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Treatment Strategies for COVID-19 in Pregnancy: Short Review of Current Recommendations

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Abstract

Since the emergence of COVID-19 in Dec. 2019, our knowledge of disease and treatment modalities has evolved significantly. Pregnancy poses a unique challenge in the context of the management of infectious diseases because of the effect of the disease and treatment modalities on the mother and fetus. There has been a lack of active inclusion of pregnant women in various trials including vaccination trials in COVID-19; hence most information on treatment strategies became available from adult non-pregnant population. This article outlines the short review on current management strategies available to the adult pregnant population with COVID-19 in light of available evidence until 30th April 2021.

Keywords

COVID-19 in Pregnancy, Vaccinations, Management of COVID-19, Trials in COVID-19

1. Introduction

Since the initial identification of SARS CoV-2 (COVID-19) in China in December 2019, it has rapidly spread across the world with its devastating effects [1]. At the same time, efforts to study the disease and develop vaccinations against the virus have also accelerated worldwide.

As our knowledge of the disease and treatment modalities has evolved, we became aware that pregnant women are not more susceptible to acquiring the infection compared to non-pregnant population, but may be at higher risk of developing severe symptoms especially in the third trimester because of the

physiological changes, relative immune-compromised state of pregnancy, and risk of consequent iatrogenic preterm deliveries [2]. Women with high BMI, multiple pregnancies, co-morbidities like hypertension, diabetes, cardiac or chronic kidney disease and those from Black, Asian and minority ethnic groups may be more susceptible to severe disease [3].

There has been a lack of active inclusion of pregnant women in various trials including vaccination trials; hence most information on treatment strategies became available from adult non-pregnant population [4] [5] [6].

This article outlines the short review on current management strategies available to the adult pregnant population with COVID-19 in light of available evidence until 30th April 2021.

2. Management Strategies

Assessing and predicting the course of COVID-19 in pregnancy includes a multidisciplinary approach involving medical and obstetric teams. Clinical assessment must consider the risk of deterioration, hypoxia, need for ventilatory support and decisions of ongoing care versus delivery plans. Different blood markers used in the general population in determining the severity of the disease, such as raised CRP, lymphopenia, increased LDH, ferritin and D-dimers have variable significance in pregnancy and immediate postnatal population, hence may not be as useful to predict severity or progression in isolation. This also applies to using risk stratification of admitted patients using the ISARIC WHO clinical characteristic protocol [7]. D-Dimers should not be used to risk assess for prophylaxis and treatment of venous thromboembolism in pregnancy and should be based on clinical judgment, risk factors and where appropriate clinical imaging for diagnostic purposes [8]. Chest x-ray and CT scans are safe to be used in pregnancy when they are required to help predicting disease severity and progression.

1) *Thromboembolism:*

Royal college of Obstetricians and Gynaecologists and several other guidelines recommend COVID-19 to be scored as a transient risk factor in venous thromboembolism (VTE) risk assessment as outpatient and inpatient attendances [9]. All inpatients with COVID-19 infection should be offered VTE prophylaxis, unless delivery is imminent within 12 hours. Based on expert consensus, NICE recommends increasing to intermediate dose prophylaxis for high-risk patients managed on critical care units, although one recent randomised controlled trial suggests this may not confer any benefit over standard dose prophylaxis [10] [11]. The VTE treatment should be started promptly after hospital admission and continue for the duration of inpatient stay and 10 days on discharge [3] [9]. Consider extended courses if women have additional risk factors.

2) *Steroid treatment:*

Initially, there was a reluctance to use steroids in the COVID-19 patients because of concerns with the progression of the infection due to reduced viral

clearance from the body. However, this was refuted by the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial [4]. This trial also included six pregnant women and the results demonstrated that the use of steroids significantly reduced the mortality within 28 days as well as the duration of invasive ventilation in patients who required mechanical ventilation or oxygen supplementation. It did not find any benefit in those who don't require respiratory support. Saad *et al.* [12] also recommends that any pregnant female with COVID-19 infection who requires oxygen support, should be started on steroid treatment.

The steroid regimen for pregnant women who require oxygen or ventilatory support includes prednisolone 40 mg administered by mouth (or intravenous hydrocortisone 80mg twice daily) for 10 days or until discharge [4].

If a preterm delivery is anticipated, dexamethasone as intramuscular injections is administered as per RCOG guidance.

3) ***Antibacterial, antimalarial, antiviral and immune modulators and monoclonal antibody agents:***

These agents have been studied in multiple randomised trials, including RECOVERY (UK), ACTT-1 (USA) and WHO SOLIDATORY trial [13].

There is no strong evidence that antibiotics are effective in preventing disease progression in the early stages of COVID-19 infection, however when a patient first presents it can be very difficult to differentiate between bacterial and viral pneumonia. Lobar pneumonia and neutrophilia may suggest bacterial infection, but their absence does not exclude it. When using antibiotics; Co-amoxiclav, Doxycycline or Clarithromycin have been suggested as treatment strategies [7]. The risk of teratogenicity with doxycycline is very low. They are historically not encouraged as first line because of cosmetic staining of primary dentation in foetuses exposed during the second and third trimesters and manufacturer concerns regarding possible enamel hypoplasia and depression of fetal bone growth. Hence, on balance, Amoxicillin and Clarithromycin are kept the first and second choice in these cases.

Hydroxychloroquine did not show any benefit in decreasing disease progression or mortality; hence it's not recommended [4] [13].

Remdesivir is safe to be used in pregnancy and postnatal period. Initial studies suggested some benefit in shortening the median recovery time to 10 days [14], but it has not shown any benefit in reducing mortality [13].

Tocilizumab, a common treatment for rheumatoid arthritis, has been subject to many studies in COVID-19. The adaptive randomised controlled trial REMAP-CAP trial demonstrated an absolute reduction in mortality of 8.5% when it was administered within 24 hours of admission to critical care [10]. The recovery trial found an absolute mortality reduction of 4% when it was given to patients with hypoxia (oxygen saturation < 92% on air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein [CRP] ≥ 75 mg/L) [15]. Mortality improvements have been confirmed in subsequent meta-analyses,

and Tocilizumab is recommended in guidelines for patients fitting these criteria, although more work is needed to understand which patient populations benefit most [5] [15] [16].

Tocilizumab has been used in pregnant population with other medical indications and can be offered to pregnant women including in the first trimester. Women receiving medicine after 20 weeks are advised to avoid live neonatal vaccinations (BCG, Rotavirus) for 6 months after delivery.

Others: There are currently new arms studied in several studies including aspirin, newer antibiotics like azithromycin, anti-viral drugs, immunomodulators, and anti-SARS-CoV-2 monoclonal antibodies directed against the spike protein of SARS-CoV-2, to block the virus attachment and entry into human cells. The REMAP-CAP trial is also evaluating the use of convalescent plasma for COVID-19. Libster *et al.* indicated that early treatment with convalescent plasma reduces the risk of progression to severe disease by 48% [17].

Future studies will also explore treatments to prevent the longer-term morbidity and mortality associated with "Long COVID" [18].

COVID-19 Vaccination: The Joint Committee on Vaccination and Immunisation (JCVI) UK has revised its advice on vaccination in pregnancy in mid-April 2021 [19] [20] [21]. They advise that all pregnant women should be offered the COVID-19 vaccine at the same time as the rest of the population, based on their age and clinical risk group. There is no evidence, and no theoretical reason, that any of the vaccines can affect the fertility of women or men [22]. There are no fetal or neonatal side effects or malformations reported even for women who got pregnant soon after receiving their vaccination. If women still wish to be cautious, they can either consider vaccination before planning pregnancy or delay their vaccine in early pregnancy until 12 weeks when organogenesis happens and consider it after the first trimester.

There have been no safety concerns raised at present with any of the vaccines in relation to pregnancy. In the USA, around 90,000 pregnant women have been vaccinated mainly with Pfizer and Moderna vaccines and no safety concerns have been identified.

A recent study from the USA including 131 reproductive-age vaccine recipients (84 pregnant, 31 lactating, and 16 non-pregnant) concluded that COVID-19 mRNA vaccines generated robust humoral immunity in pregnant and lactating women, with immunogenicity and reactogenicity similar to that observed in non-pregnant women. Vaccine-induced immune responses were significantly greater than the response to natural infection. Immune transfer to neonates occurred via placenta and breastmilk [23].

Since the new statement from JCVI and MHRA of a notification of rare side effects of risk of thrombosis and thrombocytopenia following the first dose of AstraZeneca vaccination, healthcare professionals are advised to continue to offer vaccinations to at-risk general population group and discuss the benefits and risks including rare side-effects including alternatives for under 40 years old,

where available and it does not cause substantial delays in being vaccinated. Women who had AstraZeneca vaccine in pregnancy, no such serious side effects have reported compared to the risk of immune thrombosis and thrombocytopenia seen in non-pregnant adult population.

As there's more data available for the Pfizer and Moderna vaccine in pregnancy hence these vaccines are now being recommended as first line in pregnancy in the UK from mid-April onwards. If a woman chooses to have a particular vaccine, then this choice should be facilitated [24].

RCOG recommends that pregnant women who might be eligible for vaccination should notify their local maternity unit when it is received. This is so that maternity staff can report it to the UKOSS/UKTIS vaccine registry (vaccination in pregnancy study in UK) [25] [26] [27].

3. Conclusions

All women with symptomatic and asymptomatic COVID-19 infection should be encouraged to inform their health care professionals of their diagnosis, to devise their individual care plan including advice about their health, VTE risk assessment and neonatal wellbeing. Women with co-morbidities and those from Black, Asian and ethnic minority groups should be offered extra support, including discussions about the availability of COVID-19 vaccination, and advice to seek help promptly if their clinical condition deteriorates.

There should be a low threshold to start steroids, immunomodulatory agents, antiviral and antibiotic treatments where appropriate when treating symptomatic COVID-19 pregnant women requiring oxygen or ventilatory support. Women should be supported in breast feeding as there is no evidence about the risk of neonatal transmission.

Women at high risk of infection should be offered and supported in vaccinations. Contraception should be discussed with postnatal women with severe illness to avoid unintended pregnancies and to give them time to recuperate physically as well as mentally.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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