COVID-19: can we treat the mother without harming her baby?

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Abstract

Medical care is predicated on 'do no harm', yet the urgency to find drugs and vaccines to treat or prevent COVID-19 has led to an extraordinary effort to develop and test new therapies. Whilst this is an essential cornerstone of a united global response to the COVID-19 pandemic, the absolute requirements for meticulous efficacy and safety data remain. This is especially pertinent to the needs of pregnant women; a group traditionally poorly represented in drug trials, yet a group at heightened risk of unintended adverse materno-fetal consequences due to the unique physiology of pregnancy and the life course implications of fetal or neonatal drug exposure. However, due to the complexities of drug trial participation when pregnant (be they vaccines or therapeutics for acute disease), many clinical drug trials will exclude them. Clinicians must determine the best course of drug treatment with a dearth of evidence from either clinical or preclinical studies, where at least in the short term they may be more focused on the outcome of the mother than of her offspring.

Background

Since the beginning of 2020, when most of us had not heard of COVID-19, as of 8 October 2020,[1] there have been over 36 million cases of SARS-CoV-2 and 1 million deaths from COVID-19 globally. The devastating impact of COVID-19 on communities worldwide is clear. Although vaccination is a key part of our global response to this crisis, we need a more immediate armamentarium of safe drugs to treat those infected with SARS-CoV-2 now, and during the months or years ahead whilst vaccine development progresses. There is no definite timeline on vaccine development. Even if a vaccine against SARS-CoV-2 is developed, its success depends on the development of lasting immunity, stability of the virus, availability and efficacy of the vaccine, and the willingness of the population to be vaccinated.

Furthermore, it remains important to acknowledge that we as a population are susceptible to novel coronaviruses, with three life-threatening variants emerging in the past 20 years. These novel viruses will require treatment and thus understanding the impact of the disease, its vaccine and treatment on the fetus and child will future-proof our pharmaceutical toolbox. In 2017, the WHO identified 17 diseases for which vaccine development was a priority: MERS and SARS, both coronaviruses, were highly ranked,[2] yet neither have an effective vaccine. Of 224 candidate vaccines, only 2.7% have advanced to Phase 1 trials.[3] Thus, despite vaccine candidates for SARS-CoV-2 entering human safety trials, there may be some time before an effective vaccine is available. Vaccines for SARS have been complicated by hyperimmune responses following infection in vaccinated individuals, likely due to antibodies that target the spike protein on the virus.[4] Over the last 20 years, despite societal awareness and engagement, progress with vaccine development programmes (such as for HIV[5] and Zika virus[6]) has been slow, and proportional engagement in clinical trial participation across ethnic and socio-economic groups may not have been achieved.[7] Even if a safe, effective SARS-CoV-2 vaccine is found, significant vaccine hesitancy and refusal remains an important issue for both health care workers[8,9] and the wider community which may limit vaccine uptake[10] and virus elimination strategies.[11]

Critically, whilst vaccine-preventable disease is a major health initiative, pregnant women are traditionally amongst the last to access new vaccinations due to the inherent ethical implications and concerns around potential fetal toxicity. Many vaccines, such as those recommended for seasonal influenza, need to be administered annually, as prior immunisation confers limited longevity of protection, thus immunisation *prior* to pregnancy is not assured of offering protection *during* pregnancy. There is emerging evidence of reinfection,[12–14] which suggests that vaccination for SARS-CoV2 may last for a limited period; however, we are too early in our learnings to fully appreciate the duration of immunity after contracting SARS-CoV-2 or receiving an

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effective vaccine. Thus, even if current claims of an approved vaccine by the end of 2020 are realised, ensuring global access to an effective vaccine will take far longer, and, even if available, vaccination uptake may be lower than required to slow the spread with a vaccine that is only partially effective, especially in women of reproductive age. Indeed, women of reproductive age, particularly those aged 20–29 years are also the group most likely to be SARS-CoV-2-positive.[15] Thus, we must be prepared to provide the best care to pregnant women whilst also reducing harm to their baby. Regardless of whether a vaccine is available, effective and safe, there will be a need to treat pregnant women with symptomatic COVID-19 and/or the next novel coronavirus that enters the human population through zoonotic infection comes along. Understanding the safety of these drugs for pregnant women and their babies will future-proof our clinical toolbox against COVID-19.

COVID-19 in pregnancy

There is evidence for unique immunological changes in each stages of pregnancy that result in a different response to viral infections compared to non-pregnant women,[16] and pregnant women are identified as being part of a vulnerable population by RANZCOG.[17] Specifically, they are more susceptible to respiratory infections and thus it is possible they may also be more susceptible to SARS-CoV-2[18], although susceptibility varies.[19] Whilst there is evidence that pregnancy is not related to severity of disease,[19–21] poor maternal outcomes such as ventilation and ECMO have been reported.[22,23] The prevalence of SARS-CoV-2 in a community is an important factor when determining risk of exposure[24,25] and this will vary both across and within countries. In the US and UK, 7–15% of women presenting at hospital for term delivery tested positive for SARS-CoV-2 in March/April 2020.[24,26,27] In New York, 10% of 675 pregnant women (>20 weeks) tested positive and concerningly 78% of them were symptomatic.[26] In contrast, other studies suggest that 14–70% of pregnant women who tested positive are asymptomatic.[28–30] The course of COVID-19 in pregnancy has been described and includes fever, coughing and dyspnea with severe cases including acute respiratory disease.[19,25,27,31–34] Pregnant women may have more pulmonary infiltrate than non-pregnant women,[29] although most experience mild disease.[19,35,36] A systematic review has highlighted the increased risk of ICU support needed for pregnant women with COVID-19 compared to non-pregnant women of equivalent age.[27] Symptomatic pregnant women with COVID-19, particularly those who develop pneumonia, may be at increased risk of delivering their baby preterm by caesarean section due to maternal complications.[25,27,30,34,35,37–40] Preterm delivery puts the neonate at increased risk of poor immediate and longer-term outcomes.[41] There is also evidence that these pregnancies are associated with greater risk of fetal distress, stillbirth, miscarriage, low birth weight and respiratory distress in the newborn.[30,32,33,36,42] Overall, however, for term-born infants whose mothers have COVID-19, neonatal outcomes are good,[36] despite a higher risk of bacterial pneumonia[43] and, although rates of admission to neonatal intensive care units are high,[27] few neonatal deaths have been reported.[33] Based on the time course of the appearance of SARS-CoV-2 across the globe (Fig. 1), most publications to date report data on women who contract COVID-19 in the third trimester.[30,34,35,44] Thus, the feto-maternal complications of infection with SARS-CoV-2 in the first or second trimester are currently uncertain.[26] Understanding the impact of the timing of infection on the course of a pregnancy and long-term outcomes in the offspring will take many years in the clinical population.

Furthermore, few studies have included contemporaneous SARS-CoV-2-negative pregnancies as a control group, reducing the impact of the data. For example, meta-analysis of studies that included a pregnant SARS-CoV-2-negative control group shows no significant relationship between SARS-CoV-2 infection and preterm delivery.[45] Lastly, there are many systematic reviews of small studies with overlapping reporting dates. Thus, for all who we know regarding SARS-CoV-2 in pregnancy, the true impact is not clear. From this perspective, prevention of SARS-CoV-2 is the best option,[39] and an effective vaccine may allow this to occur.

Vertical transmission of COVID-19 in pregnancy

Many studies have focused on whether COVID-19 is vertically transmitted from mother to her fetus or if the risk of exposure to the baby occurs during the postnatal period. Theoretically, vertical transmission remains possible. Angiotensin converting enzyme 2, a target of SARS-CoV-2 cell entry, and the spike glycoprotein of SARS-CoV2 have been found on the syncytiotrophoblast cells of the placental villi that form the interface between mother and fetus in the placenta.[51] Many case or small studies have been performed and systematic reviews of these studies have not identified evidence for vertical transmission.[24,26,29,32,43,52–61] There is no evidence that vaginal delivery, breastfeeding or remaining with the mother postnatally increase the risk of neonatal infection, as long as appropriate contact precautions are meticulously applied, whilst the mother remains infectious.[62] However, this issue focuses on the concept that the only risk of a SARS-CoV2-positive mother to the fetus is that the fetus/baby may also get COVID-19. Crucially, we do not know the impact of maternal COVID-19 and/or the pharmacological treatment of COVID-19 on the pregnant woman on the developing fetus and how this will impact the offspring across the course of their lives. The principles of developmental origins of health and disease (DOHaD) highlight the importance of taking a life course approach and understanding the mechanisms linking exposures during pregnancy on offspring health in infancy, childhood, adulthood and old age,[63–65] and this must be considered in the case of COVID-19.

Drug safety in pregnancy

Historically, most Phase 3 drug trials have included men, and in recent times, non-pregnant women. In many cases, information about the safety of drug use during pregnancy in terms of birth outcomes is collected many years after the drug comes onto the market and is obtained through surveillance programmes such as the now defunct Motherisk programme.[66–69] The problem with this long delay from the drug entering the market and the slow gathering of, in most instances, negative outcomes makes it difficult to understand the true prevalence of poor outcomes and the mechanisms that underlie them. This delays an understanding of the actual impact of drug exposure during pregnancy to the offspring and thus delays changes in practice such as use of another drug, a change in dosing or discussion about termination of pregnancy.[66–69] Inclusion of women of reproductive age and pregnant women in clinical trials is an important feature of minimising harm to the fetus. A recent white paper has been released by the WHO that uses learnings from HIV to propose guidelines for accelerating such data and the key use of physiologically based pharmacokinetic data to inform clinical trials in pregnant women.[70]

Any drug given to a pregnant woman, as well as its metabolites, will be distributed to both the maternal and fetal compartments.
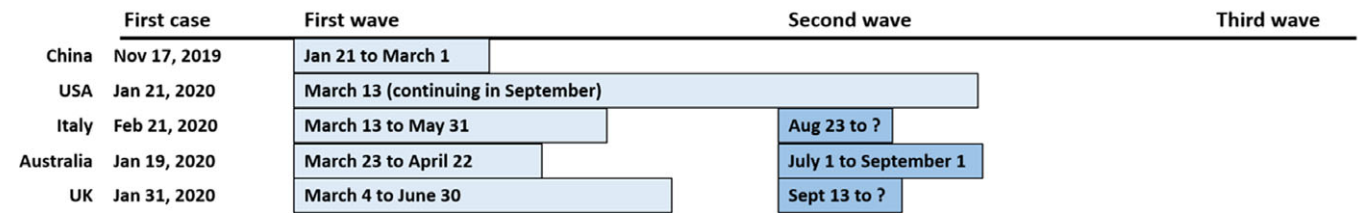
Fig. 1. Timeline showing the appearance and progression of COVID-19 globally in relation to gestation length to illustrate our current inability to understand the true impact of COVID-19 on offspring. Data sourced from Refs. 46–50.
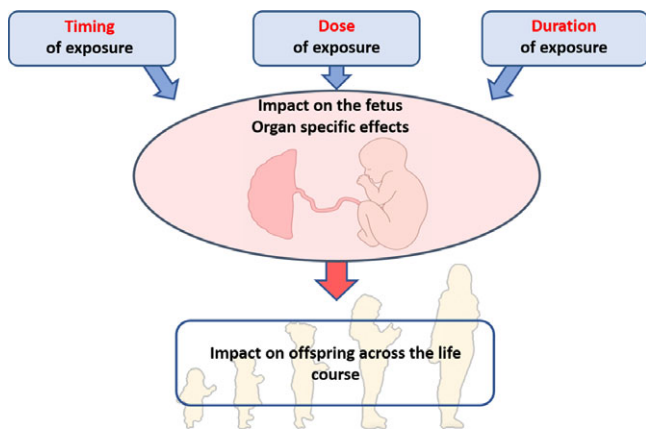

Fig. 2. The timing, dose and duration of fetal exposure to medications to treat the symptoms of COVID-19 in the mother will interact to determine the impact on the fetus with organ-specific effects that will impact health across the life course of the offspring. Adapted from Refs. 78 and 79.

Fetal development is a dynamic process; the consequences of drug exposure are dependent on the specific stage of fetal development at the time of the exposure. Thus, it is necessary to consider that, in addition to the mother, the fetus is also a patient who will be exposed to the drug.[71] Exposure to toxic drug effects may lead to fetal demise, miscarriage, disruption of organ formation (for instance, as seen with devastating consequences with thalidomide[72]), impaired fetal growth or altered organ function. These all have adverse implications for the wellbeing of the baby and may result in lifelong health impairment. This highlights the importance of the timing of drug exposure during pregnancy (Fig. 2) and the need for preclinical studies that are specifically designed to address questions around safety of maternal drug treatment, at different periods of gestation, on the baby.[73] These studies cannot simply look for congenital malformations, as drugs may be more nuanced effects with the true extent of problems only manifesting later in life. For example, our previous work has shown that maternal treatment with antidepressants can result in changes in body composition in childhood.[74–77] Some medications proposed for treatment of COVID-19 in pregnancy already have a widely characterised maternal and infant safety profile (e.g., antiretroviral drugs used to reduce vertical transmission rates of HIV), which enables better decision-making between clinicians and their patients. However, many important knowledge gaps around the safety of other drugs that may potentially be used to treat pregnant women infected with SARS-CoV-2 remain.

Drug treatment of SARS-CoV-2

Until now, treatment of COVID-19 has focused on the use of antiviral medications (e.g., remdesivir[80]) and immunomodulators (e.g., dexamethasone, hydroxychloroquine, tocilizumab and anakinra) to dampen an exaggerated immune response to SARS-CoV-2 infection in acutely unwell patients.[81] Other than the use of dexamethasone in patients with severe COVID-19, there is no conclusive evidence that any of these therapies increase survival, although most of the trials that have been conducted have yet to report their findings. Prophylaxis against infection will no doubt be a strategy that is explored, although early positive signs with hydroxychloroquine were followed by evidence of a lack of efficacy[82] and concerns about increased mortality, development of cardiac arrythmias and cardiac death.[83]

Selection criteria for drugs to treat the symptoms of COVID-19 in pregnant women

When a pregnant woman requires management of COVID-19, the clinician will be presented with two patients: a pregnant woman and a fetus. However, it is the pregnant woman who will be experiencing the symptoms of COVID-19 and who will require treatment with the primary concern being the mothers' wellbeing. Her symptoms of COVID-19 may result in hypoxemia, hyperthermia or hypoglycemia in the fetus, and these could all have negative consequences during fetal as well as postnatal life. However, it is important to consider that some treatments for the symptoms of COVID-19 in the mother may have greater or fewer effects on the fetus. These effects may be short or long term and may manifest as congenital malformations, or changes in the structure and function of organ systems that persist throughout the life course and confer a greater risk of chronic disease later in life. This later point raises concerns for COVID-19 in the context of the DOHaD hypothesis (Fig. 3). Thus, it is important to ensure that preclinical studies are performed to fill the gaps in our knowledge about the effects of these drugs on the pregnant mother, the developing fetus and the offspring from childhood to adulthood. This will allow the clinician the opportunity to pair this knowledge with the best evidence around treatment of COVID-19 to select a
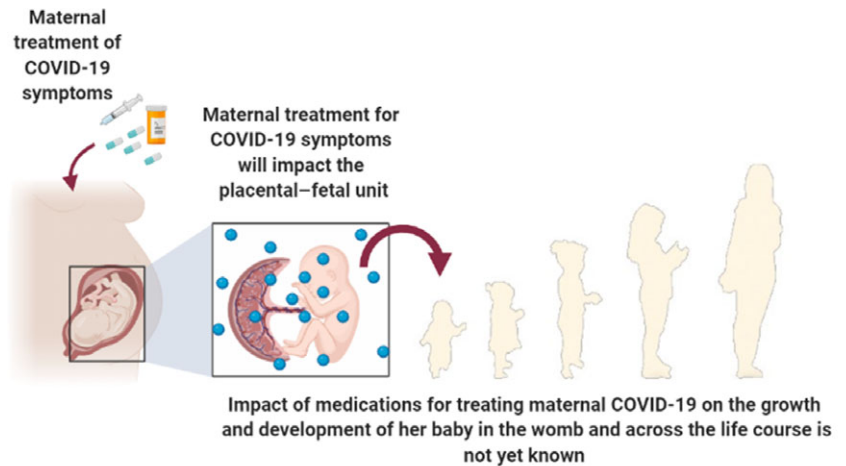
Fig. 3. It is necessary to identify COVID-19 drug therapies for pregnant women who do not harm their babies' growth and development or the health of their offspring throughout their life. Studies in humans will take years to decades to perform, but preclinical studies in appropriate models will accelerate our knowledge.

treatment strategy that will result in the best outcomes for the pregnant woman with the least risk of negative outcomes for the offspring.

We referred to the current guidelines for care of COVID-19 patients and inspected the clinical trials registries (e.g., ClinicalTrials.gov and ANZCTR.org.au) as well as publications on emerging clinical evidence for effectiveness in treatment of COVID-19. Here, we summarise some of the medications used in the treatment of COVID-19 and the knowledge base about their use in pregnancy and the impact on the fetus and offspring. Clearly, this is a dynamic area, and drugs for use in treating COVID-19 may change as data emerge from ongoing clinical trials, and thus Table 1 is not comprehensive but reflects the current knowledge base.

No or limited data of many of the medications in clinical trials for the treatment of COVID-19 in pregnant women and their offspring

Clinical prioritisation means that in most settings, the immediate health needs of the mother outweigh theoretical health implications of drug exposure to the fetus. For example, a PubMed search of 'Remdesivir and pregnancy' produced 13 results (6 October 2020), including 4 case reports with polypharmacy treatment of COVID-19 which contained little to no fetal outcome data and one case series of 64 pregnant women with severe or critical COVID-19, 16 of whom received remdesivir (including 65% of those women assessed as being critical) an average of 10.5 days after symptoms emerged.[80,84] In this case, series pregnancy and neonatal outcomes were reported, but the sample was not large enough to disentangle the effects of a mother with COVID-19 from those of exposure to remdesivir (and other treatments) on the fetus and there was no follow-up after birth. Concerningly, despite an absence of knowledge of placental transfer, remdesivir is deemed safe for the treatment of COVID-19 in pregnancy based on very limited data, with evidence of safety in pregnancy arising from a single study in a pregnant patient with Ebola, published in 2017.[85,86]

Many of the candidate drugs are also used in other immune-mediated or inflammatory conditions, many of which affect women of reproductive age. Thus, even if these drugs are not used in COVID-19, better understanding of the effects of these drugs in pregnancy will be a significant and clinically valuable contribution to fetal safety of drugs used in women. There is an urgent need to utilise appropriate animal models, rather than women facing life-threatening illness, to establish the acute and longer-term outcomes of fetal drug exposure.

Preclinical models for determining the safety of drug treatments in pregnancy

Unfortunately, many studies of the effects of drugs during pregnancy in humans simply focus on gross pregnancy outcomes (e.g., gestational age at birth) and the overall physical condition of the baby at birth (e.g., congenital malformations). The long latency and other confounding factors between fetal drug exposure and later-life wellbeing prohibit most human long-term follow-up studies. Preclinical studies of the effects of maternal drug treatment on her offspring prior to birth and throughout the life course (Fig. 2) must be performed in a species where the timing of fetal development aligns with that of humans. Although non-human primates such as *Macaca fascicularis*[87] may be the gold standard for drug testing, due to ethical concerns and logistical constraints, they may not be appropriate for characterisation of fetal impact of drug exposures (myometrial contraction after fetal surgery for catheter placement and technical limitations of fetal size (adults weigh 1.5–2 kg)).

Sheep and guinea pigs have been extensively used in preclinical studies that have been used to build an evidence base for therapies in obstetrics and paediatrics,[88,89] most notably the use of antenatal steroids in women at risk of preterm delivery. The effects of a range of maternal drug treatments, including antidepressants,[90–93] rosiglitazone,[94] resveratrol,[95] betamethasone[96,97] and methamphetamine,[98] on physiological outcomes in the fetus and juvenile have been studied in sheep and guinea pigs. There are advantages and disadvantages to each model. In sheep models, fetal surgery can be performed to allow collection of paired blood samples from the maternal and fetal circulation and determine the fetal response to maternal drug treatment in real time.[90–93,99] In guinea pigs, one can comprehensively assess the longer-term effects of fetal drug exposure to primary school age equivalency[97,98,100–103] or

Table 1. Drug treatments for COVID-19 and our knowledge about their safety for use in pregnancy

Candidate drugs	Mechanism of action	Dose and mode of delivery	Evidence of efficacy in treating COVID-19 in RCTs	Pregnancy outcomes	Birth outcomes	Childhood outcomes
Antivirals						
Remdesivir	Viral RNA polymerase inhibitor (antiviral)	Initial dose of 200 mg; then 100 mg for 9 days; intravenous (IV).	5, not 10, day course may improve outcome.[112–114]	Case report of neonate admitted to NICU with persistent pulmonary hypertension and patent ductus arteriosus.[115]	Preclinical data: negative effects on kidney.	No data
Ritonavir and lopinavir	Protease inhibitors	Oral 100 mg twice daily for 14 days in combination with oral 400 mg twice daily for 14 days.	No significant benefit compared to standard care with respect to 28-day mortality (−5.8%, 95% CI − 17.3 to 5.7) or clinical improvement (HR 1.31, 95% CI 0.95 to 1.8) of combination of ritonavir and lopinavir in severe COVID-19.[116] Addition of an interferon −1b and ribavirin led to shorter time to negative nasopharyngeal swab.[117]	Limited data but has been used in pregnancy to prevent viral transmission. Low placental transfer.[86]	Two large population studies that showed no association with premature delivery, low birthweight and congenital abnormalities.[118,119] Higher rate of preterm births compared to zidovudine monotherapy[120] and when compared to a combination of three nucleoside reverse transcriptase inhibitors.[121]	No data
Immunomodulators						
Dexamethasone	Anti-inflammatory	6 mg/day (oral or IV) for up to 10 days.[122]	Rate ratio of 28-day death rate compared to usual care of 0.83 (95% CI 0.75–0.93). Differences were greater in those who received mechanical ventilation and oxygen, but not amongst those who received no respiratory support.[29]	Use the lowest effective dose for the shortest possible time. Placental transfer is greater with dexamethasone compared to other corticosteroids (Australian Medicines Handbook).	Used in suspected preterm birth to mature fetal lungs (4 doses 6 apart; 6 mg IM). Evidence that repeated doses have negative outcomes.[123–125]	Not known in the dosing strategy used in COVID-19.
Tocilizumab	Anti-interleukin 6 immunomodulator	8 mg/kg; second dose if condition worsens; IV (ClinicalTrials.gov NCT04320615).	In COVID-19-associated cytokine storm syndrome, patients given high-dose methylprednisolone +/- tocilizumab were more likely to improve clinically, less likely to die or require mechanical ventilation. Controls were historical rather than concurrent.[126]	Crosses the placental barrier and found in cord blood, newborn plasma and breast milk (n = 2).[127] Two small, uncontrolled studies did not identify increased risk of spontaneous abortion, preterm or stillbirth or malformations.[128,129]	Little data	No data

(Continued)

Table 1. (*Continued*)

Candidate drugs	Mechanism of action	Dose and mode of delivery	Evidence of efficacy in treating COVID-19 in RCTs	Pregnancy outcomes	Birth outcomes	Childhood outcomes
Anakinra	Anti-interleukin 1 (immunomodulator)	Up to 100 mg via subcutaneous (SC) or intravenous (IV) injection 4 times a day.	Case series and cohort studies in patients with severe COVID-19 suggest clinical improvement, reduced ICU admission, invasive mechanical ventilation and mortality.[130–138] No prospective or direct comparisons with other therapies/standard of care.	Small case series (n = 43) of pregnancies and breastfed neonates (n = 14) exposed to IL-1RA therapy did not identify developmental abnormalities. European Guidelines recommend to discontinue and/or switch to an alternate agent before conception, pregnancy or breast-feeding.[139]	Little data	No data
Baricitinib	JAK-STAT inhibitor	4 mg/d for 7–14 days; oral.	Uncontrolled and historically controlled studies demonstrate reduced disease progression when given to patients with moderate to severe COVID-19.[140,141] No prospective comparisons with other therapies/standard of care.[140,142]	Small molecule likely to cross the placenta. Tofacitinib recommended to be stopped prior to conception.	Contraindicated[143]; 1 case report[144]	No data
Antibiotic						
Azithromycin	Macrolide antibiotic	Oral/IV	Meta-analysis of mostly non-randomised studies identified increased mortality with azithromycin + HCQ (33%) compared to baseline (26%) and HCQ alone (22%).[145]	Azithromycin (B1), erythromycin (A) and roxithromycin (B1) are considered safe to use (Australian Medicines Handbook).	Azithromycin crosses the placental barrier in sheep and non-human primates. Cohort study suggests increased cardiac (first trimester) and genital (any trimester) malformations in pregnancies exposed to macrolides compared to those exposed to penicillins.[146,147]	No data
Antiparasitic						
Ivermectin	Antihelmintic	Various, including 0.6 mg/kg once daily by IV injection and 12–15 mg orally as single doses in addition to other therapies.	No direct evidence of efficacy.	Not associated with an increased risk of congenital abnormalities (Australian Medicines Handbook). ADEC Category B3. Limited fetal exposure in sheep models of pregnancy.[148]	Very low-level evidence suggests no evidence of increased risk of stillbirth, spontaneous abortion or congenital abnormalities.	No data
Monoclonal antibodies						
Regeneron	Monoclonal antibody against SARS-Cov 2-Spike protein (being developed by multiple biotech companies).	Dose TBD, intravenous use.	Currently in Phase 1–3 clinical trials showing promising initial results.[149]	No data. However, monoclonal antibodies are known to cross placenta in third trimester and are found in cord blood and breast milk.	No data	No data

adulthood.[104–106] Detailed fetal physiological studies are not possible in human pregnancy and similarly, waiting several years for the effects of fetal exposure in humans to become manifest is unethical and may result in ongoing harm whilst pregnant women continue to receive drugs that are not appropriate for use in pregnancy.

Separation of vertical versus early postnatal transmission of SARS-CoV-2 remains challenging.[37,38] However, the impact of COVID-19 on the fetus *per se* appears to primarily relate to the overall clinical condition of the mother. Thus, the primary aim of preclinical studies is to identify which of the potential therapeutic options for COVID-19 are likely to have minimal or no effect on the fetus and thus the child and later life adult. Some agents under review for use in COVID-19 are already used in pregnancy for other conditions (e.g., lopinavir and ritonavir are used in HIV treatment). However, despite widespread clinical use, it is not always clear whether any adverse effects on her child are due to the effects of maternal viral infection, the mothers' other co-morbidities, or the effects of the candidate drug on fetal or childhood growth or physiological function; such studies must be performed in rigorous preclinical models of pregnancy in a physiologically relevant species.

It is known that up to 99% of women take a prescribed or over the counter medication during pregnancy.[107,108] In addition to this existing medication use, women with COVID-19 will be treated with a range of medications for symptom management. Furthermore, as social isolation is known to adversely impact on mental health, pregnant women during the pandemic, with or without COVID-19, may therefore also require treatment for mental health disorders.[109] Thus, complications relating to polypharmacy is a concern, especially if access to usual health care providers is hampered as a result of the pandemic. SARS-CoV-2 infection and the need for pharmacological intervention need to account not only for the medications required to treat the infection, but their interaction with a panoply of medications needed to treat other non-COVID-19 diseases.

Concluding remarks

If clinicians have the choice of medications believed to have equitable efficacy for maternal symptoms, the fetal and postnatal impact of the drug will inform important maternal therapy choices. Ensuring rigorously tested, high-quality information is available for clinicians, women and their families is paramount to avoid the unintended consequences of poorly designed, inappropriately tested drug regimens becoming an accepted part of clinical care.[110] Treatment of COVID-19 represents a profound challenge to physicians across the globe. The best treatments are yet to be established, leading to an unprecedented explosion in new drug therapy trials. Pregnant women are especially vulnerable to the effects of COVID-19, yet we are without clear guidance on drugs that are effective for the mother but are also safe for her developing fetus. Given the well-documented issues surrounding drug research participation during pregnancy,[111] pregnant women, despite vulnerability to COVID-19, are likely to be amongst the last clinical groups to have access to robust scientific evidence to guide clinical decision-making.[110] Simply waiting for an effective vaccine to become available, or for herd immunity to take effect, is an unacceptably risky strategy. To reduce the latency in human safety and efficacy trials, we highlight the need to capitalise on well-established perinatal translational platforms to firstly test the acute fetal effects (sheep[88]) and secondly assess any adverse pregnancy or longer-term outcomes on offspring (guinea pigs[89]).

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