C  NSIGN

Covid-19 infectiOn aNd medicineS In preGNancy

Deliverable by the EU PE & PV Research Network under a Framework contract following procurement procedure EMA/2017/09/PE/11 (Lot 4). Study on impact of COVID-19 infection and medicines in pregnancy.

Deliverable 2b: Description of international collaboration in the area of medicines use and effects in COVID-19 affected pregnancies

This document can be referenced as:

Sturkenboom MCJM, Nordeng H, Klungel O, Margulis A, Poblador B, Siiskonen SJ, Perez-Gutthann S, Gardarsdottir H, Rivero E, Jordan S, Lupatelli A, Franzoni C, Engjbom H, Andersen M for the CONSIGN consortium. Description of international collaboration in the area of medicines use and effects in COVID-19 affected pregnancies. December 2020.

Document history

name	version	comments
Miriam Sturkenboom	0.1	1st draft
Hedvig Nordeng, Olaf Klungel, Andrea Margulis, Beatriz Poblador, Satu Siiskonen, Susana Perez-Gutthann, Helga Gardarsdottir, Elena Rivero, Sue Jordan, Angela Lupatelli, Carla Franzoni, Hilde Engjbom, Morten Andersen		edits
Miriam Sturkenboom	1.0	
Miriam Sturkenboom	1.1	Insertion comments from EMA, FDA & Health Canada

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Table of Contents

Executive summary

This document describes ongoing initiatives and opportunities for international collaboration in the area of medicines use and their effects on management of COVID-19 in pregnancy. We will call this CONSIGN-International.

In chapter 1 we start with an overview of the recommendations of key international organizations. We observe that, as of December 2020, evidence provided about impact of COVID-19 on pregnancies differs across international organizations, possibly reflecting the fact that evidence is emerging and it is difficult to give a complete and consistent picture, as yet. Studies may suffer from right censoring (not all outcomes can be observed until sufficient time has elapsed to observe and study outcomes of pregnancies exposed to COVID-19 in the first and second trimesters).

In chapter 2, we list and describe many individual initiatives and networks plus opportunities for collaboration based on 1) secondary use of health care data, which will mostly capture outpatient treatment, and 2) based on primary data collection from health clinics. We did not include initiatives that are based on self-reported pregnancies from women, as these might over-represent pregnancies with adverse perinatal outcomes.

Table 1: Overview of ongoing projects and opportunities (those that have been explored already in green) for collaboration by country and type of data collection. Orange: identified & connected but not yet asked (as per December 2020)

Continent	Country	Study /network Name	Primary data collection	Secondary use of EHR	Approach to collaboration
North America	USA	Sentinel		x	FDA/Harvard Pilgrim Health Care Institute
	USA	VSD		x	CDC: Shimakaburo
	USA	CDC surveillance (SET-NET)	x		CDC
	USA	Washington state COVID-19	x		Emily Smith MA
	USA	NICHD MFMU	x		Emily Smith MA/Diana Bianchi
	Canada	CNODES		x	Health Canada/McGill
	Canada	CANCOVID	x		Emily Smith MA
South & middle America	Chile	Gestocovid	x		Emily Smith MA
	Colombia	Recogest	x		Emily Smith MA
	Suriname	INOSS			CONSIGN
Europe	Netherlands	INOSS	x		CONSIGN
	Norway	INOSS/U Oslo	x	x	CONSIGN
	Sweden	INOSS/KI	x	x	CONSIGN
	Denmark	INOSS/Aarhus	x	x	CONSIGN
	Germany	GEPARD		x	CONSIGN
	Italy	INOSS/ARS	x	x	CONSIGN
	Iceland	INOSS	x		CONSIGN
	Ireland	ROI-COVID-19	x		
	Finland	INOSS	x		CONSIGN
	Romania	INOSS	x		CONSIGN
	Slovakia	INOSS	x		CONSIGN
	Belgium	INOSS	x		CONSIGN
	France	INOSS/BPE (SNDS data)	x	x	CONSIGN
	UK	INOSS/Swansea	x	x	CONSIGN
	Spain	Madrid hospital based registry			Emily Smith MA
		FISABIO		x	CONSIGN
		Aragon		x	CONSIGN
		CatOSS	x		CONSIGN
		Obs COVID	x		
Africa	Kenya		x		Emily Smith MA

	Mali	CCV	x		Emily Smith MA
	Uganda	PERICOVID			Emily Smith MA
	Malawi	PERICOVID			Emily Smith MA
	The Gambia	PERICOVID			Emily Smith MA
	Mozambique	PERICOVID			Emily Smith MA
	Kenya	PERICOVID			Emily Smith MA
	Ethiopia	INOSS			CONSIGN
	Ghana	INOSS			CONSIGN
	South Africa	INOSS			CONSIGN
Oceania	New Zealand	CHOPAN	x		Emily Smith MA
		INOSS	x		
	Australia	CHOPAN			Emily Smith MA
		INOSS			
Asia	China and HK COVID Registry	China	x		Emily Smith MA
		Hong Kong	x		Emily Smith MA
	India	PREGCOVID	x		
Multiple continents		COVI-PREG	x		CONSIGN
		INOSS	x		CONSIGN
		NICHD network	x		Emily Smith MA/Diana Bianchi
		InterCOVID	x		
		OHDSI		x	Talita Duarte Salles

This table shows that CONSIGN international is in contact with a large number of the key investigators/data collections, and also that there are still initiatives to reach out to.

In chapter 3, we summarize the proposal to move forward and the potential approaches. CONSIGN-international will focus on two key objectives

1) Use of medicines to treat COVID-19 in pregnancy
2) Effects of medicines used to treat COVID-19 in pregnancy on pregnancy, perinatal and neonatal outcomes.

Based on our review and to our best knowledge no initiative is specifically focusing on the impact of medicines in COVID-19 affected pregnancies, and collaboration would have great benefits to learn more about the treatments used and their effects on pregnancy outcomes.

In short: analysis plans need to be shared, sites need to agree to participation, common data need to be mapped, and funding to support the work needs to be identified.

1. Current statements from international organizations

The topic of COVID-19 and pregnancy is well debated and the focus of many scientific articles as well as policies and recommendations. A review of current public recommendations as of Dec 11, 2020 and evidence shows there is heterogeneity in conclusions, evidence listed and recommendations, US reports that pregnant women are at higher risk of severe illness whereas European organizations do not state this.

We list the current statements (mostly verbatim) thus all should be between quotes

European Center for Disease Control & prevention (ECDC)[1] public statement
Are pregnant women more at risk than adults of similar age? Can the virus be transmitted to the baby?

- Pregnant women are not more at risk of developing COVID-19 or suffering from a more severe disease than other adults of similar age.
- There is no evidence that the virus can be transmitted to the unborn child during pregnancy, or during childbirth.
- Babies and young children are known to only experience mild forms of COVID-19.

National Health Service (UK)[2] public statement

- There's no evidence that pregnant women are more likely to get seriously ill from coronavirus
- But pregnant women have been included in the list of people at moderate risk (clinically vulnerable) as a precaution.
- This is because pregnant women can sometimes be more at risk from viral diseases like the flu.
- It's not clear if this happens with coronavirus. But because it's a new virus, it's safer to include pregnant women in the moderate-risk group.
- It may be possible for a pregnant woman to pass coronavirus to her baby before the baby is born. But when this has happened, the babies have got better.
- There's no evidence that coronavirus causes miscarriage or affects how a baby develops in pregnancy.

RCOG[3] public statement

The clinical evidence relating to the risks of coronavirus (COVID-19) infection and pregnancy is contained within the substantive Coronavirus (COVID-19) infection in pregnancy clinical guidance available on the RCOG website. It is important to note that:

- Pregnant women of any gestation are at no more risk of contracting the virus than any other non-pregnant person who is in similar health
- For those women who are 28 weeks pregnant and beyond, there is an increased risk of becoming severely ill should you contract COVID-19 (this is true of any viral illness contracted, such as flu).

US CDC[4] public statement

- Based on what we know at this time, pregnant people are at an increased risk for severe illness

[1] https://www.ecdc.europa.eu/sites/default/files/documents/Leaflet-Covid-19_pregnant-women.pdf (accessed Dec 11, 2020)
[2] https://www.nhs.uk/conditions/coronavirus-covid-19/people-at-higher-risk/pregnancy-and-coronavirus/
[3] https://www.rcog.org.uk/globalassets/documents/guidelines/2020-09-10-occupational-health-statement-rcog-rcm-fom.pdf
[4] https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fspecial-populations%2Fpregnancy-data-on-covid-19.html#pregnant-population

from COVID-19 compared to non-pregnant people.
- Pregnant people with COVID-19 might be at increased risk for other adverse outcomes, such as preterm birth.

CDC reports that much is still unknown about the risks of COVID-19 to newborns born to mothers with COVID-19. We do know that:

- Infections causing COVID-19 in newborns born to mothers with COVID-19 are uncommon.
- Some newborns have tested positive for the virus that causes COVID-19 shortly after birth. It is unknown if these newborns got the virus before, during, or after birth from close contact with an infected person.
- Most newborns who tested positive for the virus that causes COVID-19 had mild or no symptoms and recovered. However, there are a few reports of newborns with severe COVID-19 illness.
- Preterm birth (birth at less than 37 completed weeks gestation) and other problems with pregnancy and birth have been reported among women who tested positive for COVID-19 during pregnancy. It is unknown whether these problems were related to the virus that causes COVID-19.

American College of Obstetricians and Gynecologists[5] public statement

- Available data suggest that symptomatic pregnant women with COVID-19 are at increased risk of more severe illness compared with nonpregnant peers (Ellington MMWR 2020 (CDC surveillance n=23,434), Collin 2020 (Sweden n=53), Delahoy MMWR 2020 (COVID-NET: n=598 hospitalized cases), Panagiotakopoulos MMWR 2020 (VSD n=105), Zambrano MMWR 2020 (CDC surveillance n=23,434).
- Given the growing evidence, CDC now includes pregnant women in its "increased risk" category for COVID-19. Specifically, these data indicate a small but significant risk of ICU admissions, mechanical ventilation, and death reported in pregnant women with symptomatic COVID-19, when compared with symptomatic non-pregnant women (Zambrano MMWR 2020).
- Pregnant patients with comorbidities such as obesity and gestational diabetes may be at an even higher risk of severe illness consistent with the general population with similar comorbidities (Ellington MMWR 2020, Panagiotakopoulos MMWR 2020, Knight 2020 (UKOSS see 4), Zambrano MMWR 2020).
- Analyses so far are limited by a large amount of missing data. Similar to the general population, Black and Hispanic individuals who are pregnant appear to have disproportionately high SARS CoV-2 infection and death rates (Ellington MMWR 2020, Moore MMWR 2020, Zambrano MMWR 2020).

Although these data from the CDC suggest an increase in risk of severe outcomes in pregnant women with symptomatic SARS-CoV-2 infection, the absolute risk is still substantially lower than that of pandemic H1N1 influenza infection during pregnancy. During the H1N1 influenza pandemic, pregnant women made up 5% of deaths, despite only making up 1% of the population and pregnancy risk of ICU admission was reported as high as a 7-fold increase (Rasmussen 2012; Mosby 2011). ACOG recognizes the critical need for further analysis and peer review literature on SARS-CoV-2 infection during pregnancy.

WHO[6] public statement

- Pregnant women or recently pregnant women who are older, overweight, and have pre-existing medical conditions such as hypertension and diabetes seem to have an increased risk

[6] https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-pregnancy-and-childbirth

of developing severe COVID-19. When pregnant women develop severe disease, they also seem to more often require care in intensive care units than non-pregnant women of reproductive age.

- Due to changes in their bodies and immune systems, we know that pregnant women can be badly affected by some respiratory infections. It is therefore important that they take precautions to protect themselves against COVID-19, and report possible symptoms (including fever, cough or difficulty in breathing) to their healthcare provider.

2.Data collections and opportunities for collaboration

CONSIGN implements various analyses to estimate the use of medicines and their effects in COVID-19 affected pregnancies to guide decision-making by EMA and its committees about vaccine indications, vaccination policies, and treatment options for COVID-19 disease and associated complications.

CONSIGN builds on ongoing primary data collections in the EU initiated COVI-PREG and INOSS networks, and secondary use of data based on the IMI-funded ConcePTION tools and network.

Rationale for collaboration
Based on initial publications from UKOSS & NETHOSS, we know that medicines use specific for COVID-19 in pregnant women is quite infrequent and changing over time, collaboration to assess the impact of medicines is therefore very important.

UKOSS reports on first (March-mid April 2020) 427 hospitalized pregnancies with COVID-19
"Nine (2%) women were treated with an antiviral agent. Eight of them were given oseltamivir, one of whom also received lopinavir/ritonavir. One woman was given remdesivir. All women managed with antivirals were discharged home. Sixty-four (15%) women were given corticosteroids for fetal lung maturation, of whom 47 (73%) had given birth".

ItOSS reports on 147 hospitalized pregnancies with COVID-19 (25 February to 22 April)
72 women received various combinations of hydroxychloroquine, antivirals, antibiotics and antenatal corticostereoids. Seven women were admitted to intensive care units, all were discharged home[7].

NETHOSS update Dec 4, 2020[8]
NETHOSS reports on their website that 3057 cases have been notified, information has been obtained on 2614 women, 208 were treated (8%), 68 received antibiotics, 5 received antivirals such as tamiflu or remdesivir, 3 women received dexamethasone.

OHDSI network analysis[9]
Data from an OHDSI network analysis up to June 2020, including US, French and Spanish data, showed in hospital treatment in hospitalized women in USA (Optum database) to be azithromycin (18.1%) and hydroxychloroquine (5.1%). Conversely, the use of adjunctive therapies in hospital were common, including systemic corticosteroids (29.6%), anti-thrombotics (enoxaparin [24.0%,] heparin [15.8%] and aspirin [7.0%]), famotidine (20.9%), immunoglobulins (21.4%), and additional antibiotics (ceftriaxone [7.9%] and amoxicillin [3.5%]). Other data sources had no information on in-hospital treatment.

[7]Maraschini A, Corsi E et al. Observational Study Italy Ann Ist Super Sanita. 2020 Jul-Sep;56(3):378-389. doi: 10.4415/ANN_20_03_17.
[8] https://www.nvog.nl/actueel/registratie-van-covid-19-positieve-zwangeren-in-nethoss/
[9] https://www.medrxiv.org/content/10.1101/2020.10.13.20211821v1.full-text

Many organizations and initiatives are collecting information on COVID-19 in pregnancy. Data collections on self- reported pregnancies are not included because of the risk of selection and misclassification.

2.1 Population based electronic health care databases

CONSIGN is to our knowledge the only initiative focusing on medicines evaluation in COVID-19 affected pregnancies; all other studies appear to be focusing on disease impact. In our view this, combined with the limited numbers of pregnant women treated with individual medicines, strengthens the case for collaborating internationally.

2.1.1 FDA: Sentinel projects on COVID-19

Through the International Collaboration for Medical Regulatory Agencies (ICMRA), FDA has announced to have an interest to participate in a collaboration on the effects of medicines in pregnancies through the Sentinel system. Interest was also expressed by Harvard Pilgrim Health Care.

According to the Sentinel website Sentinel is comprised of health care organizations in the United States, known as Data Partners, that have medical billing information and electronic health records. This data is collected routinely with every healthcare encounter and is used to answer FDA's medical product safety questions. Each Data Partner keeps their own data and controls who can access it. Each Data Partner runs analyses through a script and sends the deidentified results to the Sentinel Operations Center. The Sentinel System's distributed approach maintains patient privacy and data security[10]. The Sentinel Distributed Database has a total of 351.8 million unique patient identifiers spanning the 2000 to 2020 time period. If patients move between health plans, they may have more than one patient identifier. 228.7 million patients have at least one day of drug and medical coverage.

Pregnancies: The Sentinel Distributed Database contains 5.1 million live birth deliveries with a mother-infant linkage, the algorithm to detect pregnancy cases is based on the identification of only live birth[11]

COVID-19 work by Sentinel: Most of the Sentinel COVID-19 activities relate to coagulopathies, natural history of COVID-19 disease and treatment[12]. There is currently no published project on COVID-19 & pregnancy on the Sentinel website (Dec 11, 2020).

Opportunity for collaboration: to discuss the WP1 protocol and ask for implementation in Sentinel, with pooling of estimates in a meta-analysis, and exploration whether pregnancy algorithm will be extended to capture also non-live births.

2.1.2 Health Canada and CNODES

Through the International Collaboration for Medical Regulatory Agencies, Health Canada has announced to have an interest to participate in a collaboration on the effects of medicines in pregnancies potentially through DSEN network. The Drug Safety and Effectiveness Network (DSEN) is a pan-Canadian network of independent investigators established as a partnership between the Canadian Institutes of Health Research (CIHR) and Health Canada. DSEN has the mandate, expertise

[10] https://www.sentinelinitiative.org/about/how-sentinel-gets-its-data
[11] https://www.sentinelinitiative.org/methods-data-tools/methods/identification-pregnant-women-sentinel-distributed-database-and
[12] https://www.sentinelinitiative.org/assessments/coronavirus-covid-19?page=1

and capacity to systematically conduct "real-world" drug safety and effectiveness research required by decision makers. This group has the potential to be leveraged for work related to COVID-19 infection and medicines on pregnancy in the future, the Canadian Network for Observational Drug Effect Studies (CNODES), a project of DSEN has built an extensive network of over 100 scientists, including pharmaco-epidemiologists, clinicians, statisticians, data analysts and other researchers to ensure the safety and effectiveness of drugs for Canadians. By establishing partnerships and negotiating data access with each province, CNODES studies have access to administrative healthcare data on millions of medicine users across the country as well as internationally: the UK CPRD and the US MarketScan. CNODES is funded by the Canadian Institutes of Health Research (CIHR, Grant #DSE – 146021)[13]. The work at CNODES uses population databases from seven Canadian provinces and two international databases (UK CPRD and US MarketScan), with additional databases from the Atlantic provinces on the way. Altogether, these databases include over 100 million patients[14].

Data availability is listed in the table below (obtained from CNODES website)

	BC	AB	SK	MB	ON	QC	NS	NL	CPRD	MSCAN
Health insurance registry	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Long-term care residents	✓	✓	✓	✓	✓	✓	✓	✓		✓
Prescription drug data	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hospital service data	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physicians claims	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cancer registry			✓	✓	✓		✓		✓	
Vital statistics	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Emergency data	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Laboratory data	✓	✓	✓	✓	✓			✓	✓	✓
Imaging data	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Linked survey data	✓	✓	✓	✓	✓			✓	✓	
Pregnancy data	✓			✓	✓		✓	✓	✓	

Figure 1: Available data for the different CNODES sites

Pregnancies: Pregnancy data are available in 5 of the 8 provinces. A study on isotretinoin and pregnancy has been conducted in CNODES, with data from 4 provinces. Pregnancies were identified by code lists focusing on the end of pregnancy[15]

COVID-19 work by CNODES: There is currently no project on COVID-19 & pregnancy listed on the CNODES website (Dec 11, 2020).

[13] Suissa S, Henry D, Caetano P, Dormuth CR, Ernst P, Hemmelgarn B, Lelorier J, Levy A, Martens PJ, Paterson JM, Platt RW, Sketris I, Teare G; Canadian Network for Observational Drug Effect Studies (CNODES). CNODES: the Canadian Network for Observational Drug Effect Studies. Open Med. 2012 Oct 30;6(4):e134-40. PMID: 23687528; PMCID: PMC3654509.
[14] https://www.cnodes.ca/about/data-sources/
[15] https://www.cmaj.ca/content/cmaj/suppl/2016/04/25/cmaj.151243.DC1/151243-res-1-at.pdf

Opportunity for collaboration: to discuss the WP1 protocol and ask for implementation in CNODES, with pooling of estimates in a meta-analysis. There is precedent for collaboration between the EU PE&PV research network and CNODES.

The EU PE&PV research network completed an EMA tendered study on the risk of bleeding in users of direct oral anticoagulants (DOACs). This study has also been extended in a collaboration between EMA and Health Canada. The CNODES investigators have replicated the common protocol (EUPAS16014) of the EU PE&PV research network on DOACs and the results have recently been assessed by the CHMP (EMA Press release 27/03/2020)

- Rottenkolber M, Schmiedl S, Ibánez L, Sabaté M, Ballarín E, Vidal X, Leon-Muñoz LM, Huerta C, Martin Merino E, Montero D, Gasse C, Andersen M, Aakjaer M, De Bruin ML, Gerlach R, Tauscher M, Souverein PC, van den Ham R, Klungel O, Gardarsdottir H; PE&PV consortium. Prescribers' compliance with summary of product characteristics of dabigatran, rivaroxaban and apixaban-A European comparative drug utilization study. Basic Clin Pharmacol Toxicol. 2020 Oct 10. doi: 10.1111/bcpt.13517. Epub ahead of print. PMID: 33037766.,
- Souverein PC, van den Ham HA, Huerta C, Merino EM, Montero D, León-Muñoz LM, Schmiedl S, Heeke A, Rottenkolber M, Andersen M, Aakjaer M, De Bruin ML, Klungel OH, Gardarsdottir H. Comparing risk of major bleeding between users of different oral anticoagulants in patients with nonvalvular atrial fibrillation. Br J Clin Pharmacol. 2020 Jul 6. doi: 10.1111/bcp.14450. Epub ahead of print. PMID: 32627222.
- Ibáñez L, Sabaté M, Vidal X, Ballarin E, Rottenkolber M, Schmiedl S, Heeke A, Huerta C, Martin Merino E, Montero D, Leon-Muñoz LM, Gasse C, Moore N, Droz C, Lassalle R, Aakjaer M, Andersen M, De Bruin ML, Groenwold R, van den Ham HA, Souverein P, Klungel O, Gardarsdottir H. Incidence of direct oral anticoagulant use in patients with nonvalvular atrial fibrillation and characteristics of users in 6 European countries (2008-2015): A cross-national drug utilization study. Br J Clin Pharmacol. 2019 Nov;85(11):2524-2539. doi: 10.1111/bcp.14071. Epub 2019 Sep 4. PMID: 31318059; PMCID: PMC6848911.).
- Arlett P, Kurz X, Soltys K, Blum MD. International Collaboration in Real-World Evidence Generation for Direct Acting Oral Anti-Coagulants. Clin Pharmacol Ther. 2020 Aug 28:10.1002/cpt.1999. doi: 10.1002/cpt.1999. Epub ahead of print. PMID: 32857416; PMCID: PMC7461174.

CNODES is now moving towards use of the Sentinel CDM, which can also be mapped to ConcePTION for running of scripts.

2.1.3 MHRA & CPRD

Through the International Collaboration for Medical Regulatory Agencies, MHRA has announced to have an interest to participate in a collaboration on the effects of medicines in pregnancies potentially through the CPRD system.

Clinical Practice Research Datalink (CPRD) is a real-world research service supporting retrospective and prospective public health and clinical studies. CPRD is jointly sponsored by the Medicines and Healthcare products Regulatory Agency and the National Institute for Health Research (NIHR), as part of the Department of Health and Social Care.

CPRD collects anonymised patient data from a network of GP practices across the UK. Primary care data are linked to a range of other health related data to provide a longitudinal, representative UK population health dataset. The data encompass 50 million patients, including 16 million currently registered patients.

Pregnancies: A pregnancy algorithm was recently published by Minassian et al. focusing on multiple steps, starting with the identification of delivery or pregnancy losses. The algorithm identified 5.8

million pregnancies among 2.4 million women in CPRD GOLD[16]

COVID-19 work by CPRD: There are special facilities to rapidly conduct COVID-19 research

Opportunity for collaboration: to discuss the CONSIGN WP1 protocol and ask for implementation in CPRD, with sharing of results or pooling of estimates in a meta-analysis. CPRD has been mapped to ConcePTION CDM in the ConcePTION and ACCESS projects.

2.1.4 CDC and VSD

The Vaccine Safety Datalink (VSD) is a collaboration between CDC's Immunization Safety Office and nine U.S. health care organizations serving more than 12 million persons each year. It recently published a first analysis on pregnancy & COVID-19. Hospitalizations with a patient diagnosis of COVID-19 were identified using COVID-19 International Classification of Diseases, Tenth Revision, Clinical Modification, (ICD-10-CM) and site-specific internal diagnosis codes during March 1–May 30, 2020. Pregnant women were identified using a validated algorithm based on ICD-9 diagnosis and procedure codes that has been modified for ICD-10[17]. For this study, medical records of women hospitalized with COVID-19 were reviewed by abstractors and adjudicated by a physician to identify the primary reason for hospital admission, pregnancy characteristics, COVID-19 complications, and birth outcomes among women who delivered before July 31, 2020.

Opportunity for collaboration: to discuss the WP1 protocol and ask for implementation in VSD, with sharing of results or pooling of estimates in a meta-analysis. VSD CDM can be mapped to ConcePTION CDM quite easily as the structures do not differ too much.

2.1.5 Nordic Coherence

The Nordic Collaborative Health Register Network for Covid-19 Epidemiology (Nordic COHERENCE)
Is an internationally unique multi-country database network with data from healthcare registers in Denmark, Norway, Sweden and Scotland with the purpose of conducting epidemiological studies on Covid-19. Focus in COHERENCE will be on risk factors for severe Covid-19 (disease leading to hospitalisation, intensive care or fatal outcome), identifying vulnerable populations and characterising the disease course, also pertaining to long-term sequelae among survivors of severe Covid-19. Additionally, COHERENCE will investigate collateral effects of the pandemic on healthcare and drug utilisation in the general population to assess secondary effects on public health.

Opportunity for collaboration:
All of the listed Nordic countries are participating in CONSIGN WP1, except for Scotland. We will explore that option.

2.1.6 OHDSI

The Observational Health Data Sciences and Informatics (or OHDSI, pronounced "Odyssey") program is a multi-stakeholder, interdisciplinary collaborative to bring out the value of health data through large-scale analytics. OHDSI has established an international network of researchers and observational health

[16] Minassian C, Williams R, Meeraus WH, Smeeth L, Campbell OMR, Thomas SL. Methods to generate and validate a Pregnancy Register in the UK Clinical Practice Research Datalink primary care database. Pharmacoepidemiol Drug Saf. 2019 Jul;28(7):923-933. doi: 10.1002/pds.4811. Epub 2019 Jun 13. PMID: 31197928; PMCID: PMC6618019.
[17] Naleway AL, Gold R, Kurosky S, et al. Identifying pregnancy episodes, outcomes, and mother-infant pairs in the Vaccine Safety Datalink. Vaccine 2013;31:2898–903

databases with a central coordinating center housed at Columbia University[18]. Much of the initiation and maintenance was supported by Janssen Research. Currently data from more than 19 countries have been mapped to OMOP common data model, which allow the community to conduct research together.

Data sources who have converted their data into the OMOP common data model, may participate in network studies. The community is open to subscribe to studies.
As part of the COVID-19 response an initial study on pregnancy was conducted, using two European databases (SIDIAP and French IQVIA database).

Opportunity for collaboration: to discuss the WP1 protocol and ask for implementation in OHDSI, with sharing of results or pooling of estimates in a meta-analysis. OMOP CDM can be mapped to ConcePTION CDM quite easily as the structures do not differ too much.

2.2 Case based primary data collections on pregnancy & COVID-19

2.2.1 COVI-PREG

The purpose of COVI-PREG is:

- to launch a prospective structured data collection to allow future research projects leading to a better characterization of the risks associated to SARS-CoV-2 infection in pregnancy.
- to create a responsive data collection system through a health care facilities network to ensure a rapid assessment of the risks linked to future emergent pathogens.

Inclusion criteria:

- any pregnant patient SUSPECTED OF SARS-CoV-2 infection during pregnancy.

Exclusion criteria:

- patients considered as minor in their jurisdiction
- patients who have not given their informed consent
- patients not able to consent for themselves

The data collected and coded will be made available to any research group in the world following the data-sharing agreement initiative, provided that they have a clear, non-redundant research question and a biomedical research Ethics committee approval (a list of on-going research projects will be kept available). Anyone supporting the registry by providing well-documented cases will be listed as a collaborator of the COVI-PREG registry in any future peer reviewed scientific publication having used data from the registry[19].

The global network which was established as part of the Zika investigations and has been repurposed for COVID-19 is described in a publication by Panchaud et al[20]. Figure 2 below shows the distribution of health care facilities as of April 2020.

[18] https://ohdsi.org
[19] https://www.chuv.ch/fr/dfme/dfme-home/recherche/femme-mere/materno-fetal-and-obstetrics-research-unit-prof-baud/covi-preg
[20] Panchaud, AliceAnn-Christin, Tallarek et al. An international registry for emergent pathogens and pregnancy The Lancet, Volume 395, Issue 10235, 1483 - 1484

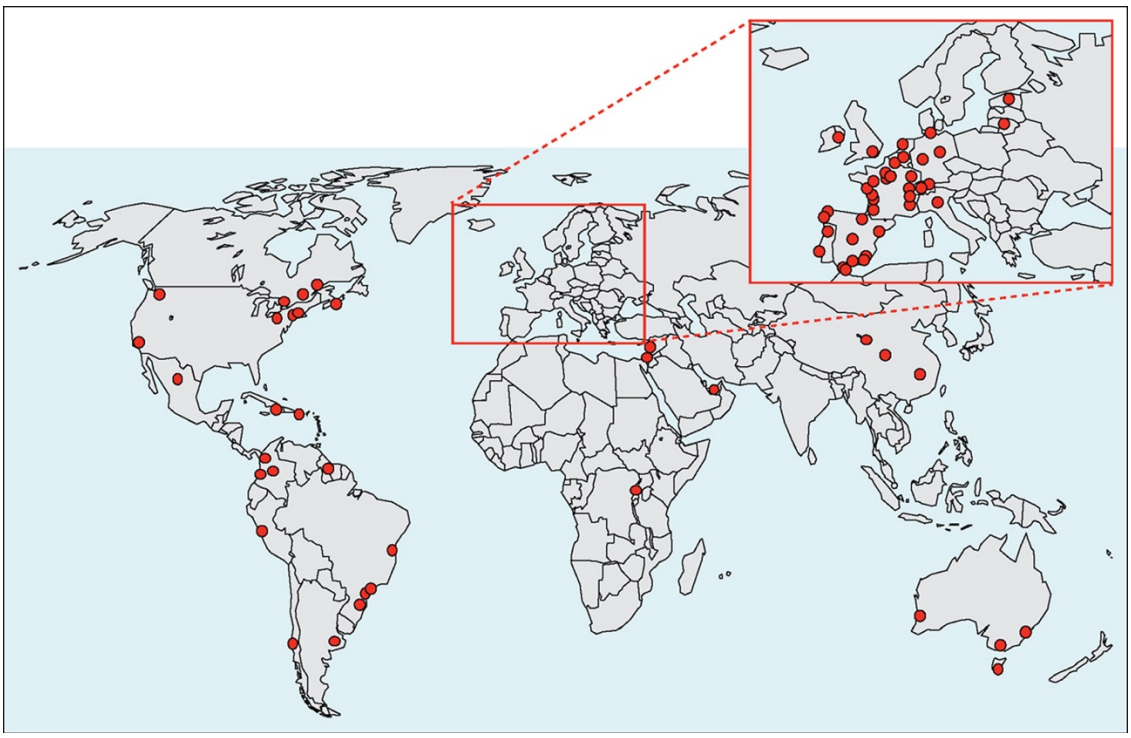

Figure 2: Participating facilities in COVI-PREG (from Panchaud et al. Lancet 2020)

Opportunity: COVI-PREG initiators are members of the CONSIGN project. Data from sites are shared in REDCAP that is held in University Lausanne. Data from across the world can be included in WP3 analyses directly conditional on the approval of the site and listing as co-author.

Data collected: data code book is available from the following link
Study population: Pregnant women who are tested for SARS-CoV-2 infection within facilities with antenatal clinics following their pregnancy. The women are followed from the recruitment visit (baseline) until 6 months after birth.

Data collection
Data is collected at each visit.
Enrolment: Baseline demographics: age, marital status, ethnicity, education, country of residence, region of residence
SARS-CoV-2 maternal testing: date performed, result, other tests performed (influenza, respiratory-syncytial virus)
Ongoing pregnancy information: date of last menstrual period, gestational age at enrolment, gravidity, parity, multiple gestation, first trimester screening date and results
Maternal comorbidities: BMI, diabetes (pre-gestational, gestational with or without medicine), thyroid function imbalances, hypertension, coronary heart disease, chronic obstructive lung disease, other illness, alcohol-tobacco-recreational drug used during pregnancy, maternal medicines
Maternal serological and immunization status when available at enrolment: toxoplasmosis, cytomegalovirus, varicella zoster virus, herpes simplex virus, rubella, syphilis, HIV, hepatitis C, hepatitis B, lymphocytic choriomeningitis virus, influenza vaccine, pertussis vaccine
Maternal and neonatal genetic testing when available at enrolment: trisomy screening, non-invasive prenatal testing (i.e. analysis of foetal DNA in maternal blood), invasive genetic testing performed (amniocentesis, chorionic villus sampling)
Follow-up: SARS - CoV-2 testing, Amniotic fluid testing: date performed, result Placenta testing: date performed, result Products of foetal loss if applicable: date performed, result

New-born testing: date performed, result Human Milk: date performed, result
Maternal outcomes: Abnormal lab result: thrombocytopenia, lymphocytopenia, anaemia, C-reactive protein, lactate dehydrogenase U/L (>245), ALT, U/L (>40)
Imaging: X-ray, CT scan, MRI (Date, result)
COVID-19 treatment: antiviral (name, duration), antibiotic (name, duration), corticosteroids (name, duration), chloroquine (yes, no, duration), intravenous immunoglobulin (name, duration), Hospital admission (yes, no, duration, time from illness onset), High-flow nasal cannula oxygen therapy (yes, no, duration, time from illness onset), ICU admission (yes, no, duration, time from illness onset), non-invasive mechanical ventilation (yes, no, duration, time from illness onset), invasive mechanical ventilation (yes, no, duration, time from illness onset), ECMO (duration, time from illness onset), renal replacement therapy ((yes, no, duration, time from illness onset),
Complication: sepsis, respiratory failure, acute respiratory distress syndrome, heart failure, septic shock, coagulopathy, renal failure, and disseminated intravascular coagulopathy, other
Pregnancy outcomes: multiple gestation, pregnancy termination (elective or spontaneous), stillbirth, preterm
Prenatal imaging: dating US results and measurements, subsequent US results and measurements, if abnormal: IUGR type, anomalies (description)
Infant outcomes: gestational age at delivery, mode of delivery, sex, weight, height, OFC, APGAR scores, umbilical arterial and venous blood pH, physical examination (if abnormal, neurological exam, splenomegaly, hepatomegaly, congenital malformation, NICU admission, feeding method and other immediate outcomes). The Ages and Stages Questionnaire (third edition) scores for communication, motor, problem solving and social development and child health outcomes at 6 months.
Imaging and further investigations: blood count results, screening for other infectious diseases, magnetic resonance imaging, other abnormalities
Early neurodevelopmental outcomes: Mothers will provide information on their child's development at 6 months of age.

2.2.2 INOSS

The International Network of Obstetric Survey Systems (INOSS) is a multi-country collaboration formed to facilitate studies of uncommon and severe complications of pregnancy and childbirth. Collaborations such as INOSS offer many benefits in the study of rare complications. The use of uniform case definitions, common datasets, specifically collected detailed data and prospectively agreed comparative and combined analyses all add to the validity of studies and their utility to guide policy and clinical practice and hence improve the quality of care. Such multi-national collaborations allow for the conduct of robust studies less subject to many of the biases attributed to typical observational studies. For very rare conditions such collaborations may provide the only route to providing high quality evidence to guide practice[21]

Opportunity: as part of the CONSIGN work Individual Patient Data Meta-analysis of the International Network of Obstetric Survey Systems (INOSS) population-based data in 18 countries (12 in Europe) on maternal and perinatal outcomes of COVID-19 disease can be pooled on individual level upon a clear data management plan. The study population in INOSS member countries in Europe will be approximately 2 million births per year, by the end of 2020 we estimate approximately 8000 cases in these countries.

Europe

[21] Knight M; INOSS. The International Network of Obstetric Survey Systems (INOSS): benefits of multi-country studies of severe and uncommon maternal morbidities. Acta Obstet Gynecol Scand. 2014 Feb;93(2):127-31. doi: 10.1111/aogs.12316. Epub 2013 Dec 30. PMID: 24382256.

- NOSS Denmark (Professor Lone Krebs, Dr Anna Aabakke)
- NOSS Finland (Professor Maija Jakobsson, Dr Outi Äyräs)
- NOSS Norway (Professor Kari Klungsøyr, Dr. Hilde Marie Engjom)
- NOSS Sweden (Professor Karin Källén, Dr Teresia Svanvik)
- NOSS Iceland (Dr Eva Jonasdottir)
- ROSS Romania (Dr. Lucian Puscasiu
- SOSS Slovakia (Dr. Alexandra Kristufkova
- B.OSS Belgium (Dr. Griet VandenBerghe,
- ITOSS Italy (Dr. Serena Donati)[22] (approx. 1500 cases as of Dec 13)
- CatOSS, Spain (Dr Montse Palacio) (approx. 500 cases pr 2 Oct)
- NETHOSS Netherlands (Professor Kitty Bloemenkamp, Professor Thomas van den Akker, Dr Ageeth Schonewille-Rosman[23] (as of Dec 4, 3057 cases)
- France, INSERM (Dr. Catherine Deneux-Tharaux)
- UKOSS United Kingdom (Professor Marian Knight, NPEU, University of Oxford) approx. 3000 cases pr 13 Dec)

Non-EU

- AMOSS Australia (Professor Elisabeth Sullivan)
- EthOSS Ethiopia (Dr. Abera Kenay Tura, Dr. Delayehu Bekele)
- GHANOSS Ghana (Dr. Emmanuel Srofenyoh)
- AMOSS New Zealand (Dr. Clare McLintock)
- SAOSS South Africa (Professor Salome Maswime, Dr. Laura Yates, Dr. Samantha Budhram)
- SUROSS Suriname (Dr. Lachmi Kodan, Dr. Kim Verschueren)

Data collection: In INOSS Covid-19 data is collected in a standardized fashion using the CRF that has been defined at the start of the pandemic by UKOSS. Any woman admitted to hospital (as inpatient or ambulatory care) with confirmed COVID-19 infection in pregnancy is eligible. Data is collected when the women is admitted and completed at the end of the pregnancy.

Baseline data: age, marital status, ethnicity, country of residence, employment, height weight, smoking Previous medical history: Asthma, other comorbidities, influenza vaccinations
Pregnancy information: estimated date of delivery, gravidity, prior problematic pregnancies, parity, multiple gestation, hospitalization
Diagnosis of COVID-19: symptoms, virological tests, imaging, source contact
Treatments in hospital: antiviral medicines, other medicines, steroids for foetal lung maturation, ECMO, SARS - CoV-2 testing,
Amniotic fluid testing: date performed, result Placenta testing: date performed, result Products of foetal loss if applicable: date performed, result
Delivery: miscarriage, termination, induction, caesarean section Pregnancy outcomes: multiple gestation, pregnancy termination (elective or spontaneous), stillbirth, preterm
Maternal outcomes: level 3 critical care, major maternal morbidity, death
Infant outcomes: gestational age at delivery, mode of delivery, sex, weight, height, OFC, APGAR scores, NICU admission, COVID-19, congenital anomalies, death

2.2.3 CDC surveillance

Surveillance for Emerging Threats to Mothers and Babies network collects information on pregnant

[22] https://www.medrxiv.org/content/10.1101/2020.06.11.20128652v1.full.pdf+html
[23] https://www.nvog.nl/actueel/registratie-van-covid-19-positieve-zwangeren-in-nethoss/

women and their children through the first 3 years of life[24]. This system aims to figure out how health threats, such as COVID-19, hepatitis C, syphilis, and Zika, affect these populations. It may also track congenital anomalies, developmental problems, and other disabilities as these children age. CDC scientists use these data to:

- Monitor and improve the health of pregnant women and infants;
- Link families to medical and social services to get recommended care;
- Strengthen laboratory and clinical testing to find emerging health threats quickly; and
- Ensure public health departments are ready and prepared to meet the needs of pregnant women and infants during emergencies.

This surveillance builds upon the US Zika Pregnancy and Infant Registry. A key part of this unique surveillance is the ability to find exposures during pregnancy and link them with health outcomes of pregnant women and infants.

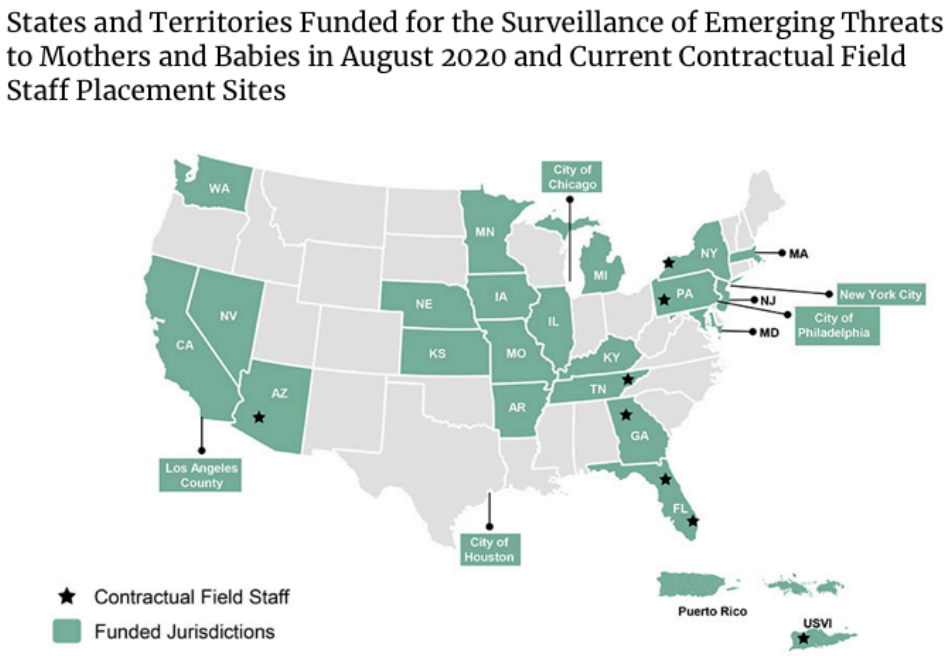

Figure 3: States and territories participating in SET-NET

Data on laboratory-confirmed and probable COVID-19 cases[25] are electronically reported to CDC using a standardized case report form[26] or NNDSS[27] as part of COVID-19 surveillance efforts. Data are reported by health departments and can be updated by health departments as new information becomes available. Information on demographic characteristics, pregnancy status, underlying medical conditions, symptoms, and outcomes is collected. Pregnancy status is ascertained by a pregnancy field on the COVID-19 case report form or through records linked to the Surveillance for Emerging Threats to Mothers and Babies Network (SET-NET) optional COVID-19 module[28]. Data up to 4 treatments of COVID-19 is collected in SET-NET, but not in the COVID-19 case report form:

[24] https://www.cdc.gov/ncbddd/aboutus/pregnancy/emerging-threats.html
[25] https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/08/05/
[26] https://www.cdc.gov/coronavirus/2019-ncov/downloads/pui-form.pdf
[27] https://wwwn.cdc.gov/nndss/covid-19-response.html
[28] https://www.cdc.gov/coronavirus/2019-ncov/downloads/cases-updates/case-report-form-pregnancy-module.pdf

Treatment for COVID-19:

☐ Remdesivir **Date started:**__/__/____ (MM/DD/YYYY)
☐ Other 1 (**Specify medicines**: _____) **Date started**:__/__/____ (MM/DD/YYYY)

☐ Other 2 (**Specify medicines**: _____) **Date started**:__/__/____ (MM/DD/YYYY)

☐ Other 3 (**Specify medicines**: _____) **Date started**:__/__/____ (MM/DD/YYYY)

CDC reports as of Dec 11, 2020 a total of 44,183 exposed pregnancies and 57 maternal deaths. Among the 44,183 cases, 8,511 pregnant women were hospitalized (19.2%).
Because only about a third of case report forms include information on pregnancy status, these numbers likely do not include all pregnant women with COVID-19 in the United States and must be interpreted with caution. The completeness of this variable continues to improve each week. Increases in the total number of cases of COVID-19 among pregnant women are largely due to the updating of pregnancy status among already reported cases.

2.2.4 Prospective meta-analysis of ongoing studies

Smith et al. are conducting a large prospective meta-analysis to study the impact of COVID-19 on pregnancy outcomes. Through a wide search 19 studies taking place in 21 countries were identified that prospectively agreed to pool data for this analysis[29].

Among these 19 prospectively included studies, ten are COVID-19 registry studies, seven are cohort or surveillance studies, and two are case-control studies. More than 74,000 pregnant women are expected to contribute to the completed analysis. These studies include data from 21 countries: Australia, Bangladesh, Canada, Chile, China and Hong Kong, Colombia, The Democratic Republic of Congo, Guatemala, India, Kenya, Malawi, Mali, Mexico, Mozambique, Pakistan, Spain, The Gambia, Uganda, United Kingdom, United States, Zambia.

Outcomes of Interest - Maternal Health according to published protocol

Mortality outcomes of interest for women include: all-cause mortality, COVID-19 specific mortality, and pregnancy-related mortality.

Morbidity outcomes of interest for women include COVID-19 related clinical signs and symptoms (fever, cough, shortness of breath, dizziness or fainting, body aches, runny nose, sore throat, loss of sense of smell, loss of sense of taste, sneezing, fatigue, nausea, vomiting, diarrhea, headache) and pregnancy-related clinical signs and symptoms (hypertensive disease of pregnancy (including preeclampsia/eclampsia), gestational diabetes, hyperemesis, intrauterine growth restriction, abnormal placentation (placental previa/accreta/percreta), placental abruption, bacterial infection prior to hospital visit, preterm contractions (not in labour), preterm labour, preterm rupture of membranes, haemorrhage (antepartum/intrapartum; postpartum; abortion-related), embolic disease, anaesthetic complications).

Other morbidity-related healthcare outcomes include hospitalization, admittance to an intensive care

[29] Emily R. Smith, Siran He, Erin Oakley, Lior Miller, James M. Tielsch. Protocol for a Sequential, Prospective Meta-Analysis to Describe COVID-19 in Pregnancy and Newborn Periods medRxiv 2020.11.08.20228056; doi: https://doi.org/10.1101/2020.11.08.20228056

unit or requiring critical care, and requiring intensive ventilation. Adverse pregnancy outcomes of interest include: stillbirth (categorized as both foetal death >28 weeks per WHO), early preterm birth (<34 weeks' gestation), preterm birth (<37 weeks' gestation), small-for-gestational-age birth (<10th percentile per the Intergrowth new-born reference values), and low birthweight (<2500 g). We will assess SARS-CoV-2 viral load in maternal biological specimens including: amniotic fluid, placenta (maternal or foetal side), cord blood, vaginal swab, faeces or rectal swab, nasopharyngeal swab, pregnancy tissue (foetus or pregnancy sac and placenta) in the case of foetal demise or induced abortion, breastmilk, and maternal blood.

Outcomes of Interest - Neonatal Health

Neonatal outcomes of interest include congenital anomalies, namely neural tube defects, microcephaly, congenital malformations of ear, congenital heart defects, orofacial clefts, congenital malformations of digestive system, congenital malformations of genital organs, abdominal wall defects, chromosomal abnormalities, reduction defects of upper and lower limbs, talipes equinovarus/clubfoot.

Smith et al. will measure early neonatal (7 day), neonatal (28 day), and six-week infant mortality (42 days). They will also measure perinatal death defined as a stillbirth or early neonatal death.

Mother-to-child transmission of SARS-CoV-2 will also be measured in the project of Smith et al., with an effort to differentiate intrauterine versus intrapartum or early peripartum infection. These definitions will be aligned with the WHO consensus case definitions once they become available.

Table 2: Overview of the studies that have agreed to participate in the meta-analysis by Smith et al.

Lead investigator	Name of study	Country	Design	Outcomes	Expected number
C. Whitehead	CHOPAN[30]	Australia & New Zealand	Cohort: Pregnancies with confirmed COVID-19		50
Akela V	ARC Kenya	Kenya/Kisumu	Cohort of pregnant women SARS-Cov2 +/-	Maternal	2500
Flaherman V[31]	USA priority Pregnancy CoRonavIrus Outcomes RegIsTrY	USA (100 hospitals)	Self-reported case series of pregnant women SARS-Cov2 +/- until 6 wks post-partum	Maternal Neonatal	1500 (enrolment closed October 2020)
Gale C	Neonatal complications study	UK	Case series of neonates COVID-19 positives or born from mothers COVID-19 positive	Neonatal	500
Gil M	Madrid hospital-based registry	Spain	Case series of pregnant women SARS-Cov2 +/-	Maternal Neonatal	54
Hernandez O	Gestovocovid	Chile	Case series of pregnant women SARS-Cov-2 + recruited at hospitals	Neonatal	1200
Knight M	UKOSS	UK	Case series of pregnant women SARS-Cov-2 + attending consultant led maternity units	Maternal	1000
Kottoff K	CCV Mali	Mali	4 different cohorts ANC vistis, DSS surveillance, **COVID-19 cohort,** delivery cohort	Maternal Neonatal (6 months)	
Doare KL	PERICOVID-PREPARE[32]	Uganda Malawi The Gambia	Cohort study, pregnant women	Maternal & Neonatal (6	70,000

[30] https://ranzcog.edu.au/news/national-registry-for-australian-women-infected-wi

[31] Flaherman VJ, Afshar Y, Boscardin J, et al. Infant Outcomes Following Maternal Infection with SARS-CoV-2: First Report from the PRIORITY Study [published online ahead of print, 2020 Sep 18]. Clin Infect Dis. 2020;ciaa1411. doi:10.1093/cid/ciaa1411

[32] https://www.pericovid.com/pericovid-in-africa

		Mozambique Kenya	with COVID-19[33]	wks)	
Waldorf KA	Washington state COVID-19	35 hospitals Washington State	Retrospective cohort of pregnant women with COVID-19	Maternal & Neonatal	240
McClure	NICHD Global network[34]	Bangladesh Kenya Guatemala DRC India Zambia USA	Cohort study in pregnant women: SARS-Cov-2 +/- (determined at delivery)	Maternal & Neonatal	2000 from each site
Metz T	NICHD MFMU network[35]	USA	Cohort of pregnant women with confirmed COVID-19 later on sample of all pregnancies	Maternal	2,000
Money D	CANCOVID Canadian Surveillance of COVID-19 in Pregnancy: Epidemiology, Maternal and Infant Outcomes[36]	Canada	Cohort of pregnant women with SARS-COV-2 + [37]	Maternal & Neonatal (6-8 wks.)	2134
Poon L	China and HK COVID Registry	China Hong Kong	Cohort of pregnant women SARS-COV-2 +		
Sann J	RECOGEST	Colombia	Cohort of pregnant women SARS-COV-2 +	Maternal & Neonatal	400

*orange rows: seem self-reported and not eligible for CONSIGN

2.3. Other studies

2.3.1 ROI COVID-19 Study, Ireland[38]

Data on COVID-19 in pregnant women were submitted by 16 maternity units/hospitals. N=70

2.3.2 PregCOVID, The National Registry of Pregnant Women with COVID-19 in India[39]

PregCovid (National Registry of Pregnant Women with Covid-19 in India) is a study of pregnant women & women in post-partum period with SARS-CoV-2 infection. This study is a joint collaboration between ICMR-National Institute for Research in Reproductive Health (NIRRH), Medical Education & Drugs Department (MEDD), Government of Maharashtra & Topiwala National Medical College & B.Y.L. Nair Charitable Hospital, Mumbai. This study is being done by Medical Education & Drugs Department (MEDD), Government of Maharashtra, Municipal Corporation of Greater Mumbai (MCGM) & other government agencies to formulate the strategies for effective management of Covid-19 & pregnancy

[33] https://13c77cd8-1721-4f9d-baec-3acff86b5bf0.filesusr.com/ugd/c9aac3_2b6d1cd078db4937b29a088e8c6677ed.pdf
[34] https://www.nichd.nih.gov/research/supported/COVID
[35] https://www.nichd.nih.gov/newsroom/news/051920-MFMU-COVID-19
[36] https://ridprogram.med.ubc.ca/cancovid-preg/
[37] https://med-fom-ridresearch.sites.olt.ubc.ca/files/2020/04/COVID-19-Canadian-Pregnancy-Surveillance-Protocol-_2020APR21-1-1.pdf
[38] https://www.ucc.ie/en/npec/roicovid-19study/
[39] https://pregcovid.com

2.3.3 Obs Covid Spain[40]

Prospective observational study of pregnant women in whom SARS-CoV-2 infection is suspected at any time during pregnancy with positive test results for SARS-CoV-2, in order to create a registry of baseline characteristics of the pregnant woman, aspects related to the course of pregnancy and delivery, and related to the new-born, with an observation period of up to 14 days after delivery.

2.3.4 InterCOVID[41]

The researchers will be recruiting women who have been exposed and not-exposed to SARS-CoV-2 at any stage of pregnancy, and following them and their new-borns until hospital discharge to quantify the risks associated with the exposure. Exposed pregnant women are defined as having:

a) laboratory confirmed Covid-19;
b) radiological findings suggestive of Covid-19;
c) symptoms compatible with Covid-19 according to a predefined list, or;
d) no symptoms, whilst in close interaction with a person(s) with confirmed Covid-19 infection (a proxy for asymptomatic cases, one of the main problems in controlling the pandemic).

60 medical institutions in 29 countries have agreed to participate, which means the study should have sufficient power to provide invaluable answers, in a short time period, regarding the risks to pregnant women who are exposed to SARS-CoV-2.

3. Conclusions and recommendations for next steps forward

CONSIGN-International should focus on the following objectives:

1) To describe medicines used to treat COVID-19 in pregnancy
2) Compare the effects of COVID-19 medicinal treatment on maternal and neonatal outcomes

To our awareness none of the current activities is focusing on medicines in COVID-19 affected pregnancies and there is an great potential for collaboration.
We summarize opportunities for collaboration based on two types of data collection.

1) Retrospective secondary use of health care data

Eligible for participation:
Networks of or single data sources with access to population based electronic health care databases, which can identify pregnancy end and start and are able to link to medicines and COVID-19 disease.

Opportunities identified
Sentinel system, CNODES, OHDSI, CPRD, COHERENCE, ConcePTION data sources (those not yet in CONSIGN). We will ensure that data sources will not be included more than once, as they may be present in multiple networks

Method/design

[40] https://osf.io/k82ja/?view_only=61d3773cc12f423b8568ff11acb0fa44We
[41] https://www.ox.ac.uk/news/2020-04-24-global-study-assess-effects-covid-19-pregnancy-launched

DAPs could use the CONSIGN WP1 protocol, or parts of it, especially objectives 1 and 3 focusing on medicines use and effects.
http://www.encepp.eu/encepp/openAttachment/fullProtocol/39437

Exposures: All medicines, identified by outpatient prescription/dispensing codes will be described by therapeutic class (ATC-level 2) and when sufficient exposures, on an individual drug level (ATC-level 5).
Risk/protective factors for COVID-19: trimester of infection, age, obesity, smoking, parity, co-morbidity (e.g. cardiovascular, respiratory, diabetes, rheumatic diseases, cancer, mental disorder), vaccinations (e.g. influenza), timing during the pandemic.
Pregnancy outcomes: congenital anomalies, preterm birth, low birth weight, small for gestational age/ intrauterine growth restriction, spontaneous abortions, stillbirth, type of delivery, microcephaly, low APGAR score at 5 min, induced terminations of pregnancy for foetal anomaly (TOPFA).
New-born outcomes: Infection (e.g. SARS-CoV-2 infection), neonatal complications, neonatal death.

Analyses

1) Descriptive analysis on monthly prevalence rates of medicines use, and prevalence of pregnancy outcomes.
2) Nested case control analysis in cohorts to assess the effect of medicines and COVID-19 on pregnancy outcomes. Timing of COVID-19 infection in pregnancy as well as medicines use and risk factors for the outcome will be considered.

Data sharing

Data may be shared using a distributed approach with a common protocol, the ConcePTION common data model may be used and common analytics may be utilized. Cross-mapping of Sentinel & OMOP common data models to ConcePTION CDM structure can be conducted such that CONSIGN R-scripts can be utilized directly or data sources can program themselves. Otherwise local coding needs to be conducted.

Next steps:

- Organize a joint meeting with the interested investigators to discuss the CONSIGN protocol and analysis
- Find modalities & agreements with ICMRA regulators to support the studies in their areas
- Assess whether sites will program themselves or want to use the CONSIGN scripts
- Find funding for implementation

2) Sharing of primary data collected in different ongoing cohorts/registries of SARS-COV-2 exposed pregnancies around the world

Many initiatives are ongoing. None of the initiatives seems to be specifically focused on assessing the effects of medicines on maternal and neonatal outcomes.

There is an opportunity to collaborate with an ongoing initiative that aims to conduct individual patient data meta-analysis, coordinated by Smith et al.[42]

Inclusion criteria for analysis

[42] https://www.medrxiv.org/content/10.1101/2020.11.08.20228056v1.full-text

Participants enrolled in the study should meet the following inclusion criteria:

- Pregnant person positive for SARS-COV-2 at any point during pregnancy using RT-PCR who has provided informed consent
- Inclusion period: date of COVID-19 diagnosis during pregnancy between January 1, 2020-December 31, 2020

Data collection

Data is collected locally and collaborators will be asked to transfer the data locally in a structurally and semantically harmonized data set.
To synergize with ongoing initiatives this could follow the modules proposed by Smith et al. in their Global Data Harmonization Data Modules and Core Questions / Variables for Pregnancy & Perinatal COVID-19 Registries or Cohorts, which is funded by the Bill & Melinda Gates Foundation, with additional details on treatments.

Data analysis

Drug utilization: describing the type of treatment for COVID-19 disease in hospital/clinics by seriousness of COVID-19, trimester of infection, country.
Medicines effects: nested case control study in pregnancy COVID-19 cohorts, matched on seriousness of COVID-19, trimester of infection, country and maternal pregnancy history.
Severity of COVID-19: classified according to WHO1 scale as follows:

Level 1: any recorded diagnosis;
Level 2: hospitalization for COVID-19 (confirmed or suspected);
Level 3: ICU admission in those with COVID-19 related admission;
Level 4: Acute respiratory distress requiring ventilation (ARDS) during a hospitalization for COVID-19;
Level 5 death during a hospitalization for COVID-19 (any cause)

Outcomes: pregnancy outcomes and neonatal outcomes.
Exposures: antivirals, antibiotics, adjunctive therapies.

Data sharing

Statistical analysis & data management plan for collaborative analysis to be agreed by all participating organizations.
Preferred option (if enough cases): analysis to data rather than data to analysis, only pooling of results (on digital research environment).
Requires local capacity to run R-scripts.

Next steps:

- Detailed analysis plan in collaboration with partners to be discussed in a remote meeting in January 2021 with key investigators organized by CONSIGN.
- Mapping of data dictionaries to common modules provided by Emily Smith., which was verbally agreed by the Smith Research group
- Collecting approvals for potential participation & reach out to key investigators.
- Funding for additional work.

Timing:

Allowing for pregnancies during the second wave of COVID-19 to end, we will be able to start analyses end of 2021/beginning of 2022.