
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Microbiology and Infection 28 (2022) 51–57

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

# Tocilizumab for coronavirus disease 2019 in pregnancy and lactation: a narrative review

Sarah C.J. Jorgensen [1, 2, *], Stephen E. Lapinsky [3, 4]

[1] Department of Pharmacy, Mount Sinai Hospital, Toronto, ON, Canada
[2] Institute of Medical Science, University of Toronto, Toronto, ON, Canada
[3] Division of Respirology, Mount Sinai Hospital, Toronto, ON, Canada
[4] Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

ARTICLE INFO

*Article history:*
Received 2 June 2021
Received in revised form
13 August 2021
Accepted 16 August 2021
Available online 23 August 2021

Editor: J. Rodriguez-Baño

*Keywords:*
Tocilizumab
Pregnancy
Breastfeeding
Lactation
COVID-19
SARS-CoV-2

ABSTRACT

*Background:* Tocilizumab is a monoclonal antibody that interrupts interleukin-6 signalling, reducing downstream effects on inflammation and the innate immune response. It was shown to reduce mortality in patients with severe or critical coronavirus disease 2019 (COVID-19). Pregnant and breastfeeding people were largely excluded from clinical trials and hence, the extent to which results can be applied to these populations is not clear.

*Objectives:* To synthesize published data on tocilizumab in pregnancy and lactation, highlight important knowledge gaps, and help inform clinical decision-making about tocilizumab's use in these populations with COVID-19.

*Sources:* PubMed was searched for studies evaluating tocilizumab in pregnancy and lactation for COVID-19 and other indications. Literature on pharmacokinetics and reproductive/fetal safety of monoclonal antibodies in general was also sought. The US Food and Drug Administration and the European Medicines Agency guidance for the industry and regulatory approval documents were reviewed.

*Content:* Published data on tocilizumab in pregnancy include 610 cases ($n = 20$ with COVID-19) together with seven mother–infant breastfeeding pairs. Higher rates of spontaneous abortion and premature birth have been reported compared with the general population, but multiple confounding variables limit interpretation. There is little data on tocilizumab exposure in the second and third trimesters when transplacental transport is highest. The effects of tocilizumab on the developing immune system are unclear. Pregnant patients with COVID-19 who received tocilizumab were often critically ill and corticosteroid use was uncommon. Neonatal follow up was limited. Tocilizumab appears to be compatible with breastfeeding.

*Implications:* Although the available data do not raise serious safety signals, they have significant limitations and are not sufficient to delineate the complete spectrum of potential adverse outcomes that may be associated with tocilizumab exposure during pregnancy and lactation. Diligent follow up and documentation of pregnancy outcomes will be important moving forward. A more effective regulatory framework to ensure equitable inclusion of pregnant people in research is clearly needed. **Sarah C.J. Jorgensen, Clin Microbiol Infect 2022;28:51**



## Background

Pregnancy has been recognized as a risk factor for complications of multiple infectious diseases since the pre-antibiotic era [1]. Early in the coronavirus disease 2019 (COVID-19) pandemic it was unclear if pregnancy itself was associated with more severe illness. However, there is now mounting evidence demonstrating that pregnant people have an elevated risk of severe COVID-19-related

* Corresponding author. Sarah C.J. Jorgensen, 600 University Avenue, Toronto, ON, M5G 1X5, Canada.
*E-mail address:* sarah.jorgensen@utoronto.ca (S.C.J. Jorgensen).

https://doi.org/10.1016/j.cmi.2021.08.016
1198-743X/

complications compared with their non-pregnant, age-matched counterparts [2–6]. In addition, COVID-19 has been associated with increased preterm birth and neonatal morbidities [2,3,5–8].

Physiological and immunological changes associated with pregnancy coupled with ethical considerations arising when treating an expectant mother and her developing fetus present unique challenges for clinicians [1,9]. These challenges are compounded by the paucity of scientifically rigorous data about drug safety and efficacy in pregnant people [9]. Despite a clear medical need, pregnant people continue to be a marginalized research population in the COVID-19 pandemic [9,10].

Tocilizumab is a recombinant humanized monoclonal IgG1 antibody that interrupts interleukin-6 (IL-6) signalling, reducing downstream effects on inflammation and the innate immune response [11]. It is licensed in over 75 countries for rheumatoid arthritis and related rheumatological diseases as well as for chimeric antigen receptor (CAR) T-cell therapy-associated cytokine release syndrome. An excessive host inflammatory response, characterized by elevated levels of a variety of pro-inflammatory cytokines, including IL-6, is thought to contribute to many pathophysiological features of severe COVID-19, providing a rationale for evaluating tocilizumab in this setting. At least nine published randomized controlled trials (RCTs) have examined the effects of tocilizumab in patients with COVID-19 and had inconsistent results [12–20]. However, in two large adaptive platform RCTs, tocilizumab was shown to reduce short-term mortality in severe or critical COVID-19 when added to corticosteroids [12,20], and it is now recommended by several consensus guideline committees [21–24].

Only one RCT, the RECOVERY trial, included pregnant people [12]. However, they made up just 0.2% ($n = 10$) of the total study population and specific maternal and neonatal outcomes were not reported [12]. Hence, the extent to which tocilizumab RCT results can be applied to pregnant people with COVID-19 is not clear.

The aim of this narrative review is to summarize published data on tocilizumab in pregnancy and lactation and highlight important knowledge gaps to help inform clinical decision-making about its use in these populations with COVID-19. Although the focus is on tocilizumab in COVID-19, where relevant, we draw on experience in pregnancy for other indications together with the use of monoclonal antibodies in general in pregnancy and lactation.

## Sources

Literature searches of PubMed were conducted between 15 May and 31 May 2021 and were updated on 11 August 2021 using various combinations of the search terms tocilizumab, interleukin-6, interleukin-6 receptors, pregnancy, lactation, breastfeeding, monoclonal antibodies, IgG1, pharmacokinetics, reproductive studies, COVID-19 and SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). Reference lists of relevant articles were examined to identify sources not captured in the electronic literature search. Additional data were obtained from the European Medicines Agency, and the US Food and Drug Administration guidance for the industry on reproductive/toxicology studies and regulatory approval review documents.

## The role of IL-6 in pregnancy

The consequences of IL-6 blockade in pregnancy are difficult to predict. IL-6 is widely expressed in the female reproductive tract and gestational tissue where it has been implicated in a range of regulatory functions involved in embryo implantation, placental development and immune tolerance to pregnancy [25]. For example, elevated IL-6 levels are characteristic of the cytokine profile found in infertility, recurrent miscarriage, pre-eclampsia and preterm delivery [25]. On the other hand, diminished local IL-6 bioavailability, due to altered IL-6 receptor expression, may contribute to many of these same complications [25]. Finally, parturition is associated with significant increases in IL-6 in the cervix and myometrium [26]. Data suggest that IL-6 inhibition may interfere with cervical ripening and dilatation and myometrial contractile activity, potentially leading to delays of parturition [26].

## Preclinical data

Evaluating the impact that IL-6 inhibition by monoclonal antibodies in animal models poses many challenges. First, human antibody placental transfer is not uniform across gestation. As a result of their large size and hydrophilicity, monoclonal antibodies cannot cross the placenta by simple diffusion and instead rely on active transport facilitated by binding of the IgG FC region to the neonatal Fc receptor (FcRn) on the syncytiotrophoblast [27]. During the first trimester, FcRn is barely detectable and maternofetal antibody transport is limited. FcRn expression and antibody transport then increase as pregnancy progresses, being greatest in the third trimester [27]. This means the period of greatest susceptibility to the effect of maternal monoclonal antibody exposure in humans will be during the second and third trimesters when growth and maturation occur, rather than during the early embryonic period when organogenesis occurs. Developmental and reproductive studies are most informative when dosing extends beyond the embryonic period [27,28]. This is especially relevant for immune modulating antibodies like tocilizumab since many components of the immune system continue to develop and mature during the fetal and postnatal periods.

Cynomolgus monkeys have generally been used preferentially in non-clinical reproductive and developmental toxicity studies of antibodies targeting the immune system because the immune systems of the two species are similar [28,29]. Furthermore, maternofetal IgG transfer in cynomolgus monkeys is comparable to that in humans in terms of timing, with antibody transfer mainly occurring during the final 50 days of gestation, equivalent to the second and third trimesters in humans [28,29]. However, monkey antibody levels in offspring may be lower than in humans and, with respect to tocilizumab in particular, monkey maternal IL-6 expression is more limited under normal conditions [11]. Finally, tocilizumab tissue cross-reactivity is greater in humans compared with cynomolgus monkeys where binding in the latter is restricted to inflammatory, endothelial and epithelial cells [11].

The rodent immune system, by contrast, is developmentally immature at the time of birth compared with primates and certain aspects develop predominantly in the postnatal period [30]. Antibodies are effectively transported in breast milk in rodents and absorbed across the neonatal gut by FcRn, meaning dosing in rodent studies should be extended into lactation to simulate human exposure in the fetal period [11,30]. Other barriers to using rodent models include the inability of tocilizumab to bind to non-primate IL-6 receptors and the high levels of anti-tocilizumab antibodies produced by rodents, which neutralize the effect of tocilizumab [11,30]. To overcome these problems an analogous rat anti-mouse IL-6 receptor antibody (MR16-1) was developed and used in prenatal/postnatal toxicity mouse studies [11,30]. The affinity of MR16-1 to the mouse soluble IL-6 receptor is approximately 14-fold lower than the affinity of tocilizumab for human soluble IL-6 receptor. Despite this, MR16-1 can still suppress the acute phase response to IL-6 at low exposures in mice [11,30]. A limitation of this model however, is that many mice develop fatal immune reactions to low doses of MR16-1 and therefore outcomes are typically only evaluable with much higher relative doses than used in humans [11].

With these limitations in mind, there was no evidence of teratogenicity with the administration of tocilizumab between days 20 and 50 of gestation in a cynomolgus monkey embryo–fetal toxicity study [11]. However there was a dose-related increase in the incidence of abortion or embryo–fetal death at high relative exposures [11]. Unfortunately, because there was no dosing beyond day 50 of gestation, this study is only of relevance in identifying maternally mediated effects, which might have indirect adverse effects on embryo development.

The second major series of reproductive studies for tocilizumab used the MR16-1 mouse model [11]. In these prenatal/postnatal studies, as noted previously, the low-dose group had a high incidence of fatal immune reactions and was not evaluable. No reproductive abnormalities were observed in offspring of the high dose group however [11]. Offspring did show reductions in white blood cell, lymphocyte and neutrophil counts as well as CD45 and CD49 markers, indicating mild immune suppression [11].

## Clinical data

Studies of patients treated with tocilizumab during pregnancy are summarized in Table 1. The experience includes 11 studies with 610 pregnant people, although there may be repeated patients between studies [31–41]. Most studies were retrospective without an appropriate control group. Further, as can be seen in Table 1, most patients were treated with tocilizumab for rheumatological diseases and interpretation of outcomes is complicated by underlying illness and concomitant medications, some of which are known teratogens.

Most of the clinical data on tocilizumab use in pregnancy come from (a) Roche's Global Safety Database, which included prospective ($n$ = 180) and retrospective ($n$ = 108) reports from clinical trials, non-interventional studies, spontaneous submissions and other post-marketing literature [35] and (b) the European League Against Rheumatism (EULAR) taskforce report, which complied cases from registration data and abstracts reported at scientific conferences ($n$ = 218) [37].

With regards to the Global Database, over 90% of patients were treated with tocilizumab for rheumatoid arthritis and most received their last dose pre-conception or early in the first trimester, when tocilizumab transplacental transfer would be expected be negligible [35]. Not surprisingly considering the timing of exposure, there was no apparent increase in congenital malformations (4.5%) [35] compared with the background rates of 3%–4% in the general population [42,43]. Furthermore, there was no distinct pattern of malformations among the cases. This is consistent with the most recent EULAR report, where a low rate of congenital malformations (3.9%) was documented [37].

Spontaneous abortions were higher in both the Global Database (21.7%) and the EULAR report (21.6%) than in the general population (15%–20%) [35,37]. Concomitant methotrexate, which was prescribed to approximately 20% of patients and is a known teratogen and abortifacient, may have contributed to these outcomes [35].

The rate of prematurity was also increased (31.1%) compared with the background rates in the general population (10%–15%) [35,44]. In addition, a lower mean birthweight, which was only partly explained by gestational age, was observed. Although pregnancy outcomes in stable rheumatoid arthritis patients are comparable the general population, high rheumatoid arthritis disease activity has been associated with preterm birth [35,45]. Disease activity was not recorded in this database, but early discontinuation of effective therapies may have played a role in outcomes.

In total, 17 pregnant people whose outcomes were captured in the Global Database continued or resumed tocilizumab beyond the first trimester [35]. All gave birth to live neonates and in prospective cases ($n$ = 11), the median gestational age at birth was $36^{+4}$ weeks, i.e. approximately half were preterm deliveries. A small number of cases in other reports received tocilizumab beyond the first trimester but outcomes were generally not reported separately (Table 1).

There have been four reports of tocilizumab use in pregnant patients with COVID-19 ($n$ = 20) (Table 1) [31,32,36,41]. Tocilizumab administration frequently occurred in the third trimester, many patients were critically ill, and corticosteroid use was uncommon. In the largest series from Spain ($n$ = 12), all pregnancies resulted in live births, but most had limited neonatal follow up [31]. There was one case of maternal cytomegalovirus reactivation and congenital infection [31]. A dose-related increase in the incidence of secondary opportunistic infections was identified among patients receiving long-term tocilizumab in rheumatoid arthritis trials [37]. This has not been observed in clinical trials of tocilizumab for COVID-19 [12–19], although follow up has been limited and this remains an area of uncertainty for both pregnant and non-pregnant patients. Guidance from Public Health England recommends that live vaccines not be administered before 6 months of age following in utero exposure to biological immunosuppressant agents [38].

## Pharmacokinetics

The pharmacokinetics of tocilizumab have not been characterized in pregnancy. However, based on what is known about monoclonal antibody pharmacokinetics in general, together with pregnancy-associated pharmacokinetic changes [46,47], several reasonable predictions can be made about tocilizumab pharmacokinetics in pregnancy. First, because of their large size and hydrophilicity, monoclonal antibodies reside almost exclusively in the blood plasma and extracellular fluid [46]. The increase in blood volume associated with pregnancy (~40%) [47] may reduce tocilizumab plasma concentrations. Next, monoclonal antibodies are primarily eliminated by intracellular degradation after target binding and to a lesser degree by proteolytic catabolism [46]. The former is related to target expression levels, i.e. IL-6 receptor expression, which is approximately 40% higher throughout pregnancy [48], suggesting that tocilizumab may be eliminated more rapidly in pregnancy. Together, these pregnancy-associated changes suggest that higher doses or additional doses may be necessary to match exposures achieved in non-pregnant patients. However, the clinical importance of potentially altered exposure in pregnancy is unclear because pharmacokinetic/pharmacodynamic efficacy and toxicity targets have not been established.

## Breastfeeding

In general, maternal IgG1 does not transfer well into breast milk (large molecular size, limited transport mechanisms), although concentrations are higher in the colostrum from mothers of preterm infants [49,50]. Furthermore IgG oral bioavailability is low because of proteolytic degradation in the infant digestive tract. Undigested IgG molecules can pass into the neonatal circulation via gut-derived FcRn, which is most relevant for preterm infants who digest less IgG in their stomach compared with term infants [49,50].

Data on tocilizumab in breastfeeding is limited to three prospective case series/reports, which included a total of seven mother–infant pairs [33,34,51]. Tocilizumab was either stopped in the first trimester and resumed after delivery or continued throughout pregnancy and postpartum. All women delivered healthy term infants. In all cases, tocilizumab was excreted into breast milk and reached peak levels 3–5 days after administration. However, transfer was low with trough milk-to-serum ratios

**Table 1**
Studies of tocilizumab in pregnant people for COVID-19 and other indications

| First author, publication year | Design | Setting | Number of Patients<br>Gestational age at last tocilizumab dose<br>Tocilizumab indication | Concomitant medications/biologics | Tocilizumab dose | Maternal COVID-19 severity | Birth outcomes | Maternal adverse effects |
|---|---|---|---|---|---|---|---|---|
| Jinenez-Lorano I 2021 (31) | Case series | Spain | $n = 12$<br>Median $27^{+5}$ weeks gestation (range 18 $-36^{+3}$ weeks)<br>COVID-19 | 12/12 hydroxychloroquine<br>9/12 lopinavir/ritonavir<br>8/12 azithromycin<br>1/12 interferon beta-1B<br>2/12 methylprednisolone | Before March 2020<br>600 mg IV, then 600 mg (≥80 kg) or 400 mg (<80 kg) IV, 12 hours after the first dose<br>Mid-March 2020 and onwards<br>600 mg (>75 kg) or 400 mg (≤75 kg) IV. A second dose was considered in patients with poor early response | 7/12 high flow oxygen<br>3/12 mechanical ventilation<br>5/12 intensive care unit | 12/12 live births<br>Median $38^{+6}$ weeks gestation<br>7/12 caesarean delivery<br>2/12 preterm<br>1/12 congenital cytomegalovirus infection<br>1/12 *Klebsiella pneumoniae* conjunctivitis<br>12/12 neonates SARS-CoV2 (−)<br>1/12 congenital abnormalities (cleft lip and palate) confirmed before COVID-19 and tocilizumab | 1/12 maternal cytomegalovirus infection<br>2/12 cytolytic hepatotoxicity |
| San-Juan R 2020 (32) | Subgroup of single-centre retrospective cohort study of pregnant people with COVID-19 | Spain | $n = 5$<br>Median (IQR) 29 (25–34) weeks gestation for overall cohort<br>COVID-19 | 1/5 methylprednisolone | 400–600 mg IV<br>2/5 1 dose<br>3/5 2 doses | 3/5 high flow oxygen<br>1/5 mechanical ventilation<br>1/5 intensive care unit | 2/5 urgent caesarean delivery<br>1/5 preterm<br>Other pregnancy outcomes not reported separately for patients that received tocilizumab | 5/5 recovered |
| Abdullah S 2021 (41) | Case series | United Arab Emirates | n = 2<br>24 weeks and 35 weeks gestation<br>COVID-19 | 2/2 hydroxychloroquine<br>1/2 lopinavir-ritonavir<br>1/2 acetylcysteine<br>1/2 favipiravir<br>1/2 azithromycin | 400 mg IV × 1 dose<br>600 mg IV × 1 dose | 1/2 high flow oxygen<br>1/2 mechanical ventilation<br>1/2 intensive care unit | 1/2 elective caesarean delivery following recovery from COVID-19, initial neonatal assessment was unremarkable<br>1/2 urgent caesarean delivery, initial and 6-week neonatal assessments were unremarkable | 2/2 recovered 1/2 discharged on hospital day 35<br>1/2 unclear length of admission |
| Naqvi M 2020 (36) | Case report | USA | $n = 1$<br>$22^{+6}$ weeks gestation<br>COVID-19 | Remdesivir | 400 mg IV × 1 dose | Supplemental oxygen | Ongoing at publication | Recovered and discharged on hospital day 8 |
| Hoeltzenbein M 2016 (35) | Prospective and retrospective cohort study<br>Roche Global Safety Database | Global<br>29% Europe<br>26% North America<br>23% Asia<br>15% South America | $n = 288$<br>90% rheumatoid arthritis<br>180 prospective<br>108 retrospective cases with pregnancy outcomes<br>Prospective cohort: 112/180 tocilizumab administered after conception<br>Median gestational age at tocilizumab discontinuation was 5 weeks<br>11/180 tocilizumab continued beyond first trimester<br>Retrospective cohort: Gestational age not consistently reported<br>6/108 tocilizumab continued beyond first trimester | Prospective:<br>38/180 methotrexate<br>Retrospective: not reported | Most common regimen<br>8 mg/kg IV every 4 weeks | Not applicable | Prospective:<br>68/112 live birth, 20/112 spontaneous abortion, 24/112 elective termination of pregnancy, 0 stillbirth<br>Median (IQR) gestational age at birth ($n = 55$), 39 (37–40) weeks<br>16/55 pre-term<br>Median (IQR birthweight $n = 39$, 2800 (2300–3320) g<br>Malformations 5/111, 4.5%<br>Neonatal death 2/111<br>Second/third trimester exposure:<br>11/11 live births at median $36^{+4}$ weeks; median (IQR) birthweight $n = 7$, 2590 (2060–2835) g<br>Retrospective:<br>55/108 live births<br>31/108 spontaneous abortions<br>22/108 elective termination of | Not reported |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | pregnancy<br>Second/third trimester exposure<br>6/6 live births<br>2/6 preterm | |
| Gotestam Skorpen C 2016 (37) | Register data, 2 case reports | Global | 218 including<br>180 prospective cases and 38 retrospective cases | Not reported | Not reported | Not applicable | 47/218 miscarriages<br>5/128 congenital malformations | Not reported |
| Nakajima K 2016 (38) | Retrospective cohort study<br>Chugai safety database | Japan | $n = 61$ (50 with pregnancy outcomes)<br>87% rheumatoid arthritis<br>10/61 tocilizumab discontinued before the last menstrual period<br>30/61 first trimester exposure<br>2/61 tocilizumab continued throughout pregnancy | Not reported for overall cohort<br>Concomitant methotrexate in 5/9 pregnancies that resulted in spontaneous abortion<br>Concomitant methotrexate in 2/6 pregnancies that resulted in neonatal abnormalities | Most common regimen 8 mg/kg IV every 4 weeks | Not applicable | 36/50 deliveries<br>10/36 term; 2/36 preterm; 24/36 unknown<br>0/36 congenital abnormalities<br>6/36 neonatal abnormalities<br>1/6 neonatal asphyxia; 5/6 low birthweight <2500 g − 3/5 considered fetal growth restriction<br>9/50 spontaneous abortions<br>5/50 induced abortions − 1/5 due to fetal abnormality −caudal regression syndrome | Not reported |
| Saito J 2018 (34) | Case report | Japan | $n = 2$<br>2/2 rheumatoid arthritis<br>2/2 tocilizumab discontinued at 6 weeks gestation | Etanercept<br>Prednisolone | 400 mg (8 mg/kg) IV every 4 weeks | Not applicable | Vaginal delivery at 36 and 37 weeks gestation<br>2/2 healthy infants | None |
| Saito J 2019 (33) | Case report | Japan | $n = 1$<br>Adult onset Still's disease<br>Tocilizumab continued throughout pregnancy | Prednisolone<br>Tacrolimus | 400 mg IV every 4 weeks | Not applicable | Vaginal delivery at $40^{+5}$ weeks gestation<br>Birthweight 2792 g<br>Apgar scores at 1 and 5 minutes 10<br>No congenital or neonatal abnormalities | Not reported |
| Weber-Schoendorfer C 2016 (40) | Prospective cohort study<br>Embryotox Berlin Program | Germany | $n = 16$ (12 with pregnancy outcomes)<br>100% rheumatoid arthritis<br>Median 9 weeks gestation<br>All patients had first trimester tocilizumab exposure and/or exposure before last menstrual period | 1/16 hydroxychloroquine<br>2/16 leflunomide<br>1/16 methotrexate<br>1/16 sulfasalazine<br>6/16 prednisolone | Most common regimen 8 mg/kg IV every 4 weeks | Not applicable | 11/12 live births<br>7/11 cesarean delivery<br>Median birthweight 3130 g<br>Median gestation 39 weeks<br>1/11 preterm<br>4/16 spontaneous abortions<br>1/16 elective abortion<br>0 major malformation<br>1 spontaneous abortion complicated by hydrops fetalis | Not reported |
| Kaneko K 2016 (39) | Case series | Japan | $n = 4$<br>rheumatoid arthritis<br>4 days to 3 weeks gestation<br>1/4 resumed tocilizumab at 10 weeks gestation and continued during pregnancy | 1/4 prednisolone | 8 mg/kg IV every 4 weeks | | 3/4<br>37−38 weeks gestation<br>1/4 partial molar pregnancy and miscarriage at 11 weeks gestation − tocilizumab resumed at 10 weeks gestation and continued during pregnancy | Not reported |

Abbreviations: COVID-19, coronavirus disease 2019; IQR, intraquartile range; IV, intravenous.

ranging from 0.00082 to 0.0015 [33,34,51]. In one report, the umbilical cord blood, infant serum and breast milk concentrations were measured [33] Overall transfer to the infant was minimal; the tocilizumab umbilical cord blood concentration was 17% of the maternal blood concentration and at 5 days post-delivery, the infant serum tocilizumab concentration was 5% of the maternal concentration. By week 4, tocilizumab was undetectable in the infant serum despite exclusive breastfeeding and continued maternal tocilizumab use. No adverse effects were observed in any of the infants including no infections, although only two reports ($n = 3$) followed infants longitudinally for 6–13 months. Early childhood vaccines were administered on schedule to two infants [34]. Rotavirus vaccine and the bacillus Calmette–Guérin vaccine were delayed to 6 months after delivery in the third (with in utero tocilizumab exposure) because of concerns over safety with live vaccines in the setting of possible tocilizumab-associated immunosuppression [33,52]. Vaccination details were not reported for the other cases [51].

## Conclusions

Although our understanding is still evolving, available data strongly suggest that pregnant people with COVID-19 infection experience a higher severity of illness and increased rates of complications compared with age-matched non-pregnant individuals; neonatal morbidities are also increased [2–8]. Effective prevention and treatment strategies are therefore critically important to improve maternal and neonatal outcomes, but regressive policies excluding pregnant people from participating in biomedical research persist [9,10]. Clinicians and pregnant people are left with the difficult task of deciding whether potential benefits of a treatment outweigh potential harms to the fetus based on very little information. Data so far indicate that COVID-19-specific therapies are used infrequently in pregnant patients including the critically ill [5].

To assist in decision-making, we reviewed information on tocilizumab in pregnancy and lactation from a variety of sources. Although our review does not reveal serious safety signals, it is clear that the available data have significant limitations and are not sufficient to delineate the complete spectrum of potential adverse outcomes that may be associated with exposure to tocilizumab during pregnancy and lactation. Importantly, there are very few data on tocilizumab exposure in the second and third trimesters when most pregnant people with COVID-19 have been hospitalized and transplacental passage is highest [3,5]. Questions also remain about the impact of tocilizumab on the developing immune system. Diligent follow up and documentation of pregnancy outcomes will be important moving forward. A more effective regulatory framework to ensure equitable inclusion of pregnant women in research is clearly needed.

## Transparency declaration

SCJJ has received a speaker's honorarium from Sunovion, outside this work. SEL has received payments from Cambridge University Press and Sage Publications Inc., outside this work.

## Funding

No funding was received for this work.

## Authors' contributions

SCJJ wrote the original draft, and SCJJ and SEL review and edited the article and the conceptualization.

## References

[1] Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. N Engl J Med 2014;371:1077.
[2] Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ 2020;370:m3320.
[3] Money D. Canadian Surveillance of COVID-19 in pregnancy: epidemiology, maternal and infant outcomes. Report #2. Public Health Agency of Canada; 2021. Available at: http://med-fom-ridprogram.sites.olt.ubc.ca/files/2021/01/CANCOVID_Preg-report-2-ON-AB-BC-QC-data_15JAN2021_FINAL.pdf. [Accessed 24 May 2021].
[4] Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22–October 3,2020. MMWR Morb Mortal Wkly Rep 2020;69:1641–7.
[5] Knight M, Ramakrishnan R, Bunch K, Vousden N, Kurinczuk J, Sarah Dunn S, et al. Females in hospital with SARS-CoV-2 infection, the association with pregnancy and pregnancy outcomes: a UKOSS/ISARIC/CO-CIN investigation. 2020. Available at, https://www.gov.uk/government/publications/ukossisaricco-cin-females-in-hospital-with-sars-cov-2-infection-the-association-with-pregnancy-and-pregnancy-outcomes-25-march-2021. [Accessed 25 May 2021].
[6] Gurol-Urganci I, Jardine JE, Carroll F, Draycott T, Dunn G, Fremeaux A, et al. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: national cohort study. Am J Obstet Gynecol 2021. epub ahead of print.
[7] Woodworth KR, Olsen EO, Neelam V, Lewis EL, Galang RR, Oduyebo T, et al. Birth and infant outcomes following laboratory-confirmed SARS-CoV-2 infection in pregnancy – SET-NET, 16 Jurisdictions, March 29–October 14, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1635–40.
[8] Vouga M, Favre G, Martinez-Perez O, Pomar L, Acebal LF, Abascal-Saiz A, et al. Maternal outcomes and risk factors for COVID-19 severity among pregnant women. Sci Rep 2021;11:13898.
[9] Malhame I, D'Souza R, Cheng MP. The moral imperative to include pregnant women in clinical trials of interventions for COVID-19. Ann Intern Med 2020;173:836–7.
[10] Taylor MM, Kobeissi L, Kim C, Amin A, Thorson AE, Bellare NB, et al. Inclusion of pregnant women in COVID-19 treatment trials: a review and global call to action. Lancet Glob Health 2021;9:e366–71.
[11] Center for Drug Evaluation and Research, Department of Health and Human Services Food and Drug Administration. Actemra™ (tocilizumab). Pharmacology NDA review and evaluation. 2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125276s000PharmR.pdf. [Accessed 5 May 2020].
[12] Group RC. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021;397:1637–45.
[13] Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. JAMA Intern Med 2021;181:32–40.
[14] Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of Tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. JAMA Intern Med 2021;181:24–31.
[15] Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. N Engl J Med 2021;384:20–30.
[16] Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. N Engl J Med 2020;383:2333–44.
[17] Veiga VC, Prats J, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ 2021;372:n84.
[18] Rosas IO, Brau N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. N Engl J Med 2021;384:1503–16.
[19] Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, et al. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. Lancet Respir Med 2021;9:511–21.
[20] Investigators R-C, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. N Engl J Med 2021;384:1491–502.
[21] COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. Available at, https://www.covid19treatmentguidelines.nih.gov/. [Accessed 31 May 2021].
[22] National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing COVID-19 NICE guideline [NG191]Published. 2021. Last updated: 27 May 2021. Avaialable at, https://www.nice.org.uk/guidance/ng191/chapter/Recommendations. [Accessed 31 May 2021].

[23] National COVID-19 Clinical Evidence Taskforce. Clinical care living guidelines v39.1. 2021. Available at: https://covid19evidence.net.au/. [Accessed 31 May 2021].
[24] Ontario COVID-19 Drugs and Biologics Clinical Practice Guidelines Working Group. Clinical practice guideline summary: recommended drugs and biologics in adult patients with COVID-19. Ontario COVID-19 Science Advisory Table. 2021. https://doi.org/10.47326/ocsat.cpg.2021.2.0. Version 2.0. Available at: . [Accessed 31 May 2021].
[25] Prins JR, Gomez-Lopez N, Robertson SA. Interleukin-6 in pregnancy and gestational disorders. J Reprod Immunol 2012;95:1–14.
[26] Winkler M. Role of cytokines and other inflammatory mediators. BJOG 2003;110:118–23.
[27] Stewart J. Developmental toxicity testing of monoclonal antibodies: an enhanced pre- and postnatal study design option. Reprod Toxicol 2009;28:220–5.
[28] FDA Center for Drug Evaluation and Research. Guidance for the industry. S6 preclinical safety evaluation of biotechnology-derived pharmaceuticals. 1997. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals. [Accessed 27 May 2021].
[29] Martin PL, Breslin W, Rocca M, Wright D, Cavagnaro J. Considerations in assessing the developmental and reproductive toxicity potential of biopharmaceuticals. Birth Defects Res B Dev Reprod Toxicol 2009;86:176–203.
[30] Sakurai T, Takai R, Burgin H, Ishihara K, Sakamoto Y, Amano J, et al. The effects of interleukin-6 signal blockade on fertility, embryo-fetal development, and immunization in vivo. Birth Defects Res B Dev Reprod Toxicol 2012;95:304–17.
[31] Jimenez-Lozano I, Caro-Teller JM, Fernandez-Hidalgo N, Miarons M, Frick MA, Batllori Badia E, et al. Safety of tocilizumab in COVID-19 pregnant women and their newborn: a retrospective study. J Clin Pharm Ther 2021. epub ahead of print.
[32] San-Juan R, Barbero P, Fernandez-Ruiz M, Lopez-Medrano F, Lizasoain M, Hernandez-Jimenez P, et al. Incidence and clinical profiles of COVID-19 pneumonia in pregnant women: a single-centre cohort study from Spain. EClinicalMed 2020;23:100407.
[33] Saito J, Yakuwa N, Kaneko K, Takai C, Goto M, Nakajima K, et al. Tocilizumab during pregnancy and lactation: drug levels in maternal serum, cord blood, breast milk and infant serum. Rheumatol (Oxford) 2019;58:1505–7.
[34] Saito J, Yakuwa N, Takai C, Nakajima K, Kaneko K, Goto M, et al. Tocilizumab concentrations in maternal serum and breast milk during breastfeeding and a safety assessment in infants: a case study. Rheumatol (Oxford) 2018;57:1499–501.
[35] Hoeltzenbein M, Beck E, Rajwanshi R, Gotestam Skorpen C, Berber E, Schaefer C, et al. Tocilizumab use in pregnancy: analysis of a global safety database including data from clinical trials and post-marketing data. Semin Arthritis Rheum 2016;46:238–45.
[36] Naqvi M, Zakowski P, Glucksman L, Smithson S, Burwick RM. Tocilizumab and remdesivir in a pregnant patient with coronavirus disease 2019 (COVID-19). Obstet Gynecol 2020;136:1025–9.
[37] Gotestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis 2016;75:795–810.
[38] Nakajima K, Watanabe O, Mochizuki M, Nakasone A, Ishizuka N, Murashima A. Pregnancy outcomes after exposure to tocilizumab: a retrospective analysis of 61 patients in Japan. Mod Rheumatol 2016;26:667–71.
[39] Kaneko K, Sugitani M, Goto M, Murashima A. Tocilizumab and pregnancy: four cases of pregnancy in young women with rheumatoid arthritis refractory to anti-TNF biologics with exposure to tocilizumab. Mod Rheumatol 2016;26:672–5.
[40] Weber-Schoendorfer C, Schaefer C. Pregnancy outcome after tocilizumab therapy in early pregnancy-a case series from the German Embryotox Pharmacovigilance Center. Reprod Toxicol 2016;60:29–32.
[41] Abdullah S, Bashir N, Mahmood N. Use of intravenous tocilizumab in pregnancy for severe coronavirus disease 2019 pneumonia: two case reports. J Med Case Rep 2021;15:426.
[42] Pregnancy outcomes working group of the FDA pregnancy labeling taskforce in the center for drug evaluation and research (CDER) and the center for biologics evaluation and research (CBER). Reviewer guidance evaluating the risks of drug exposure in human pregnancies. 2005. Available at: https://www.fda.gov/media/71368/download. [Accessed 27 May 2021]. accessed.
[43] Centers for Disease C, Prevention. Update on overall prevalence of major birth defects—Atlanta, Georgia, 1978–2005. MMWR Morb Mortal Wkly Rep 2008;57:1–5.
[44] Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health 2019;7:e37–46.
[45] Smith CJF, Forger F, Bandoli G, Chambers CD. Factors associated with preterm delivery among women with rheumatoid arthritis and women with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2019;71:1019–27.
[46] Ryman JT, Meibohm B. Pharmacokinetics of monoclonal antibodies. CPT Pharmacomet Syst Pharmacol 2017;6:576–88.
[47] Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. Front Pharmacol 2014;5:65.
[48] Matsuzaki N, Neki R, Sawai K, Shimoya K, Okada T, Sakata M, et al. Soluble interleukin-6 (IL-6) receptor in the sera of pregnant women forms a complex with IL-6 and augments human chorionic gonadotropin production by normal human trophoblasts through binding to the IL-6 signal transducer. J Clin Endocrinol Metab 1995;80:2912–7.
[49] Koenig A, de Albuquerque Diniz EM, Barbosa SF, Vaz FA. Immunologic factors in human milk: the effects of gestational age and pasteurization. J Hum Lact 2005;21:439–43.
[50] Hurley WL, Theil PK. Perspectives on immunoglobulins in colostrum and milk. Nutrients 2011;3:442–74.
[51] Saito J, Yakuwa N, Kaneko K, Nakajima K, Takai C, Goto M, et al. Clinical application of the dried milk spot method for measuring tocilizumab concentrations in the breast milk of patients with rheumatoid arthritis. Int J Rheum Dis 2019;22:1130–7.
[52] Cheent K, Nolan J, Shariq S, Kiho L, Pal A, Arnold J. Case Report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. J Crohns Colitis 2010;4:603–5.