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Placental transfer and safety in pregnancy of medications under investigation to treat coronavirus disease 2019

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OBJECTIVE: Treatment of coronavirus disease 2019 is mostly symptomatic, but a wide range of medications are under investigation against severe acute respiratory syndrome coronavirus 2. Although pregnant women are excluded from clinical trials, they will inevitably receive therapies whenever they seem effective in nonpregnant patients and even under compassionate use.

METHODS: We conducted a review of the literature on placental transfer and pregnancy safety data of drugs under current investigation for coronavirus disease 2019.

RESULTS: Regarding remdesivir, there are no data in pregnant women. Several other candidates already have safety data in pregnant women, because they are repurposed drugs already used for their established indications. Thus, they may be used in pregnancy, although their safety in the context of coronavirus disease 2019 may differ from conventional use. These include HIV protease inhibitors such as lopinavir/ritonavir that have low placental transfer, interferon that does not cross the placental barrier, and hydroxychloroquine or chloroquine that has high placental transfer. There are also pregnancy safety and placental transfer data for colchicine, steroids, oseltamivir, azithromycin, and some monoclonal antibodies. However, some drugs are strictly prohibited in pregnancy because of known teratogenicity (thalidomide) or fetal toxicities (renin-angiotensin system blockers). Other candidates including tocilizumab, other interleukin 6 inhibitors, umifenovir, and favipiravir have insufficient data on pregnancy outcomes.

CONCLUSION: In life-threatening cases of coronavirus disease 2019, the potential risks of therapy to the fetus may be more than offset by the benefit of curing the mother. Although preclinical and placental transfer studies are required for a number of potential anti-severe acute respiratory syndrome coronavirus 2 drugs, several medications can already be used in pregnant women.

Key words: coronavirus disease 2019, placenta, pregnancy, severe acute respiratory syndrome coronavirus 2

Introduction

The current coronavirus disease 2019 (COVID-19) pandemic is a global health emergency that affects all populations, including pregnant women.[1,2] COVID-19 can result in maternal morbidity and mortality from pneumonia and acute respiratory distress syndrome (ARDS),[3] similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) infections and influenza.[4,5] Studies on pregnancy complications are still lacking, although a high preterm birth rate has been reported. This is mostly caused by iatrogenic preterm birth owing to the diagnosis of COVID-19[6] principally preterm cesarean deliveries.[7–9] Whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly contributes to spontaneous preterm birth or medical complications such as preeclampsia that require iatrogenic preterm birth is less clear. Perinatal transmission may occur but seems rare.[6] There is little evidence of in utero or intrapartum exposure, because most amniotic fluid, cord blood, neonatal plasma, and oropharyngeal and placental specimens have been reported to indicate negative results,[7–9] but a case has been reported of a positive result for a reverse transcription polymerase chain reaction (RT-PCR) in a nasopharyngeal swab from a neonate born by elective cesarean delivery and immediately isolated from the mother.[10] Postnatal exposure is possible through respiratory and skin contact, but breast milk samples reported negative results in most studies. Anti–SARS-CoV-2 immunoglobulin M was reported in 8 newborns of infected mothers in 2 studies,[11,12] but these may be false-positive results for immunoglobulins[10] because the RT-PCR results were negative. In a Chinese report of 33 neonates born to women with COVID-19, 3 positive PCR test results were reported.[13]

There is currently no specific antiviral treatment recommended for COVID-19 in general or specifically for pregnant women.[3,14–16] Pregnant women remain

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AJOG MFM at a Glance

Why was this study conducted?

Although pregnant women can be severely affected by coronavirus disease 2019 (COVID-19), they are generally excluded from clinical trials because of concern about fetal safety. We have data on transplacental transfer of drugs that are currently under investigation to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Key findings

The medications considered to treat COVID-19 are repurposed drugs that are in use for other indications, most of which have data on placental transfer and pregnancy safety. Lopinavir and ritonavir, hydroxychloroquine or chloroquine, colchicine, steroids, oseltamivir, azithromycin, and some monoclonal antibodies can be used in pregnant women. Renin-angiotensin system blockers should not be used. Data are lacking for interleukin 6 (IL-6) inhibitors and remdesivir.

What does this add to what is known?

Some of the therapies considered for COVID-19 can be used in pregnant women, but there is a crucial need for research on placental transfer and safety of important investigational drugs including remdesivir.

excluded from all clinical trials to date. Remdesivir, lopinavir/ritonavir, interferon, and hydroxychloroquine or chloroquine are under investigation in several large phase 3 trials, including the Discovery trial of the REACTing consortium[17] and the World Health Organization worldwide open-label trial.[18] These studies are multicenter, adaptive, randomized, open clinical trials on the safety and efficacy of treatments for hospitalized adults with COVID-19. Data on their use in pregnant women are already available for several of these drugs, including lopinavir/ritonavir studied in women living with HIV,[19,20] interferon beta (in inflammatory diseases), chloroquine (in malaria prophylaxis), or hydroxychloroquine (in inflammatory diseases). However, for other drugs, there are no data of their use during pregnancy. This is the case with remdesivir, which is generally not considered in pregnant women because of its renal and liver toxicity profile.

Given the potential severity of COVID-19 in pregnant women, there is an urgent need to know which therapies may be used. Placental transfer for each medication is key background information, because the placenta is an active barrier[21] that lets variable amounts of drugs cross into the fetal circulation[22]. The objective of this study was to review the toxicity profiles in pregnancy and the placental transfer of medications under consideration as therapy against SARS-CoV-2.

Materials and methods

We conducted a review of the literature concerning the drugs investigated against SARS-CoV-2 in published or ongoing clinical studies worldwide, with a total of 502 clinical studies registered on the ClinicalTrials.gov website from March 01, 2020 to May 30, 2020. We described the characteristics of drugs based on the French national drug safety agency (ANSM) database (https://www.ansm.sante.fr/) and the pharmacokinetic parameters using the PubChem database and the Human Metabolome Database. We searched pregnancy safety and placental passage data from the PubMed database with keywords pregnancy, placenta, fetus, or newborn for each individual study drug. In vitro efficacy of drugs was defined by their 50% effective concentration (EC50).[23–25] Promising drugs with in vitro antiviral effect against SARS-CoV-2 of EC50<10 μM have been reported.

Results

For the principal medications currently under investigation against SARS-CoV-2, safety data in pregnant women, placental transfer, and neonatal outcome are summarized in the Table.

Azithromycin

Azithromycin is an antibiotic of the macrolide class. It has a molecular mass of 749 g/mol, is sparsely soluble in water, and has 20% protein binding. It has in vitro activity against Zika virus[21,22] but has not proved significant efficiency against Ebola virus[63] nor in decreasing the 90-day mortality in MERS infection in a retrospective cohort of 136 infected patients.[64] Nevertheless, azithromycin has an in vitro EC50 of 2.12 μM[25] and has been used in patients infected by SARS-CoV-2.[65] The combination of azithromycin with hydroxychloroquine seemed to be more effective than hydroxychloroquine alone.[66] Currently, several studies are underway to conclude on its effectiveness against COVID-19. The main toxicity in adults is QT interval prolongation and torsade de pointe.

Regarding pregnancy, azithromycin crosses the placental barrier in sheep[67] and nonhuman primate[68] models, with a maternal-fetal plasma concentration ratio of 3.2 after intravenous administration. Placental transfer in humans was lower in a clinical study[26] and in the human ex vivo cotyledon perfusion model.[28]

Regarding safety, most studies found no increase in major congenital malformations in the event of exposure during the first trimester (risk ratio [RR], 1.19; 95% confidence interval [CI], 0.98−1.44; 120 cases exposed)[31] and no cardiac malformation (RR, 0.7; 95% CI, 0.4−1.3) if any macrolide is used during the first trimester.[29] An association between prenatal macrolide exposure and pyloric stenosis has been reported, but remains controversial.[29,30,32] A recent English cohort study reported an increased risk for fetal malformations when using macrolides during the first trimester of pregnancy (compared with the use of penicillin: RR, 1.55; 95% CI, 1.19−2.03) and in particular cardiovascular anomalies (RR, 1.62; 95% CI, 1.05−2.51) and genital anomalies, regardless of the trimester of exposure (RR, 1.58; 95% CI, 1.14−2.19).[27]

TABLE

Transplacental drug transfer in humans and safety data in women and neonates exposed to medications used for the treatment of patients with coronavirus disease 2019

Transplacental drug transfer			Safety in pregnant women and neonates		
	Study design	**Main results**		**Study design**	**Main results**
Azithromycin					
Sutton et al[26]	In vivo[a]	n=30 women Result: detectable in cord blood	Fan et al[27]	Type of study: retrospective cohort study Population: exposed to macrolides, n=104 604 children Control group: exposed to penicillin	Exposed during the first trimester: • Major malformation (RR, 1.55; 95% CI, 1.19–2.03) • Cardiovascular malformation (RR, 1.62; 95% CI, 1.05–2.51) Exposed in any trimester: • Major malformation (RR, 1.13; 95% CI, 0.94–1.36) • Genital malformation (RR, 1.58; 95% CI, 1.14–2.19)
Heikkinen et al[28]	Ex vivo[b] Open circuit	n=21 term placentas Transplacental transfer rate[d]: 2.6%	Lin et al[29]	Type of study: retrospective cohort study Population: congenital malformation, heart defect (n=4132) and pyloric stenosis (n=735) Control group: infants without any malformation	Macrolides (without erythromycin): • Cardiac malformation (OR, 0.7; 95% CI, 0.4–1.3) • pyloric stenosis (OR, 1.7; 95% CI, 0.6–4.6)
			Almaramhy and Al-Zalabani[30]	Type of study: meta-analysis of cohort studies Population: exposed to macrolides, n=739 children Control group: general population or unexposed women	• Pyloric stenosis (OR, 1.47; 95% CI, 1.03–2.09; I^2, 29.3%)
			Almaramhyand Al-Zalabani[30]	Type of study: meta-analysis of case-control studies Population: exposed to macrolides, n=9000 Control group: general population or unexposed women	• Pyloric stenosis (OR, 1.02; 95% CI, 0.66–1.58; I^2, 51.2%)
			Bérard et al[31]	Type of study: retrospective cohort study Population: exposed to azithromycin at first trimester, n=120 Control group: children of unexposed women	• Major malformation (RR, 1.19; 95% CI, 0.98, 1.44)

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(continued)

TABLE

Transplacental drug transfer in humans and safety data in women and neonates exposed to medications used for the treatment of patients with coronavirus disease 2019 *(continued)*

Transplacental drug transfer			Safety in pregnant women and neonates		
	Study design	**Main results**		**Study design**	**Main results**
			Cooper et al[32]	Type of study: retrospective cohort study Population: exposed to macrolides without erythromycin, n=621 Control group: general population	• Pyloric stenosis (OR, 2.77; 95% CI, 1.22–6.30)
Chloroquine					
Law et al[33]	In vivo[a]	n=19 women F/M concentration ratio[c]: Chloroquine: 110% DECQ: 120%	Osadchy et al[34]	Type of study: analysis of 12 studies Population: exposed to chloroquine or hydroxychloroquine, n=588 Control group: rheumatic disease unexposed patients	Notably, 5 studies with a total of 251 exposed children reported no clinical visual abnormalities in any case
			Silva et al[35]	Type of study: retrospective cohort study Population: exposed women to chloroquine for malaria, n=20 Control group: unexposed malarial patient	• Risk for failing in the hearing screening (RR, 5.64; 95% CI, 1.17–27.3)
Colchicine					
Amoura et al[36]	In vivo[a]	n=1 woman F/M concentration ratio[c]: 15%	Diav-Citrin et al[37]	Type of study: prospective cohort study Population: Mediterranean fever/ Behcet's exposed women, n=238 Control group: unexposed women	• Major congenital anomalies: 4.5% vs 3.9% (P=.648) • Preterm birth: higher, 15.0% vs 5.9% (P<.001) • Birthweight: lower, 3000 g vs 3330 g (P<.001)
Hydroxychloroquine					
Costedoat-Chalumeau et al[38]	In vivo[a]	n=11 women F/M concentration ratio[c]: 104% (51–182)	Costedoat-Chalumeau et al[39]	Type of study: retrospective cohort study Population: connectivitis exposed patients, n=133 Control group: connectivitis unexposed patients	• Abortion: 11.3% vs 10% (P=.78) • Fetal death: 0.8% vs 2.9% (P=.27) • Live birth: 88% vs 84.3% (P=.46) • Premature birth: 28% vs 17% (P=.21) • Full-term birth 72% vs 67% (P=.21)
			Cimaz et al[40]	Type of study: retrospective cohort study Population: exposed children, n=6 Outcome: electroretinography results	Results were normal in all cases.

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(continued)

TABLE

Transplacental drug transfer in humans and safety data in women and neonates exposed to medications used for the treatment of patients with coronavirus disease 2019 *(continued)*

Transplacental drug transfer			Safety in pregnant women and neonates		
	Study design	**Main results**		**Study design**	**Main results**
Interferon beta (IFN-β)					
Waysbort et al[41]	Ex vivo[b] Open circuit	n=4 placentas No transplacental transfer rate[d] was observed	Hellwig et al[42]	Type of study: retrospective cohort study Population: IFN-β exposed women, n=1348 Control group: EUROCAT and MACDP database	Among known pregnancies outcomes: • Spontaneous abortion: 11.9% (n=160) • Stillbirth: 1.5% (n=20) Among known live birth outcomes (82%): • Congenital birth defects: 1.4% (n=14) (RR, 0.61; 95% CI, 0.31, 0.94)
Duma et al[43]	Ex vivo[b] Open circuit	n=1 placenta No transplacental transfer rate[d] was observed	Coyle et al[44]	Type of study: retrospective cohort study Population: IFN-β exposed women, n=96 Control group: unexposed women	• Spontaneous abortion: 11.5% (n=11; *P*=.86) Among 96 birth outcomes (3 twins): • Spontaneous abortion: 11.1% (n=11) • Congenital birth defects: 5.8% (n=5; *P*=.092)
Pons et al[45]	In vivo[a]	n=2 women Result: undetectable in cord blood			
Interleukin inhibitors					
Tocilizumab					
Tada et al[46]	In vivo[a]	n=1 woman F/M concentration ratio[c]: 89% in cord blood and 78% in newborn	Nakajima et al[47]	Type of study: retrospective cohort study Population: exposed neonates, n=36 neonates Control group: none	• Noncongenital anomalies
			Hoeltzenbein et al[48]	Type of study: retrospective cohort study Population: rheumatoid and juvenile idiopathic arthritis, n=288 Control group: none	Prospective data (n=180): • 109 live births (60.6%) • 39 spontaneous abortions (21.7%) • 1 stillbirth • Malformations: 4.5% • Preterm birth (31.2%) Retrospective data (n=108): • 55 live births (50.9%) • 31 spontaneous abortions (28.7%) • Preterm birth (20%)

Louchet. Medication for coronavirus disease 2019 in pregnancy. AJOG MFM 2020. *(continued)*

TABLE

Transplacental drug transfer in humans and safety data in women and neonates exposed to medications used for the treatment of patients with coronavirus disease 2019 *(continued)*

Transplacental drug transfer			Safety in pregnant women and neonates		
	Study design	Main results		Study design	Main results
Interleukin-1 inhibitors					
No specific data on transplacental transfer in human			Youngstein et al[49]	Type of study: retrospective cohort study Population: autoinflammatory disease, n=31 (8 with canakinumab and 23 with anakinra) Control group: none	• Miscarriage: n=2/31 • No serious neonatal infection • One case of renal agenesis • Preterm birth (20%)
Ivermectin					
			Nicolas et al[50]	Type of study: meta-analysis Population: mostly African women, n=893 Control group: unexposed women	• Preterm birth: not reported • Spontaneous abortion or stillbirth: OR of 1.15 (0.75, 1.78) in observational studies OR of 0.62 (0.18, 2.14) in randomized controlled trials • Congenital anomaliesOR of 1.69 (0.83, 3.41) in observational studies OR of 1.10 (0.07, 17.65) in randomized controlled trials
Leflunomide					
			Bérard et al[51]	Type of study: administrative database cohort study Population: exposed women, n=73 Control group: unexposed women	• Spontaneous abortion: aOR, 1.09 (0.90, 1.32) • Major congenital malformation: aOR, 0.97 (0.81, 1.16) • Prematurity: aOR, 4.03 (0.91, 17.85) • Low birthweight: aOR, 1.06 (0.90, 1.25)
Lopinavir/ritonavir					
Gavard et al[52]	Ex vivo[b]	n=25 placentas Transplacental transfer rate[d] (albumin concentration): 23.6% (2 g/L) and 3.3% (40 g/L)	Sibiude et al[19]	Type of study: prospective HIV cohort study Population: Exposed to LPV/RIT, n=3704 Control group: Exposed to other or no antiretroviral drugs	• No association between birth defects and lopinavir or ritonavir with a power of >85% for an OR of 1.5

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(continued)

TABLE

Transplacental drug transfer in humans and safety data in women and neonates exposed to medications used for the treatment of patients with coronavirus disease 2019 *(continued)*

Transplacental drug transfer			Safety in pregnant women and neonates		
	Study design	**Main results**		**Study design**	**Main results**
Ivanovic et al[53]	In vivo[a]	n=11 placentas Undetectable	Tookey et al[20]	Type of study: Prospective HIV cohort study Population: exposed to LPV/RIT, n=4864 pregnancies Control group: pregnancy as the unit of observation	• 13% were at <37 weeks' gestation • 2.5% were at <32 weeks' gestation • 15% had birthweight of <2500 g • 2.3% had birthweight of <1500 g • 2.9% had ≥1 congenital abnormality
Marzolini et al[54]	In vivo[a]	n=1 placenta Undetectable			
Oseltamivir					
Huang et al[55]	Ex vivo[b]	n=20 placentas Transplacental transfer rates[d] of 12.39% (oseltamivir) and 10.17% (its metabolite)	Ehrenstein et al[56]	Type of study: retrospective cohort study Population: exposed to oseltamivir, n=1898 pregnancies Control group: general population	After first-trimester exposure (n=449 pregnancies) • Major malformation (OR, 0.94; 95% CI, 0.49–1.83) • Congenital heart defect (OR, 1.75; 95% CI, 0.51–5.98)
			Chambers et al[57]	Type of study: prospective cohort study Population: exposed to oseltamivir, n=112 pregnancies Control group: general population	• Major birth defects (RR, 0.84; 95% CI, 0.19, 2.80) • Spontaneous abortion: none reported • Preterm delivery (RR, 0.65; 95% CI, 0.26, 1.63)
Ribavirin					
No specific data on transplacental transfer			Sinclair et al[58]	Type of study: retrospective cohort study Population: HCV-infected women treated with ribavirin in pregnancy, general population, n=272 pregnant women Control group: MACDP	Direct exposure (n=133): • Live birth: 85/134 (63.4%) • Miscarriage: 23/134 (17.2%) • Birth defects: 7/85 (8.2%) (95% CI, 3.4–16.2) Indirect exposure (n=139) • Live birth: 95/134 (68.3%) • Miscarriage: 18/139 (12.9%) • Birth defects: 4/95 (4.2%) (95% CI, 1.2–10.4)

Louchet. Medication for coronavirus disease 2019 in pregnancy. AJOG MFM 2020. *(continued)*

TABLE
Transplacental drug transfer in humans and safety data in women and neonates exposed to medications used for the treatment of patients with coronavirus disease 2019 *(continued)*

Transplacental drug transfer			Safety in pregnant women and neonates		
	Study design	Main results	Study design	Main results
Sildenafil				
Russo et al[59]	Ex vivo[b] Closed circuit	n=6 placentas F/M concentration ratio[c]: 91% to 95%	Dunn et al[60]	Type of study: meta-analysis Population: exposed women, n=165 Control group: unexposed	Maternal effects: • Headache: 49/107 (46%) • Visual trouble: 14/81 (17%) • Hypotension: 0/39 (0%) • Cesarean delivery: 55/66 (83%) Neonatal outcome: • Nursery admission: 35/52 (67.3%) • Stillbirth: 3/69 (4.3%) • Neonatal death: 5/129 (4%) • Congenital malformations: 0/35 (0%)
Russo et al[61]	In vivo[a]	Undergoing	Ferreira et al[62]	Type of study: meta-analysis Population: exposed women with preeclampsia (n=139) or fetal intrauterine growth restriction (n=275) Control group: unexposed	• Birthweight: +223 g with high heterogeneity, I=96% • No difference in gestational age at birth, I=93% • No significant difference in neonatal death • No difference in headache, I=69%

aOR, adjusted odds ratio; *CI*, confidence interval; *COVID-19*, coronavirus disease 2019; *DECQ*, desethylchloroquine; *EUROCAT*, European Registration of Congenital Anomalies and Twins; *F/M*, fetal-to-maternal; *HCV*, hepatitis C virus; *IFN-β*, interferon beta; *LPV/RIT*, lopinavir/ritonavir; *MACDP*, Metropolitan Atlanta Congenital Defects Program; *OR*, odds ratio; *RR*, risk ratio.

[a] Corresponds to blood samples in mothers and neonates.; [b] Corresponds to perfused placenta model.; [c] Corresponds to comparison of fetal and maternal concentrations, expressed as ratio of concentration or transfer rate (%).; [d] Transplacental transfer rate corresponds to ratio of fetal-to-maternal molecule. It includes parameters such as flow rate or compartment volumes (concentration x flow rate/concentration x flow rate). This formula is often used in open cotyledon circuits.[200]

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Chloroquine and hydroxychloroquine

Chloroquine is an antimalarial drug derived from 4-aminoquinoline. Its molecular mass is 319.9 g/mol; it is lipophilic and has a protein binding of 50%. It has been reported to have antiviral properties in vitro. Chloroquine is able to inhibit influenza A in vitro[69] but previous randomized trials in humans with influenza reported no efficacy vs placebo.[70] Chloroquine has in vitro activity against coronaviruses by interfering with the glycosylation of the SARS-CoV-2 receptor angiotensin-converting enzyme 2 (ACE2) and reduces viral replication[71–73] with an EC50 of 9.12 μM.[24] It inhibits the replication of SARS-CoV-1 at the plasma concentrations conventionally used for malaria treatment.[74] Recently, chloroquine has proved in vitro efficacy against SARS-CoV-2, blocking infection[75] and virus replication with an EC50 of 9.12 μM.[24] Chloroquine is under investigation in several clinical studies for the treatment of COVID-19.[76]

Chloroquine cardiac toxicities include restrictive cardiomyopathy reported in several case reports[77–80] and, in case of an overdose, the risk for hypotension and cardiac conduction disorder (prolongation of the QT space and enlargement of the QRS).

Concerning pregnant women, pharmacokinetic studies report an increase in clearance of chloroquine and its active metabolite desethylchloroquine (DECQ), especially in the second and third trimesters.[81,82] Coadministration of azithromycin modestly decreases exposure to DECQ without modifying exposure to chloroquine.[81] Its use in pregnant women could be responsible for ototoxicity reported in a small study (RR, 5.64; 95% CI, 1.17–27.3).[35] Chloroquine crosses the placenta[33,83–86] with a mean ratio of cord-to-maternal concentrations of 1.1 for chloroquine and 1.2 for DECQ. With regard to pregnancy outcomes including miscarriages, no increased risk has been reported.[87] In humans, studies have not reported any teratogenic or fetotoxic effect in the event after in utero exposure; in particular, no risk for ocular damage in newborns was found in a meta-analysis of 588 infants.[34]

Hydroxychloroquine is also an antimalarial drug derived from 4-aminoquinoline with an anti-inflammatory action. It has a molecular mass of 335.9 g/mol, is lipophilic, and has a protein binding of 45%. It has indicated antiviral activity against SARS-CoV-2 in small in vitro studies[88,89] and some studies have reported that hydroxychloroquine reduces viral excretion.[66,90] Compassionate use has been authorized in patients with COVID-19,[91] and a large number of observational studies that have been performed worldwide published conflicting conclusions on its efficacy and safety on COVID-19,[92−100] and randomized clinical trials are currently underway (53 studies with randomized statement criteria are available in ClinicalTrials.gov website, including NCT04329923, NCT04307693, Chi CTR2000029559, ChiCTR2000 029898-99, and ChiCTR2000029992).

Hydroxychloroquine is recommended for patients with rheumatoid arthritis and lupus. It obtained marketing authorization in these indications in 1997.[101] Hydroxychloroquine toxicities are retinopathy in case of long-term treatment at high doses (prevalence from 2%−8%),[102,103] heart conduction disorders,[104] and more rarely ventricular tachyarrhythmia or QT prolongation.

Hydroxychloroquine has been reported to be safe for use in pregnant women at doses of 200 mg once or twice a day. It crosses the placenta by passive diffusion with a strong correlation between maternal and fetal concentrations and a fetal-to-maternal concentrations ratio of 1.04 (range, 0.51−1.82).[38] Pregnancy outcomes in the event of exposure are similar to those of untreated women with the same conditions (number of miscarriages and rate of malformation in particular).[39,105,106] There has been no reported increase in visual disturbances in newborns of exposed women.[40]

Lopinavir/ritonavir

The fixed combination lopinavir/ritonavir has been widely used for the treatment of adults living with HIV. Lopinavir has a molecular mass of 1349.7 g/mol, is practically insoluble in water, and has a protein-binding rate of 98% to 99%. Lopinavir is a protease inhibitor prescribed in combination with ritonavir, an inhibitor of the isoform CYP3A4 of cytochrome p450 which is used as a booster to obtain therapeutic plasma concentrations. It has in vitro and in vivo efficiency against SARS-CoV-1 and MERS infections.[107,108] It is considered as an option for COVID-19 treatment in several trials, although the first randomized, open-label, controlled study to be published reported no significant benefits of lopinavir/ritonavir.[109]

The tolerability of lopinavir/ritonavir is poorer than of other HIV protease inhibitors, especially regarding digestive disorders and lipid abnormalities.[85] In the randomized controlled trial from China in adults with severe COVID-19 infection,[109] treatment (400 mg/100 mg twice a day) had to be stopped early for 13.8% (n=13) of patients because of adverse events (primarily gastrointestinal adverse events). This incidence of severe adverse events was higher than what was reported in HIV infection at the same dose. Lopinavir/ritonavir exposure increases plasma concentrations of CYP3A4-metabolized drug taken concurrently.

In pregnant women living with HIV, lopinavir/ritonavir was for several years the most widely used antiretroviral therapy, with a nucleoside reverse transcriptase backbone,[86] and used as monotherapy (at 400 mg/100 mg, twice daily).[110] During pregnancy, the clearance of the free form of lopinavir/ritonavir has not changed and experts do not recommend increasing the dosage of the drug (generally 400 mg of lopinavir/100 mg of ritonavir twice a day).[111] Lopinavir/ritonavir crosses the placenta but poorly. Fetal transfer rates with perfused cotyledon model are around 20% to 25%[52] and the level in cord blood is undetectable in studies with cord-to-mother ratios.[53,54] This is caused by strong protein binding for protease inhibitors and to the efflux mechanism of the placental membrane transporters and in particular to P-glycoprotein.[112−114]

Pregnancy outcomes were reported to be similar to those of control women living with HIV.[19,20] There was no increase in the rate of congenital malformations after first-trimester exposure. A large randomized trial has reported a higher rate of preterm births in the groups treated with lopinavir/ritonavir-based antiretroviral treatment (ART) than monotherapy of zidovudine.[115] This has already been described in a randomized trial comparing lopinavir/ritonavir-based ART with a combination of 3 nucleoside reverse transcriptase inhibitors.[116]

In addition, several cases of lopinavir/ritonavir toxicity have been described in treated preterm infants, in particular signs suggesting adrenal insufficiency with hyponatremia and hyperkalemia.[117] These undesirable effects led to an alert by the Food and Drug Administration (FDA) in 2011 to contraindicate this drug in premature babies.[85]

Remdesivir

Remdesivir (GS-5734) is a prodrug of a nucleoside analog antiviral. It has a molecular mass of 602.9 g/mol with a protein-binding rate of 85% to 92% in animal studies. It is metabolized by the liver and has a renal and biliary excretion. Its water solubility is not yet available on the PubChem website. It is metabolized into its active form GS-441524. It competes with adenosine triphosphate and inhibits the viral RNA polymerase.[118] Remdesivir was initially developed against Ebola virus, with efficacy in a clinical phase 3 trial.[119] It has also been studied to treat MERS-CoV and SARS-CoV-1 infections.[120] Its efficacy against SARS-CoV-2 has been proven in vitro[75,121] with EC50 of 11.41 or 6.25 μM associated with emetine[23,24] and in vivo in animals.[122] Its mechanisms of action (shortening of the DNA chain or modification of excision activity) remain to be explained in detail.[120,123] A number of clinical trials are underway to determine the efficacy and safety of remdesivir to treat COVID-19 (NCT04252664, NCT04257656, NCT04280705, NCT04292730, and NCT04292899). Notably, 2 double-blinded randomized clinical trials have been published using an intravenous

loading dose of 200 mg followed by 100 mg daily for 10 days.[124,125] Both indicated a reduction of time to clinical improvement.[124] Similar results have been reported in its compassionate use for severely ill patients.[126]

To date, tolerance data in humans are sparse. There is a risk for renal dysfunction[127,128] and elevated liver enzymes, a possible effect on mitochondrial functions,[127] and a case of cardiac arrest in a clinical trial on Ebola infection.[119] Thus, investigators recommended biological monitoring of liver and kidney functions. Clinical trials on COVID-19 disease also report adverse effects with an incidence ranging from 21% to 66%.[124–126]

In a clinical study on the Ebola disease, 6 pregnant women who were treated with remdesivir had positive pregnancy tests,[119] but these cases were not described. We found no study addressing the safety of remdesivir in pregnant women or its placental transfer. Considering its small molecular weight and its high protein-binding rate, we may expect that remdesivir crosses the placenta.

Other antiviral drugs

Several antiviral drugs commonly used in clinical practice have been proposed,[129] although some in vitro studies of antiviral effects on SARS-CoV-2 replication failed to indicate an effect of oseltamivir, favipiravir, ribavirin or darunavir.[23,130]

Oseltamivir is widely recommended to treat influenza in children or adults who are considered at risk for severe manifestations, including pregnant women. According to the ex vivo human placental perfusion, oseltamivir and its metabolite oseltamivir carboxylate cross poorly the placenta with transfer rates of 12.39% and 10.17%, respectively.[55] Retrospective studies with large population do not provide evidence of risk for any major congenital malformation or heart defect.[57] No evidence of increased risk for preterm birth nor small for gestational age infants was reported in another prospective study.[57,131] We did not find any information about pregnancy and zanamivir, which is another neuraminidase inhibitor.

Favipiravir is an antiviral drug approved in Japan and China for influenza which inhibits the RNA polymerase enzyme.[132,133] It has indicated efficacy against Ebola virus in animals and humans.[134,135] A potential synergistic benefit of favipiravir associated with oseltamivir has been described in influenza.[136,137] Favipiravir is under investigation for treating SARS-CoV-2 in several clinical trials (NCT04310228, NCT04358549). We found no information about the use of favipiravir in pregnant women but caution is needed because of a warning by the Japanese drug agency on a teratogenic risk in preclinical animal studies.[132,138]

The combination of interferon alpha and ribavirin (which is an antiviral mainly used to treat hepatitis C) is also under investigation in COVID-19, even though it has not been proven to reduce mortality for the treatment of MERS-CoV.[139,140] In pregnant women, ribavirin is usually contraindicated because of its possible teratogenic role in the event of direct or indirect exposure (preconception or in the event of father's treatment). There are some reassuring data,[141] but the number of exposures is too small to conclude on safety.

Some HIV protease inhibitors are under consideration (NCT04252274), in addition to lopinavir discussed previously. Darunavir with a ritonavir boost has been the most widely used therapy for HIV in pregnant women in Europe and America for nearly a decade, and there are data from prospective cohort studies. There is no increase in the risk for congenital malformations. However, the use of boosted protease inhibitors has been associated with an increased risk for preterm delivery, although it is not clear whether the effect is related to any specific drug or other confounding factors.[142] Nelfinavir is a selective inhibitor of HIV protease which has been reported to inhibit SARS-CoV replication in vitro.[143] The placental transfer of nelfinavir is low.[54] There is no increase in the risk for congenital malformations.

Arbidol hydrochloride (umifenovir) is an immunomodulator and a broad-spectrum antiviral drug. Arbidol is able to block viral fusion against influenza viruses and has been reported to have antiviral activity in vitro against SARS-CoV.[144] It has been reported to increase the effect of lopinavir/ritonavir treatment on SARS-CoV-2 excretion at 7 and 14 days in a retrospective cohort study (n=33 patients),[145] but clinical outcomes have not yet been assessed.[146] Comparison of arbidol with lopinavir/ritonavir or oseltamivir is under investigation in a randomized controlled phase 4 study (NCT04255017). A study reports its use, in association with other antiviral drugs, in 7 pregnant women with SARS-CoV-2 infection.[147] We found no information on safety of umifenovir in pregnancy.

Clevudine (NCT04347915) is used in hepatitis B infection in Asian countries. We found no information on its safety profile in pregnancy or its placental transfer.

Other antiinfective drugs

Ivermectin, usually used to treat parasite infections, is currently under investigation in COVID-19 clinical trials (NCT04390022 and NCT04381884). Transplacental transfer has been proven in sheep with limited fetal exposure.[148] Data on safety for pregnant women and neonates are sparse, and a recent meta-analysis has concluded to insufficient evidence for its safety profile in pregnancy.[50] Nitazoxanide is another antiparasitic drug under consideration (NCT04343989) for which we found no specific data on specific use in pregnant women.

The FDA-approved antihelminthic drug niclosamide has indicated in vitro antiviral efficacy against SARS-CoV-2.[24] As mentioned previously, the amebicide emetine inhibits SARS-CoV-2 replication[23,24] and has been studied in association with remdesivir.

Interferon

Interferons beta and lambda are both studied as COVID-19 therapy but most information concerns interferon beta. Interferon beta is a cytokine with antiviral, antiproliferative, and immunomodulatory activities. It is commonly used to treat multiple sclerosis. It is a glycoprotein that works after it has

attached to the cell membrane by triggering a cascade of intracellular signaling with, in particular, the induction of enzymes that could inhibit viral replication in infected cells. Interferon beta has been proposed as immune-modulatory treatment to control the massive inflammation resulting in lung injury in SARS-CoV-2 infection.

There is a long experience of safety and tolerability of interferon in nonpregnant adults and the most frequently reported adverse events are injection site reactions, asthenia, flu-like symptoms, headache, and lymphopenia.[149]

Pregnancy outcomes in women treated with interferon beta have been documented in prospective and retrospective pharmacovigilance studies on 1348 and 99,948 pregnant women, respectively.[42,44,150] The prescribed subcutaneous doses ranged from 30 μg/0.5 mL per week to 30 μg/0.5 mL 3 times a week. These studies did not find an increased risk for miscarriage or congenital malformation associated with treatment with interferon beta. Other perinatal outcomes were not described.

We did not find any study on the transplacental passage of interferon beta. However, interferons have high molecular weights and it has been reported that interferon alpha does not cross the placenta in humans, according to data from the ex vivo cotyledon perfusion model[41,43] and neonatal cord blood samples.[45] By analogy, we can assume that interferon beta does not cross the placental barrier.

Convalescent plasma

Transfusion of immunoglobulins from patients who have recovered from the disease is a passive immunotherapy. Convalescent plasma transfusion has been previously described as a therapeutic option in the management of Ebola and previous coronavirus infections.[151,152] It was not associated with a significant improvement in survival in Ebola patients[153] but was useful in the treatment of SARS-CoV infection with a higher discharge rate (control group with usual care represented with 418 patients previously treated in the same center), especially if given at the early phase of the disease (n=80).[154] There have been case reports on the use of convalescent plasma transfusion in association with supportive care and antiviral drugs.[145,146] Recently, convalescent plasma has been approved by the FDA to treat critically ill patients with COVID-19[44,149,150] and clinical trials are currently being conducted (NCT0432142, NCT04321421 [ongoing], and NCT04333355 [ongoing]). Previous studies included pregnant women with SARS-CoV-2 (n=1)[155] and Ebola infection (n=8)[153] but the authors recognized that pregnancy was incompletely recorded in the control group. Concerning transplacental transfer of immunoglobulins, it is well known that transfer of maternal immunoglobulin G (IgG) to the fetus plays an important role in preventing neonatal infections. Antibodies are transported across the placenta with mediation of the neonatal Fc receptor[156] and transfer increases with gestational age, mostly in the third trimester.

Inactivated vaccines are also currently under investigation (NCT04352608). Safety in pregnant women has obviously not been assessed.

Immune modulators

The leading cause of mortality from COVID-19 is respiratory failure from severe acute respiratory syndrome. Accumulating evidence suggests that patients with severe COVID-19 have a cytokine storm, which is a hyperinflammatory syndrome characterized by a fulminant and fatal hypercytokinemia and multiorgan failure and previously described with SARS-CoV infection.[157] Other approaches to anti-inflammatory therapy include cytokine blockers, steroids, and other potent anti-inflammatory agents.

Interleukin 6 (IL-6) is a proinflammatory cytokine that participates in the cytokine storm which characterizes ARDS in COVID-19. Therefore, the following anti−IL-6 therapies are being considered in COVID-19 pneumonia: tocilizumab (NCT04317092, NCT04331795, NCT04332913); and other antiinterleukin molecules such as clazakizumab (NCT04343989), levilimab (NCT04397562), olokizumab (NCT04380519), sarilumab (NCT04315298, NCT04321993, NCT04357808), and siltuximab (NCT04330638, NCT04329650). Tocilizumab is a humanized monoclonal antibody that binds to IL-6 receptors and inhibits the signal transmitted by the cytokine. Anti−IL-6 therapy is usually used as an immunosuppressant in rheumatoid arthritis and its use requires monitoring of liver function. Tocilizumab crosses the placental barrier and is found in cord blood assays (89% of maternal plasma dosage), plasma assays in newborns (78%), and breast milk (11%)[46] with a peak in breast milk reached on the third day after injection.[158] There does not seem to be an increased risk for congenital anomalies[47,48] but the interpretation of the data is difficult because there is often coexposure with methotrexate. In 2016, at the European Congress of Rheumatology, specialists recommended against tocilizumab in pregnancy judging the data insufficient in terms of fetal safety.[159] Even fewer data are available regarding sarilumab/siltuximab. Similar to other IgG antibodies of the IgG_1 subclass, they cross the placenta. Immune response may be impaired in infants with in utero exposure. A registry has been established to monitor outcomes after exposure to anti−IL-6 monoclonal antibodies during pregnancy. Other antiinterleukin inhibitors (anti−IL-1) that are also under investigation are canakinumab (NCT04362813) and anakinra (NCT04362813). A retrospective study on 31 exposed women has reported global sparse reassuring data with no neonatal infection but renal agenesis in 1 fetus after anakinra exposure.[49]

The sphingosine-1-phosphate receptor regulator fingolimod (FTY720) is an immune modulator which prevents lymphocytic contribution to autoimmune reaction. It also has been proposed in COVID-19 therapy (NCT04280588). Fingolimod has been widely used in severe multiple sclerosis. It is generally well tolerated and has a long-term safety profile (including infection or malignancy rates)[160,161] but serious cardiac adverse effects have been reported in

patients at risk for heart failure. Data on the safety in pregnant women do not indicate any increase in major malformation rates among live births in comparison with the general population and the multiple sclerosis population (n=91 pregnancies and 75 live births).[162] We found no data on placental transfer of fingolimod.

Baricitinib, a Janus kinase (JAK) and adaptor-associated kinase inhibitor, was found capable to reduce or interrupt the passage of the virus into target cells (endocytosis into pulmonary cell) and to inhibit the JAK1- and JAK2-mediated cytokine release, constituting the rationale to perform a trial on patients with mild to moderate COVID-19.[2,163] The drug was licensed for the treatment of rheumatoid arthritis at the daily dose of 4 mg orally, with excellent results in terms of clinical response and a good safety profile.[163] Because baricitinib does not interact with antivirals owing to its prevalent renal elimination, it may be used in combination with antiviral therapy. As a biological and small molecule, baricitinib is contraindicated in pregnancy, awaiting larger studies to assess its safety.[164,165] Another anti-JAK molecule is also tested in current studies, that is, ruxolitinib (NCT04377620, NCT04334044, NCT04334044).

Infliximab is also under consideration for severe COVID-19 pneumonia (NCT04333420). There are data from retrospective cohorts on the safety of infliximab in pregnant women treated for Crohn's disease.[166] It crosses the placenta in the second and third trimesters and has been detected in newborn samples 6 months after delivery.[167,168]

Leflunomide is an immune suppressor used in rheumatoid arthritis that is also under investigation for COVID-19 (NCT04361214). It is teratogenic in an animal model and thus is to be avoided if possible, although a small retrospective study[36] reported no association with major congenital malformation after 5 cases of first-trimester exposure or adverse pregnancy outcomes after 15-second and third-trimester exposures. We found no data on placental transfer of leflunomide.

Additional immune therapies under investigation to treat the cytokine storm in COVID-19 include lenzilumab, which is a humanized monoclonal antibody that blocks the granulocyte-macrophage colony−stimulating factor (NCT04351152), and the human IgG_1 monoclonal antibody gimsilumab (NCT04351243).

Colchicine is a powerful anti-inflammatory drug. It is under investigation in a simple, pragmatic randomized controlled trial for its immunomodulatory and anti-inflammatory effects, which may reduce the cytokine storm and inflammatory cascade activation in severe forms of COVID-19 (NCT04328480, NCT04326790). To date, it has not been proven to be effective as a treatment or prevention of COVID-19 disease.[169−171] Colchicine has been approved for the treatment of various inflammatory diseases such as gout, familial Mediterranean fever, Behcet's disease, and some dermatologic indications (chronic urticaria, cutaneous vasculitis, and psoriasis). Regarding pregnant women, colchicine is not contraindicated during pregnancy.[159] Colchicine crosses the placenta.[36] A meta-analysis reported no increase in the incidence of miscarriage or major fetal malformations in exposed women compared with nonexposed women with familial Mediterranean fever (4 studies and 554 pregnancies with colchicine exposure).[172] However, in 1 retrospective study, there was an increased risk for preterm deliveries at ≤36 weeks' gestation (15% [n=32/214] vs 5.9% [n=51/867]; $P<.01$) and a lower median birthweight in singleton full-term children (3090 g vs 3315 g; $P<.01$).[37]

The use of steroids is still controversial for the treatment of SARS-CoV-2 infection. Methylprednisolone and dexamethasone are being studied in prospective randomized controlled trials (NCT04273321, NCT04325061, and NCT04329650). In addition, the glucocorticosteroid ciclesonide has indicated in vitro antiviral efficacy against SARS-CoV-2.[24] In pregnant women, fluorinated glucocorticosteroids (usually betamethasone with 2 doses of 12 mg) are recommended in case of a high risk for preterm delivery to accelerate fetal lung maturation. Their placental transfer is high.[173] In contrast, prednisone is inactivated by placental 11β-hydroxysteroid dehydrogenase.[174,175] Betamethasone and dexamethasone increase blood glucose level but are considered safe for pregnant women. Their clinical benefits have been proven in numerous studies including a meta-analysis of 18 trials and more than 3700 babies.[176] Steroids reduce mortality (odds ratio [OR], 0.60; 95% CI, 0.48−0.75) and respiratory distress syndrome (OR, 0.53; 95% CI, 0.44−0.63), and they may also reduce the risk for severe intraventricular hemorrhage.

Medications modifying the renin-angiotensin-aldosterone system

Drugs that regulate the renin-angiotensin-aldosterone system have important potential to treat COVID-19.[177] ACE was identified as a SARS-CoV receptor in 2004.[178] Thus, ACE inhibitors are considered as a therapeutic approach to limit the endocytosis of the viral complex[179] and thereby the number of cells infected with SARS-CoV-2. Losartan, an angiotensin II receptor blocker, is under investigation in patients with COVID-19 (NCT04318418). Another angiotensin receptor blocker, telmisartan, is also being studied (NCT04355936). In pregnancy, drugs that block the renin-angiotensin system can damage the fetal kidneys, leading to renal failure with oligohydramnios, deformations, and lung hypoplasia.[180,181] These drugs modifying the renin-angiotensin cascade could also affect placental functions leading to growth retardation.[182]

Other drugs with vascular impact

Sildenafil, a phosphodiesterase type 5 inhibitor, is a vasodilator used to treat erectile dysfunction and pulmonary arterial hypertension. It is under investigation in patients with COVID-19 (NCT04304313) because pulmonary hypertension is a complication of ARDS. In pregnant women, as in nonpregnant patients, the adverse effects are headache and visual disturbance.[183] It crosses the

placenta at a high rate in ex vivo model,[184] and thus, it is considered in antenatal care to prevent pulmonary hypertension in case of congenital diaphragmatic hernia.[185] Sildenafil has also been studied for the prevention of fetal growth restriction in case of maternal vascular disease such as preeclampsia, and a meta-analysis has reported a significant increase in fetal weight at birth.[186] No increases of neonatal death or congenital anomalies have been described in another meta-analysis.[183] However, the Sildenafil Therapy in Dismal Prognosis Early-Onset Intrauterine Growth Restriction group which was gathered in 2011 to explore effects of sildenafil on fetal growth restriction recommended against the prescription of sildenafil.[187,188]

Bevacizumab (NCT04305106) is an anti−vascular endothelial growth factor antibody. It has been used in cases of ovarian cancer in pregnancy with no maternal and fetal adverse effects[189] but it is still recommend to avoid its use.[190] It has also been used during pregnancy to treat intravitreal hemorrhage with local injection[191,192] with no pregnancy-related complications. We found no information on the placental transfer of bevacizumab.

Anticancer agents

Thalidomide is under consideration for COVID-19 (NCT04273529 and NCT04273581), but it is definitively contraindicated in pregnancy because of its proven teratogenicity.[193,194]

Another anticancer agent, plitidepsin, is also under investigation for COVID-19 (NCT04382066). There is no information on pregnancy use, but in view of its high molecular mass (1110 g/mol), we may expect that it would not cross the placenta.

The topoisomerase II blocker etoposide, which is proposed for a clinical study on COVID-19 (NCT04356690), has been reported in few case reports to treat gestational trophoblastic disease or malignant teratomas.[195−197] Data on exposure during completed pregnancy are sparse[198] and evidence of adverse effect is difficult to conclude because women received combinations of drugs. We found no data on placental transfer of etoposide.

Other approaches

A large variety of other drugs are also currently under consideration against SARS-CoV-2. Dapagliflozin is an antidiabetic medication of the sodium-glucose cotransporter 2 inhibitor class which is under consideration to treat COVID-19−related respiratory failure, sepsis, and multiorgan failure in a clinical trial (NCT04350593). We found no specific data on its use during pregnancy.

Another therapeutic approach under investigation is the use of fetal-derived cells to reduce inflammation and fibrosis in COVID-19−related lung infection. The study registered as NCT04319731 is a pilot study of nebulized human amniotic fluid. Umbilical cord−derived mesenchymal stromal cells are used in several studies (NCT04333368, NCT04315987, NCT04288102). There is no data available on their safety in pregnancy.

Discussion

Among the medications under investigation to treat COVID-19, some already have sufficient safety data to allow their use in pregnant women. These include the HIV protease inhibitors such as lopinavir/ritonavir, interferon, and hydroxychloroquine. In addition, there are reassuring safety data for use of colchicine, steroids, oseltamivir, azithromycin, and to some extent monoclonal antibodies such as infliximab and possibly tocilizumab. Some drugs are strictly prohibited in pregnancy because of known teratogenicity (thalidomide) or fetal toxicities (renin-angiotensin system blockers). Other candidates have insufficient pregnancy data, including IL-6 inhibitors, umifenovir, and favipiravir. Importantly, remdesivir remains an investigational drug with restricted use in the absence of preclinical data concerning pregnancy in view of its toxicity profile (hypotension during injection, renal and liver dysfunction). The range of medications under consideration to treat COVID-19 is rapidly evolving.

An unusual aspect of clinical trials on COVID-19 is the fact that most of the drugs under investigation are repurposed and thus are already used in pregnant women for their established indications. Because pregnant women are usually excluded from clinical trials, pregnancy follow-up data were obtained from off-label use. Although some follow-up data are obtained from structured cohort studies, most studies are from retrospective registers with limited endpoints and delayed and disparate collection of clinical data. Importantly, the doses used may differ and the diseases treated differ widely, so that drug toxicities may be quite different. This is of particular concern in patients with severe organ or multiorgan failure.

The use of medications in pregnancy must take into account a number of important issues. First, there is potential for increased toxicities to the patient herself and pharmacokinetic and pharmacodynamic differences with nonpregnant individuals. Physiological changes include increased volume of distribution, lower albumin concentrations, and hormone-induced susceptibility to hepatic toxicities.[199] In addition, there may be an effect on placental functions and potential adverse pregnancy outcomes, such as abortion, fetal growth restriction, and preterm delivery. The most important are the potential risks for the fetus, such as teratogenicity, fetal toxicities, and long-term effect on the child's health.

Clinical trials usually exclude pregnant women and newborns even when benefits are expected for this population type. This precautionary principle has been denounced as unjust.[183] Pregnant women, according to the principle of autonomy, should be able to take responsibility and provide consent for participation in clinical trials,[184] even for drugs with potential teratogenic risk.[185] Excluding pregnant women from clinical trials usually prevents us from obtaining reliable safety data from the use of drugs during pregnancy. This makes it very difficult to take care of pregnant patients with the prescription of drugs without proof of efficacy or tolerance established during pregnancy. Thus, it seems that the benefits of

including pregnant patients in therapeutic trials would outweigh the risks.[186]

Knowledge about placental transfer should be available early enough in the process of drug evaluation to be able to move on to use in pregnant women without needless delays. Most medications cross the placenta, but the amount of placental transfer differs. Passive diffusion is the major mechanism of transplacental transfer and depends on pharmacokinetic parameters such as small molecular weight, high water solubility, polarity, and important protein-binding rate (>90%). The other important mechanism is active transport which depends on import or export protein transporters.[201] Three types of studies have been developed to obtain information on fetal drug exposure. Placental transfer may be estimated by the concentration ratios between the umbilical cord blood and maternal blood at birth. However, these studies are based on a small number of patients. Preclinical studies on placental transfer are performed either in animals (but their placentas differ from the human hemochorial placenta) or in experimental models,[187,188] including the ex vivo human cotyledon perfusion model.[2–4] Physiologically based pharmacokinetic models have also been developed to predict fetal exposure to drugs.[202]

Because the available evidence suggests that there is little risk for vertical transmission of SARS-CoV-2, there is no need for antiviral therapies to cross the placenta. There is also no benefit to be expected from fetal exposure to immunomodulatory therapies. Thus, the optimal approaches to treating pregnant women with COVID-19 would theoretically be those with minimal fetal effect or minimal placental transfer.

The management of pregnant women with COVID-19 is essentially symptomatic. Therapies must be discussed, based on rapidly evolving data on the efficacy and safety in nonpregnant adults, also taking into account obstetrical and fetal consequences of such treatment and the consequences of lack of therapy. In severe cases, therapy should not be withheld solely because of pregnancy and should be discussed between obstetricians, intensive care and infectious disease specialists, and the patient and her partner. ■

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