RANDOMISED EVALUATION OF COVID-19 THERAPY (RECOVERY)
for pregnant and breastfeeding women
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	RECOVERY trial protocol	Adaption for pregnancy
Eligibility	Patients are eligible if all of the following are true: i. Hospitalised ii. SARS-CoV-2 infection (clinically suspected or lab confirmed) iii. No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial	Same eligibility
Interventions	**First randomisation part A** • Colchicine **First randomisation part B** • Convalescent plasma • Synthetic neutralising antibodies **First randomisation part C** • Aspirin **Second randomisation** • Tocilizumab	Same interventions *(with exception of colchicine for pregnant and breastfeeding women - do not undertake part A randomisation for pregnant women)* **Pregnant and breastfeeding women are eligible for all other treatments shown.**
Follow-up/ outcomes	Ascertained at the time of death or discharge or at 28 days after randomisation (whichever is sooner): ➢ Vital status (alive/ dead, with date and presumed cause of death, if appropriate) ➢ Hospitalisation status (inpatient/ discharged, with date of discharge, if appropriate) ➢ Use of ventilation (none/ previous/ ongoing, with days of use and type, if appropriate) ➢ Use of renal dialysis or haemofiltration (none/ previous/ ongoing)	Same follow-up and outcomes, with addition of UKOSS COVID-19 case number (for pregnancy and baby information) to allow later data linkage
		Adaptions for breastfeeding
		The same interventions *(with exception of colchicine)* should be used. UKOSS COVID-19 case number added if available.

Frequently asked questions

1. **Are the drugs safe in pregnancy?** The pregnancy leads for the trial have reviewed the safety literature (Annex A), and experience around using these drugs for other conditions, and consider that participation in the trial is reasonable for pregnant and breastfeeding women. The regulators (MHRA and HRA) have agreed to the inclusion of pregnant women for each of the agreed treatments above.
2. **Where can I find information specifically written for pregnant women about the drugs?** The links below are provided with permission from the bumps (best use of medicines in pregnancy) website, who have developed information leaflets for each of the drugs used in the RECOVERY trial. The bumps website and information are provided by the UK Teratology Information Service (UKTIS), a not-for-profit organisation funded by Public Health England on behalf of the UK Health Departments.
   - Aspirin: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Aspirin/
   - Tocilizumab: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Tocilizumab/
3. **Who has endorsed the trial?** The trial itself has been endorsed by the **Chief Medical Officer and NHS England Medical Director.** Inclusion of pregnant and postpartum women has been endorsed by NHS England, the Royal College of Obstetricians and Gynaecologists, Royal College of Midwives, Royal College of Physicians, Tommy's Charity, British Maternal and Fetal Medicine Society, Macdonald Obstetric Medicine Society, the Neonatal Society, the Reproductive Health and Childbirth Specialty Group Lead (NIHR Clinical Research Network).

4. **Who should take consent for inclusion in the trial?** Any healthcare professional with appropriate training and knowledge of the trial can take consent. Obstetricians, obstetric physicians and midwives can make their colleagues aware that pregnant and postpartum women are eligible for the trial and should be approached for participation. Consent does not need to be taken specifically by an obstetrician, obstetric physician or research midwife.
5. **Can I offer the trial to a woman who is in hospital for another reason?**
   If you are looking after a woman with a positive covid-19 swab result who was initially admitted for another reason (e.g. in labour), ask whether you are uncertain about the benefits of treatment or not for this woman, either for treatment or to prevent deterioration. If you are uncertain, then it is reasonable to provide the information to the woman, offer the trial and make a shared decision. We do not know the optimal time to offer treatment.
6. **Who collects the outcome data?** The outcome data will be collected as usual for the trial, with the exception of pregnancy-specific data, which will be collected by research nurses or research midwives as part of the ongoing **UKOSS COVID-19 study in pregnancy**, using the **UKOSS COVID-19 Data Collection Form**. All pregnant women should be reported within the UKOSS COVID-19 study (although this does not need to be started before consent to RECOVERY), and the UKOSS number should be included in the outcome data.
7. **Can we give women corticosteroids for fetal lung maturity?** Yes, if indicated, as in usual clinical obstetric practice (see **RCOG guidance in COVID-19 pandemic**)
8. **Can we take part?** Any hospital that has R&D approval for RECOVERY can take part. There are no special approvals needed for including pregnant and breastfeeding women. A 'pregnancy lead' healthcare professional has been identified in 160 sites, to work alongside the site Principal Investigator.

Annex A: Trial drugs in pregnancy and during lactation

All trial drugs recommended for pregnant women (except REGN-COV2 monoclonal antibodies) have been used in pregnant women with pre-existing medical disorders where benefits outweigh the risks to fetus or woman, including in the first trimester. The data for colchicine is outlined below. The existing data related to each drug is summarized below.

Colchicine

This is not currently recommended for inclusion in the RECOVERY trial for pregnant or breastfeeding women.

The RECOVERY trial is excluding women aged less than 55 years old, but older women (aged 55 years and older) who might be pregnant should also not have colchicine included in their randomisation. Colchicine is a drug used to treat gout (not commonly seen in women of reproductive age) and familial Mediterranean fever (which is seen in pregnant women). A systematic review of colchicine use for pregnant women with familial Mediterranean fever has reported no increased risk of adverse pregnancy outcomes,[1] and this is reflected in the UKTIS information on colchicine:
https://www.medicinesinpregnancy.org/bumps/monographs/MEDICATIONS-USED-TO-TREAT-COVID-19-IN-PREGNANCY/
However, there are theoretical concerns over use in pregnancy, as colchicine has anti-mitotic properties with evidence of teratogenicity in animals, and the BNF advises against its use in pregnancy:
https://bnf.nice.org.uk/drug/colchicine.html#pregnancy.
In light of the uncertainty, we are not recommending colchicine for use in pregnant women (or those of reproductive age), but if a pregnant woman is unintentionally exposed to the drug, then the usual pathway should be followed (e.g. referral to a Fetal Medicine Unit and/ or discussion with the UK Teratology Information Service for advice).

Convalescent plasma (prepared with Dr Sue Pavord, Consultant Haematologist)

Convalescent plasma is plasma from people who had confirmed COVID-19 (SARS-Cov-2) infection, and have now recovered and been free of the infection for 28 days. The plasma contains antibodies that their immune systems have produced in fighting the virus. It is hoped that giving this plasma will help speed up recovery of a patient with active infection and improve their chances of survival. Plasma is already used as a treatment in pregnant patients who are bleeding,[2] or have particular blood conditions.[3, 4] The plasma being used in this trial is from a selected donor and hopefully contains anti-SARS-Cov-2 antibodies, but is otherwise no different. Plasma infusions can

occasionally cause side effects. Mostly this is a rise in temperature, itching or a rash, and in very extreme cases, anaphylaxis. Other potential complications include breathlessness and changes in blood pressure. Monitoring of pulse and blood pressure takes place before and after the infusion. There is no risk of miscarriage or fetal loss, preterm birth, preterm rupture of membranes, perinatal mortality or low birthweight, from plasma transfusions and there are no concerns with breast feeding.

REGN-COV2 Monoclonal antibodies (prepared with Dr Ken Hodson, Medical Director, UKTIS)
Monoclonal antibodies have been used as therapeutic agents in pregnancy over recent years, for a variety of conditions. Human monoclonal antibodies in use in pregnancy include anti-TNF agents, such as adalimumab, indicated for a variety of chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. Data have recently accumulated from a variety of cohort and registry studies indicating that such exposure in pregnancy was not associated with an increased risk for adverse pregnancy outcomes, when compared to unexposed pregnancies with the same underlying medical diseases.[5] This is supported by a consensus report on immunosuppressives and biologics during pregnancy and lactation, confirming no evidence of elevated adverse pregnancy outcomes or malformation risks.[6] Some monoclonal antibodies are transported across the placenta (and may also enter breast milk) but as REGN10933 and REGN10987 do not have any human targets such exposure should not be associated with risk of harm. Pregnant women, just like other patients with COVID-19, are at significant risk from the infection itself (particularly those in the third trimester.[7, 8] All pregnant women in RECOVERY are entered into the UK Obstetric Surveillance System which follows all pregnancies to their conclusion.[8] Given the early safety experience with REGN10933+REGN10987 it would appear appropriate not to exclude pregnant women from this aspect of the trial (as such exclusion would inhibit the development of treatments for this population).[9]

Aspirin
Aspirin is widely used for the prevention of pre-eclampsia in pregnant women at increased risk of the disease. A recent Cochrane meta-analysis on this topic included seventy-seven trials (40,249 women) taking aspirin at doses between 60 and 150mg daily.[10] In most trials, aspirin was started from 12 weeks' gestation, although a more recent meta-analysis has reported eight trials (1426 women) in which aspirin was initiated in the first trimester.[11] In light of the clear evidence of effectiveness, 75-150mg aspirin is recommended for pre-eclampsia prophylaxis in NICE guidelines for management of hypertension in pregnancy (NG133), and in the NHS England document 'Saving Babies' Lives for women at increased risk of placental dysfunction disorders.[12, 13] There is some ongoing uncertainty as to the optimal dose (75mg vs. 150mg) for pre-eclampsia prophylaxis, but both doses are in widespread clinical use in pregnancy in the UK for these indications and in other conditions (e.g. in pregnant women with antiphospholipid syndrome). Aspirin can be given to pregnant women of any gestation or to breastfeeding women in the RECOVERY trial.

Second randomisation intervention: Tocilizumab
Two pharmaceutical global safety registry database studies have reported on tocilizumab use in pregnancy, including outcomes from 288 pregnancies [14] and 61 pregnancies,[15] typically for rheumatoid or other arthritides, and with the majority having received the drug in the first trimester. These data suggest that the rates of congenital abnormality, spontaneous pregnancy loss and other adverse outcomes were not higher than in the general population.[15] Small studies have shown that tocilizumab is transferred to the fetus with serum concentrations approximately 7-fold lower than those observed in maternal serum at the time of birth.[16] Very low concentrations of tocilizumab are identified in breast milk and no drug is transferred into the serum of breast fed infants.[16, 17] Women should be advised that if treated after 20 weeks' gestation, their infant should not be immunised with live vaccines (rotavirus and BCG) for the first 6 months of life. All non-live vaccinations are safe and should be undertaken.[18]

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