Covid-19 infectiON and medicineS In preGNancy

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Contributing organizations

- University Medical Center Utrecht, Utrecht, the Netherlands (UMCU)
- UKOSS, NPEU, University of Oxford, ITOSS, Rome, Italy , NOSS, Nordic countries, Inserm, France
- Universiteit Utrecht, Utrecht, The Netherlands (UU)
- Agenzia Regionale di Sanita' Toscana Italy (ARS)
- Aarhus University (AUH)
- University Copenhagen, Denmark (UCPH)
- Leibniz-Institute for Prevention Research and Epidemiology – BIPS, Germany (BIPS)
- Hospital Sanitaria Vall d'Hebron, Spain (FICF)
- Foundation for the Promotion of Health and Biomedical Research of Valencian Region (FISABIO), Spain
- Karolinska Institute, Sweden (KI)
- RTI Health Solutions (RTI-HS), Barcelona, Spain; North Carolina and Massachusetts, USA
- University Oslo, Norwegian Institute of Public Health, Norway (UiO)
- Instituto Aragonés de Ciencias de la Salud, Zaragoza Spain (IACS)
- University Swansea, UK (USWANSEA)
- University Bordeaux (BPE
- University Lausanne/Bern, (UniBern)
- University of Manchester, UK.(UMAN)

Many questions remain, 8 months into COVID-19

1. Is a pregnant woman at higher risk to get COVID-19?

2. Is a pregnant woman with COVID-19 at higher risk of severe disease?

3. Risk factors for vertical transmission of SARS-Cov-2

4. What is the impact of COVID-19 disease on pregnancy outcomes?

5. What is the impact of medicines to treat COVID-19 on pregnancy outcomes?

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Current evidence from large studies

- Initial evidence based on case series from China seemed re-assuring

- Additional case series showed severe covid-19 is associated iatrogenic preterm delivery

- CDC surveillance analysis: 326,335 women aged 15 to 44 years with positive test results for SARS-CoV-2 (June 25, 2020)

  - Pregnant women with COVID-19 seemed more likely to be hospitalized

  - Pregnant women 1.5 times (95%CI1.2-1.8) more likely to be admitted to ICU (absolute risk 1.5%) than those who were not pregnant

  - No increase in death of pregnant women with COVID-19, Hispanic and black women disproportionally affected

- UKOSS study 427 pregnant women admitted to 197 obstetric units across the United Kingdom between March and April 15, 2020 (https://www.ncbi.nlm.nih.gov/pubmed/32513659)

  - Incidence of admission: 4.9/1000 maternities

  - Mostly 2nd and third trimester infections (was March-April)

  - 10% of women needed critical care, 1% died

  - 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.

  - Sixty four (15%) women were given corticosteroids for fetal lung maturation

Current evidence

UK St Georges Hospital pregnancy outcomes (irrespective of COVID-19 infection) historical controls

Table 2. Comparison of the Study Outcomes Between the Prepandemic Period (October 1, 2019, to January 31, 2020) and the Pandemic Period (February 1, 2020, to June 14, 2020)

Outcomes	Prepandemic period (n = 1681 births)[a]	Pandemic period (n = 1718 births)[a]	Difference (95% CI)	P value
Stillbirths, No./total No. (No. per 1000 births)	4/1681 (2.38)	16/1718 (9.31)	6.93 (1.83 to 12.0)	.01
Excluding late terminations for fetal abnormality, No./total No. (No. per 1000 births)	2/1681 (1.19)	12/1718 (6.98)	5.79 (1.54 to 10.1)	.01
Preterm birth, No./total No. (%)				
Prior to wk 37	113/1655 (6.8)	127/1692 (7.6)	−0.68 (−2.43 to 1.07)	.46
Prior to wk 34	42/1655 (2.5)	62/1692 (3.7)	1.13 (−0.05 to 2.30)	.07
Cesarean delivery, No./total No. (%)	423/1655 (25.6)	419/1692 (24.8)	−0.79 (−3.73 to 2.14)	.60
Admission to neonatal unit, No./total No. (%)	103/1677 (6.1)	106/1702 (6.2)	0.09 (−1.53 to 1.71)	.94

[a] Discrepancies between the denominator for some of the categories and the number of pregnancies included in the study are due to missing data.

Current evidence for management?

Management of COVID-19 in the Setting of Pregnancy

- Potentially effective treatment for COVID-19 should not be withheld from pregnant women because of theoretical concerns related to the safety of therapeutic agents in pregnancy **(AIII)**.

- Decisions regarding the use of drugs approved for other indications or investigational agents for the treatment of COVID-19 in pregnant patients must be made with shared decision-making between the patient and the clinical team, considering the safety of the medication for the woman and the fetus and the severity of maternal disease. For detailed guidance on the use of COVID-19 therapeutic agents in pregnancy, please refer to Considerations in Pregnancy in the Antiviral Therapy and Immune-Based Therapy sections of these Guidelines.

- To date, most SARS-CoV-2-related clinical trials have excluded, or included only a very few, pregnant women and lactating women. This limitation makes it difficult to make evidence-based recommendations on the use of SARS-CoV-2 therapies in these vulnerable patients and potentially limits their COVID-19 treatment options. When possible, pregnant women and lactating women should not be excluded from clinical trials of therapeutic agents or vaccines for SARS-CoV-2 infection.

Overview NIH (August 27, 2020) based on CDC, ACOG and Society for Maternal-Fetal-Medicine (https://www.covid19treatmentguidelines.nih.gov/special-populations/pregnancy/)

Remdesivir SmPC (EMA, June 2020)

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of remdesivir in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Remdesivir should not be used during pregnancy unless the clinical condition of the women requires treatment with it.

Women of child-bearing potential have to use effective contraception during treatment.

Breast-feeding

It is unknown whether remdesivir is excreted in human milk or the effects on the breast-fed infant, or the effects on milk production.

In animal studies, the nucleoside analog metabolite GS-441524 has been detected in the blood of nursing rat pups of mothers given remedesivir. Therefore, excretion of remdesivir and/or metabolites into the milk of lactating animals can be assumed.

Because of the potential for viral transmission to SARS-CoV-2-negative infants and adverse reactions from the drug in breast-feeding infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Remdesivir therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Aim for EMA to launch the tender

To guide evidence based decision-making about COVID-19 vaccine indications, vaccination policies, and treatment options for pregnant women by regulators.

Will real world 'evidence' be good enough?

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Objectives CONSIGN

- Assess use of medicines for COVID-19 treatment

- Describe severity and clinical outcomes of COVID-19 disease

- Assess and compare pregnancy and neonatal outcomes in different COVID-19 antiviral and immune based treatment groups

- To establish collaborations with other global initiatives and allow for pooling of evidence

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CONSIGN works with strong networks in pregnancy field

Innovative Medicines Initiative - funded project with 88 partners aiming to build an ecosystem in Europe for monitoring medicines safety in pregnancy and lactation https://www.imi-conception.eu

Multinational collaboration of organisations conducting prospective population-based studies of serious illnesses in pregnancy and childbirth, doi: 10.1111/aogs.12316. Epub 2013 Dec 30.
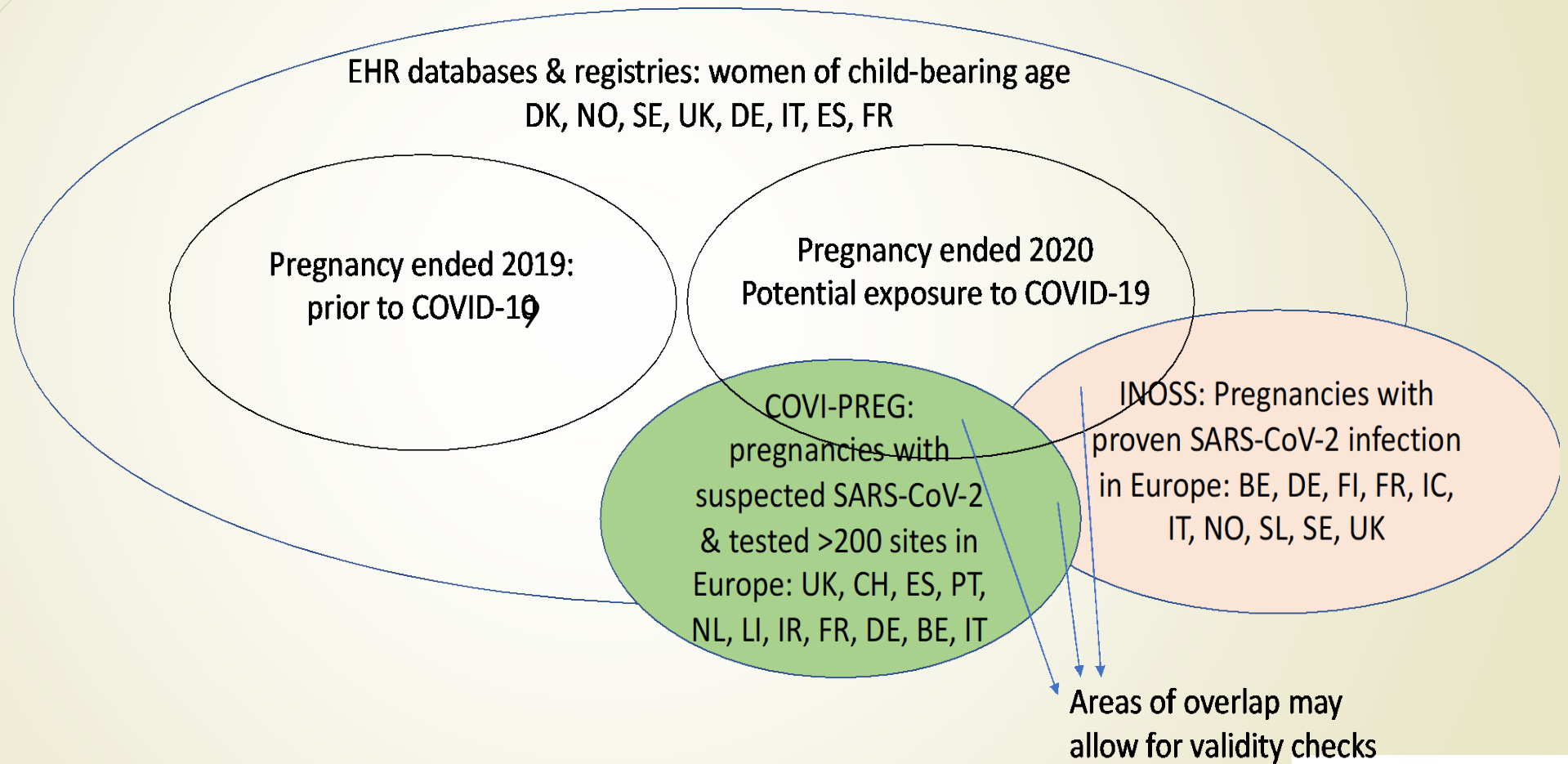

An international registry for emergent pathogens and pregnancy https://doi.org/10.1016/S0140-6736(20)30981-8

Approach

- **Primary data collection** (specific for purpose)
  - **INOSS**: ongoing standardized data collection at delivery for women with COVID-19 during pregnancy in INOSS countries
  - **COVI-PREG**: ongoing standardized data collection in health clinics at each visit for pregnant women with suspected COVID-19 in > 200 health facilities
  - Data recording and sharing through REDCAP
- **Secondary use of real world data collected in health care**
  - 9 Population based electronic health and medical birth registers in 8 countries, covering more than 1 million births per year
  - Women of childbearing age
  - Using ConcePTION tools (distributed analytics) and common data model to harmonize

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Overlaps and differences

EHR databases & registries: women of child-bearing age
DK, NO, SE, UK, DE, IT, ES, FR

Pregnancy ended 2019:
prior to COVID-19

Pregnancy ended 2020
Potential exposure to COVID-19

COVI-PREG:
pregnancies with
suspected SARS-CoV-2
& tested >200 sites in
Europe: UK, CH, ES, PT,
NL, LI, IR, FR, DE, BE, IT

INOSS: Pregnancies with
proven SARS-CoV-2 infection
in Europe: BE, DE, FI, FR, IC,
IT, NO, SL, SE, UK

Areas of overlap may
allow for validity checks

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Complementarity, harmonization & synergies

- **Primary data collection: prospective dedicated for COVID-19**
  - **INOSS**: Uses standardized CRF, collect <u>at delivery</u> pregnancy outcomes and what happened during hospitalization for COVID-19 (medicines in hospital) & with open reporting what was used otherwise. No direct comparison group (option for historical controls)
    - Opportunity to describe drug use in hospital
    - Opportunity to conduct case control studies on pregnancy outcomes and match on COVID-19 trimester and other maternal characteristics
  - **COVI-PREG**: Extensive data collection <u>at each visit</u> (longitudinal, from enrollment), outpatient and inpatient data on drug use, for suspected COVID-19 cases, will be extended with follow-up after delivery (6 months).
    - Opportunity to compare between SARS-COV-2 test positive and test negative pregnancies,
    - no data on non-pregnant women
    - Opportunity for longitudinal analysis of medication data both inpatient and outpatient
- **Secondary use of health data: retrospective analysis of recorded health data**
  - Opportunity to analyse & compare medicines use and outcome in women with COVID-19 (confirmed and/or suspected), without COVID-19, and historically
 - May miss data on in hospital medication use

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Collaboration: size matters

- **Collaboration with other international initiatives to increase sample size, and investigate true heterogeneity**
  - UKOSS analysis:
    - 5/1000 pregnancies admitted for COVID-19 (highly dependent on infection rate)
    - Mostly were second and third trimester (we need to wait for first trimester evidence)
    - Amongst those hospitalized only 2% received antivirals
    - Adverse pregnancies outcomes are rare
  - We need pooling
    - In Europe: retrospective data on a source of 130 million: at most 4000 hospitalized COVID-19 pregnancies (assuming constant hospitalization rate), only 75-100 may be exposed to antivirals in hospital, and outpatient will be lower

Pooling of information with

- Sentinel
- CNODES (Health Canada)
- Other ICMRA available options
- INOSS network outside of Europe
- COVI-PREG sites outside of Europe

https://doi.org/10.1016/S0140-6736(20)30981-8
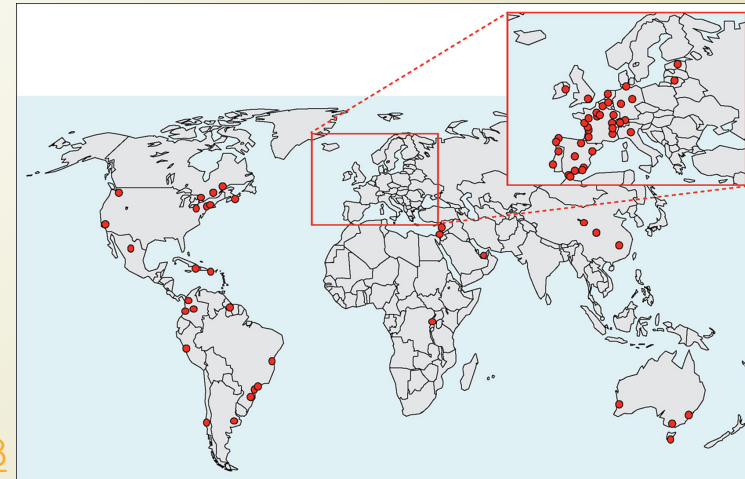
Will the real world evidence be enough for regulatory decision making?

- CONSIGN will use all its clinical, epidemiological and analytical expertise to generate high quality evidence in a transparent manner

    - **Report on quality of data** according to ConcePTION quality processes
        - Level 1: Distributions of data that are collected
        - Level 2: Logical checks
        - Level 3: Benchmarking with external data and between datasources

    - **Review of design of studies** and definition of variables with ICMRA group and the associated networks (ConcePTION, INOSS, COVI-PREG…..)

Questions please send to

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