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Clinical practice guidelines on the use of aspirin in pregnancy: Systematic review

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ABSTRACT

Background: Placental related disorders, including preeclampsia and fetal growth restriction (FGR) are among the main determinants of adverse maternal and perinatal outcomes in both singleton and twin pregnancies. In view of its relevance, aspirin administration is commonly recommended to women at high risk for preeclampsia or FGR by the various national and international guidelines.

Objectives: To establish the clinical heterogeneity among the clinical practice guidelines (CPGs) on aspirin use in pregnancy and to investigate the quality of these CPGs.

Methods: We performed a systematic review of Clinical practice guidelines on main databases searching for all peer-reviewed guidelines into the literature, analyzing the following aspects related to use of aspirin in pregnancy: indications for aspirin administration, dosage, starting of therapy, ending of therapy, safety and side effects. The assessment of risk of bias and quality assessment of the included CPGs were performed using "The Appraisal of Guidelines for REsearch and Evaluation (AGREE II)" tool.

Results: 16 CPGs were included. There was an overall general agreement among the published CPGs as regards to the indication for aspirin intake in pregnancy, with prior preeclampsia, chronic hypertension, autoimmune disease, and diabetes mellitus type 1 or 2 recognized as solitary major risk factors for Aspirin administration in 93.7% (15/16) of CPGs.

There was heterogeneity in the recommendations provided by the different CPGs as regards the gestational age at which aspirin should be commenced.

Conclusion: There is general agreement in the reported indications for aspirin intake in pregnancy, with prior preeclampsia and maternal medical co-morbidity associated with increased risk of preeclampsia being the major indications for aspirin intake. Conversely, there was heterogeneity in the recommended dose, gestational age at initiation and discontinuation of therapy among the different CPGs.

Introduction

Placental related disorders, including preeclampsia and fetal growth restriction (FGR) are among the main determinants of adverse maternal and perinatal outcomes in both singleton and twin pregnancies [1]. Accurate risk stratification and early screening for preeclampsia and FGR could contribute to improve perinatal outcome [2]. Previous systematic reviews and randomized controlled trials have reported a significant reduction of preeclampsia and FGR in women receiving aspirin, with higher dosages and early gestational age at administration being associated with a higher magnitude of its effect [3–6].

In view of its relevance, aspirin administration is commonly

Abbreviations: **FGR**, fetal growth restriction; **PE**, preeclampsia; **CPGs**, clinical practice guideline; **AGREE II**, The Appraisal of Guidelines for REsearch and Evaluation tool.

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recommended to women at high risk for preeclampsia or FGR by the various national and international guidelines [7–22]. 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. The Appraisal of Guidelines for REsearch and Evaluation tool (AGREE II) is the most widely utilized tool to appraise the quality of CPGs, and it has been considered as the 'gold standard' for CPG quality assessment [23]. The published literature on aspirin in pregnancy is highly heterogeneous with regards to the indications for administration, gestation at starting of therapy and dosage. It is yet to ascertained whether there is agreement among the published CPGs on these aspects of aspirin use in pregnancy.

The aim of this systematic review was to evaluate the clinical heterogeneity among the published CPGs on aspirin use in pregnancy and to investigate their quality.

Methods

Search strategy

This review was performed according to a protocol recommended for Systematic Review of Clinical Guidelines [24]. PRISMA guidelines were followed [25] and its checklist was provided in the Supplementary Materials. This review was registered a priori on PROSPERO before the literature search (CRD42022327611). The literature search was conducted in the MEDLINE (PubMed), Scopus, ISI Web of Science databases to identify all relevant CPGs published before the end of June 2022. Combinations of the following keywords and MESH search terms were used: ("management" OR "managing") AND ("aspirin" OR "fetal growth" OR "preeclampsia") AND ("twin pregnancy" OR "single pregnancy" OR "pregnant women" OR "during pregnancy") AND ("Clinical trial" OR "Clinical trials" OR "ASPRE TRIAL" OR "observational study" OR "observational studies") AND ("guidelines"). No restrictions for geographic location were applied. The reference lists of relevant recommendations and considerations were also hand-searched to complement database search. The search was restricted to guidelines published in English language.

Selection of studies

Only CPGs including recommendations on the use of aspirin in pregnancy were considered eligible for the inclusion in this systematic review. Two reviewers (RDG, SA) independently evaluated titles and abstracts. Disagreements were resolved by discussion among authors (AK, FS, GMM, GR, ML), and if required, with the involvement of a third author (FDA). When more than one version was available, the most updated version was included. Any non-CPG articles or CPGs where aspirin was not mentioned 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, date of publication, last revision, Differentiation between early and late preeclampsia and FGR when described and type of methodology adopted. The outcomes were extracted and reported in an online Google sheet 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 Appraisal of Guidelines for REsearch and Evaluation (AGREE II)" tool [23].

The AGREE II tool comprehends 32 items divided in six quality domains:

1. Scope and purpose
2. Stakeholder involvement
3. Rigor of development
4. Clarity of presentation
5. Applicability
6. Editorial independence

Each of the 23 items targets various aspects of the quality of the practice guideline. Each item was evaluated on a seven-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 two, and preferably four appraisers review each clinical guideline to increase the reliability of the assessment. The standardized domain score would be 0 % if each appraiser scored 1 for all the items included in this domain (https://www.agreetrust.org/resource-centre/agree-ii). Reaching consensus method to score the items was applied. After reviewing 23 items and the comprehensive judgement of the reviewers, the evaluation of the CPGs was divided into three categories according to the AGREE II score (recommended, recommended after revision, and not recommended).

Outcomes measures

The following outcomes related to use of aspirin in pregnancy were addressed:

1. Indications for Aspirin administration
2. Dosage
3. Gestation at starting therapy
4. Gestation at ending of therapy
5. Safety and side effects

Statistical analysis

Statistical analysis was carried out as descriptive statistic. We calculated frequencies and raw proportions to summarize the main recommendations on the use of aspirin in pregnancy. In addition, we analyzed the guidelines evaluating other issues addressed, such as aspirin indications, duration, dosage, risk factors, starting dose and ending therapy, 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 advice on how to define scores. To define a CPG as of good quality we adopted the cut-off score according to Amer et al. [26]: if the overall guideline score was greater than 60 %, the CPGs was recommended; if the overall guideline score was 40 % to 60 %, the CPGs was recommended after modification; and if the guideline score was < 40 %, it was not recommended. The analysis was performed using Excel 16.57 (© 2021 Microsoft Corporation. All rights reserved.) statistical software.

Results

Study characteristics and quality assessment

A total of 761 articles were identified and screened, 42 were assessed with respect to their eligibility for inclusion and 16 CPGs [7–22] were included in the analyses (Table 1, Fig. 1). The main recommendations were extracted and reported in Table 2. CPGs excluded and the main

Table 1
General characteristic of the Clinical Practice Guidelines (CPGs) included in the systematic review.

Authors	Society	Country	Year at publication	Last revision	Differentiation between early and late preeclampsia and FGR	Methodology
Mehta L.S. et al. [7]	ACC/AHA	USA	2020	2020		scientific statement
Society for Maternal–Fetal Medicine [8]	ACOG	USA	2013	2020	×	expert consultation
Brennecke S.P. et al. [9]	Australasian Society for the Study of Hypertension in Pregnancy	Australia	1995	1995		Evidence Review and Evidence Review Committees
Bates S.M. et al. [10]	American College of Chest Physicians	USA	2012	2012		expert consultation
Poon L.C. et al. [11]	FIGO	International	2019	2019	×	Results were restricted to systematic reviews, randomized controlled trials, controlled clinical trials, and observational studies. Expert consultation
Davidson K.W. et al. [12]	USPSTF	USA	2014	2021	×	Results were restricted to systematic reviews, randomized controlled trials, controlled clinical trials, and observational studies
Lowe S.A. et al. [13]	SOMANZ	Australia	2008	2014		Results were restricted to systematic reviews, randomized controlled trials, controlled clinical trials, and observational studies
Webster K. et al. [14]	NICE	UK	2010	2019	×	NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the guideline committee's experience and opinion of what constitutes good practice.
Regitz-Zagrosek V. et al. [15]	ESC	Germany	2018	2018		Results were restricted to systematic reviews, randomized controlled trials, controlled clinical trials, and observational studies. Expert consultation.
Metin Gülmezoglu A. et al. [16]	WHO	Switzerland	2011	2011	×	GREAT
Magee L. et al. [17]	SOGC	Canada	2014	2014	×	Results were restricted to systematic reviews, randomized control trials, controlled clinical trials, and observational studies
Brown M.A. et al. [18]	ISSHP	International	2018	2018	×	Expert consultation
Queensland Clinical Guidelines [19]	Queensland Clinical Guidelines Steering Committee Statewide Maternity and Neonatal Clinical Network	Australia	2021	2021		Expert consultation
Stepan H. et al. [20]	DGGG	Germany	2008	2013	×	A Guidance Manual and Rules for Guideline Development
Vayssiere C. et al. [21]	FCGO	France	2014	2015	×	Expert consultation
Gillon T.E.R. et al. [22]	The Association of Ontario Midwives	Canada	2001	2015	×	AGREE II

FGR: fetal grow restriction, ACC/AHA: the American College of Cardiology (ACC) and American Heart Association (AHA); ACOG: The American College of Obstetricians and Gynecologists; FIGO: The International Federation of Gynecology and Obstetrics; USPSTF: U.S. Preventive Services Task Force; SOMANZ: Society of Obstetric Medicine of Australia and New Zealand; NICE: National Institute for Health and Care Excellence; ESC: European Society of Cardiology; WHO: World Health Organization; SOGC: Society of Obstetricians and Gynecologists of Canada; ISSHP: International Society for the Study of Hypertension in Pregnancy; DGGG: German Society of Gynaecology and Obstetrics; FCGO: French College of Obstetrics and Gynecologists; GREAT: Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge; AGREE-II: Appraisal of Guidelines Research and Evaluation.

reasons are summarized in Supplementary materials (Supplementary Table 1). The CPGs included in this systematic review consisted of Expert opinion, Review of literature, expert panel consensus and were representative of different countries (14 National, 2 International). Thirty-one point two five percent (5/16) were published before 2010 and 68.7 % (11/16) were published after 2010.

Synthesis of results

There was an overall general agreement among the published CPGs with regards to the indications of aspirin intake in pregnancy. Prior preeclampsia, chronic hypertension, multiple gestations, autoimmune disease, and pre-pregnancy diabetes mellitus type 1 or 2 were recognized as solitary major risk factors for preeclampsia and for aspirin administration in 93.7 % (15/16) of CPGs. Conversely, prior FGR, high-blood pressure at booking and positive FMF screening for preeclampsia were listed as major indication for aspirin intake in only 18.7 % (3/16) of the CPGs included in the present systematic review. Among the moderate risk factors, advanced maternal age was reported as a contributory risk factor in 56.1 % (9/16), increased maternal body mass index (BMI) in 62.5 % (10/16), *in vitro fertilization* (IVF) pregnancy in 50 % (50 %) and nulliparity in 68.7 % (11/16) of the CPGs included in the present systematic review, while black ethnicity, raised uterine artery Doppler pulsatility index in the first trimester and maternal smoking in

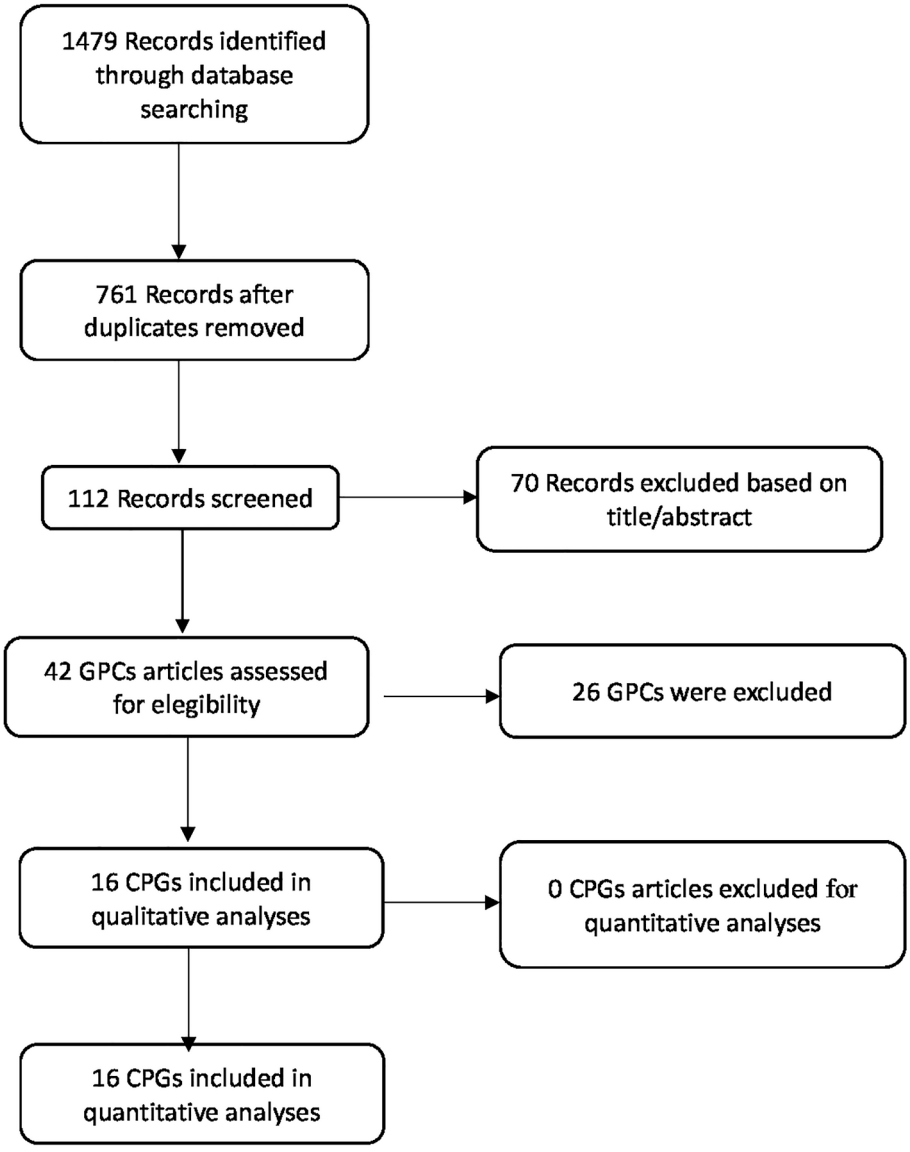

Fig. 1. PRISMA flow chart.

31.2 % (5/16) and 12.5 % (2/16) of CPGs, respectively.

There was heterogeneity in the recommendations with regards to the gestational age at which aspirin should be commenced. Namely, 43.7 % (7/16) CPGs recommend starting aspirin prior to 16 weeks (43.7 %), 31.2% (5/16) before 12 weeks, while 25 % (4/16) generally reported that aspirin should be started before or after 20 weeks of gestation. Regarding the gestational age at which aspirin should be discontinued, 18.7 % (3/16) recommended discontinuation at 34–35 weeks of gestation, 25 % (4/16) at 36–37 weeks another 25% (4/16) recommended discontinuation at delivery, while the other 31.2 % did not report any specific gestational age cut-off. There was also heterogeneity in the recommended aspirin dose in pregnancy: 25 % of the CPGs included in the present review reported a daily dosage of 50–150 mg, 18.7 % (3/16) 100–150 mg, 12.5 % (2/16) 81 mg, while one CPG 75 mg and 60 mg, respectively. Regarding the time at administration, 12/16 of CPGs (75 %) recommended bedtime intake. Finally, only one CPGs mentioned the increased risk of ante and post-partum hemorrhage in women taking the large dose of aspirin.

Methodological quality of CPGs

The AGREE II domains are summarized in Table 3. The average AGREE II standardized score for each domain is reported below (mean ± SD).

CPGs of high quality reached cut-off >60 % and it was showed in green (Table 3). A medium quality (with 40 %-59 % cut-off) was reported in yellow and a CPGs of low quality were showed in red.

One CPG [16] reported the use of the Guideline development, Research priorities, Evidence synthesis, Applicability of evidence, Transfer of knowledge (GREAT) approach, while another one [22] reported the use of AGREE II tools.

The AGREE II standardized domain scores for the first overall assessment (OA1) had a mean of 57 % (SD ± 15.1 %). Six CPGs [9,11,14,16,20,22] scored more than 60 % and revealed a consensus agreement between the reviewers on recommending the use of these CPGs. Finally, there was a general agreement in considering aspirin safe (11/16, 68.7 %) and with limited side effects.

Table 2
Summary of the main findings of Clinical Practice Guidelines (CPGs) included (n = 16).

characteristics	outcome	value
High risk factors	Previous preeclampsia	15 (93.7)
	Previous fetal growth restriction	3 (18.7)
	Chronic hypertension	13 (81.2)
	Autoimmune disease	13 (81.2)
	Multiple gestation	13 (81.2)
	Previous fetal death	2 (12.5)
	Pre-pregnancy diabetes (type 1 or 2)	13 (81.2)
	High blood pressure at booking	3 (18.7)
	FMF screening result for early preeclampsia	3 (18.7)
	Need for at least 1 factor	8 (50)
Moderate risk factors	Advanced maternal age	9 (56.2)
	o $\geq$ 35 years	4/9 (44.4)
	o $\geq$ 40 years	4/9 (44.4)
	o Age not specified	1/9 (11.1)
	Previous fetal growth restriction	1 (1.6)
	Increased maternal BMI	10 (62.5)
	o $\geq$ 30Kg/m	9 (0.9)
	o $\geq$ 35Kg/m^2	1 (0.1)
	Maternal smoking	2 (12.5)
	IVF pregnancy	8 (50)
	Nulliparity	11 (68.7)
	Black ethnicity	5 (31.2)
	Adverse pregnancy outcome	7 (43.7)
	Lower inter-pregnancy interval (<10 years)	6 (37.5)
	Low socioeconomic income	5 (31.2)
	High uterine artery Doppler PI in the first trimester	5 (31.2)
	Need for at least 2 factors	8 (50)
	o Yes	6/8 (75)
	o Clinical judgment	1/8 (12.5)
	o Consider but not mandatory	1/8 (12.5)
Aspirin Therapy	Starting therapy	
	o Before 12 weeks	5 (31.2)
	o Before 16 weeks	7 (43.7)
	o Before or after 20 weeks	4 (25)
	Ending therapy	
	o 34-35 weeks	3 (18.7)
	o 36-37 weeks	4 (25)
	o Until delivery	4 (25)
	o Not specified	5 (31.2)
Aspirin Recommended dose (mg/day)	50-150	1 (1.6)
	75-150	4 (25)
	75	1 (1.6)
	150	2 (12.5)
	100-150	3 (18.7)
	60	1 (1.6)
	81	2 (12.5)
	Not specified	2 (12.5)
Time at administration (Night vs day)	night is preferred	3 (18.7)
	day is preferred	1 (1.6)
	Not specified	12 (75)
Side effects and safety	Safe	11 (68.7)
	Not safe: Increment of neonatal intracranial hemorrhage	0 (0)
	Not safe: Increment of antepartum hemorrhage*	1 (0.1)
	Not safe: Increment of postpartum hemorrhage*	1 (0.1)
	Safety not mentioned	4 (25)

*Same study.
BMI: body mass index; FGR: fetal grow restriction; FMF: fetal medicine foundation; IVF: in vitro fertilization; PI: pulsatility index.

Discussion

Main findings

The findings from this systematic review of CPGs showed that there is a general agreement in the reported indications of aspirin intake in pregnancy, with prior preeclampsia and chronic disease being the major indication for aspirin intake. Conversely, there was heterogeneity in the recommended dose, gestational age at initiation and discontinuation of therapy among the different CPGs.

Results in the context of what is known

Pregnancies complicated by preeclampsia and FGR are at higher risk of short and long-term adverse outcomes, including maternal and perinatal mortality and morbidity, as well as the future risk of cardiovascular disease later in life [27,28]. Administration of aspirin has been recognized as a major contributor in reducing the risk of preeclampsia and FGR in pregnancies at risk [29]. Therefore, early identification of these pregnancies is likely to target antenatal surveillance and intervention to optimize their outcomes [30]. This is particularly important as the magnitude of preventative effect of aspirin in reducing the risk of placental related disorders is higher when therapy is started in the early second trimester of pregnancy [31]. Nevertheless, there is still large heterogeneity in several aspects of aspirin use in pregnancy, including the recommended dose, timing at administration and gestation at discontinuation of therapy [7–22]. The recently published ASPRE trial has reported that administration of a dose of 150 mg per day from 11 to 14 weeks of gestation until 36 weeks of gestation was associated with a significant reduction of preterm preeclampsia compared to placebo (preeclampsia occurred in 13 participants (1.6 %) in the aspirin group, as compared with 35 (4.3 %) in the placebo group (odds ratio in the aspirin group, 0.38; 95 % confidence interval, 0.20 to 0.74; P = 0.004) [32]. Similarly, a systematic review by Roberge et al. including 45 RCT for a total of 20,909 pregnant women randomized to between 50 and 150 mg of aspirin daily has reported that, when aspirin was initiated at or prior to 16 weeks' gestation, there was a significant reduction (Relative Risk, 0.57; 95 % confidence interval, 0.43–0.75; P <.001; R2, 44 %; P =.036) and a dose–response effect for the prevention of preeclampsia, severe preeclampsia, and FGR with higher dosages of aspirin being associated with greater reduction of these outcomes. Conversely, when aspirin was initiated after 16 weeks, there was a smaller but significant reduction of preeclampsia but not FGR without relationship with aspirin dosage [33]. In the present systematic review, we reported a relatively high heterogeneity among the published CPGs with regards to the aspirin dosage and gestational age at which such therapy should be commenced. It is the collective authors' opinion, that in view of the predictive accuracy of first trimester screening for preterm preeclampsia including demographic characteristics, risk factors, maternal blood pressure, uterine artery Doppler and biomarkers such as placental growth factor, aspirin should be started following a positive screening test.

Clinical and research implications

In the present systematic review, multiple pregnancy was among the most common indications for aspirin administration to prevent

Table 3
AGREE-II score.

Guidelines	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
ACC/AHA [7]	33 %	41 %	44 %	14 %	48 %	29 %	38 %	Y (n = 0) YWM (n = 0)
ACOG [8]	86 %	43 %	46 %	55 %	32 %	63 %	50 %	N (n = 2) Y (n = 0) YWM (n = 2)
Australasian Society for the Study of Hypertension in Pregnancy [9]	81 %	43 %	38 %	39 %	70 %	64 %	60 %	N (n = 0) Y (n = 1) YWM (n = 1)
American College of Chest Physicians [10]	67 %	53 %	44 %	39 %	32 %	49 %	39 %	N (n = 0) Y (n = 0) YWM (n = 0
FIGO [11]	70 %	65 %	43 %	74 %	75 %	50 %	66 %	N (n = 2) Y (n = 2) YWM (n = 0)
USPSTF [12]	86 %	76 %	59 %	67 %	57 %	43 %	59 %	N (n = 0) Y (n = 1) YWM (n = 1)
SOMANZ [13]	86 %	76 %	59 %	67 %	57 %	43 %	59 %	N (n = 0) Y (n = 1) YWM (n = 1)
NICE [14]	90 %	81 %	65 %	90 %	61 %	69 %	80 %	N (n = 0) Y (n = 2) YWM (n = 0)
ESC [15]	86 %	62 %	64 %	52 %	54 %	36 %	52 %	N (n = 0) Y (n = 1) YWM (n = 1)
WHO [16]	90 %	67 %	70 %	62 %	54 %	43 %	75 %	N (n = 0) Y (n = 2) YWM (n = 0)
SOGC [17]	43 %	38 %	38 %	48 %	35 %	41 %	33 %	N (n = 0) Y (n = 0) YWM (n = 1)
IHSSP [18]	43 %	43 %	38 %	35 %	50 %	50 %	47 %	N (n = 1) Y (n = 0) YWM (n = 2)
Queensland Clinical Guidelines Steering Committee Statewide Maternity and Neonatal Clinical Network [19]	81 %	38 %	59 %	67 %	43 %	64 %	50 %	N (n = 0) Y (n = 0) YWM (n = 2)
DGGG [20]	90 %	67 %	70 %	62 %	54 %	43 %	75 %	N (n = 0) Y (n = 2) YWM (n = 0)
FCGO [21]	43 %	38 %	38 %	48 %	57 %	50 %	43 %	N (n = 0) Y (n = 0) YWM (n =

(continued on next page)

Table 3 (*continued*)

Guidelines	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
								2)
The Association of Ontario Midwives [22]	90 %	67 %	77 %	68 %	54 %	59 %	84 %	N (n = 0) Y (n = 2) YWM (n = 0)
MEAN	73 %	56 %	53 %	55 %	52 %	50 %	57 %	N (n = 0)
SD		0,15530078	0,13508022	0,18224411	0,12151646	0,11304866	0,15134811	

ACC/AHA: the American College of Cardiology (ACC) and American Heart Association (AHA); ACOG: The American College of Obstetricians and Gynecologists; FIGO: The International Federation of Gynecology and Obstetrics; USPSTF: U.S. Preventive Services Task Force; SOMANZ: Society of Obstetric Medicine of Australia and New Zealand; NICE: National Institute for Health and Care Excellence; ESC: European Society of Cardiology; WHO: World Health Organization; SOGC: Society of Obstetricians and Gynecologists of Canada; ISSHP: International Society for the Study of Hypertension in Pregnancy; DGGG: German Society of Gynaecology and Obstetrics; FCGO: French College of Obstetrics and Gynecologists; OA1: Overall Assessment 1; OA2: Overall Assessment 2; Y: Yes; YWM: Yes, with modifications (YWM); N: No.

preeclampsia and FGR. The rate of preeclampsia is higher in twins than singleton pregnancies with an overall rate around 9.5 %, about two- to threefold increased risk compared to singletons. Furthermore, preeclampsia in twin pregnancies has been reported to occur generally earlier than in singletons [34]. However, most CPGs on the management of twin pregnancies do not generally recommend aspirin administration [7–22]. In fact, authors believed that guidelines should have twin pregnancies section dedicated and explain the importance of aspirin use in their management. However, assessing the actual role of aspirin in reducing the risk of preeclampsia and FGR in twins is challenging as these pregnancies can also be complicated by other conditions commonly associated with placental related disorders, such as IVF and nulliparity, or co-morbidities as chronic diseases [35,36]. Therefore, CPGs should improve in exploring the role of aspirin in reducing the risk of preeclampsia according to different maternal and pregnancy risk factors.

Aspirin intake in pregnancy is generally safe irrespective of the timing and length of its administration [37]. Although the CPGs included in the present systematic review briefly mentioned the safety profile of aspirin use in pregnancy, most of them did not mention the possible side effects. In a recent Swedish population study including more than 300,000 women, the authors have reported that women taking aspirin had a significantly higher risk of intrapartum bleeding (2.9 % in aspirin users vs 1.5 % non-users), postpartum hemorrhage (10.2 % vs 7.8 %), and postpartum hematoma (0.4 % vs 0.1 %). The risk of a neonatal intracranial hemorrhage was also significantly increased (0.07 % vs 0.01 %). Finally, after stratifying by mode of birth, a higher incidence of bleeding among aspirin users was present in those who had a vaginal birth but not those who had a cesarean delivery [38]. Although the beneficial effects of aspirin in preventing preeclampsia are higher than the risk of bleeding complications, which is a relatively uncommon, we believe that future updates of CPGs should highlight these risks, as well as support the evidence in favor of aspirin administration.

Strengths and limitations

This is, to the best of our knowledge, the first systematic review exploring the methodological quality and clinical heterogeneity of CPGs on the use of aspirin in pregnancy using the AGREE-II tool. Other strengths included the thorough literature search and assessment of the multitude of aspects of aspirin use in pregnancy. The methods for development of the guidelines were not reported in detail in some of the included CPGs, making assessment of Domain 3 using AGREE-II challenging, thus limiting an objective evaluation of the included CPGs. It has been suggested that that Domains 3 and 5 (applicability), in addition to domain 6 (editorial independence) may have the strongest influence on the results of the 2 overall assessments. Finally, we did not consider CPGs written in non-English language.

Conclusions

Although there is a general agreement in the published CPGs with regards to the indications of aspirin administration, there is still heterogeneity in some aspects of its use in pregnancy, including dosage, timing at initiation and discontinuation of therapy. The findings from this systematic review highlight the need for a standardization of the general recommendations by the different societies in order to make management of these pregnancies homogeneous. Although uncommon, the side effects of aspirin therapy should be highlighted.

CRediT authorship contribution statement

Raffaella Di Girolamo: Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Sara Alameddine:** Data curation. **Asma Khalil:** Investigation, Supervision, Writing – review & editing. **Francesca Santilli:** Investigation. **Giuseppe Rizzo:** Supervision, Supervision, Writing – review & editing, Writing – review & editing. **Giuseppe Maria Maruotti:** Writing – review & editing. **Marco Liberati:** Supervision, Writing – review & editing. **Francesco D'Antonio:** Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2022.12.032.

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