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Pregnancy, COVID-19 and Emerging Therapeutic Options

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Introduction

Coronavirus-19 disease (COVID-19) continues to spread across the world, creating an unprecedented international public health crisis. With 131 million women giving birth annually, governments have taken steps to safeguard this group, earmarking them as at risk1. Although a low absolute risk of adverse outcomes have been reported, emerging data from the UK and US highlights an increased risk of pregnant women with COVID-19 requiring intensive care admission[2,3,4]. With new and faster spreading severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) variants adding urgency to the vaccine push, we explore how the needs of pregnant women can be managed by the drug development community[5]. In this article we discuss the risks COVID-19 poses to pregnant women, the foetus and the newborn. We review current epidemiology, therapeutic options and focus on the specific drug development needs of this group during a pandemic.

Clinical manifestations of COVID-19 in pregnant women, the foetus and neonate

Women of reproductive age are reported to comprise 21% of all COVID-19 cases, 9% of whom were pregnant at the time[6]. Viral respiratory illnesses are associated with a higher risk of obstetric complications and adverse perinatal outcomes, including pneumonia, preterm labour and low birth weight[7,8,9,10]. The previous coronavirus infections: severe acute respiratory syndrome and Middle East respiratory syndrome demonstrated higher rates of maternal and foetal complications and mortality, warranting close attention to pregnant women in the current pandemic[11]. Data from prospective cohort studies suggested that maternal outcomes overall in COVID-19 were similar to non-pregnant [12,13]. The incidence of hospitalisation of UK pregnant women with symptomatic SARS-CoV-2 has been estimated as 2.0 per 1000 maternities (March to 31 August 2020)[2]. The clinical situation is, however, evolving and results from a large and regularly updated US dataset suggest pregnant women with COVID-19 are at significantly higher risk of severe outcomes compared with non-pregnant women, including intensive care treatment, invasive ventilation, extracorporeal membrane oxygenation and death[4]. Although this retrospective study does have limitations, such as substantial missing data and pregnancy status ascertained in 36% of women of reproductive age only, it flags risks that cannot be ignored, particularly in the light of more infectious strains of SARS-CoV-2. Data from the UK has also recently indicated the proportion of pregnant women admitted to intensive care is increasing, especially in comparison to the first wave of COVID-19[3].

As with non-pregnant individuals, advanced age, obesity, pre-existing hypertension and diabetes are significant risk factors and increase the chances of a more severe disease presentation and evolution[6,15]. Interestingly, a recent living systemic review identified pregnant women as less likely to present with fever and myalgia[15]. This may be due to routine testing of all pregnant women and therefore the identification of asymptomatic sufferers.

SARS-CoV-2 infection may increase the risk of pre-term delivery to manage obstetric or medical complications, but rates of spontaneous pre-term labour do not appear to be elevated[15]. The incidence of stillbirth and neonatal death do not seem to be

higher than the background rate[2,4,15]. Admission to neonatal units was noted to be increased in studies[2]. The rationale for this may include local policies on observation and quarantine of infants with exposure to SARS-CoV-2.

In utero vertical transmission has been reported in case studies and although rare, the SARS-CoV-2 genome has been found in umbilical cord blood, amniotic fluid, maternal vaginal mucosa and full term placenta[16]. Fortunately, infection of foetuses, newborns and infants is uncommon[17]. If neonates do become infected, most cases are asymptomatic or mild and outcomes are favourable[18,19]. Most complications in neonates born to COVID-19 positive mothers are a result of prematurity rather than COVID-19 infection[20]. Interestingly, both IgG and IgM antibodies against COVID-19 have been found in seronegative neonates born to COVID-19 infected mothers[21]. As IgM antibodies cannot cross the placenta, the suggestion of a foetal immune response against the virus is possible[21].

Therapeutic options and specifics of drug development in pregnancy

Researchers around the world are working at record pace to progress treatment and prophylactic options for COVID-19. Any drug or vaccine candidate needs to be evaluated for risk/benefit to the pregnant women plus potential effects on the foetus, newborn and breastfed infant. As pregnant women are usually excluded from pre-registration clinical trials, other ways to accelerate the understanding of risk/benefit should be considered at the earliest opportunity and include the conduct of developmental and reproductive toxicity (DART) studies and using already established pregnancy and post-marketing registries[22].

Vaccines

There are over 200 vaccines in development, with 63 vaccines in clinical stage evaluation[23]. A handful of vaccines are rolling out in select countries, including the novel mRNA immunisations by Pfizer-BioNTech and Moderna, plus AstraZeneca-University of Oxford's viral vector vaccine. The phase 3 results from Janssen's one dose vaccine are also expected shortly. These and other currently recruiting large scale vaccine studies have not actively recruited pregnant women, leading to limitations in safety data in a group that is potentially at risk.

Inclusion of pregnant women in vaccine trials, especially those looking to rapidly deliver results, is challenging but maternal immunisation is a successful tool and can, critically, provide dual protection. The influenza vaccine protects both the mother and infant and pertussis vaccines given in pregnancy afford passive protection to the infant[24]. The prospect of passive immunity through IgG transfer from a vaccinated pregnant mother is an attractive additional benefit for COVID-19 vaccines.

Phase 2 and 3 trials for vaccine studies include thousands of female subjects. Extrapolating data from women of childbearing age in clinical trials and those who inadvertently become pregnant offers invaluable insights. 49.4% of the Pfizer-BioNTech BNT162b2 Phase 3 trial were women and as of the 14th November 2020 datacut, 23 participants reported intercurrent pregnancy, outcomes of which are actively being followed[25]. DART studies can be conducted early in a clinical development plan and offer crucial safety insights of a drug's effects on pregnancy and the foetus[22]. DART studies with BNT162b2 have revealed no vaccine-related effects on female fertility, pregnancy, or embryo-foetal development[25]. This data is also a useful safety indicator for other vaccines with similar mechanisms of action. The early completion of DART studies is critical and offers a catalytic step to earlier recruitment of pregnant women in trials of vaccines and novel agents.

The data on currently approved vaccines does not indicate any safety concerns, allowing the MHRA and FDA to recommend that clinicians undertake case by case assessment for the use of COVID-19 vaccines by pregnant women, particularly those with other high risk comorbidities[26]. SARS-CoV-2 variants have arisen in several

locations including the UK and South Africa and although the current crop of vaccines are likely be effective for these, a Brazilian variant has been identified with changes to the receptor binding domain[27,28]. Drug developers from the 200 other vaccines in development should aim to evaluate safety markers in pregnancy and follow the successful precedent set by the approved vaccines to advance the inclusion of pregnant women in COVID-19 trials.

Medical treatments

Repurposing drugs with known safety profiles in pregnancy has been an attractive first approach with COVID-19. Remdesivir was used to treat pregnant women during the Ebola and Marburg virus epidemics[29] and although the recent trial in COVID-19 did not include pregnant women, there were no significant safety concerns reported in women of childbearing potential[30]. Remdesivir has not shown a mortality benefit but has some clinical benefit in shortening the time to recovery, particularly in those requiring supplemental oxygen[30]. Remdesivir's subsequent use by hospitalised pregnant women suffering with severe COVID-19 disease has occurred via expanded access programs[31]. Evaluation of the first 86 pregnant women to use the drug from 5 countries has been favourable, demonstrating high recovery rates within 28 days and low rates of serious adverse events[31]. The RECOVERY trial demonstrated a mortality benefit of low dose dexamethasone in patients with COVID-19 who required respiratory support[32]. This trial included pregnant and breastfeeding subjects and no pregnancy associated adverse outcomes were reported. The use of steroids and remdesivir are now included in national guidelines[33]. There are several trials looking at interferon (IFN) alpha and beta use in COVID-19, mostly in addition to antivirals. Results with injectable forms have been disappointing[34]. An investigational inhaled nebulised IFN beta-1a (SNG001) has however, shown some promise. When administered to hospitalised patients with COVID-19 in a phase 2b study, the likelihood of recovery by day 15 compared with placebo was increased[34]. Several studies (mostly in multiple sclerosis) have shown no increase in congenital abnormalities with INF use[35], this coupled with the potentially to bypass the placenta makes nebulised IFN beta-1a an attractive option for pregnant women. DART studies should also be conducted with

this investigational product to allow further insights to the risk/benefit in pregnant women. The use of other agents, such as monoclonal antibody therapies have shown some promise in clinical trials and case-reports of use in pregnant women are growing[36,37]. Given the potential for higher risk in pregnant women, in the absence of absolute contraindications, it may be reasonable to include pregnant women in clinical trials of these therapeutic approaches.

Conclusion

The race to find appropriate treatments and vaccines for COVID-19 is progressing swiftly, but with the urgency of more transmissible variants and more intensive care admissions, strategies to enrol pregnant women earlier into clinical development plans should be utilised. To ensure safety of pregnant women and neonates, drug developers should prioritise early initiation of DART studies followed by systematic review of inadvertent pregnancies during clinical trials in the general population. This, coupled with industry supported pregnancy registries and close collaboration with regulators and government bodies, will allow pregnant women to have access to investigational clinical trials whilst mitigating potential risks. The authors will continue to review developments for pregnant women during the COVID-19 pandemic.

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