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Cohort profile: The Covid-19 in pregnancy in Scotland (COPS) dynamic cohort of pregnant women to assess effects of viral and vaccine exposures on pregnancy

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Authors:

Sarah J Stock¹ 0000-0003-4308-856X*

Jade Carruthers² 0000-0002-2777-6824

Cheryl Denny² 0000-0003-4616-4732

Jack Donaghy² 0000-0002-6137-1601

Anna Goulding² 0000-0002-1288-3256

Lisa E M Hopcroft² 0000-0002-7022-1322

Leanne Hopkins² 0000- 0002- 7487- 4363

Rachel Mulholland¹ 0000-0003-1020-3373

Utkarsh Agrawal³ 0000-0001-5181-6120

Bonnie Auyeung⁴ 0000-0003-1741-0949

Srinivasa Vittal Katikireddi⁵ 0000-0001-6593-9092

Colin McCowan³ 0000-0002-9466-833X

Josie Murray² 0000-0002-1511-7944

Chris Robertson^{2,7} 0000-0001-6848-5241

Aziz Sheikh¹ 0000-0001-7022-3056

Ting Shi¹ 0000-0002-4101-4535

Colin R Simpson^{8,1} 0000-0002-5194-8083

Rachael Wood² 0000-0003-4453-623X

¹ Usher Institute, University of Edinburgh, Edinburgh, UK.

² Public Health Scotland, UK.

³ School of Medicine, University of St Andrews, St Andrews, UK.

⁴ School of Philosophy, Psychology and Language Sciences, University of Edinburgh, Edinburgh, UK.

⁵ MRC/CSO Social & Public Health Sciences Unit, University of Glasgow, Glasgow, UK.

⁶ Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK.

⁷ Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK.

⁸ School of Health, Wellington Faculty of Health, Victoria University of Wellington, Wellington, New Zealand.

*Corresponding author: Sarah J Stock, Usher Institute, University of Edinburgh

NINE Edinburgh BioQuarter, 9 Little France Road, Edinburgh EH16 4UX

sarah.stock@ed.ac.uk

Key Words: Pregnancy; COVID-19; Miscarriage; Stillbirth; Neonatal Death; Vaccine;

Key features:

- COVID-19 in Pregnancy in Scotland (COPS) is a new national prospective dynamic cohort utilising Scotland's maternity and health care data. It is unique in that it is a national surveillance platform using routinely available population data to capture near-complete pregnancies in Scotland, covering the whole pregnancy from conception to the end of the puerperium for women (41 days postpartum) and the end of the neonatal period (27 days postnatal) for babies.
- COPS was created to describe the epidemiology of COVID-19 in pregnancy, the effect of SARS-CoV-2 infection on pregnancy outcomes and investigate the safety and effectiveness of COVID-19 vaccines among pregnant women. COPS includes all women in Scotland who were pregnant on 1st March 2020 or have subsequently become pregnant and thus could be potentially exposed to SARS-2-CoV or COVID-19 vaccination in pregnancy. The dynamic cohort is updated with new pregnancies and pregnancy outcomes monthly.
- The cohort is generated by linking primary care records to maternity records, national birth and mortality records, other secondary health care data, together with laboratory results and vaccination information. Combining these data sources allows comprehensive capture of the outcomes of all births and all pregnancy losses in women who attended healthcare services (except very early miscarriages where medical or midwifery advice was not sought). Thus, COPS provides a robust platform for the study of viral effects and pharmacoepidemiologic research.
- As of 16th September, 2021, the dynamic cohort included 123,004 women with 134,070 completed or ongoing pregnancies.
- Pre-pandemic outcome rates for analyses can be calculated from an approved retrospective extension of the cohort to 1st January 2015.
- Data are hosted in the Public Health Scotland's (PHS) trusted research environment (TRE). Code and meta-data are available through our study website (1). To access the data, the applicants must submit an enquiry to phs.edris@phs.scot.

Why was the cohort set up?

Understanding the effects of SARS-CoV-2 infection on maternal, pregnancy, and neonatal health is essential to inform public health policy (2, 3). The epidemiology of COVID-19 in pregnancy remains incompletely understood as, to date, most studies have included selected cohorts of pregnant women who have required treatment for COVID-19 rather than population-based data (4-7). SARS-CoV-2 transmission from mother to baby (antenatally or intrapartum) appears to be possible, but the proportion of pregnancies affected and its clinical significance is uncertain (8, 9). Potential effects of the virus on early pregnancy losses, congenital anomalies and fetal growth remain largely un-investigated, whilst studies have reported conflicting findings on associations between COVID-19 and late miscarriage, preterm birth and stillbirth (4, 9).

Understanding the effects of COVID-19 in pregnancy and perinatally at different stages will help inform policy and advice to pregnant women and those considering pregnancy, and provides a platform for studies of long-term effects. It is also essential to inform immunisation strategies via assessing the safety and effectiveness of vaccination in pregnancy. Pregnant women have been largely excluded from clinical trials of COVID-19 vaccines, thus despite pregnant women being considered as a vulnerable group, it was initially unclear whether vaccination should be offered to pregnant women (10, 11), This early lack of clarity regarding vaccine recommendations to pregnant women has contributed to low uptake of COVID-19 vaccination in this group, despite evidence of vaccine effectiveness and safety from observational studies (10,11).

COPS (12) is a sub-study of the EAVE II cohort (Early Pandemic Evaluation and Enhanced Surveillance of COVID-19), an observational study using linked Scottish national data (13-

20), funded by the Medical Research Council and Scottish Government Director-General for Health and Social Care, Tommy's charity and Wellcome Trust.

An overview of the cohort is provided in Figure 1.

Who is in the cohort?

COPS is a national dynamic cohort of all women who were pregnant on, or became pregnant after, 1st March 2020 (12). Ongoing pregnancies are identified from antenatal booking records. Completed pregnancies are identified from general and maternity hospital discharge records, GP records, statutory termination of pregnancy records, and statutory live and stillbirth registrations (see Table 1 for an overview of data sources; a more detailed description of how the pregnancy cohort was set up is available in Appendix S1). Hospital and GP records capture women who have early pregnancy losses (miscarriage, molar pregnancy or ectopic pregnancy) and receive care from a healthcare provider. Women who had a very early pregnancy loss and who do not attend or notify their GP or attend hospital for care will not be included. However, we anticipate that these numbers will be small, as, in Scotland: i) the National Health Service (NHS) provides free healthcare to all women; ii) pregnant women are advised to see their GP or attend an early pregnancy unit if they have any signs of a miscarriage; and iii) clinicians and miscarriage support groups have informed us that only a small minority of women have a miscarriage and do not seek care (21-23). As statutory birth records are used, we capture all births including home births (<2% of births in Scotland), although clinical maternity data may be missing for a proportion of home births. There are no private obstetric services in Scotland.

The cohort is updated monthly, allowing near 'real-time' identification of pregnant and recently pregnant women. There are differences in source data latency to the unified COPS dataset (see Appendix S1), which means that data for the most recent months are most

unstable with potential for missing conceptions and end of pregnancy events; and initial findings may be 'overruled' over time as more detailed records accrue. Data are generally complete for conceptions and end of pregnancy events occurring up to 3-4 months previously.

As of 16th September 2021, the cohort included 123,004 women with 134,070 completed or ongoing pregnancies. We have completed pregnancy outcomes for the first wave COVID-19 cohort, which included women who were pregnant on the 1st March 2020 and those who became pregnant up to 30th June 2020 (n = 60,402 pregnancies). The cohort continues to be updated and the end date depends on the course of the pandemic and requirement to support future pandemic preparedness.

How often have they been followed up?

Data are collected from women throughout their pregnancy to 41 days postpartum, and data on their babies are collected up to the end of the neonatal period (27 days after birth).

Women enter the cohort on identification of a pregnancy from one or more sources of routinely collected healthcare data from primary and secondary care settings (see Table 1). Pregnancy outcome (i.e. ectopic pregnancy, molar pregnancy, miscarriage, termination of pregnancy, stillbirth or live birth) is obtained from the same datasets, and data are linked to a number of other sources (also summarised in Table 1) to investigate maternal demographics and comorbidities. Further information on fetal and neonatal outcomes (congenital anomaly, preterm birth, very preterm birth, small for gestational age, severe small for gestational age, microcephaly, severe microcephaly, low Apgar score, very low Apgar score, Neonatal SARS-CoV-2 infection [see Table S1 for definitions], neonatal mortality and extended perinatal mortality) and maternal outcomes (COVID-19 disease, severe COVID-19 disease

[see Table S1 for definitions], any maternal death, thromboembolic disease, hypertensive disorders of pregnancy) also come from the same datasets.

New pregnant women are added to the cohort and new outcomes are identified at monthly updates. Women who have given birth, and their babies, remain in the cohort. Pregnant women who leave Scotland before pregnancy end will have the pregnancy outcome recorded as unknown, but will remain in the cohort. Linkage through a universal health care identifier (Community Healthcare Index or CHI) will allow further follow-up of women and children unless they leave Scotland permanently.

What has been measured?

The data sources provide comprehensive information on pregnancy, maternal and neonatal outcomes, as well as complications, pre-existing and pregnancy risk factors, clinical vulnerability to COVID-19, COVID-19 diagnosis and vaccination status. An overview of the maternal and pregnancy characteristics and pregnancy and neonatal outcome data that are collected are in Table 2. A high-level summary of other key exposure and outcome data being collected is provided in Supplementary Table S1. Detailed description and definitions of outcomes can be found in the COPS data dictionary (1).

What has it found?

There were 38,106 ongoing pregnancies in Scotland on 1 March 2020. As of the 16th September 2021, data on a further 95,964 pregnancies conceived from 1st March 2020 onwards have been added to the cohort. The COVID-19 first wave cohort with women who were pregnant on 1st March 2020 or who subsequently became pregnant up until 30th June 2020 includes a total of 60,402 pregnancies.

Figure 2 shows gestational age distribution of ongoing pregnancies on 1 March 2020 (panel a) and the conceptions each month from 1st March 2020 onwards (panel b). Figure 3 shows the outcomes of all pregnancies in the dynamic cohort by month of conception. Maternal characteristics, pregnancy and selected neonatal outcomes of the participants in the dynamic cohort to 16th September 2021 and the COVID-19 first wave cohort are shown in Table 2.

The COPS cohort has been linked to COVID-19 vaccination data which show the changing pattern of uptake of COVID-19 vaccinations by pregnant women (24).

What are the main strengths and weaknesses?

To our knowledge, this is the first near complete population level platform capturing all pregnancy outcomes from conception to the end of the puerperium and neonatal period. Linkage of GP records to established birth records and secondary care records has allowed early pregnancy losses to be included. This linkage has enriched the cohort by identifying 4,208 early pregnancy outcomes that are not captured in secondary care records. Linkage to other datasets allows capture of rich data on maternal demographics and comorbidities, COVID-19 disease and COVID-19 vaccination. The potential for future linkage to long term child and maternal healthcare data and primary and secondary care prescription data enables a robust platform for future pharmacoepidemiology studies.

Weaknesses of the cohort include the fact that women with early pregnancy loss who do not seek medical advice will not be included. In addition, clinical maternity data on a proportion of home births (which make up <2% of births overall in Scotland) will not be available, although the births themselves will be included. Although a key strength is that we have population-based data on all women with confirmed or probable COVID-19 in pregnancy, and are not restricted to women and babies admitted to hospital, we acknowledge that

restriction of viral PCR testing early in the pandemic to healthcare workers and patients ill enough to require hospital admission may have limited ascertainment of all cases at that time.

Can I get hold of the data? Where can I find out more?

Data are available to researchers for analysis after securing relevant permissions from the data holders. Enquiries regarding data availability should be directed to phs.edris@phs.scot.

Ethics approval

COPS is a sub-study of EAVE II, using unconsented data, which is covered by National Research Ethics Service Committee, South East Scotland 02 approval reference REC 12/SS/0201: SA 2. COPS has been approved by the Public Benefit and Privacy Panel approval reference 2021-0116. Public Health Scotland and the Chief Medical Officer for Scotland are both (independent) data controllers for the national Abortion Act Scotland (AAS) database of termination of pregnancy notifications, thus the Chief Medical Officer has been informed of the use of AAS records for this study and permission to access to the AAS database was granted.

All permissions to link the datasets were received by 31st August 2020.

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Author Contributorship

SJS, RW, CR and AS contributed to the conception of the study. SJS, DM, EV, CRS, UA, CM, JD, LR, CR, AS, LH, LEMH, AG, JC and RW contributed to the study design. SJS, DM, EV, CRS, UA, CM, LH, JD, LR, CR, AS, RM, SVK and RW contributed to drafting the protocol. JD, AG, CD, LH, LEMH, and JC performed data analysis. SJS, DM, EV, CRS, UA, CM, LH, LR, CR, AS, AG, CD, LEMH, JC, BA and RW interpreted the data and revised the manuscript for important intellectual content. SJS, DM, EV, CRS, UA, CM, LH, JD, LR, CR, AS, AG, CD, LEMH, JC, BA, SVK, and RW gave final approval of the version to be published.

Conflict of interest statement

SJS declares funding (paid to the institution) from NIHR, Wellcome Trust and Tommy's charity during the conduct of this study. AS is a member of the Scottish Government Chief Medical Officer's COVID-19 Advisory Group, NERVTAG's risk stratification subgroup and AstraZeneca's Thrombotic Thrombocytopenic Advisory Group; all roles are unremunerated. CRS declares funding from the Medical Research Council, the National Institute for Health Research, the Chief Scientist Office and the New Zealand Ministry for Business, Innovation and Employment and Health Research Council during the conduct of this study.

Tables

Table 1

Overview of the datasets used to create the cohort

Table 2

Maternal characteristics, pregnancy and selected neonatal outcomes of the participants in the cohort to mid- September 2021 and the COVID19 first wave cohort

Figures

Figure 1 Overview of the creation of the COPS cohort

CHI: Community Health Index; COVID: COVID-19 [Coronavirus disease 2019]; ICU: Intensive Care Unit; COPS: COVID-19 in pregnancy in Scotland.

Figure 2 Gestational age of pregnant women on 1st March 2020 (A) and conceptions each month from 1st March 2020 onwards (B)

Figure 3 Pregnancy outcomes of the dynamic cohort by month of conception as of mid - September 2021

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