correlations, retrospective registry analyses are limited by incomplete data, imbalances in baseline factors, and ascertainment bias that can confound outcomes. Although COVID-19 registry analyses represent a rich repository of COVID-19 data, it should be recognized that these registries tend to capture outcomes of symptomatic cases of COVID-19 and do not account for the many asymptomatic or mildly symptomatic cases in individuals who opted out of testing and recovered at home. Additionally, as these databases are designed to capture COVID-19 data, ancillary data such as pregnancy status and hospital outcomes will be more limited. For instance, the analysis by Zambrano et al. used most often to guide current pol-icy had pregnancy status data available for only 36% of the 1,300,938 women potential-ly eligible for inclusion[1]. Furthermore, data on ICU admission status was only available for 24% to 27% of eligible women in this study and for only 8.2% of eligible individuals in the analysis by Martinez-Portilla et al[1,4]. Considering that these databases are designed for symptomatic COVID-19, they should be interpreted with caution when drawing conclusions on the risk for individuals with asymptomatic infections and for those who are pregnant.

Imbalances in baseline factors are also a concern when retrospectively analyzing registry data. Zambrano et al. used a multi-variate analysis and Martinez-Portilla et al. used propensity score matching to address this issue[1,4]. Both analyses failed to recognize that pregnancy on its own is also a well-recognized risk factor for increased morbidity and mortality[5,6]. In an observational cohort study of SARS-CoV-2-positive pregnant women, 24% of ICU admittances were for an indication other than COVID-19 and two out of six deaths were not deemed related to COVID-19 (for a rate of COVID-19-related mortality of 0.3%)[7]. The Zambrano et al. analysis also failed to adjust for severe obesity, another well-recognized risk factor for poor outcomes, which was twice as common among the pregnant versus non-pregnancy study group (2.2% vs. 1.1%)[1]. Although Martinez-Portilla et al. considered a wider range of factors in their analysis, this approach is typically limited by the potential for unmeasured variables that can affect outcomes[4,8,9]. These studies also tend to be poorly implemented in the medical literature and their reliability is difficult to assess in the absence of sensitivity analyses[8–10]. The influence of these limitations and other factors, known to be strongly associated with severe outcomes, that define high-risk subgroups and that may be driving the overall effect (for example, older pregnant women had a four- and two-fold greater risk of invasive ventilation and death, respectively, relative to non-pregnant women in the Zambrano et al. study) may partially or fully explain the reported in-creased risk in pregnant

women, underscoring the importance of well-controlled randomized trials to confirm findings[1].

Hospital database analyses of pregnant women with symptomatic COVID-19

Hospital databases provide a more complete picture of pregnancy status and hospitalization outcomes for risk evaluation. Knight et al. and Pineles et al. recently published retrospective analyses of hospital databases to assess the risk of severe disease from COVID-19 among hospitalized pregnant women[2,3]. Knight et al. analyzed data from the COVID-19 Clinical Information Network (CO-CIN) including over 300 Nation-al Health Service hospitals across the United Kingdom (UK), the UK Obstetric Surveil-lance System (UKOSS), and from the surveillance system known as Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) [2]. COVID-19 events were assessed in 1,134 pregnant women and 6,810 non-pregnant women and men aged 20-39 years who were hospitalized with COVID-19. The dataset was over 94% complete for COVID-19 status, pregnancy status and relevant outcomes (ventilation, ICU admission, and death rates). Unlike the CDC analysis, the CO-CIN study found lower rates of ICU admission (11.4% vs. 23.5%), invasive ventilation (3.7% vs. 8.8%) and death (0.8% vs. 3.1%) among symptomatic pregnant women versus non-pregnant persons. Similar outcomes were seen in the overall study cohort that also included asymptomatic SARS-CoV-2-infected patients.

Pineles et al. conducted a large analysis of an all-payer hospital network data repository from 853 hospitals that captured 20% of all hospitalizations in the United States to determine the risk of severe outcomes for women hospitalized with COVID-19 and viral pneumonia[3]. The study showed that in-hospital deaths occurred less frequently among pregnant (n=1,062) compared with non-pregnant women (n=9,815) (8 vs. 35 per 1,000) and that pregnant women tended to be younger and less likely to have comorbid conditions[3]. Overall, recently published cohort analyses relying on databases that provide more complete pregnancy and hospitalization outcome data fail to confirm an increased risk of ICU admittance, invasive ventilation, and mortality for pregnant women compared with non-pregnant persons hospitalized for COVID-19.

Finally, a prospective cohort study of the UKOSS representing all 194 obstetrics units was conducted by Knight et al.; this group identified 427 pregnant women hospitalized between March 1 and April 14, 2020 that tested positive for COVID-19 after becoming symptomatic[11]. They found that the estimated incidence of admission to a hospital with symptomatic COVID-19 was low (4.9 per 1,000 maternities) and that most women did not need critical care (90%) and were healthy when discharged (93%). They did note, however, that the majority of hospitalized women were black or other ethnic minorities (56%), overweight or obese (69%), 35 years or older (41%) and/or had pre-existing comorbidities (34%).

Medical database analyses of pregnant women with asymptomatic infections with SARS-CoV-2

Single cohort studies of asymptomatic patients provide important insights into rates of asymptomatic infections with SARS-CoV-2 and COVID-19 outcomes among pregnant women. A number of small retrospective studies of obstetrics units conducting universal COVID-19 testing published by Woods et al., Sutton et al. and Maru et al. showed that the vast majority of those testing positive for SARS-CoV-2 did not have clinical evidence of disease (72% to 98%)[12–14]. Retrospective reviews of hospital databases were conducted by Delahoy et al. and Cruz-Lemini et al. to determine the risk of severe outcomes from COVID-19 among pregnant women and neonates hospitalized with COVID-19[15,16]. Delahoy et al. analyzed the COVID-19-Associated Hospitalization Surveillance Network (COVID-NET), which included 598 hospitalized pregnant women infected with SARS-CoV-2. The study found that the majority of pregnant women were asymptomatic (54.5%) and required no ICU admissions or invasive ventilation requirements, with no deaths reported[15]. Cruz-Lemini et al. of the Spanish Obstetric Emergency Group prospectively screened 11,728 pregnant women admitted to 42 hospitals, including a small fraction of SARS-CoV-2-positive patients (n=279, 2.4%) and among these, those with asymptomatic infections (n=174, 62%). They found no significant differences in neonatal outcomes from asymptomatic pregnant women infected with SARS-CoV-2 compared with those testing negative for infection (n=430), with the exception of pre-labor rupture of membranes at term[16]. The authors concluded that "Pregnant asymptomatic women testing positive for COVID-19 at admission for delivery should be reassured by their healthcare workers." Studies that include outcomes among women with asymptomatic infections with SARS-CoV-2 show that most infected pregnant women remain asymptomatic, and their neonates are not at an increased risk of severe outcomes from COVID-19.

Summary

The CDC analysis has been suggested to show a higher risk of severe COVID-19 outcomes such as ICU admittance, invasive ventilation, and death among symptomatic pregnant women, although the overall risk was low. Outcomes from this analysis should be interpreted with caution as they were based on limited pregnancy status and hospital outcome data and did not fully control for baseline factors such as severe obesity which is a well-known risk factor for severe COVID-19 outcomes. Our review of studies assessing the risk of severe COVID-19 outcomes among pregnant women underscores the importance of not ascribing causation based on association and appropriately extrapolating outcomes, in addition to the importance of properly controlled trials to confirm findings prior to policy implementation. Finally and perhaps most importantly, these studies do not account for the role of prophylaxis using safe and effective therapies like hydroxychloroquine, which can help mitigate severe outcomes of COVID-19[17]. Although it is reasonable to adopt greater caution given the substantial global health issue that COVID-19 represents, available data fail to definitively support the claim that all pregnant women are at increased risk for developing severe outcomes from this disease.

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Conflicts of Interest:

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Steven Pelech is the majority shareholder and President and Chief Scientific Officer of Kinexus Bioin-formatics Corporation, which has been developing serological tests for detection of antibodies against SARS-CoV-2 proteins.
All other authors declare no conflicts of interest.

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