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Starting a regional collaborative research group for COVID-19 in pregnancy: the Southern Michigan experience

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Abstract: The outbreak of the SARS-CoV-2 elicited a surge in publications. Obstetric reports were with few exceptions characterized by small sample sizes with potentially limited generalizability. In this review, evidence suggests increased susceptibility to COVID-19 in pregnancy; common pregnancy comorbidities may help explain worse outcomes. While the risk of death is low, pregnancy may be associated with increased need for ventilation. Prematurity rates seem to be increased but may be accounted for in part by higher cesarean rates, to a large degree accounted for by elective decision to shorten the course of the labor. Though fetal/neonatal complication rates may be higher in the presence of COVID-19 infection, survival rates seem unaffected and vertical transmission is rare. As the outbreak continues in the USA with resurgence in many other western countries that achieved initial success in suppressing the virus, much remains to be learned. For example, the question related to the degree to pregnancy modifying symptomatology remains open. Currently, routine polymerase chain reaction testing remains limited by supply shortages possibly delaying diagnosis until later in the course of the disorder and thus altering the symptom complex at presentation. To add to the knowledge base, we initiated a regional COVID-19 in pregnancy collaborative observational study with a coordinating center, standardized data collection and a shared database. This was facilitated by a longstanding tradition of collaboration among regional obstetric services. Over an anticipated two-year study duration, we expect to study 400 documented and suspected COVID-19 pregnancies with time and site of services controls for cohort effect and high power to detect several adverse maternal/infant outcomes. We include a complete listing of variables in our database, which, along with our experience in setting up our regional collaborative, we hope and believe will be of use in other settings.

Keywords: COVID-19; fetus; observational study; pregnancy; prematurity; registry collaborative; SARS-CoV-2.

Introduction

The outbreak of the SARS-CoV-2 resulted in an unprecedented surge in publications in every conceivable discipline. In obstetrics, these early reports were invaluable in forming the basis for counseling, management and prognostication at the time. Notwithstanding the above benefits, early reports had significant limitations. These included small case numbers and with a disproportionate number of initial reports from Asia, in which health systems, obstetric practices and the underlying health status of the population may differ significantly from those in the United States (US) and Western Countries. In addition, advances in care, virus mutation leading to altered infectivity and disease morbidity as well as changing demographics (e.g., younger patients) of the affected populations have the significant potential of altering disease severity and outcomes. Addressing the limitations of earlier reports, revealed the necessity to conduct a larger and continuous collaborative study including national data that has been recently published in the U.S. [1] Based on these considerations we embarked on a collaborative statewide study in Michigan, the southern region of which began in March 2020 and became an epicenter of the US outbreak during the spring.

In this paper, we briefly summarize our knowledge at the time of writing in areas of clinical importance in COVID-19 pregnancies and, in particular, areas in which
significant gaps in knowledge exist. The summary information presented is culled almost exclusively from systematic reviews and meta-analyses, and where available national-level or large collaborative studies. The systematic reviews do however have the limitation of overlap of study subjects, but, given the more robust patient numbers, often allow meaningful statistical analysis of the accumulated data. In the second part of this manuscript, we provide information on how we created a COVID-19 in Pregnancy Registry, that we quickly decided to transform into a Regional Collaborative Research Group by adding a control group. We hope that this review and our experience will be useful to others who may wish to set up a COVID-19 in pregnancy clinical study.

Review of the literature

Susceptibility in pregnancy

Whether there is increased susceptibility to SARS-CoV-2 infection in pregnancy remains a subject of discussion. Several lines of evidence support this view. These include changes in the respiratory system such as hyperventilation increasing the intake of air and potentially viral particles, immune changes such as reduced number and activity of T-cells in the blood compromising antiviral capability, and increased expression of ACE 2, the cellular receptor for the SARS-CoV-2 virus [2]. On the other hand, severe and critical COVID-19 disease is often due in large part to the overproduction of inflammatory cytokine rather than direct viral damage, the so-called 'cytokine storm'. Much of pregnancy is dominated by an anti-inflammatory state with the production of anti-inflammatory cytokines promoted by multiple pregnancy hormones including progesterone, hCG, and estrogen [3]. Nonetheless, recent clinical data supports negative outcomes in pregnancy. A study from the Center for Disease Control and Prevention (CDC) [4] evaluated US national data, which included 91,412 laboratory-confirmed SARS-CoV-2 cases, of whom 8,207 (9%) were pregnant women. The pregnant women were hospitalized at a higher rate (31.5 vs. 5.8%) compared to non-pregnant cases. The indications for hospitalization, pregnancy vs. coronavirus-related were unstated, however. Outcomes assessed appeared to be worse in pregnant women.

COVID-19 symptomatology in pregnancy

Due to a national shortfall in testing capacity, unresolved at the time of this writing, a large percentage of and possibly a majority of COVID-19 cases are diagnosed based on symptomatology. Given the negative outcomes in pregnant women, the question of the impact, if any, of pregnancy on presenting symptoms assumes practical significance. The only national level data addressing this issue [1] found that based on 12 potential symptoms, 2.9% of pregnant women were asymptomatic vs. 3.1% of non-pregnant cases. The frequency of cough and shortness of breath were similar, while pregnant women had lower frequencies of fever, chills, muscle ache, headaches, and diarrhea. Thus, reliance on a flu like illness – fever, chills and myalgia – could potentially lead to underdiagnosis of pregnant women. As high as 32.6% of cases have been reported asymptomatic on presentation [5], but such reports include smaller case numbers and represent a compilation of studies in which it is likely that patients were queried about a less comprehensive list of symptoms.

Accuracy of laboratory diagnosis of COVID-19 infection in pregnancy

The current gold standard uses reverse-transcriptase-polymerase chain reaction (RT-PCR) to detect viral nucleic acid. The impact, if any, of pregnancy on test accuracy is unclear. There are numerous sources of variation that may increase the false negative rate of the test. These include inadequate sample collections, site from which the sample is obtained, disease stage and inherent test inaccuracy. In pregnant patients with a diagnosis of COVID-19, as high as 23% were reported to have negative PCR testing [5]. This emphasizes the need for repeat swabbing if clinical suspicion is high and potentially including swabbing or testing other anatomical areas. In cases of negative laboratory testing with suspicious symptoms, radiological diagnosis has been relied on in some centers. Systematic reviews report high sensitivity with the use of chest CT, in excess of 96% [5, 6]. Chest X rays were reported to also have comparable sensitivity at 100% in one review [7]. The role of imaging in symptomatic, test negative pregnant women needs further investigation.

Should routine PCR testing of asymptomatic pregnant women be performed?

Routine testing in pregnant women is a justifiable clinical recommendation in view of the potentially severe consequences of SARS-CoV-2 infection. Unfortunately, the ongoing national shortage of testing reagents, particularly for the rapid test, have put many institutions in the difficult position of rationing the use of this resource. In those unfortunately common circumstances, is there a role for
screening based on symptoms with targeted testing of symptomatic pregnant women? The initial support for routine PCR testing was based on an early report from New York City, USA, which found a 13.5% test positive rate among 211 asymptomatic obstetric patients [8] who were being admitted. This was followed by another study in the same region which found a 14.4% test positive rate among admitted pregnant women [9]. The number of symptoms evaluated could not be assessed in the first study [8], while the number of symptoms queried were limited in the second [9]. Subsequent studies using an expanded symptom list and larger case numbers found PCR positive rates <3% in asymptomatic pregnant women [10]. A CDC report [1], which evaluated 12 symptoms in a large number of pregnant patients, found that only 2.9% of test positive patients were asymptomatic. This suggests that comprehensive symptom screening could lower the rate of PCR testing when there is a shortage of testing kits. Further large prospective studies are needed to address the issue of reduced availability of tests.

What are the sources of infection in pregnant women?

Very little attention has been paid to this issue in the literature. Epidemiologically, however, this is of paramount importance as it facilitates the development of effective public health strategies to reduce the risk of exposure in pregnancy. One systematic review [11] reported that 41.3% of positive cases reported contact with sick individuals. Details of whether these were household or outside contacts and the potential sources of the other infections were not available, however.

Do co-morbidities account for worse outcomes in pregnancy?

Underlying comorbidities are well recognized to be a driver of worse outcomes and could potentially explain, rather than the pregnancy per se, the worse outcomes reported pregnant women. In a CDC study [4], some comorbidities now known to be associated with worse outcome in COVID-19 were more common in pregnant than in non-pregnant women between age 15 and 44 years. These included diabetes (12.3 vs. 6.4%), chronic lung disease (21.8 vs. 10.3%), cardiovascular disease (14.0 vs. 7.1%) and immunocompromised status (3.5 vs. 2.8%) in pregnant vs. non-pregnant women. In a national cohort of infected pregnant women admitted to hospital in the UK, 34% had pre-existing co-morbidities while 34% were obese, another risk factor for complications in SARS-CoV-2 infection [12]. Given the high rate of co-morbidities in pregnant women in the US, the role of co-morbidities vs. pregnancy per se in explaining poor outcomes in this group needs to be further elucidated.

Maternal treatment and outcomes

The pandemic continues to evolve and several factors including improved therapeutics have resulted in improved outcomes over time. Contemporary data needs, therefore, to be generated to inform treatment and patient counseling. A significant percentage of infected individuals including those pregnant are asymptomatic and require no specific treatment. For those pregnant women who are hospitalized the available data suggest an overall good outcome. A systematic review, primarily of cases from China found that 70.7% received antibiotics, 37% antivirals and 17.6% were treated with corticosteroids with a smaller percentage receiving other therapeutic agents [6]. A large multi-center study from France [13] found that 15% of admitted patients received nasal oxygen or non-invasive ventilation, with 12.4 % receiving non-invasive ventilation in a separate review [6]. In two large national studies the need for invasive ventilation was <5% [13]. After controlling for confounders (age, co-morbidities, race/ethnicity), pregnant women were significantly more likely to receive mechanical ventilation (aRR = 1.7 [1.2–2.4]) [1]. Intensive/critical care was needed in 10% of pregnant cases in the UK national study [12] and higher risk of ICU admission was found in pregnant women (aRR 1.5 [1.2–1.8]) in the CDC study [4].

In the larger health population or national-level studies reviewed, the maternal death rate appeared fortunately to be low at 0.2% [4, 13], and 1% [12], while the risk of death was not increased (aRR = 0.9 [0.5–1.5]) in the CDC study [4]. A systematic review by de Sousa et al. [14] found seven deaths in 421 maternal cases, while a database review [15] found 25 maternal deaths in 125,218 overall coronavirus cases in Brazil indicating a low mortality risk. Updated reports of the risks for these severe outcomes are needed.

What are the current estimates of pregnancy issues and outcomes in COVID-19 pregnancies?

The systematic review of Juan et al. [6] showed relatively low rates of gestational diabetes, hypertensive disorders of pregnancy and preeclampsia, 8.2, 6.2, and 1.7%,
respectively. Early reports of high prematurity rates have been an area of ongoing concerns. However, one systematic review found a 6.4% spontaneous and 16.0% iatrogenic prematurity rate [11]. More importantly, in the large French study, the prematurity rate increased significantly with COVID-19 disease severity with high rates in critical patients [13]. Asymptomatic or mild cases constitute the vast majority of pregnant patients appear to be at comparatively low risk for preterm birth. Low rates of pregnancy related complications have been reported in other systematic reviews [16]. High cesarean delivery rates are another area of concern. While this has been reported in coronavirus infections, compilation of data primarily from Chinese cases found that 55% of cesareans were performed primarily for COVID-19 [6], while a UK national study found that with an overall cesarean rate of 59.5%, only 26.9% of these surgeries were performed primarily due to COVID-19 indications [12]. This demonstrates that different practice patterns need to be considered when reporting cesarean rates as some institutions, at least earlier in the epidemic, considered SARS-CoV-2 disease as an indication for cesarean delivery.

Fetal and newborn outcomes

Relatively high rates of fetal distress [16] and NICU admissions [11] have also been reported on systematic review of the existing literature. However, the latter has significant potential for overestimation on the impact of the coronavirus itself for pregnancy outcomes since a distinction between admission for observation purposes, rather than for severe illness, cannot be teased out of the data. In addition, much of the neonatal morbidity reported in published series is likely due to prematurity rather than coronavirus infection per se. An objective assessment of newborn outcomes suggests that the impact on the average neonate is not likely to be severe. Neonatal death rates at ~0.3–0.5‰ [13] appear consistent with non-COVID rates.

What is the risk of vertical transmission of the SARS-CoV-2 virus?

Vertical transmission of SARS-CoV-2 has been an area of focus since the outbreak of the current pandemic. A relatively small number of newborns in reported series have been undergoing PCR testing. This has introduced variability in reported positivity rates. In a review of 493 infant outcomes, a 2% test positive rate was found [14]. Other systematic reviews and a national study of 190–310 newborns report neonatal test positive rates of from 0 to 4% [11]. There is clearly therefore a possibility of vertical transmission though this appears to be relatively small. Sufficient justification however exists for routine SARS-CoV-2 testing of the newborns of infected mothers and larger datasets need to be accumulated.

Overall, significant advances in our understanding of the impact of COVID-19 in pregnancy has been achieved. Larger series that can more precisely guide counseling and treatment and that are relevant to a particular neonatal context are clearly warranted.

Designing and implementing a regional COVID-10 in pregnancy registry, quickly

Introduction and summary of progress

Investigators in the collaborative, noted the rapid increase in COVID-19 cases in our region, recognized early in the US as a “hot spot,” along with an explosion in the number of documented and suspected COVID-19 cases on the respective obstetric services. Upon reviewing the literature, which at the time (five months ago) was very limited, the dearth of US data on maternal outcomes in pregnant women who contracted the SARS-CoV-2 infection was apparent. The collaborators concluded that the absence of significant US data to guide obstetric and medical practitioners in this country needed to be urgently addressed. An agreement on establishing a regional registry in the hopes of addressing some of these deficiencies was quickly reached. Of great value was the fact that much of the Obstetric and Maternal-Fetal Medicine leadership in the Greater Detroit/Southeast Michigan region had trained at and/or served as faculty at Hutzel Hospital/Wayne State University with RJS. This made obtaining enthusiastic cooperation and agreement to participate relatively straightforward. In total, at the time of this writing 14 obstetric services with a total of approximately 50,000 deliveries per year have become a part of this collaborative. This includes all four university-affiliated/related services in the region, as well as large community-based hospital services that provide a significant percentage of obstetric care in our region. Based on experience on these services, it is estimated that data for at least 400 cases of COVID-19 in pregnancy (in addition to the two to three times that number of controls) will be collected over the two year study period, a large number compared with any reports in the literature, suggesting it
would be possible to have a large enough sample size to avoid missing important but low frequency outcomes because of inadequate statistical power. The tasks of the collaborative were, deciding on the objectives, agreeing on the design and getting the group together for weekly phone meetings, and initiating and obtaining Human Investigation Committee Institutional Review Board (IRB) approval at each institution. This process has moved forward relatively rapidly. Furthermore, we welcomed and anticipate that several more obstetric services in the region may opt to join us. Given the potential for cyclic and recurrent outbreaks in the pandemic and the duration of pregnancies an average of 39–40 weeks, we planned the study to extend over two years to facilitate adequate time to fully manifest the maternal and pregnancy outcomes of cases infected with the COVID-19 virus. This joint effort is expected to provide the robust patient population needed for adequate power to study COVID-19 pregnancies and to be significantly more impactful than publications from individual hospitals.

**Study design**

The overall study objective was to characterize maternal and fetal/neonatal morbidities and quantify these risks in COVID-19 pregnancies. When we began there was insufficient data and specifically a dearth of US data by which the frequency of these complications can be reasonably estimated. Such information will be pivotal for counseling patients and families and for developing medical, obstetric and newborn management strategies. Our objectives for the registry include the following:

- To determine the frequency of maternal pregnancy, fetal and newborn complications in COVID-19 infection and whether they are significantly increased over those in control pregnancies.
- Determine whether the frequency of prematurity is significantly increased in COVID-19 pregnancies relative to an unaffected cohort controlled for timing and hospital of delivery.
- Document the frequency of other obstetrical complications in COVID-19 pregnancies.
- Document the frequency of maternal medical complications in COVID-19 pregnancies.
- Document the frequency of newborn complications in COVID-19 pregnancies.
- Accounting for the reported substantial false negative rates of viral PCR testing, determine maternal, pregnancy and newborn risks and outcomes in symptomatic, clinically suspicious pregnant patients with negative cultures.
- Document the frequency of maternal medical adverse outcomes.
- Document the frequency of obstetric, fetal and newborn complications in this group.

To accomplish these goals and aims, we planned a retrospective review of cases of COVID-19 positive and suspected pregnant women who delivered in the participating institutions. While many registries only enroll patients with a given disease, this approach limits the value of any findings, which basically are multi-case reports. Statistically, having a control group allows calculation of an adequate sample size to avoid an underpowered study, helping avoid a type 2 error, particularly an issue with relatively rare outcomes. To support enhanced statistical inference, after group discussion, we opted for inclusion of a control group, thus changing the design from a Registry into a Regional Collaborative Research Group Observational Study. Index cases of COVID-19 pregnancy are matched with the next three deliveries in the labor and delivery unit in which the index case was delivered. Controls were defined as individuals not suspected of or diagnosed with COVID-19 infection. We decided to fix the number of cases and controls to be powered to meet the requirements for the anchoring outcome i.e., preterm birth, which correlates with other important pregnancy complications. Simultaneously, outcomes for individuals with symptomatology suggestive of COVID-19 infection, but who had negative or equivocal PCR test results for infection, are being collected. The frequency of such cases in pregnancy is currently unknown so it is not possible to perform a valid power analysis for these comparisons (see below). The objective is to assess the rates of maternal and perinatal complications in this group, just as we are doing for the COVID-19 positive cases.

The study proposed the establishment of a multi-institutional clinical database, based on extraction of the relevant pregnancy, newborn and hospital outcomes from the medical records of pregnant women who delivered at the participating institutions. Given the high rate of infection observed among healthcare workers in the US and in Southern Michigan, the high infectivity of the virus, chronic issues of inadequate quantities and quality of personal protective equipment and given that the study is based entirely on chart review and results are only to reported jointly with protection of patient anonymity, we judged that the need for consent would introduce additional health risks without additional research benefit. Therefore, we requested and have received a waiver for additional patient consent from each IRB. It is worth noting, parenthetically, that working with multiple IRBs
may seem inefficient, but having the local principal investigators (regional collaborators) deal directly with their own committees has been advantageous, both with regard to the granting of waivers and working through data use agreements for the study.

Data collected includes demographic information, the obstetric course, maternal medical complications, pregnancy and newborn outcomes and placental histology. The categories of clinical and laboratory data for extraction from the medical records of pregnant patients and their newborns are detailed in Table 1 (the full listing of variables is available on-line in Appendix 1). Variables to be included were chosen from extensive literature review plus regional experience as our experience ballooned.

### Table 1: Redcap research database categories from South East Michigan Regional COVID-19 in pregnancy.

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification numbers</td>
<td>Identification as a case or a control</td>
</tr>
<tr>
<td>Demographics</td>
<td>Hospital, patient age, race/ethnicity, insurance status, location of residence, highest educational level, employment status, marital status of patient and partner, maternal weight, height and BMI</td>
</tr>
<tr>
<td>Past history</td>
<td>Gravidaity, parity, term births, preterm births, abortions, living children, prior preterm birth with Gestational age</td>
</tr>
<tr>
<td>Pre-existing medical disorders</td>
<td></td>
</tr>
<tr>
<td>Smoking, history and present</td>
<td></td>
</tr>
<tr>
<td>Current obstetric history</td>
<td>Estimated due date, prenatal care? Ob disorders this pregnancy, number of fetuses</td>
</tr>
<tr>
<td>COVID-19 details</td>
<td>Date of admission and days since first Michigan case, contact with positive individual and symptoms?</td>
</tr>
<tr>
<td>Gestational age at symptom onset</td>
<td></td>
</tr>
<tr>
<td>Trimester of COVID-19 infection</td>
<td></td>
</tr>
<tr>
<td>Signs and symptoms (20 + other)</td>
<td>Lab testing for virus and response</td>
</tr>
<tr>
<td>Additional respiratory diagnosis</td>
<td></td>
</tr>
<tr>
<td>Laboratory findings (up to 14 entries for each of 26 lab assays potentially affected in COVID-19 infection with final interpretation of lab abnormality)</td>
<td></td>
</tr>
<tr>
<td>Imaging findings</td>
<td>Chest X-ray and CT scan, brain MRI and EEG</td>
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<tr>
<td>CNS abnormality</td>
<td></td>
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<tr>
<td>COVID-19 disease severity on admission and during hospitalization</td>
<td></td>
</tr>
<tr>
<td>Critical care admission? When?</td>
<td></td>
</tr>
<tr>
<td>ECMO? CPAP? Antibiotics</td>
<td>COVID-19 treatment with 13+other drugs, including corticosteroids and anticoagulants</td>
</tr>
<tr>
<td>Same information for first admission and second through fifth admissions</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Maternal outcome, or any of 14 or other adverse outcomes, reason for maternal ICU admission, date and primary cause(s) of maternal death, if discharged before delivery, gestational age, adverse pregnancy outcomes (9 + other), significant persistent FHR abnormality, anesthesia, intrapartum complications, delivery type, induced and reason(s)? Cesarean indication(s)</td>
</tr>
</tbody>
</table>

### Table 1: (continued)

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at delivery</td>
<td></td>
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<tr>
<td>Length of delivery hospitalization</td>
<td></td>
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<tr>
<td>Newborn gender, weight and length</td>
<td></td>
</tr>
<tr>
<td>Premature birth status and newborn findings</td>
<td></td>
</tr>
<tr>
<td>Major birth defects</td>
<td></td>
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<tr>
<td>Newborn testing for Cov-19 with diagnosis</td>
<td></td>
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<tr>
<td>Newborn complications including NICU admission and reason(s)</td>
<td></td>
</tr>
<tr>
<td>Neonatal death with date and cause(s), including neurologic condition</td>
<td></td>
</tr>
<tr>
<td>Neonatal serum IgM antibodies</td>
<td></td>
</tr>
<tr>
<td>Neonatal secondary bacterial infection</td>
<td></td>
</tr>
<tr>
<td>Placental analysis and histology</td>
<td></td>
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<tr>
<td>Rooming in and breastfeeding with duration?</td>
<td></td>
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</tbody>
</table>

Recognizing the need for a coordinating center

For major National Institutes of Health sponsored inter-institutional studies, funding of a data coordinating center is a prevailing standard in the US. Our observational study initiative was much smaller, regional and not externally funded, so this issue was not top of mind. The need for a computerized database and the magnitude of the data to be collected, entered, cleaned and analyzed that made the need for a Coordinating Center obvious. This could have been a major “sticking point,” since while clinical research projects such as this can be done by individual physician scientists gratis in their own institutions. For a more substantial project, lack of a dedicated research database system, such as Redcap, and knowledgeable individuals to manage it would have been fatal. Fortunately, such resources were made available by one of the Co-Principal
Investigators (SSH), who provided in kind funding through the Wayne State University Office of Women’s Health, which she directs. Going forward it is clear that we will need additional funding to operate effectively and efficiently; we will need to approach agencies and foundations for such support.

**Power analysis**

Having detailed the regional collaborative feeding data into the registry and the data collected, we turn our attention to the number of patients planned for inclusion and the duration of data collection. The review of Schwartz et al. [17] yielded a prematurity rate of 28.2%, while the review of published cases by Dashraath et al. [18] found a prematurity rate of 43% in COVID-19 pregnancies. The estimate by Schwartz et al. [17] was used for our power calculation as it was more conservative, and the study provided more details for calculation of the prematurity rate. In the review of 38 cases (five case series) by Schwartz et al. [17] they reported a prematurity rate (primarily from Wuhan City, China) of 28.2% for COVID-19 pregnancies. Data on the prematurity rate in Hubei Province before the epidemic [19] was estimated at 9.4%. This would represent a three-fold increase in prematurity among COVID-19 infected women. The prematurity rate in the State of Michigan, US, from which the participating centers in this study originate was 10% in 2019 [20].

Based on the report of Schwartz et al. [17] the prematurity rate in these COVID-19 cases in our proposed study would be ~30% i.e., a three-fold increase over non-infected cases using Michigan data. The sample size needed to detect a 3-fold increase in the prematurity rate in COVID-19 positive cases at a power of 0.9 and a significance level of p<0.01 is 121 cases and 121 controls. However, this does not take patient transfers, based on acuity and resource availability, into account. The consequences are that both high acuity and low acuity COVID-19 patients could be transferred out from the initial institution of admission to hospitals within and outside a particular hospital system. This could challenge our ability to complete data acquisition on many patients. This is in addition to the underlying challenges of abstracting complete data (sufficient for analysis) from all patients even if the patient receives all her care in a single institution. This is an inherent challenge of performing retrospective chart-review based studies.

Based on the above, we estimated that incomplete data could result in limiting the utility of ~30% of cases. Based on this estimate, to achieve the power threshold of 121 cases for actual analysis we expect to need to review 160 case charts and 160 control charts to determine whether there is a three-fold increase in the frequency of prematurity in COVID-19 infected pregnancies. As the other complications such as stillbirth and neonatal death are significantly less common than the prematurity rate, a substantially larger number of cases would be needed to ascertain significant changes in these outcomes. We therefore have planned that all COVID-19 cases and clinically suspicious/equivocal cases that are admitted to the institutions for the duration of the outbreak (two years) be eligible for inclusion.

**Planned data analysis**

To achieve our goals and improve aims and hopefully to learn enough to improve care and outcomes for pregnant women with COVID-19, we will be doing the following analyses once data cleaning has been accomplished:

- The principal comparison will be between laboratory (PCR) test positive COVID-19 pregnancies (study cases) and asymptomatic control pregnancies. The principal outcome compared will be the prematurity rates. Other adverse obstetric outcomes will be evaluated as well.

- Secondly, the sensitivity, specificity and accuracy of the laboratory tests used to establish the diagnosis of COVID-19 infection (primarily nucleic acid tests) is variable and uncertain. Even with a good performing test, poor technique (inadequate sampling) and low number of viral replicons (often in the early stage of disease) may reduce sensitivity. Published data suggest a potential for a high false negative rate even in a laboratory setting i.e., sensitivity of 53.6–73.3% and thus a false negative rate of ~26.7–46% [21]. In other words, there could be a significant number of affected individuals with symptoms who will have an initial negative or equivocal test yet have clinical symptoms consistent with COVID-19 infection. This may be particularly so for those with mild symptoms (suspected or probable COVID-19 cases) and low viral counts. The extent of the problem is currently unknown as are the pregnancy outcomes in such equivocal cases. Also, with immunological testing coming on-line in the later part of the Michigan epidemic, the diagnostic accuracy and reproducibility has not yet been established. Consequently, data for this cohort of patients (delivered during this period with symptoms consistent with COVID-19 infection, but with negative or equivocal PCR test results, will be entered and analyzed. For this group as with PCR positive COVID-19 cases, three matched controls i.e., the next three deliveries in that particular hospital labor and delivery unit, will be used to compare pregnancy outcomes. Evidence of a signal from this study suggesting significant rates of maternal or adverse pregnancy outcomes with ‘equivocal’ cases...
could prompt significant changes in clinical management e.g., maternal and newborn isolation and the wearing of full personal protective equipment by healthcare workers involved with these patients. As for PCR positive cases, PCR negative or equivocal but with symptoms consistent with COVID-19 infection will be assessed for the prevalence of maternal and pregnancy complications will be collected over the two-year duration of the study. Bivariate and multivariable statistical analyses will be performed as appropriate with focus on describing COVID-19 risks for adverse perinatal outcomes, the impact of comorbidities and detecting any positive or negative impact of pregnancy management, such as cesarean delivery, and COVID-19 treatments, such as antivirals, corticosteroids and anticoagulants.

Comment

As academic Obstetricians and Maternal-Fetal Medicine subspecialists, the authors believe that an important part of their responsibilities is to advance knowledge that will improve maternal-fetal outcomes. That consideration encouraged preparation of this manuscript for publication. We hope our experience in working to delineate the risks of COVID-19 in pregnancy will help pave the way for others. Of particular note, we would highlight

- Keeping one’s eyes open for opportunities to contribute is as relevant for Emeritus Professors as for Assistant Professors.
- Longstanding personal relationships should be mined to facilitate clinical research, as in life in general.
- Bringing available resources to bear can accelerate research.
- The value of disease registries can be enhanced by data collection for appropriate control patients as well, turning them into observational cohort studies.

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