



SPOR Evidence Alliance
Strategy for Patient-Oriented Research

Alliance pour des données probantes de la SRAP 
Stratégie de recherche axée sur le patient

Strategy for Patient-Oriented Research

SPOR
Putting Patients First 



COVID-END
COVID-19 Evidence Network
to support Decision-making
... in Canada

Pregnancy related risks associated with COVID-19

A rapid review

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EXECUTIVE SUMMARY

Objectives: *The purpose of this review was to provide evidence on the following:*

Key Question:

1. *Has there been a change in the rate of pregnant persons admitted to the ICU/developing severe COVID outcomes?*

Supporting Questions:

2. *What is the risk of pregnant women acquiring COVID-19, developing severe illness, being hospitalized, requiring ICU admission or death?*
 - a) *Does the risk differ between trimesters?*
 - b) *Does the risk differ between COVID-19 genomic variants (e.g., variants of interest, concern or high consequence)?*
 - c) *What risk factors related to pregnancy, based on intersecting conditions of social and/or material disadvantage or certain health conditions (e.g., obesity, diabetes, hypertension, chronic respiratory illness), are associated with a higher risk?*
3. *What is the association of physiological changes during pregnancy (e.g., increased risk of thromboembolic events, natural state of immunosuppression) with increased risk of acquiring COVID-19, developing severe illness, being hospitalized, requiring ICU admission or death?*

Design: *Rapid review*

Method: *We searched four bibliographic databases (Medline, Embase, CovidLit and CochraneCovid). One reviewer selected studies for inclusion, extracted data and assessed the quality of systematic reviews using the AMSTAR tool.*

Results: *From 12760 citations identified through our search, we included 343 studies that met our inclusion criteria (62 systematic reviews/ clinical practice guidelines, 158 clinical studies, 123 editorials, opinions, commentaries, and narrative reviews). Numerous systematic reviews have been identified that provided evidence on the key questions and all were considered to be of 'low' to 'critically low' quality. Additional primary studies (n = 158) were identified that were not captured by previous evidence syntheses (mostly cohort studies and case reports/ series).*

In summary, only low summary evidence was available to answer the key and supporting questions:

1. Has there been a change in the rate of pregnant persons admitted to the ICU/developing severe COVID outcomes?

Pregnant persons testing positive for COVID-19 are more likely to be admitted to the ICU and there is some evidence that the rates were higher in the second wave compared with the first wave in the UK. Maternal deaths were shown to be higher during the pandemic compared to pre-pandemic.

2. What is the risk of pregnant women acquiring COVID-19, developing severe illness, being hospitalized, requiring ICU admission or death?

There is a large variability in the reported event rates for:

- Developing severe illness (Median = 11.7%; IQR = 6.7%, 18.0%; Range: 1.4% - 22.0%),
- Requiring ICU admission (Median = 5.6%; IQR = 3.6%, 10.8%; Range: 1.9% - 29.0%),
- Death (Median = 1.0%; IQR = 0.2%, 1.7%; Range: 0.0% - 11.3%).

a. Does the risk differ between trimesters?

Most COVID-19 diagnoses during pregnancy occurred in the third trimester:

- 1st trimester (Median = 1.8%; IQR = 1.4%, 2.5%; Range: 0.0% - 28.3%),
- 2nd trimester (Median = 8.2%; IQR = 6.3%, 18.5%; Range: 3.2% - 97.8%),
- 3rd trimester (Median = 90.2%; IQR = 73.9%, 92.6%; Range: 2.2% - 100.0%).

b. Does the risk differ between COVID-19 genomic variants (e.g., variants of interest, concern or high consequence)?

Scant data is available on the association of genomic variants and outcomes during pregnancy with only one clinical study identified that reported more ICU admissions in the 2nd wave compared to the 1st wave.

c. What risk factors related to pregnancy, based on intersecting conditions of social and/or material disadvantage or certain health conditions (e.g., obesity, diabetes, hypertension, chronic respiratory illness), are associated with a higher risk?

Most common comorbidities discussed were obesity, diabetes, and maternal hypertension. There is no consensus on whether these conditions may be associated with higher risk of acquiring COVID-19 or having more severe complications.

3. What is the association of physiological changes during pregnancy (e.g., increased risk of thromboembolic events, natural state of immunosuppression) with increased risk of acquiring COVID-19, developing severe illness, being hospitalized, requiring ICU admission or death?

These complex physiologic adaptive changes (e.g., altered immune response) during pregnancies make pregnant individuals at a high-risk for viral respiratory infections. These changes include a gestational shift in the Th1-Th2 immune response, and a lower WBC count. With regards to hypercoagulability, there is less certainty and consensus if COVID-19 complicated pregnancies are at a higher risk of coagulopathy and thromboembolism.

Conclusion: While there are many evidence syntheses, their poor quality and lack of including numerous potentially relevant studies, reflects the need for more well-conducted evidence syntheses and prospective cohort studies to answer the questions of relevance to this review.

Methods

This rapid review was conducted according to World Health Organization guide for rapid reviews,¹ and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.² The primary research questions for this review were as follows:

Key Question:

1. Has there been a change in the rate of pregnant persons admitted to the ICU/developing severe COVID outcomes?

Supporting Questions:

2. What is the risk of pregnant women acquiring COVID-19, developing severe illness, being hospitalized, requiring ICU admission or death?
 - a) Does the risk differ between trimesters?
 - b) Does the risk differ between COVID-19 genomic variants (e.g., variants of interest, concern or high consequence)?
 - c) What risk factors related to pregnancy, based on intersecting conditions of social and/or material disadvantage or certain health conditions (e.g., obesity, diabetes, hypertension, chronic respiratory illness), are associated with a higher risk?
3. What is the association of physiological changes during pregnancy (e.g., increased risk of thromboembolic events, natural state of immunosuppression) with increased risk of acquiring COVID-19, developing severe illness, being hospitalized, requiring ICU admission or death?

We utilized a hierarchical approach to the evidence synthesis with a focus on previously conducted systematic reviews (SRs), scoping reviews (ScRs), rapid reviews (RRs), meta-analyses (MAs), and clinical practice guidelines (CPGs)/ policy guidance statements (e.g., from governmental organizations or specialized societies). In addition, we identified primary clinical studies (CS) that were not captured by the previously conducted evidence syntheses. Lastly, we highlighted some key findings from Editorials, Commentaries, Opinions, and Narrative reviews (ECONs) that provided additional insight for the key questions.

Search strategy for identification of studies

A knowledge synthesis librarian prepared the original search for Medline (Ovid) and it was peer-reviewed using the PRESS checklist by a second librarian. The final search was translated to the other databases. We searched general health bibliographic databases [MEDLINE (Ovid) and EMBASE (Ovid), and COVID-19 specific databases Cochrane Covid (Wiley) (<https://covid-19.cochrane.org/>) and [LitCovid (NLM) (<https://www.ncbi.nlm.nih.gov/research/coronavirus/>)]. Searches were conducted from May 17-19, 2021. Each database was searched using an individualized search strategy (Appendix 1). Finally, the reference lists of relevant narrative and systematic reviews and included studies were hand-searched for relevant citations. We performed reference management in EndNote™ (version X9, Thomson Reuters, Carlsbad, CA, USA).

Study selection

We used a two-stage process for study screening and selection using standardized and piloted screening forms. One reviewer screened the titles and abstracts of search results to determine if a citation met the inclusion criteria. Full texts (if available) of all the selected citations were examined by one reviewer.

The population of interest for this review was limited to pregnant individuals irrespective of trimester. Non-pregnant, fetal, and newborn populations were not within the scope of this review. The diagnosis of COVID-19, requirements for hospital or ICU admission were author-defined. We also did not limit to studies that only include women with laboratory-confirmed infections. Lastly, we did not limit studies to any geographic location but limited to English-language publications for feasibility.

Data abstraction and management

One reviewer summarized the findings from included study reports. We tabulated the results, which were presented descriptively. Data management was performed using Microsoft Excel™ 2010 (Excel version 14, Microsoft Corp., Redmond, WA, USA).

Assessment of methodological quality and potential risk of bias

Due to the expedited nature of this rapid review, and that most of the evidence was expected to come from lower quality, single-arm observational studies, editorials, commentaries, opinions and narrative reviews, we did not assess the methodological quality or potential risk of bias of these included studies. However, we did assess the quality of systematic reviews (as defined by Cochrane) using the AMSTAR 2 tool. These assessments were done in duplicate with one reviewer conducting the initial evaluations and a second review double-checking for errors. Discrepancies were resolved through discussion and consensus. We rated the overall confidence in the results of a review as High (Zero or one non-critical weakness), Moderate (More than one non-critical weakness), Low (One critical flaw with or without non-critical weaknesses) or Critically low) following the guidance of the developers of the AMSTAR 2 tool (<https://amstar.ca/Amstar-2.php>).

Presentation of the results

For each Key Question, we have summarized the relevant evidence below. In addition, more information is presented in the associated Excel Workbook (Evidence Summary.xlsx). For example, to identify additional summaries from the publications that provided evidence to each Key Question,

- 1) Open the Excel file named 'Evidence Summary';
- 2) Click on any of three tabs (Relevant SRs from CPGs, Additional Clinical Studies, or Editorials, Comments and Narrative Reviews);
- 3) Click on the column header for relevant Key Question (KQ);
- 4) Remove the tick marks for the 'Blanks' box leaving only the 'Yes' box checked.
- 5) This will filter the worksheet displaying only the relevant publications.

Instructions are also available in the first worksheet in the Excel Workbook titled: "Instructions".

Results

From 12,760 citations identified through the search strategy and hand-searching, 342 studies met the inclusion criteria: 61 SRs,³⁻⁶³ one CPG,⁶⁴ 157 CS,⁶⁵⁻²²¹ 123 ECONs²²²⁻³⁴⁴ (Figure 1). The included studies are summarized in the associated Excel Workbook (Evidence Summary.xlsx) and is divided based on key question and evidence source. All the systematic reviews were rated as 'low' to very 'critically low' quality studies.

Key Question:

1. Has there been a change in the rate of pregnant persons admitted to the ICU/developing severe COVID outcomes?

We identified three SRs,^{8, 19, 58} one MA²⁴⁸ and one additional CS²¹⁰ that was not captured by the SRs. The SRs were all rated as a critically low overall confidence in the results. Pregnant persons testing positive for COVID-19 are more likely to be admitted to the ICU. *Huntley et al., 2021*¹⁹ reported that pregnant persons testing positive for COVID-19 were statistically significantly more likely to be admitted to the ICU (1.9% vs. 0.1%). Similarly, *Wei et al., 2021*⁵⁸ reported that the odds ratio of ICU admission was 4.78 (95% CI 2.03 to 11.25) for pregnant women with COVID-positive compared with COVID-negative pregnant women. Even so, a cumulative MA of ICU admission by *Dubey et al, 2021*²⁴⁸ indicated no change in ICU admissions from May to August 2020.

There is little evidence from the identified studies that directly compared maternal ICU admissions at different time points in the pandemic. Albeit there is some evidence that the rates were higher in the second wave compared with the first wave in the UK. The study by *Kadiwar et al., 2021*²¹⁰ reported that ICU admission rates were higher in the second wave (62 admissions – 6 requiring extracorporeal membrane oxygenation (ECMO)) compared with the first wave (34 admissions – 1 requiring ECMO).

With regards to severe COVID outcomes, maternal deaths were shown to be higher during the pandemic compared to pre-pandemic. *Chmielewska et al., 2021*⁸ highlighted a significant increase in maternal deaths during the pandemic (530/ 1237018) compared to pre-pandemic (698/ 2224859) [OR 1.37 (95% CI 1.22 to 1.53)]. *Huntley et al., 2021*¹⁹ also reported that pregnant persons testing positive for COVID-19 were non-significantly more likely to die [0.5% (3/ 559) vs. 0.3% (8/ 3155)].

Supporting Questions:

2. What is the risk of pregnant women acquiring COVID-19, developing severe illness, being hospitalized, requiring ICU admission or death?

We identified 53 SRs,^{3, 5-7, 9-23, 25-38, 40-48, 50-56, 59, 61-63} one CPG,⁶⁴ 147 additional CSs,^{65-105, 107-118, 120-128, 130-133, 135-166, 168-170, 172-179, 181-188, 190-197, 200-209, 211-221, 345} and 102 ECONs.^{222, 223, 225-227, 229-237, 239, 240, 242, 243, 245-257, 260, 261, 263-268, 270, 272, 274-276, 278-292, 294-299, 301-311, 313-321, 323-328, 330, 331, 333, 336-339, 341-344} The SRs were all rated as a low^{6, 10, 23, 28, 37, 54, 55, 59, 61} to critically low^{3, 5, 7, 9, 11-22, 25-27, 29-36, 38, 40-48, 50-53, 56, 62, 63} overall

confidence in the results. Papanou et al., 2021⁴³ conducted an overview of 39 systematic reviews. They reported maternal ICU admission and mechanical ventilation rates of 3 to 28.5% and 1.4 to 12%, respectively; the maternal mortality rate was <2%.

Evidence from the remaining SRs identified by this review, supported by evidence from the additional CSs and ECONs, revealed that there is a large variability in the reported event rates:

- Developing severe illness^{7, 9, 10, 36, 44, 45, 59}
(Median = 11.7%; IQR = 6.7%, 18.0%; Range: 1.4% to 22.0%),
- Requiring ICU admission^{3, 5, 6, 9, 10, 12-17, 19, 23, 28, 29, 34, 36-38, 42, 44, 46, 47, 50, 52, 54, 55, 61-63}
(Median = 5.6%; IQR = 3.6%, 10.8%; Range: 1.9% to 29.0%),
- Death^{3, 5, 6, 9, 10, 12-17, 19, 21, 22, 25, 26, 28, 29, 31-35, 37, 38, 40, 41, 44-48, 50, 53-56, 61-63}
(Median = 1.0%; IQR = 0.2%, 1.7%; Range: 0.0% to 11.3%).

a. Does the risk differ between trimesters?

We identified 29 SRs,^{3, 6, 7, 11, 14-18, 21, 25-28, 30, 31, 33-38, 40, 43-45, 50, 52, 55} one CPG,⁶⁴ 61 additional CSs,^{65, 67-69, 71, 82, 83, 89, 92, 94, 95, 97-99, 105, 106, 109, 112-115, 118-120, 129, 131, 132, 134, 136-138, 142-144, 147, 153, 155, 157, 158, 161, 162, 164, 166, 168-171, 180, 184, 186-188, 193, 196, 198, 199, 202, 204, 208, 212, 221} and 15 ECONs.^{234, 239, 248, 250, 252, 264, 281, 286, 288, 303, 306, 316, 321, 327, 334} The SRs were all rated as a low^{6, 28, 37, 55} to critically low^{3, 7, 11, 14-18, 21, 25-27, 30, 31, 33-36, 38, 40, 43-45, 50, 52} overall confidence in the results. Evidence from the SRs, supported by evidence from the additional CSs and ECONs, revealed that most COVID-19 diagnoses during pregnancy occurred in the third trimester:

- 1st trimester^{3, 14, 17, 33, 34, 38, 44, 50, 52, 55, 64}
(Median = 1.8%; IQR = 1.4%, 2.5%; Range: 0.0% to 28.3%),
- 2nd trimester^{3, 17, 27, 31, 33, 34, 38, 44, 50, 52, 55}
(Median = 8.2%; IQR = 6.3%, 18.5%; Range: 3.2% to 97.8%),
- 3rd trimester^{3, 6, 7, 11, 14-17, 21, 25-28, 30, 31, 33-38, 40, 44, 50, 52, 55}
(Median = 90.2%; IQR = 73.9%, 92.6%; Range: 2.2% to 100.0%).

b. Does the risk differ between COVID-19 genomic variants (e.g., variants of interest, concern or high consequence)?

We identified one CS discussing the potential association of COVID-19 severity in pregnancy and clinical variants. In the study by *Kadiwar et al., 2021*,²¹⁰ they reported that while in the 1st wave in the UK, 34 women were admitted to the ICU and one required ECMO, during the 2nd wave the corresponding numbers were 62 and six, respectively.

c. What risk factors related to pregnancy, based on intersecting conditions of social and/or material disadvantage or certain health conditions (e.g., obesity, diabetes, hypertension, chronic respiratory illness), are associated with a higher risk?

We identified 13 SRs,^{8, 18, 19, 22, 25, 26, 28, 30, 34, 46, 51, 58, 60} 44 additional CSs,^{65, 82, 85, 90, 94, 96, 101, 118, 119, 122-124, 126, 128, 129, 131, 133, 137-139, 141, 144, 146, 148, 151, 152, 154, 158, 159, 163, 164, 175, 179, 189, 190, 192, 195-197, 201, 207-209, 212} and 27 ECONS.^{222, 224, 225, 229, 233, 234, 242, 248, 250, 258, 260, 264-266, 268, 276, 277, 281, 283, 284, 292, 304, 315, 316, 321, 335, 338} The SRs were all rated as a low^{28, 60} to critically low^{8, 18, 19, 22, 25, 26, 30, 34, 46, 51, 58} overall confidence in the results. The most common comorbidities that were discussed were obesity, diabetes, and maternal hypertension. Having said that, there was no consensus on whether these conditions may be associated with higher risk of acquiring COVID-19 or having more severe complications.

3. What is the association of physiological changes during pregnancy (e.g., increased risk of thromboembolic events, natural state of immunosuppression) with increased risk of acquiring COVID-19, developing severe illness, being hospitalized, requiring ICU admission or death?

We identified 9 SRs,^{4, 15, 20, 24, 39, 48, 49, 55, 57} one CPG,⁶⁴ 7 additional CSs,^{125, 167, 178, 179, 190, 198, 220} and 61 ECONS.^{224-226, 228, 233, 234, 236, 238, 241, 242, 244, 247, 250, 252-256, 258-260, 262, 267-269, 271-274, 276, 277, 279-281, 283, 286-289, 291, 293, 294, 296-298, 300, 302, 305, 307, 308, 311, 312, 318, 322, 329, 332, 337, 340, 341, 343, 344} The SRs were all rated as a low⁵⁵ to critically low^{4, 15, 20, 24, 39, 48, 49, 57} overall confidence in the results. Evidence from the SRs, supported by evidence from the additional CSs and ECONS, emphasized that the physiological changes during pregnancy change throughout the trimesters to suit the needs of the growing fetus. These complex adaptive changes (e.g., altered immune response), make pregnancies at a high-risk for viral respiratory infections. These changes include a gestational shift in the Th1-Th2 immune response, and a lower WBC count.

With regards to hypercoagulability, there is less certainty and consensus if COVID-19 complicated pregnancies are at a higher risk of coagulopathy and thromboembolism.

Conclusions

Overall, the quality of the evidence from previous evidence synthesis is weak and decision-making should consider looking closely at higher-quality primary studies (e.g., prospective, longitudinal studies). Large, prospective cohort studies of pregnant individuals should be continued to provide further evidence on the risks and harms of COVID-19 infections during pregnancy.

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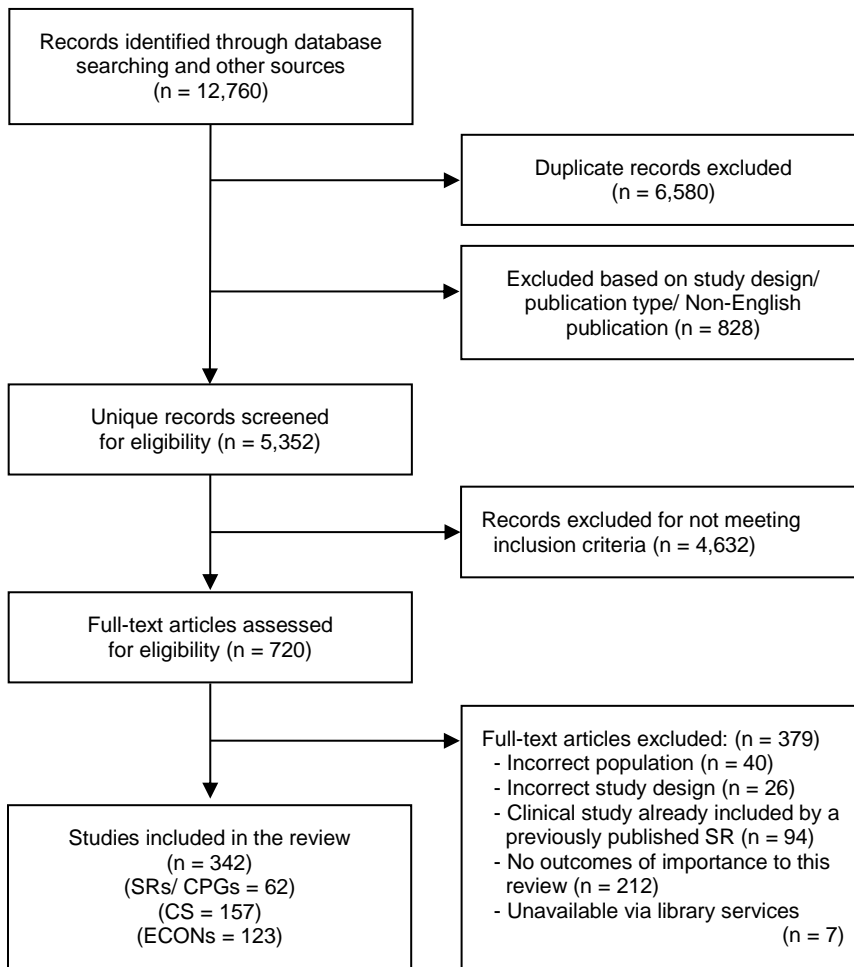
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Figure 1. Modified PRISMA flow-chart



Appendix 1. Medline (Ovid) Search Strategy

1. exp Coronavirus/ or exp Coronavirus Infections/ (96880)
2. (OC43 or NL63 or D614G or 229E or HKU1 or hcov* or ncov* or covid* or sarscov* or sars-cov* or sarscoronavir* or sars-coronavir* or 2019ncov* or 19ncov* or novel cov* or 2019novel cov* or severe acute respiratory syndrome corona*).ti,ab,kf,nm,ot,ox,rx,px. (138705)
3. ((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV)).ti,ab,kf,ot. (42496)
4. ((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf,ot. (7974)
5. ((wuhan or hubei) adj5 pneumonia).ti,ab,kf,ot. (335)
6. (COVID-19 or SARS-CoV-2).rx,px,ox,rn. or (COVID-19 or COVID-19 serotherapy or ORF7b protein, SARS-CoV-2 or ORF6 protein, SARS-CoV-2 or ORF8 protein, SARS-CoV-2 or pediatric multisystem inflammatory disease, COVID-19 related or envelope protein, SARS-CoV-2 or ORF7a protein, SARS-CoV-2 or spike protein, SARS-CoV-2 or ORF3a protein, SARS-CoV-2 or COVID-19 drug treatment or severe acute respiratory syndrome coronavirus 2 or membrane protein, SARS-CoV-2 or ORF1ab polyprotein, SARS-CoV-2 or nucleocapsid protein, Coronavirus or COVID-19 vaccine or COVID-19 diagnostic testing).os,ps,rn,rs. (7980)
7. or/1-6 (156700)
8. limit 7 to yr="2019 -Current" (140838)
9. exp pregnant women/ or exp pregnancy/ or exp pregnancy complications/ or exp maternal health services/ or exp prenatal care/ or exp perinatal care/ (959417) ()
10. (pregnan* or gestation* or gravidity or maternal or maternity or antenatal or ante natal or antepartum or ante partum or prenatal or pre natal or perinatal or peri natal or obstetric*).ti,ab,kf. (921768)
11. or/9-10 (1293208)
12. 8 and 11 (3599)
13. exp animals/ not humans.sh. (4832753)
14. 12 not 13 (3576)
15. limit 14 to english language (3472)

Appendix 2. Embase (Ovid) Search Strategy

1. exp betacoronavirus/ or coronavirinae/ or exp coronavirus infection/ (139351)
2. (OC43 or NL63 or D614G or 229E or HKU1 or hcov* or ncov* or covid* or sarscov* or sars-cov* or sarscoronavir* or sars-coronavir* or 2019ncov* or 19ncov* or novel cov* or 2019novel cov* or severe acute respiratory syndrome corona*).ti,ab,kw,hw,ot. (137391)
3. ((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,ab,kw,hw,ot. (118690)
4. ((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kw,ot. (7454)
5. ((Wuhan or Hubei) adj5 pneumonia).ti,ab,kw,ot. (370)
6. (COVID-19 or severe acute respiratory syndrome coronavirus 2).ox,dq,dj,od. (30511)
7. or/1-6 (158494)
8. limit 7 to yr="2019 -Current" (141942)
9. pregnant woman/ or exp pregnancy disorder/ or exp pregnancy/ or exp prenatal care/ or exp perinatal care/ (1090452)
10. (pregnan* or gestation* or gravidity or maternal or maternity or antenatal or ante natal or antepartum or ante partum or prenatal or pre natal or perinatal or peri natal or obstetric*).ti,ab,kw. (1128235)
11. or/9-10 (1462229)
12. 8 and 11 (4414)
13. (exp animal/ or nonhuman/) not exp human/ (6577992)
14. 12 not 13 (4381)
15. limit 14 to english language (4234)

Appendix 3. Cochrane Covid (Wiley) Search Strategy

pregnan* or gestation* or gravidity or maternal or maternity or antenatal or "ante natal" or antepartum or "ante partum" or prenatal or "pre natal" or perinatal or "peri natal" or obstetric* (2253)

Appendix 4. LitCovid (NLM) Search Strategy

pregnan* or gestation* or gravidity or maternal or maternity or antenatal or "ante natal" or antepartum or "ante partum" or prenatal or "pre natal" or perinatal or "peri natal" or obstetric* (2427)