Use of IL-6 receptor antagonists in the second and third trimester of pregnancy: an observational study

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Abstract

Background: A paucity of data exist to inform the use of interleukin-6 receptors antagonists (anti-IL6Rs) in pregnancy; particularly in the third trimester. This study aimed to describe outcomes of women and their neonates exposed to these medications given to treat COVID-19 after the first trimester.

Methods: A retrospective observational study of pregnant women with COVID-19 treated with anti-IL6Rs between 1st March 2020- 30th September 2022 was performed. Maternal and pregnancy outcomes were documented.

Findings: 25 women received an anti-IL6R for COVID-19 in pregnancy during the study period. The group described were a high-risk population with 24/25 (96%) requiring level two or three critical care. 24/25 (96%) of the women received Tocilizumab; one Sarilumab. All patients were prescribed at least three concomitant medications. 23/25 (92%) received the anti-IL6R in the third trimester of pregnancy. There were no cases of maternal neutropenia or pancytopenia, the number of women who had a rise in liver enzymes was in keeping with the severity of COVID-19 reported and all women who developed a secondary bacterial infection mounted a C-reactive protein response. There was one maternal death.

All pregnancies resulted in live births (n=26; one twin pregnancy); 16/26 (62%) of these babies were born preterm. One baby died at six months old as a consequence of complications of extreme prematurity. A transient neonatal cytopenia was described in 6/19 (32%) of babies in whom a full blood count was performed. While these findings are likely in keeping with prematurity alone, we cannot exclude the possibility that transplacental transfer of anti-IL6Rs was contributory.

Interpretation: We report further data for the use of anti-IL6Rs in the third trimester of pregnancy for the management of COVID-19 in pregnancy, which when extrapolated can inform shared decision making for women who would benefit from use of anti-IL6Rs into the third trimester of pregnancy for management of rheumatological disease.

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Introduction

Tocilizumab is a humanised monoclonal IgG1 antibody against the interleukin-6 receptor (anti-IL6R) utilised for various inflammatory rheumatic conditions including Rheumatoid Arthritis (RA), juvenile idiopathic arthritis, and large vessel vasculitis. Since 2017, the fully human IgG1 anti-IL6R sarilumab has also been licenced by the European Medicine Agency for use in RA. Tocilizumab has been demonstrated to improve survival in hospitalised COVID-19 patients with hypoxia and systemic inflammation. (1) It is therefore recommended by the World Health Organisation for the management of severe or critical COVID-19; where tocilizumab is not available sarilumab can be offered as an alternative.

A paucity of data describing the use of anti-IL6Rs exists to inform their use in pregnancy. Data in human pregnancy consist predominantly of uncontrolled case reports/series cumulatively describing around 600 exposed pregnancies (summarised in a narrative review by Jorgensen et al). (2) The reported adverse outcomes following in-utero exposure are in-keeping with the background population and in a number of cases in which adverse outcomes were reported the mother was taking concomitant teratogenic medications, such as methotrexate. Only a minority of cases include exposures in the 2nd/3rd trimester, and of these, we are not aware of any that include details on neonatal haematological parameters or C-reactive protein (CRP) response to neonatal infection. Only one case of the use of sarilumab in pregnancy is reported in the literature.

Given their large molecular weight, anti-IL6Rs are unable to cross the placenta by diffusion. From 13 weeks' of gestation, however, the placenta begins to express neonatal Fc receptors (nFcR) which facilitate transplacental passage of maternal antibodies. This process serves to establish passive immunity in the newborn – and transfer becomes more efficient as the pregnancy progresses. (3) As IgG1 based molecules, anti-IL6Rs are predicted to bind to the nFcR, thereby allowing their passage to the fetus, particularly in the second half of pregnancy. The lack of transfer in early pregnancy, during the period of fetal organogenesis, means teratogenic potential is limited but the existing data do not inform clinicians on the safety profile of use in later pregnancy. Pre-clinical animal data do not raise any concerns at doses used in humans (4), but there is a theoretical risk that use in 2nd/3rd trimesters may have adverse effects on neonatal immunity (such as cytopenias, CRP suppression) due to known transfer at later gestations. (5) Currently, this yet to be proven potential risk must be balanced against the known adverse impacts of poorly controlled inflammatory rheumatic disease in pregnancy (e.g. increased risk of preterm birth and pre-eclampsia) when deciding whether to continue anti-IL6R therapy beyond the 1st trimester.

The recent British Society for Rheumatology (BSR) guidelines on prescribing in pregnancy and breastfeeding state "limited evidence has not shown IL-6 inhibitors to be teratogenic; however, there remains insufficient evidence to be confident that they are compatible with pregnancy. Consider stopping the drug at conception. Any exposure, however, during pregnancy is unlikely to be harmful". (6) As it is well recognised that pregnant women with COVID-19 are at increased risk of severe disease, particularly when infected in the third trimester (7), organisations such as the Royal College of Obstetricians and Gynaecologists (RCOG) recommend that tocilizumab be strongly considered in pregnant women with severe COVID-19 infection on balance of benefit and theoretical risk (8). This echoes the stance of the BSR that for rheumatic indications, anti-IL6Rs "may be considered to manage severe maternal disease in pregnancy if no other pregnancy-compatible drugs are suitable".

Despite such guidance, data have demonstrated that only one-quarter of pregnant women who would benefit from evidence-based therapies such as anti-IL6Rs for severe COVID-19 are offered them (9, 10). This is likely to reflect clinician concerns regarding the safety profile of anti-IL6Rs for the fetus in later pregnancy highlighting the need for further pregnancy and neonatal outcome data to support risk-benefit discussions for patients and their clinicians. (11)

In this observational study we report maternal and neonatal outcomes for 25 women treated with anti-IL6Rs for COVID-19 in pregnancy. These data will also be of interest to rheumatologists using anti-IL6Rs for women with rheumatic disease who may benefit from continuation of the drug into the third trimester of pregnancy.

Methods

A retrospective observational study of pregnant women with COVID-19 treated with anti-IL6Rs was performed at Guy's and St Thomas' NHS Foundation Trust (GSTT) and Imperial College Healthcare NHS Trust (ICHT), two tertiary hospitals in London. All women receiving tocilizumab or sarilumab for the management of COVID-19 in pregnancy between 1st March 2020 and 30th September 2022 were included. All cases had a laboratory-

confirmed reverse-transcriptase-polymerase-chain-reaction (RT-PCR) SARS-CoV-2-positive result (in any respiratory sample).

Maternal demographics, clinical data, administered medications and maternal and neonatal outcomes were recorded from a review of patients' medical records. In some cases, neonates were born at a local hospital after the mother had been discharged from either GSTT or ICHT. Neonatal data were collected for these babies through the maternal medicine networks. Information was collected, anonymised and stored in a password protected Excel spreadsheet and data analysed using Stata v17 for Mac. Neonatal data were reviewed by and discussed with a consultant neonatologist to determine whether any adverse findings were in keeping with complications of concurrent events e.g. prematurity, or could relate to an adverse drug effect from anti-IL6Rs.

Descriptive characteristics were calculated. Continuous variables were expressed as mean ± standard deviation. Categorical data are reported as median [interquartile range]. Proportions were summarised as an absolute number and percentage.

Ethical approval and individual patient consent were not sought as this is a retrospective evaluation of patients identified in an anonymised database. There was no funding source for this study.

Results

In total, 25 women received an anti-IL6R for COVID-19 in pregnancy during the study period. Mean age at admission was 33 years ± 5·14. In total, 13 women had a medical comorbidity including type 2 diabetes mellitus, migraine, gastric bypass, asthma, hypothyroidism, IgA nephropathy, inflammatory bowel disease, Takayasu's arteritis and RA. There was one twin pregnancy (patient 19); the remainder were all singleton pregnancies. Of the patients admitted to GSTT, 9/13 (69%) women were transferred to the centre from peripheral hospitals primarily so that they could access extracorporeal membrane oxygenation (ECMO) if required; the remainder were local patients whose pregnancies were booked at this centre. All patients managed at ICHT were local patients; one was transferred to an ECMO centre for four weeks and then returned to ICHT for the duration of their inpatient stay.

In total, one patient was admitted to level one care, 5/25 (20%) level two high dependency care (although two did not require oxygen) and 19/25 (76%) were admitted to level three intensive care units. The baseline vital signs and level of respiratory support are described in Table 1. These in combination with the patients' clinical examination findings and radiological imaging on admission to hospital were consistent with a group of women with severe maternal disease.

Of the 25 women prescribed an anti-IL6R, 24/25 (96%) received Tocilizumab and 1/25 (4%) received Sarilumab. The dose of anti-IL6R and description of concomitant medications and doses are shown in Table 2. The median number of days into hospital admission that the tocilizumab was prescribed was 3 days [1-3]. In 23/25 (92%) women the tocilizumab or sarulimab was received during the third trimester of pregnancy, the remaining two received it in the second trimester.

The trend of maternal CRP and ALT are shown in Figure 1 and the area under the curve for these outcomes for each patient is reported in Appendix 1. CRP was suppressed in all patients following tocilizumab administration. Three patients went on to have a spike in CRP; patient four in response to a ventilator associated pneumonia; patient 18 an initial spike in response to klebsiella septicaemia and later a superimposed bacterial pneumonia; and patient 25 in response to a wound infection following caesarean birth. There were a number of patients who had a rise in their ALT; all were reported to be related to the COVID-19 infection and all resolved spontaneously. Patient 17 had an ALT which was on an upward trend until day six, no further results were available during the inpatient stay but the patient had bloods repeated at their follow-up appointment when they returned in labour, at which point the ALT had returned to within normal limits. Trends for maternal white cell count (WCC), haemoglobin, lymphocyte count, platelet count and neutrophils are given in Appendix 2. There were no cases of maternal neutropenia or pancytopenia.

The maximal respiratory support required by each patient is described in Table 3. In total, 24/25 (96%) women survived until hospital discharge, one woman died. This unvaccinated patient had severe COVID-19 pneumonitis requiring extra-corporeal membrane oxygenation (ECMO). She received Tocilizumab on day one of admission. Six weeks into the admission she developed myocarditis from which she subsequently had a cardiac arrest and could not be resuscitated.

Details of neonatal outcomes are described in Table 3. The gestational age at which mothers were admitted to hospital was 30+1 weeks ± 4.73. In total, 10/26 (39%) of babies were born at term (≥37 weeks' gestation), 11/26 (42%) pre-term (≥32 weeks' gestation), 3/26 (12%) very pre-term (≥28 and <32 weeks' gestation) and 2/26 (8%) extremely pre-term (<28 weeks' gestation). In total, 2/26 (8%) babies had been delivered at a local hospital prior to transfer to GSTT, 12/26 (46%) were delivered during the mother's hospital admission and 12/26 (46%) were delivered post discharge. Of the 14 babies born prior to hospital transfer or during the mother's admission with COVID-19, 12 were delivered by emergency caesarean section and the remaining two by vaginal delivery. Mode of delivery, neonatal APGAR scores and breastfeeding status are shown in Table 3.

All pregnancies resulted in live births. Half of the babies (13/26) required admission to a neonatal intensive care unit or special care baby unit; all admissions were related to complications of prematurity. In terms of immediate complications, 10 babies had evidence of respiratory distress; five of these were pre-term, three very pre-term and two extremely pre-term. Six babies were diagnosed with jaundice and three developed hypoglycaemia all of which were considered to be related to prematurity.

One baby was born with a fenestrated atrial septal defect, identified on echocardiogram, with no haemodynamic compromise. This had resolved by patient follow-up. There were no other congenital malformations reported in this series.

Six babies had cytopenias; these are described in Table 3. All of these babies were born preterm (range 22 weeks and two days gestation to 35 weeks and six days gestation. Babies 1, 3, 6 and 23 had transient cytopenias which resolved by a maximum of seven days. Baby 15 was diagnosed with thrombocytopenia on day 1, on day two (day of discharge) the platelets reached a nadir of 77 $x10^9$/L, the patient did not attend follow-up, however, when reviewed at three months the baby was found to be doing well. Baby 24, was found to have lymphopenia, thrombocytopenia and neutropenia and is described in detail below.

At the stage of data collection 27/28 (96%) of babies were reported to be alive. Baby 24 died at six months old. This baby had been born at 23 weeks and two days gestation as a consequence of maternal deterioration for severe COVID-19 pneumonitis. The baby had multiple complications as a consequence of prematurity including cerebral atrophy on cranial ultrasound, significant chronic lung disease of prematurity with continued requirement for respiratory support and necrotising enterocolitis. This baby also had hepatic failure, jaundice, hepatosplenomegaly, likely as a result of long-term parenteral nutrition and recurrent sepsis; and multiple fractures as a consequence of osteopenia of prematurity. The baby had feed intolerance and intermittent hypoglycaemic episodes. This baby required repeated platelet and red cell transfusions. The thrombocytopenia was considered likely to be related to prematurity, chronic illness and hepatic failure. They were treated with antibiotics on seven separate occasions, growing Klebsiella extended spectrum beta lactamase (ESBL) on skin swab, candida parapsilosis in urine, Klebsiella ESBL on blood cultures, and was treated for presumed klebsiella meningitis after blood contaminated cerebrospinal fluid. The TORCH screen was negative. The baby died at six months of age from multiorgan failure. The patient has been discussed with the neonatologists and paediatricians and tocilizumab has not been considered to be a cause of any of the baby's conditions; rather extreme prematurity is thought to have been the most significant factor.

Two babies were reported to have suffered infections (babies 1 and 24). Both of these babies mounted a CRP response to the infection despite being exposed to Tocilizumab six days and seven days prior to delivery respectively.

Discussion

This retrospective case series describes the maternal and neonatal outcomes of 25 women who received anti-IL6Rs in pregnancy. In total, 92% of women received the drug during the third trimester of pregnancy, a period in which there is a relative void in the reported literature. There is only one case of sarilumab reported in the literature (12), we add a further case. The outcomes for the mothers and neonates were largely reassuring; the only possible adverse outcome was a transient neonatal cytopenia described in six out of 19 babies who had a full blood count performed.

Of the 25 women prescribed an anti-IL6R, 24 received tocilizumab in line with national guidance for COVID-19 which recommends this as the first line anti-IL6R after corticosteroids (8). In one case, where tocilizumab was not available, sarilumab was used. We describe a high-risk group of individuals; GSTT is a tertiary centre in which patients are referred for consideration and use of ECMO. It is the only ECMO centre in the UK with co-located

maternity services. Queen Charlotte's and Chelsea Hospital, ICHT is also a tertiary referral centre and all the patients described received either level two or three critical care. The patients reported had standard treatment doses of both drugs. All women were receiving at least three concomitant medications, a number of which have limited safety data in pregnancy.

Elevated liver transaminases have been well described in relation to COVID-19 infection and are also recognised as a side-effect of anti-IL6R use (13, 14). It is reported that 14-53% of patients with COVID-19 infection develop elevated liver enzymes, with the degree of abnormality correlating with disease severity (20). In our series, of the 25 patients whose alanine aminotransferase (ALT) was available, 16 (64%) had an abnormal result at some stage during their admission. In all cases the ALT normalised and in all women who underwent further investigation for primary liver disease the results were normal. It is difficult to determine the relative contribution of severe COVID-19 infection, anti-IL6R administration and co-prescribed medications on transaminitis in our series, but our data demonstrate that any rise in liver enzymes in this population was self-limiting.

CRP is an acute phase reactant which is unchanged by pregnancy and elevated in severe COVID-19 infection. Anti-IL6Rs are known to blunt the acute phase response with rapid normalisation of CRP following administration, as is demonstrated in our series. In rheumatological practice, numerous case reports describe patients receiving weekly/monthly anti-IL6Rs presenting with a variety of severe infectious syndromes including septic shock, endocarditis, colonic perforation and septic arthritis with normal CRP (21, 22). There is a theoretical risk, therefore, that the use of anti-IL6Rs in COVID-19 infection could impair the recognition of secondary bacterial infections including ventilator associated pneumonias (VAPs). In our series, three women had a subsequent increase in CRP, related to a line infection, klebsiella septicaemia then a hospital acquired pneumonia and in the third to a hospital acquired pneumonia. The preservation of CRP responses to secondary infection with the single dose administration of anti-IL6Rs for COVID-19 infection is supported by other studies and offers reassurance for clinicians utilising these agents in critically unwell pregnant women (23).

There is a paucity of data relating to the use of single-dose tocilizumab in pregnancy, particularly in the third trimester. The UK Teratology Information Service (UKTIS) summarise 51 cases of late pregnancy use of tocilizumab for the management of COVID-19 in pregnancy which have been reported in the literature (4, 24-28). In the described cases dose regimens were similar to those received in our cohort and similarly patients were often prescribed multiple concomitant medications in the context of their critical illness. The cases comprise a number of small case series/reports (25, 27-30) (five administered tocilizumab in third trimester, two in second trimester, remainder unrecorded), a slightly larger Spanish series of 12 women (median gestation of tocilizumab dose 27.7 weeks) and an Emirati series of 28 women (mean gestational age 30.1 weeks) (31). The case reports and case series report good maternal outcomes apart from one maternal death. The mother was critically unwell, had had a prior caesarean birth and required emergency delivery via caesarean birth. She subsequently died of an acute bowel perforation post-partum, with contributory factors recorded as adhesions, recent surgery, COVID-19 and tocilizumab use (which is rarely associated with colonic perforation) (30). In the Spanish series all women survived to hospital discharge; complications considered to be related to tocilizumab therapy were described in three women, two related to hepatotoxicity which resolved prior to discharge and one woman who had reactivation of cytomegalovirus (CMV) (notably this woman had also been receiving corticosteroids for 15 days) (26). Tocilizumab has been reported to be associated with reactivation of viral infection and we therefore would support close monitoring, particularly in patients who are taking concomitant immunosuppressive therapy (32). The series from Dubai includes two maternal deaths from COVID-19, one pseudomonas infection, one fungal and multi-drug resistant bacterial infection and four mothers who developed pre-eclampsia.

The literature that described any dose of tocilizumab in the third trimester include 17 patients from Roche's Global Safety Database and the cases in which it was used for the management of COVID-19 described above. There were no neonatal complications reported in the global database. Some neonates were lost to follow-up in the reported case series but of the 45 babies born to mothers in which it had been used for COVID-19, all were live born; one was diagnosed with cleft palate at 20 weeks' gestation and thus prior to maternal COVID-19 infection or tocilizumab administration; and one was confirmed to have congenital CMV (born to the mother with CMV reactivation, this neonate received treatment at birth and made a full recovery) (26). All other complications were considered to be related to preterm birth. We are not aware of any studies that include details of neonatal haematological parameters or CRP response to neonatal infection.

With regards neonatal outcomes in our study, 16/26 (61·5%) of babies were born prematurely which is in keeping with the reported rates of preterm birth in this severely unwell maternal population (24). While a number of the

neonates suffered immediate complications (respiratory distress, jaundice, hypoglycaemia) these were not considered to be related to tocilizumab but rather complications of preterm delivery. One baby born at 23 weeks and two days gestation died at six months old after a prolonged admission to neonatal intensive care. Neonatal intensive care or special care baby unit admissions were also considered to be related to complications of preterm birth. We report one case of fenestrated atrial septal defect in a baby that received tocilizumab at 29+4 weeks' gestation, thus after the period of organogenesis. The baby who developed a central line related infection (Baby 1) and the baby with necrotising enterocolitis (Baby 24) both mounted CRP responses to the infection/inflammation.

There is a theoretical risk that transplacental passage of anti-IL6R could result in neonatal cytopenias and in those babies exposed to live vaccines put them at risk of disseminated infection. This is the only study, to our knowledge, that reports data on neonatal full blood counts following tocilizumab exposure in the third trimester of pregnancy. In total, a full blood count was sent on 19 babies and was abnormal in 6. This means almost one third of babies who had a full blood count checked had an abnormal result and this is of concern. It should be noted that in all but the baby born to patient 24 the abnormalities were transient. These findings were reviewed by and discussed with a neonatologist (TW) who considered that this degree of cytopenia would not be uncommon in a preterm population, however, we acknowledge that it is difficult to distinguish drug effects from prematurity effects and thus we cannot rule out a drug effect.

This study increases significantly the literature reporting outcomes of mothers and neonates exposed to anti-IL6Rs in the third trimester of pregnancy. It is limited in that the patients receiving these drugs were also taking concomitant medications some of which have limited safety data in pregnancy, thus any effects cannot be assumed to relate solely to anti-IL6Rs. While the use of anti-IL6Rs in this group were single doses for the management of COVID-19 and therefore do not relate directly to rheumatological practice, the findings are reassuring with regard to administration of anti-IL6Rs close to delivery. The outcomes described can be used to inform discussions on the merits of continuing anti-IL6Rs into the 3rd trimester for the management of RA, juvenile idiopathic arthritis and large vessel vasculitis. While not available for our patients, assessment of placental pathology would allow for further evaluation of outcomes in future studies.

Conclusion

We add further data for the use of anti-IL6Rs in the third trimester of pregnancy; data which extrapolated can inform shared decision making for women who would benefit from use of anti-IL6Rs into the third trimester of pregnancy for rheumatological disease. To our knowledge we are the first to report neonatal haematological parameters and CRP response to infection following anti-IL6Rs exposure in pregnancy. While we have described transient neonatal cytopenias these were not associated with adverse neonatal outcomes. Future studies of anti-IL6Rs throughout pregnancy should be undertaken in women with rheumatological disease, where the risk of prematurity is smaller, and thus studies in this population may be better able to delineate the impact of anti-IL6Rs on transient neonatal cytopenias.

Research in context

Evidence before this study: We searched PubMed and MEDLINE from Jan 1, 2000, to January 1, 2024, with the search terms "tocilizumab", "sarilumab", "interleukin-6 receptors antagonists", "anti-IL6Rs" and "pregnan*". We searched the reference lists of papers of interests and while we focussed on publications between 2015 and 2024 we also references important older publications.

The search revealed a paucity of data describing the use of anti-IL6Rs in pregnancy, the majority of which described exposure in the first trimester of pregnancy. To our knowledge there are no reported cases of exposure in the third trimester of pregnancy that include details of neonatal haematological parameters or C-reactive protein response to neonatal infection.

Added value of the study: This study adds 25 cases of 2nd/3rd trimester exposure to anti-IL6Rs to the literature and describes the haematological parameters in 19 neonates.

Implications: For women with inflammatory rheumatic conditions requiring anti IL-6R therapy shared decision making about whether to initiate or continue therapy in pregnancy can now be informed by this and other case series demonstrating minimal safety signals.

Author contribution statements:

MN and CNP conceived the idea of the study. MN, CNP and MD designed the study. MN, MG EC, BG and HP collected and analysed the data. All authors had full access to all the data in the study; three authors MN, MG and HP verified the underlying data reported in the manuscript. MN drafted the first draft of the manuscript which was edited by MG and BG. MD, TW and CNP approved the final version of the manuscript. All authors have seen and approved the final text and all authors had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests: We declare no competing interests.

Data sharing:

Individual study patient data will not be made available for confidentiality purposes. Anonymised data can be made available by contracting MN (melanie.nana@gstt.nhs.uk). There are no additional related documents that will be made available.

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