Steroid use in Pregnancy with Severe COVID-19

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December 21, 2021

Abstract

Managing women who are pregnant with severe COVID-19 is complex. This paper focuses on the debate surrounding steroid use in this group. Unfortunately, despite international efforts to identify treatments for COVID-19, there is very little research which has focussed specifically on pregnant women. Therefore current guidance is based on consensus and expert opinion, with variation in these guidelines worldwide, and reports that 73% of pregnant women do not receive steroids at all. There is an assumption of a steroid class-effect implicit within the UK guidelines for the mother with COVID-19 which is at odds with established within-class differences for effects on the foetus. This now warrants further discussion given the increasing numbers of pregnant women being admitted to hospital with COVID-19.

Since COVID 19 was declared a pandemic on 11th March 2020, significant international efforts have been made to identify and implement effective treatments. Arguably, the RECOVERY trial with its innovative design has been most influential; in particular its early discovery that low dose dexamethasone reduced mortality in severe infection by between a third (in ventilated patients) and one fifth (in patients requiring oxygen but not ventilation)[1]. An unintended consequence of these data being produced so rapidly was the termination of other trials investigating prednisolone and methyl-prednisolone in COVID-19 infection.

Although pregnant women were included in the RECOVERY trial, they are severely under-represented with only 4 patients recruited and 1 randomised to dexamethasone[1]. Unfortunately, over the last six months we have seen an increasing number of women who are pregnant requiring intensive care admission due to COVID-19 infection and predict this to continue into at least the mid-term[2]. This subjective view echoes the UK Obstetrics Surveillance System (UKOSS) data showing that of 3371 pregnant women admitted with COVID-19, 336 (10%) required ICU and 701 (20%) required respiratory support. The proportion of COVID-19 cases in pregnancy being moderate-severe has also increased to 50% with the delta variant compared with approximately 33% with the alpha variant and 25% in the first wave[3,4]. Given these data the evidence gap surrounding the treatment of pregnant women requiring critical care warrants discussion.

We therefore wish to open a discussion, prompted by our experience treating women in our own critical care unit, surrounding steroid use in pregnancy with COVID-19. It seems to us that the balance of risks and benefits is between:

1. The requirement to treat maternal COVID-19 in an attempt to prevent deterioration and preterm delivery, acknowledging that a good foetal outcome can only follow stability of the mother

2. The consequences to the foetus of longer-term corticosteroid treatments, all of which cross the placenta to some degree

Treatment of COVID-19

Evidence for the use of steroid treatment in COVID-19 is now well understood outside of pregnancy[1]. Our local adult protocol advises dexamethasone 6.6mg IV for 10 days along with Tocilizumab/Sarilumab if there are no contra-indications, there is also provision for utilising casirivimab in an appropriate sub-set of patients. To our knowledge there is no evidence for the use of prednisolone in COVID-19 and the evidence for use of hydrocortisone in the treatment of COVID-19 is controversial[5]. We note a meta-analysis has aggregated dexamethasone, prednisolone, hydrocortisone and methylprednisolone[6] but the case for a 'class effect' is far from certain[5–7]. Like in the placenta, the lung concentration of steroids is not uniform throughout the class. Of note, Vichyanond et al reported that 'methylprednisolone achieves higher concentrations in the lungs than prednisolone'[8] and 'transcortin carries prednisolone around the body [for which] prednisolone has a very high affinity, but it binds to it with a lower capacity'. It implies that methylprednisolone more avidly reaches the lungs than prednisolone[8].

As of 14/9/21 the RECOVERY trial had 132 pregnant or postpartum women recruited[4] which will provide new data but we note the protocol does not include dexamethasone unless lung maturation is required with no control arm for the prednisolone/hydrocortisone cohort. This leaves the possibility of dexamethasone as a first line agent for all pregnant women being superior to the study protocol. Whilst we eagerly await these data we wish to highlight the potential of under-treating this patient cohort.

Available evidence from UKOSS suggests that preterm deliveries occur in 21% of women who are pregnant and admitted to hospital with COVID-19[3]. It is not surprising that we suspect, based on our experience, that once a woman who is pregnant requires ICU admission the probability of preterm delivery is far greater than this.

Most concerningly, recent UKOSS data suggests we may have a bigger problem than steroid selection with only 27% of women who are pregnant admitted to intensive care receiving any steroids at all[3].

Antenatal steroid use

There are risks associated with prolonged or repeated steroid dosing in pregnancy although both terms are ill-defined. There is therefore concern about giving pregnant women steroids when delivery is not planned or imminent[9]. There is provision in NICE guidelines for repeated doses of steroids when gestational age, time since last course of steroids and likelihood of delivery within 48 hours are considered[10]. The advantage of lung maturation is balanced against the risks. These risks were shown in the ACTORDS trial which gave either betamethasone or placebo to women still at risk of pre-term birth prior to 32+0 weeks gestation after they had already received one course of corticosteroids[11]. This group reported growth retardation that was fully reversed by hospital discharge[12]. This is somewhat contradicted by an NICHD study utilising betamethasone which was terminated early because of severe (<10th decile) IUGR[9]. There is also concern of neurological sequelae in the child[13,14].

Evidence for antenatal glucocorticoids mimicking the usual rise in corticosteroids seen in the last weeks of pregnancy is well established with betamethasone and dexamethasone both proven to induce foetal lung maturation[10,15,16]. The recommended dose of dexamethasone is 24mg split into four 6mg IM doses 12 hours apart[10,17].

The most recent Cochrane review included 8158 infants and showed marked reduction in death, respiratory distress syndrome, necrotizing enterocolitis and the need for respiratory support, surfactant therapy and oxygen supplementation[15]. This is due to the fact that betamethasone and dexamethasone have the highest placental transfer rate in this class as they are not metabolised by placental 11-b-hydroxylase steroid dehydrogenase-2. It is thought that this is not the case for prednisolone, hydrocortisone and to a slightly

lesser extent methyl-prednisolone meaning these drugs only minimally cross the placental barrier[8,18,19]. Therefore, given repeat doses of steroids are permitted for foetal lung maturation in the non-COVID-19 setting, a woman with severe COVID-19 prescribed a full course of dexamethasone 6mg daily for 10 days receives less than double this dose.

Current guidelines for the treatment of COVID-19 in pregnancy

The Royal College of Obstetrics and Gynaecology (RCOG) advocates the use of prednisolone 40mg daily or hydrocortisone 80mg twice per day for those women with severe COVID-19 without plans for immediate (within 4 days) delivery[8]. These doses are the equivalent to 6mg of dexamethasone using the BNF steroid equivalency table[20], although this is based on the assumption of a class effect based on glucocorticoid activity and does not fully account for pharmacokinetics amongst other differences.

American guidelines suggest using a 10 day course of betamethasone or dexamethasone for pregnant women who are requiring oxygen or are mechanically ventilated[21]. Given concerns for breast-feeding others have suggested switching to methylprednisolone after the initial lung maturation dexamethasone doses[22]. The Australian National COVID-19 Clinical Evidence Taskforce guidance suggests using Dexmethasone 6mg daily for 10 days for pregnant women receiving oxygen or mechanically ventilated[23,24].

Discussion

Current UK guidelines in this area are at odds with standard adult treatment for COVID-19 and we note there are conflicting recommendations from governing bodies around the world regarding treatment of COVID-19 during pregnancy.

In emergency situations the ethos of prioritising the mother over the child is well established[25,26]. This is exemplified by the Resuscitation Council UK advocating peri-mortem delivery of the neonate during a maternal cardiac arrest increasing the probability of survival for the mother. There is, however, a continuum of 'grey' leading to the very obvious emergency of cardiac arrest.

We suggest that an ICU admission with COVID-19 during pregnancy is also an emergency where similarly the treatment of the mother should be prioritised over the child. However, we have noted locally and within the literature that this 'grey' area creates ambiguity and we fear the possibility of under-treating the mother in this emergency setting given concerns for foetal complications.

Clinical uncertainty around the likelihood of preterm birth outwith COVID-19 often leads to repeated doses of steroids for foetal lung maturation with their associated risk of complications. Given the high incidence of preterm delivery in women who are pregnant with severe COVID-19 it is unlikely that women will receive steroids without then progressing to preterm delivery.

The natural conclusion of this logic is the use of dexamethasone first-line in such a patient at the 6mg twice per day dosing for two days then 6mg once a day there-after to complete ten days. This is to give the mother the highest chance of survival and give the child the maximum chance of gaining the benefits of steroids if delivery were to become necessary. It may be a switch to methyl-prednisolone once the lung maturation dexamethasone (48hours) has been administered is non-inferior to dexamethasone but these data are currently not available and we suspect the reduction in risk to the foetus to be minimal.

The requirement to prove non-inferiority is pressing given the theoretical concerns for prednisolone being ineffective for the treatment of COVID-19. We suspect that a steroid class-effect in the treatment of COVID-19 is unlikely to be found especially given we know there are in-class-differences for the placenta and therefore foetus. We advocate for urgent research to test the assumption of 'class effect' before equipoise is lost and we are left potentially under-treating pregnant women with severe COVID-19.

At present the use of prednisolone in this setting lacks evidence. In this emergency setting the mother's health should be prioritised and the current UK guidelines likely compromise the mother for a debatable small advantage to the foetus.

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