Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Systematic review and critical evaluation of quality of clinical practice guidelines on the management of SARS-CoV-2 infection in pregnancy

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OBJECTIVE: To systematically identify and critically assess the quality of clinical practice guidelines for the management of SARS-CoV-2 infection in pregnancy.

DATA SOURCES: Medline, Scopus, and ISI Web of Science databases were searched until February 15, 2022.

STUDY ELIGIBILITY CRITERIA: Inclusion criteria were clinical practice guidelines on the management of SARS-CoV-2 infection in pregnancy. The risk of bias and quality assessments of the included clinical practice guidelines were performed using the Appraisal of Guidelines for REsearch and Evaluation II tool, which is considered the gold standard for quality assessment of clinical practice guidelines. To define a clinical practice guideline as of good quality, we adopted the cutoff score proposed by Amer et al: if the overall clinical practice guideline score was >60%, it was recommended.

METHODS: The following clinical points related to the management of pregnant women with SARS-CoV-2 infection were addressed: criteria for maternal hospitalization, recommendations for follow-up fetal growth scan, specific recommendations against invasive procedures, management of labor, timing of delivery, postpartum care, and vaccination strategy.

RESULTS: A total of 28 clinical practice guidelines were included. All recommended hospitalization only for severe disease; 46.1% (6/13) suggested a fetal growth scan after SARS-CoV-2 infection, whereas 23.1% (3/13) did not support this practice. Thromboprophylaxis with low-molecular-weight heparin was recommended in symptomatic women by 77.1% (7/9) of the clinical practice guidelines. None of the guidelines recommended administering corticosteroids only for the presence of SARS-CoV-2 infection in preterm gestation, unless specific obstetrical indication exists. Elective induction of labor from 39 weeks of gestation was suggested by 18.1% (2/11) of the clinical practice guidelines included in the present review, whereas 45.4% (5/11) did not recommend elective induction unless other obstetrical indications coexisted. There were 27% (3/11) of clinical practice guidelines that suggested shortening of the second stage of labor, and active pushing was supported by 18.1% (2/11). There was general agreement among the clinical practice guidelines in not recommending cesarean delivery only for the presence of maternal infection and in recommending vaccine boosters at least 6 months after the primary series of vaccination. The Appraisal of Guidelines for REsearch and Evaluation II standardized domain scores for the first overall assessment of clinical practice guidelines had a mean of 50% (standard deviation±21.82%), and 9 clinical practice guidelines scored >60%.

CONCLUSION: A significant heterogeneity was found in some of the main aspects of the management of SARS-CoV-2 infection in pregnancy, as reported by the published clinical practice guidelines.

Keywords: clinical practice guidelines, COVID-19, SARS-CoV-2

The COVID-19 pandemic, caused by SARS-CoV-2 infection that was first identified in December 2019, still remains a major public health concern.[1] Pregnancy is an independent risk factor for adverse outcomes in women with SARS-CoV-2 infection, especially in the presence of several comorbidities such as diabetes mellitus or preeclampsia.[2,3]

EDITOR'S CHOICE

The rapid spread of the pandemic and the higher risk of adverse maternal outcomes reported in women with SARS-CoV-2 infection underscore the importance of available evidence-based

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AJOG MFM at a Glance

Why was this study conducted?

This systematic review wants to objectively evaluate the quality of the published clinical practice guidelines on the management of SARS-CoV-2 infection in pregnancy using the Appraisal of Guidelines for REsearch and Evaluation (AGREE) II tool.

Key findings

A general agreement in the criteria for maternal hospitalization, mode of delivery, and recommendation of vaccine booster was observed. Conversely, there was large heterogeneity in several other management aspects, including type and frequency of maternal assessment after infection, ultrasound scans, timing of delivery, and type of fetal monitoring during labor.

What does this add to what is known?

The results of this systematic review indicate the need for developing shared guidelines supported, endorsed, and promoted by national and international professional societies to make management of SARS-CoV-2 infection in pregnant women more homogeneous among different countries.

guidelines for the management of this infection in pregnancy.[4–32]

Clinical Practice Guidelines (CPGs) are statements that include recommendations intended to optimize patient care. CPGs should follow a rigorous methodology to provide clinicians with the most up-to-date and objective clinical evidence. However, high-quality CPGs are methodologically complex to develop, which makes them relatively incompatible with emergency situations. Rapid Guidelines (RGs) are defined as CPGs that are developed in a 1- to 3-month time frame and are alternatives to comprehensive CPGs, providing guidance in response to an emergency.[33] Since the beginning of the pandemic, a multitude of RGs reporting different aspects of the management of SARS-CoV-2 infection in pregnancy have been released. However, the methodological robustness of such guidelines has yet to be determined.[34]

The Appraisal of Guidelines for REsearch and Evaluation (AGREE) II tool is the most widely used tool for appraising the quality of CPGs, and it has been considered as the gold standard for CPG quality assessment.[35]

The primary aim of this systematic review (SR) was to objectively evaluate the quality of the published CPGs on the management of SARS-CoV-2 infection in pregnancy using the AGREE II tool. The secondary aim was to assess and report the agreement or heterogeneity among the CPGs regarding different aspects of clinical management of SARS-CoV-2 infection.

Methods

Protocol, information sources, and literature search

This review was performed according to a protocol recommended for SRs of clinical guidelines.[36] The review protocol was not designed a priori, given the rapid evolution of the pandemic and the speed of the evidence synthesis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed (Table S1).[36] The literature search was conducted in the MEDLINE (PubMed), Scopus, and ISI Web of Science databases to identify all relevant CPGs published before February 15, 2022. Combinations of the following keywords and Medical Subject Headings (MeSH) search terms were used: ("management" OR "managing") AND ("SARS-CoV-2" OR "COVID-19" OR "coronavirus") AND ("pregnancy" OR "pregnant" OR "pregnant women" OR "during pregnancy" AND ("antenatal care" OR "prenatal" OR "vaccine" OR "ultrasound" OR "delivery") AND ("guidelines"). No restrictions for geographic location were applied. The reference lists of relevant recommendations and considerations were also hand-searched to complement the database search. The search was restricted to guidelines published in English.

Only CPGs including recommendations on the management of pregnant women with SARS-CoV-2 infection were considered eligible for this SR. Two reviewers (R.D.G., G.C.) independently evaluated titles and abstracts. Disagreements were resolved by discussion among authors, and if required, with the involvement of a third author (F.D.A.). When >1 version was available, the most updated version was included, considering newer versions methodologically as equivalent to previous versions, given that they were written using the same approach. Any CPGs on the organization of antenatal or postnatal services or information for healthcare professionals in the context of the COVID-19 pandemic were excluded.

Data extraction

The main data extracted for the present review included publication ID (first author, a research consortium, or a professional society), year of publication, country, title, society, scope of the CPG, date of publication, number of revisions, and type of methodology adopted. The outcomes were extracted and reported in an online Google Sheets document for sharing among all authors.

Risk of bias assessment and quality appraisal of guidelines

The assessment of risk of bias and quality assessment of the included CPGs were performed using the AGREE II tool,35 which comprehends 23 items grouped into 6 quality domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence.

Each of the 23 items targets various aspects of CPG quality, and was

evaluated on a 7-point scale from 1 (strongly disagree) to 7 (strongly agree).

A final overall assessment includes the rating of the overall quality of the CPG (OA1) and whether the CPG would be recommended for use in practice (OA2).

To begin the appraisal process, it is recommended that at least 2 (preferably 4) appraisers review each CPG to increase the reliability of the assessment. The standardized domain score would be 0% if each appraiser gave a score of 1 for all the items included in this domain (https://www.agreetrust.org/resource-centre/agree-ii).[35] A consensus method for scoring the items was applied. After the review of the 23 items and the comprehensive evaluation by the reviewers, the CPGs were divided into 3 categories according to the AGREE II score: recommended, recommended after revision, and not recommended.

Statistical analysis

Statistical analysis was performed using descriptive statistics. We calculated frequencies and raw proportions to summarize the main recommendations for managing perinatal care of pregnant women with SARS-CoV-2 infection and their timing of delivery. In addition, we analyzed guidelines regarding other issues addressed, such as admission to hospital, vaccination policy, etc., and calculated proportions and percentages for each issue. Moreover, we calculated the quality of CPGs using AGREE II domain scores. Mean ± standard deviation (SD) was used to summarize the scores across all the guidelines per domain. The AGREE II tool does not provide any guidelines on how to define scores. To define a CPG as of good quality, we adopted the cutoff score proposed by Amer et al[37]: if the overall CPG score was >60%, it was recommended; if the overall CPG score was 40% to 60%, it was recommended after modification; and if the CPG score was <40%, it was not recommended. The analysis was performed using Excel, version 16.57 (Microsoft Corporation, Redmond, WA).

Outcome measures

The following outcomes related to the management of pregnant women with SARS-CoV-2 infection were addressed: criteria for maternal hospitalization, recommendations for follow-up growth scan, specific recommendations against invasive procedures, use of supportive therapy (antenatal or maternal care), management of labor, indication for cesarean delivery, postpartum care, indication for vaccine booster.

Results

Study selection and characteristics

A total of 20,798 articles were identified and screened; 38 were assessed with respect to their eligibility for inclusion, and 28 CPGs[5–32] were included in the qualitative analyses, whereas 19 were included in quantitative analysis (Tables 1 and 2; Figure). Main recommendations were extracted, synthesized, and reported in Table 3. The CPGs included in this SR were obtained from expert opinions, literature reviews, and expert panel consensus recommendations, and were representative of different countries (16 national, 10 international, and 2 local). The proportion of studies that were published in 2021 was 60.7% (17/28), and 7.1% (2/28) had more than 5 revisions.

Synthesis of results

All the CPGs included in the SR did not recommend maternal hospitalization only for SARS-CoV-2 infection, and there was general agreement that admission to hospital should be restricted to women with severe infection. Fifty percent of the included guidelines specifically stated the criteria for maternal admission, including respiratory distress, respiratory rate >22/min, O_2 saturation <95%, or rapid deterioration in respiratory status.

The 46.1% (6/13) of CPGs suggested to perform a fetal growth scan after SARS-CoV-2 infection (generally after 2 weeks); 23.1% (3/13) did not support this practice, whereas the remaining 30.8% (4/13) did not address this point. The proportion of CPGs included in the present review suggesting monthly maternal assessment after the infection was 38.4% (5/13). The large majority of CPGs (80%, 4/5) did not report any contraindication in case the patient should undergo invasive procedures, whereas one suggested delaying chorionic villus sampling and opting for amniocentesis.

Thromboprophylaxis with low-molecular-weight heparin (LMWH) was recommended for symptomatic women in 77.7% (7/9) of CPGs. None of the CPGs recommended administering corticosteroids only for the presence of SARS-CoV-2 infection in preterm gestation, unless specific obstetrical indication coexists, because such corticosteroid therapy is specifically for fetal lung maturity. Management of labor in women with SARS-CoV-2 infection was addressed by 11 CPGs. Elective induction of labor (IOL) at 39 weeks of gestation was recommended by 18.1% (2/11) of the CPGs, whereas 45.4% (5/11) did not recommend elective induction unless other obstetrical indications coexist with maternal infection. Oxygen support was suggested by 75% of CPGs (9/12), and continuous fetal electronic monitoring by 58.3 % (7/12). There were 27.2% (3/11) of CPGs that recommended shortening of the second stage of labor, mainly with iatrogenic rupture of the membranes or oxytocin infusion, and active pushing was supported by 18.1% (2/11). A general agreement was recorded among the CPGs in not recommending cesarean delivery only for the presence of maternal infection, although 77.7% (7/9) of the guidelines suggested considering it in the case of severe maternal SARS-CoV-2 infection with worsening of maternal conditions. The need for postpartum thromboprophylaxis with LMWH was mentioned in only one CPG out of those included, as well as the need for sending placenta specimens to histopathology for examination. Finally, there was general agreement in recommending completion of vaccine series at least 6 months after the primary vaccine (Table 4), and 88.9% (8/9) of the included CPGs did not report any specific restrictions with regard to the gestational age at vaccination.

TABLE 1
General characteristics of the clinical practice guidelines included in the quantitative analyses of systematic review

First author or Society	Year	Country	Title	Society	Scope	Date of pubblication	Number of revisions	Method of development
CAPWHN[6]	2020	CANADA	Suggestions for the care of the perinatal population	Canadian Association of Perinatal and Women's Health Nurses	National	2020	0	Expert opinion, methods not reported
D. CHAWLA[11]	2020	INDIA	Perinatal-Neonatal Management of COVID-19 Infection	Federation of Obstetric and Gynaecological Societies of India (FOGSI), National Neonatology Forum of India (NNF), and Indian Academy of Pediatrics (IAP)	National	2020	0	Review of literature, expert panel consensus, GRADE
C. ELWOOD[12]	2020	CANADA	Committee Opinion No. 400: COVID-19 and Pregnancy	The Society of Obstetricians and Gynaecologists of Canada (SOGC)	National	2021	2	Review of literature, expert panel consensus, methods not reported
CDC[13]	2020	USA	COVID-19 Vaccines While Pregnant or Breastfeeding	Centers for Disease Control and Prevention	National	2021	3	Methods not reported
ACOG[14]	2020	USA	COVID-19 Vaccination Considerations for Obstetric–Gynecologic Care	American College of Obstetricians and Gynecologists	National	2021	3	Review of literature, expert panel consensus, methods not reported
E. Miller[15]	2020	UK	Society for Maternal-Fetal Medicine and Society for Obstetric and Anesthesia and Perinatology Labor and Delivery COVID-19 Consideration	The Society for Maternal-Fetal Medicine (SMFM)	National	2021	7	Expert opinion, methods not reported
RANZCOG[16]	2020	AUSTRALIA	Coronavirus Disease (COVID-19) in Pregnancy A guide for resource-limited environments	The Royal Australian and New Zealand College of Obstetricians and Gynaecologists	National	2020	3	Review of literature, expert panel consensus, methods not reported
NSW[18]	2020	AUSTRALIA	Guidance for maternity, newborn care and infant feeding, Medicine management for pregnant patients with COVID-19	New South Wales government Health	Local	2021	3	Review of literature, expert panel consensus, methods not reported
QUEBEC GROUP[19]	2020	CANADA	Guidelines for the management of the pregnant woman with COVID-19 admitted to the intensive care unit (ICU)	Quebec Maternal-Fetal. Medicine group	Local	2020	0	Expert panel consensus, methods not reported
Governament of India[20]	2021	INDIA	Guidelines on operationalization of maternal health services during COVID-19 pandemic	Maternal Health Division Ministry of Health & Family Welfare	National	2021	0	Methods not reported
Indian Council of Medical Research[21]	2020	INDIA	Guidance for Management of Pregnant Women in COVID-19 Pandemic	National Institute for Research in Reproductive Health (ICMR)	National	2020	0	Expert panel consensus, methods not reported

(continued)

TABLE 1
General characteristics of the clinical practice guidelines included in the quantitative analyses of systematic review *(continued)*

First author or Society	Year	Country	Title	Society	Scope	Date of pubblication	Number of revisions	Method of development
M. O. Bahtiyar[22]	2021	USA	Fetal interventions in the setting of the coronavirus disease 2019 pandemic: statement from the North American Fetal Therapy Network	North American Fetal Therapy Network (NAFTN)	National	2021	0	Expert opinion, methods not reported
L. C. Poon[25]	2020	ns	ISUOG Interim Guidance on coronavirus disease 2019 (COVID-19) during pregnancy and puerperium: information for healthcare professionals – an update	International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)	International	2020	1	Review of literature, expert panel consensus, methods not reported
T. Bourne[26]	2020	ns	ISUOG Consensus Statement on rationalization of early-pregnancy care and provision of ultrasonography in context of SARS-CoV-2	International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)	International	2020	1	Review of literature, expert panel consensus, methods not reported
RCOG[27]	2020	UK	Guidance for antenatal screening and ultrasound in pregnancy in the coronavirus (COVID-19) pandemic	Royal College of Obstetricians and Gynaecologists (RCOG)	National	2021	1.2	Review of literature, expert panel consensus, methods not reported
RCOG[28]	2021	UK	Guidance for rationalising early pregnancy services in the evolving coronavirus (COVID-19) pandemic	Royal College of Obstetricians and Gynaecologists (RCOG)	National	2021	2	Expert panel consensus, methods not reported
RCOG[29]	2021	UK	Coronavirus (COVID-19) infection and pregnancy	Royal College of Obstetricians and Gynaecologists (RCOG)	National	2022	14.3	Expert panel consensus, searching through literature
HIS[31]	2020	UK	COVID-19 position statement: Maternal critical care provision	Healthcare improvement Scotland (HIS)	National	2020	2	Expert opinion, methods not reported
SIGO/AOGOI[32]	2021	Italy	Interim guidance on pregnancy, childbirth, breastfeeding and care of infants (0-2 years) in response to the COVID-19 emergency	Italian Society of Gynaecology and Obstetrics/ Association of Italian Hospital Gynaecologists and Obstetricians	National	2021	2	Review of literature, expert panel consensus, methods not reported

Not specified (ns)

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TABLE 2
AGREE-ment scores

ID AGREE II	Domain 1 (Items 1-3)	Domain 2 (Items 4-6)	Domain 3 (Items 7-14)	Domain 4 (Items 15-17)	Domain 5 (Items 18-21)	Domain 6 (Items 22-23)	OA1	OA2
CAEP.CA[5]	86%	0%	0%	24%	32%	29%	0%	Y (n=0) YWM (n=0) N (n=2)
CAPWHN[6]	86%	43%	21%	48%	32%	64%	43%	Y (n=0) YWM (n=2) N (n=0)
AAFP[7]	86%	0%	0%	24%	32%	29%	0%	Y (n=0) YWM (n=0) N (n=2)
CPS[8]	86%	43%	21%	48%	32%	64%	43%	Y (n=0) YWM (n=2) N (n=0)
AAP[9]	43%	38%	38%	48%	50%	50%	43%	Y (n=0) YWM (n=2) N (n=0)
CDC[10]	90%	81%	59%	90%	61%	43%	71%	Y (n=2) YWM (n=0) N (n=0)
FOGSI, NNF, IAP[11]	86%	76%	64%	67%	57%	43%	71%	Y (n=2) YWM (n=0) N (n=0)
SOGC[12]	90%	57%	70%	57%	57%	43%	57%	Y (n=1) YWM (n=1) N (n=0)
CDC[13]	90%	81%	59%	90%	61%	43%	71%	Y (n=2) YWM (n=0) N (n=0)
ACOG[14]	90%	57%	70%	62%	54%	43%	57%	Y (n=1) YWM (n=1) N (n=0)
SMFM[15]	86%	43%	54%	86%	67%	50%	71%	Y (n=2) YWM (n=0) N (n=0)
RANZCOG[16]	86%	62%	64%	52%	54%	36%	57%	Y (n=1) YWM (n=1) N (n=0)
FIGO[17]	81%	38%	59%	67%	43%	64%	43%	Y (n=0) YWM (n=2) N (n=0)
NSW[18]	86%	48%	27%	52%	61%	57%	43%	Y (n=0) YWM (n=2) N (n=0)
QUEBEC GROUP[19]	43%	38%	38%	48%	50%	50%	43%	Y (n=0) YWM (n=2) N (n=0)
GOVERNAMENT OF INDIA[20]	86%	43%	21%	48%	32%	64%	43%	Y (n=0) YWM (n=2) N (n=0)
ICMR[21]	86%	0%	0%	24%	32%	29%	0%	Y (n=0) YWM (n=0) N (n=2)
NAFTN[22]	43%	38%	38%	48%	50%	50%	43%	Y (n=2) YWM (n=2) N (n=0)
EBC[23]	90%	57%	59%	52%	54%	43%	43%	Y (n=0) YWM (n=2) N (n=0)
ISIDOG[24]	43%	43%	21%	48%	32%	29%	43%	Y (n=0) YWM (n=2) N (n=0)
ISUOG[25]	90%	81%	59%	52%	61%	43%	71%	Y (n=2) YWM (n=0 N (n=0)
ISUOG[26]	90%	57%	70%	62%	54%	57%	57%	Y (n=1) YWM (n=1) N (n=0)

(continued)

TABLE 2
AGREE-ment scores *(continued)*

ID AGREE II	Domain 1 (Items 1-3)	Domain 2 (Items 4-6)	Domain 3 (Items 7-14)	Domain 4 (Items 15-17)	Domain 5 (Items 18-21)	Domain 6 (Items 22-23)	OA1	OA2
ISUOG[27]	86%	76%	64%	67%	57%	43%	71%	Y (n=2) YWM (n=0 N (n=0)
RCOG[28]	90%	57%	70%	57%	57%	50%	71%	Y (n=2) YWM (n=0) N (n=0)
RCOG[29]	90%	76%	59%	48%	61%	64%	71%	Y (n=2) YWM (n=0) N (n=0)
RCOG[30]	90%	81%	59%	90%	61%	43%	71%	Y (n=2) YWM (n=0 N (n=0)
HIS[31]	86%	43%	21%	48%	32%	64%	43%	Y (n=0) YWM (n=2) N (n=0)
SIGO/AOGOI[32]	90%	71%	59%	52%	61%	29%	57%	Y (n=1) YWM (n=1) N (n=0)
Average score for each domain (n%) *	**81%**	**51%**	**44%**	**56%**	**49%**	**47%**	**50%**	
SD for each domain (±%)	**16%**	**24%**	**23%**	**18%**	**12%**	**12%**	**21%**	

*A cut-off for high quality CPGs of 60% or more for all the 6 AGREE II domains were selected in consideration of the limitations associated with the Rapid Guidelines (RGs)' development. The cut-offs for low and moderate quality are <40% (highlighted in red) and 40%–60% (highlighted in orange), respectively. The cut-offs for high quality are >60% (highlighted in green).

CAEP.CA, Canadian Association of Emergency Physicians; AAFP, American Academy of Family Physicians; CPS, Canadian pediatric Society; AAP, American Academy of Pediatrics; CDC, Centers for Disease Control and Prevention; CAPWH, Canadian Association of Perinatal and Women's Health Nurses; FOGSI, Federation of Obstetric and Gynaecological Societies of India; NNF, National Neonatology Forum of India; IAP, Indian Academy of Pediatrics; SOGC, The Society of Obstetricians and Gynaecologists of Canada; CDC, Centers for Disease Control and Prevention; SMFM, The Society for Maternal-Fetal Medicine; RANZCOG, The Royal Australian and New Zealand College of Obstetricians and Gynaecologists; FIGO, International Federation of Gynacology and Obstetrics; NSW, New South Wales Government Health; QMFMG, Quebec Maternal-Fetal Medicine group; GOI, Government of India; ICMR, National Institute for Research in Reproductive Health; NAFTN, North American Fetal Therapy Network; ISIDOG, International Society of Infectious Diseases in Obstetrics and Gynecology; ISUOG, International Society of Ultrasound in Obstetrics and Gynecology; RCOG, Royal College of Obstetricians and Gynaecologists; JCV, Joined Commette Vaccination; RCOG, Royal College of Obstetricians and Gynaecologists; HIS, Healthcare improvement Scotland; SIGO/AOGOI, Italian Society of Gynaecology and Obstetrics/ Association of Italian Hospital Gynaecologists and Obstetricians; OA1, Overall Guideline Assessment 1; OA2, Overall Guideline Assessment 2; Y, Yes; YWM, Yes with modifications; N, No.

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Methodological quality of clinical practice guidelines

The AGREE II domains are summarized in Table 2. The average AGREE II standardized score for each domain is reported below (mean±SD).

The cutoff for CPGs of high quality was >60%, represented in green (Table 2). Medium quality (with 40% −59% cutoff) was represented in yellow and low quality in red.

Only 1 CPG[11] reported the use of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

The AGREE II standardized domain scores for the first overall assessment (OA1) had a mean of 50% (SD±21.0%). Nine CPGs scored >60%[10,11,13,15,25,27–30] and revealed a consensus agreement between the reviewers on recommending their use.

Discussion

Summary of the main findings

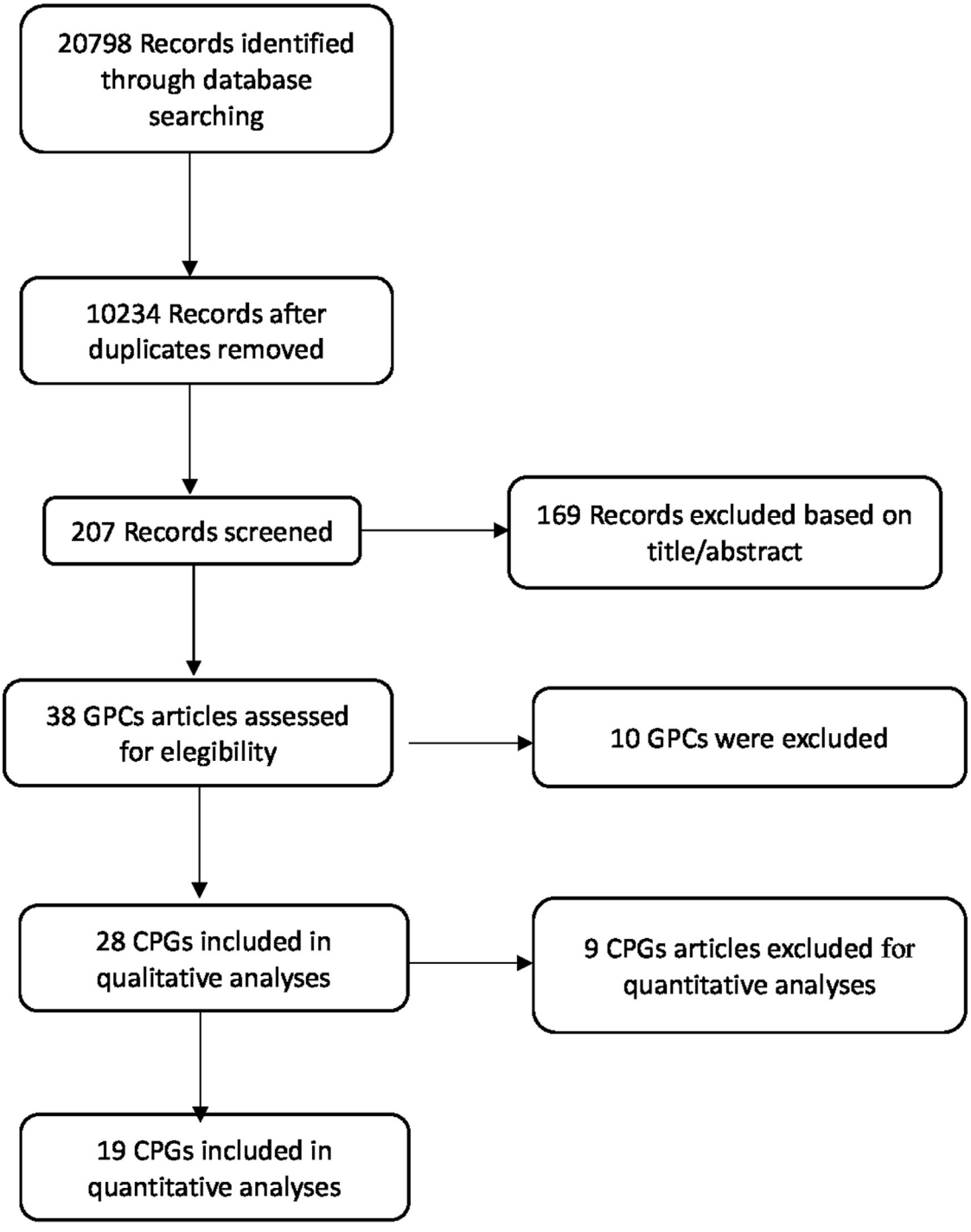
The findings of this SR of CPGs showed that significant heterogeneity and disagreement were assessed in several aspects of clinical management of SARS-CoV-2 infection in pregnancy as reported by the published CPGs. There was a general agreement in the criteria for maternal hospitalization, mode of delivery, and recommendation for vaccine booster. Conversely, a large heterogeneity was observed in several other management aspects, including type and frequency of maternal assessment after the infection, ultrasound scans, timing of delivery, and type of fetal monitoring during labor.

Strengths and limitations

This SR of CPGs on SARS-CoV-2 infection in pregnancy used a recognized tool (AGREE II) for evaluating medical guidelines. Other strengths included the thorough literature search and assessment of the multitude of management aspects of pregnancies with SARS-CoV-2 infection. The main weakness of the present review is the methodological quality of some of the included CPGs, as indicated by their low AGREE II scores.

Of note, the methods of guideline development were not reported for most of the included CPGs, making the assessment of Domain 3 with AGREE II challenging, thus limiting an objective evaluation of the included CPGs. It has been suggested that Domains 3 and 5 (applicability), in addition to domain 6 (editorial independence), may have had the greatest effect on the results of the 2 overall assessments of the CPGs. These guidelines were developed as an acute

FIGURE
PRISMA flowchart



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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TABLE 3

Graphic description of issues addressed by eligible rapid guidelines for antenatal care management of pregnant women with COVID-19

Guideline	CAPWHN[6]	FOGSI, NNF, IAP[11]	SOGC[12]	CDC[13]	ACOG[14]	SMFM[15]	RANZCOG[16]	NSW[18]	GMFMQ[19]	GOI[20]	ICMR[21]	NAFTN[22]	ISUOG[25]	ISUOG[26]	RCOG[27]	RCOG[28]	RCOG[29]	HIS[31]	SIGO[32]
Year	2020	2020	2020	2020	2020	2020	2020	2020	2020	2021	2020	2021	2020	2020	2020	2021	2022	2020	2021
Maternal hospitalization criteria for COVID-19						X		X	X		X					X			X
Maternal hospitalization criteria for Obstetric conditions	X		X							X			X	X				X	
Ultrasound scan soon after recovery										X	X		X		X		X		X
Monthly surveillance during pregnancy after recovery			X					X		X			X						X
Specific recommendations against invasive procedures												X							
Use of antenatal anticoagulation with LMWH						X			X	X	X		X				X	X	X
Send placenta to histopathology								X											
Corticosteroids for COVID-19 symptoms			X			X			X	X							X		
Other Supportive therapies during labor	X	X	X			X	X	X	X	X	X						X	X	X
Continuous fetal electronic monitoring		X	X				X	X	X		X						X		
Induction of labor at 39 weeks						X				X									
Indication for CS for COVID-19 symptoms										X	X						X		
Shortening of the second stage of labor							X				X								
Active pushing										X									
Post-partum care: is use LMWH encouraged?																	X		
Vaccine booster			X	X	X	X											X		

CS, Cesarean section; LMWH, low molecular weight heparin; CAPWH, Canadian Association of Perinatal and Women's Health Nurses; FOGSI, Federation of Obstetric and Gynaecological Societies of India; NNF, National Neonatology Forum of India; IAP, Indian Academy of Pediatrics; SOGC, The Society of Obstetricians and Gynaecologists of Canada; CDC, Centers for Disease Control and Prevention; SMFM, The Society for Maternal-Fetal Medicine; RANZCOG, The Royal Australian and New Zealand College of Obstetricians and Gynaecologists; NSW, New South Wales Government Health; QMFMG, Quebec Maternal-Fetal Medicine group; GOI, Government of India; ICMR, National Institute for Research in Reproductive Health; NAFTN, North American Fetal Therapy Network; ISUOG, International Society of Ultrasound in Obstetrics and Gynecology; RCOG, Royal College of Obstetricians and Gynaecologists; HIS, Healthcare improvement Scotland; SIGO/AOGOI, Italian Society of Gynaecology and Obstetrics/ Association of Italian Hospital Gynaecologists and Obstetricians.

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TABLE 4
Description of issues addressed by eligible rapid guidelines for antenatal care management of pregnant women with COVID-19

Issues (guidelines total=19)	N (%)
• Criteria for hospital admission (12)	
Admission in case of severe disease (not specified)	6/12 (50)
Specific criteria for admission (respiratory distress >22/min, O_2 saturation <95%, rapid deterioration in respiratory status)	6/12 (50)
• Ultrasound assessment (13)	
Ultrasound scan soon after recovery	
Recommend	6/13 (46.1)
Recommend against	1/13 (7.6)
No recommendation for or against	6/13 (46.1)
Monthly surveillance during pregnancy after recovery	
Recommend	5/13 (38.4)
Recommend against	3/13 (23.0)
No recommendation for or against	4/13 (30.7)
• Specific recommendations against invasive procedures (5)	
Recommend	1/5 (20)
Recommend against	4/5 (80)
• Use of anticoagulation with LMWH (9)	
Recommend when patient has COVID-19 symptoms	7/9 (77.7)
Recommend against	1/9 (11.1)
Recommend ever	1/9 (11.1)
• Corticosteroids for COVID-19 symptoms (8)	
Recommend, preferably using those not passing placenta	4/8 (50.0)
No recommendation for or against, but still suggested for obstetrical indications as usual	4/8 (50.0)
• Management of labor (12)	
Fluids	3/12 (25.0)
Oxygen	9/12 (75.0)
Continuous fetal electronic monitoring	7/12 (58.3)
Induction of labor at 39 wk (11)	
Recommend	2/11 (18.1)
Recommend against	5/11 (45.4)
Shortening the second stage of labor	3/11 (27.2)
Active pushing	2/11 (18.1)
• Send placenta to histopathology (19)	
No recommendation for or against	18/19 (94.7)
Recommend	1/19 (5.2)
• Indication for CD in case of symptomatic COVID-19 (9)	
Recommend against, but consider in severe or worsening course of the disease	7/9 (77.7)
Recommend against	2/9 (22.2)

(continued)

response to a period of crisis, which partially explains the lack of detailed methodological descriptions for some of the included guidelines. However, a positive sign in CPG development methodology was the application of GRADE in some of the more recent CPGs, indicating improvements in their quality and trustworthiness.

Interpretation of the study findings, clinical and research implications

The rapid spread of the pandemic has made the availability of objective evidence-based guidelines on the management of SARS-CoV-2 infection in pregnancy critical. Pregnancy represents an independent risk factor for severe SARS-CoV-2 infection, and infected women are at higher risk of adverse maternal outcomes, including mechanical ventilation, admission to the intensive care unit, and even death, compared with nonpregnant infected women.[38–40] Several risk factors have been associated with an increased risk of symptomatic infection, including obesity, hypertension, underlying respiratory disorder, and Black or Asian race.[41,42] In view of such associations, all pregnant women with SARS-CoV-2 infection should be closely monitored for the development of symptoms and signs of severe COVID-19 disease. Importantly, some of the clinical manifestations of COVID-19 overlap with symptoms of normal pregnancy (ie, fatigue, shortness of breath, nasal congestion, nausea or vomiting), which should be considered during the evaluation of afebrile symptomatic women. Nevertheless, 75% of women will experience an asymptomatic infection, not requiring hospitalization.[43] In the present review, there was general agreement on the criteria for maternal hospital admission in those with SARS-CoV-2 infection, with all the included CPGs recommending hospitalization only for severe disease. Moreover, although pregnant women still show hesitancy toward COVID-19 vaccines,[44–46] CPGs already declared the safety and efficacy of available messenger RNA vaccines against SARS-CoV-2 infection, and also the usefulness of the booster dose in reducing the rate of complications during pregnancy (Tables 3

TABLE 4
Description of issues addressed by eligible rapid guidelines for antenatal care management of pregnant women with COVID-19 *(continued)*

Issues (guidelines total=19)	N (%)
• Postpartum care: is use of LMWH recommended? (19)	
No recommendation for or against	18/19 (94.7)
Recommend	1/19 (5.2)
• Vaccine booster (5)	
Recommend, pregnant women at increased risk	1/5 (20)
Recommend, 6 mo after their Pfizer/Moderna primary series	4/5 (80)

CD, cesarean delivery; *LMWH*, low-molecular-weight heparin.

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and 4). The association between SARS-CoV-2 variants and maternal or perinatal outcomes represents another particular issue given that the risk of adverse outcomes may vary according to virus variants, thus affecting the recommendations provided by CPGs. Most of the reported data on the association between SARS-CoV-2 infection and maternal outcomes come from the early stages of the pandemic when wild-type SARS-CoV-2 predominated. A recent study carried out through the UK Obstetric Surveillance System, including over 4000 pregnant women, reported that the Alpha and Delta variants have been associated with more severe disease in pregnancy than the wild-type variant.[47] After adjustment for potential confounding factors, both Alpha and Delta were independently associated with admission to the intensive care unit. Conversely, no difference was found in the risk of perinatal outcomes (mainly stillbirth) between wild-type, Alpha, and Delta variants. The effect of the Omicron variant on maternal and perinatal outcomes is more difficult to assess because most studies included fully vaccinated women. Birol Ilter et al[48] reported that fully vaccinated pregnant women infected with SARS-CoV-2 during the Omicron wave had milder illness and were less likely to require oxygen supplementation and intensive care than their unvaccinated counterparts. Despite the apparently lower risk of adverse maternal outcomes reported in vaccinated pregnant women with SARS-CoV-2 infection, it is not possible to provide specific guidelines for women infected with the Omicron variant for various reasons. First, viral sequencing is not extensively undertaken. Second, the studies reporting the outcomes of pregnant women infected with the Omicron variant include mainly vaccinated women, thus potentially biasing their findings. Last, pregnancy represents an independent risk factor for adverse outcomes in SARS-CoV-2 infection, and COVID-19–positive women should be thoroughly followed up because the course of the infection may be unpredictable.

Recent studies and SRs have reported that a large proportion of pregnancies complicated by SARS-CoV-2 infection have placental histopathologic abnormalities consistent with placental inflammation and hypoperfusion. Although there is no standard definition of placental SARS-CoV-2 infection and no definite COVID-19–specific placental changes, the association between infection and placental signs of the disease raises the question of whether these pregnancies should undergo more intensive surveillance to identify placenta-related complications such as preeclampsia or fetal growth restriction. Indeed, it should be recommended to send placental tissue of all SARS-CoV-2–infected pregnant women to histopathology.[49] A recent meta-analysis of observational studies reported 62% higher odds of developing preeclampsia among infected patients. Furthermore, preeclampsia with severe features, eclampsia, HELLP syndrome, and preterm birth are also reported to be increased in pregnant women with SARS-CoV-2 infection, whereas the association with preterm birth is less established. Likewise, there is emerging evidence on the increased risk of stillbirth in pregnant women with SARS-CoV-2 infection. A recent report from the United States including 1.2 million births reported that the risk of stillbirth was 1.26% in infected women vs 0.64% in noninfected women. The risk of stillbirth increased with the presence of comorbidities such as chronic hypertension, multiple gestation, cardiac disease, placental abruption, acute respiratory distress syndrome, and mechanical ventilation, and was mainly due to the Delta virus variant.[50] In the present review, there was no general agreement on the need for increased maternal and fetal surveillance after the infection, with nearly half of the CPGs suggesting increased fetal surveillance starting from 15 days following maternal infection. (Tables 3 and 4)

Another important dilemma in the management of SARS-CoV-2 infection in pregnancy is the timing of birth. The recently published ARRIVE (A Randomized Trial of Induction Versus Expectant Management) trial reported that elective IOL at 39 weeks of gestation results in a significantly lower frequency of cesarean delivery in healthy pregnancies.[51] Since the beginning of the pandemic, elective delivery of women with asymptomatic or nonsevere SARS-CoV-2 infection at 39 weeks of gestation has been suggested by several authors to decrease the risk of worsening maternal status before the onset of spontaneous labor.[52] Elective IOL at 39 weeks of gestation was suggested by only 2 CPGs,[15,20] whereas the remaining CPGs did not specifically recommend this practice. Conversely, in severely symptomatic women, delivery could be indicated by the worsening of maternal clinical conditions and may be considered by 32 to 34 weeks' gestation.[20–27]

It is the collective authors' opinion that, despite the coverage offered by the COVID-19 vaccines, women with SARS-CoV-2 infection should be strictly followed up to detect early signs of severe infection. Risk stratification is crucial when assessing these mothers because some particular medical conditions, mainly preeclampsia and diabetes mellitus, represent additional independent risk

factors for the development of severe infection. In this scenario, women with such additional risk factors should undergo a closer follow-up. A growth scan within a month from the infection is advisable in view of the association between SARS-CoV-2 infection and placenta-related disorders, mainly fetal growth restriction. Last, timing of IOL should be carefully evaluated. Although elective IOL at 39 weeks' gestation in women with current or previous SARS-CoV-2 infection is not the common clinical practice in any of the authors' affiliated institutions, a closer follow-up of these women is commonly considered because of the association between infection and placenta-related disorders. This allows the identification of pregnancies at higher risk of adverse perinatal outcomes, which may benefit from elective IOL.

Conclusions

A significant heterogeneity was found in some of the main aspects of clinical management of SARS-CoV-2 infection in pregnancy, as suggested by the published CPGs, especially regarding follow-up after the infection and timing of delivery. The findings from this SR highlight the need for developing shared guidelines supported, endorsed, and promoted by national and international professional societies to make the management of SARS-CoV-2 infection in pregnant women more homogeneous among different countries. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ajogmf.2022.100654.

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