ABSTRACT

Objective: To systematically identify and critically assess the quality of clinical practice guidelines (CPGs) on management fetal growth restriction (FGR).

Data sources: Medline, Embase, Google Scholar, Scopus and ISI Web of Science databases were searched to identify all relevant CPGs on the management of pregnancies complicated by FGR.

Study selection: Clinical Practice Guidelines that include recommendations about fetal growth restriction management were included.

Data extraction and synthesis: Diagnostic criteria of FGR, use of recommended growth charts, recommendation for detailed anatomical assessment and invasive testing, frequency of fetal growth scans, frequency of fetal monitoring, criteria for hospital admission, drugs administrations, timing at delivery, indications for induction of labor, prophylactic administration of low-dose aspirin, postnatal assessment and placental histopathological were assessed. Quality assessment was evaluated by AGREE II tool. Twelve CPGs were included. Twenty-five percent (3/12) of CPS adopted the recently published Delphi consensus, 58.3% (7/12) an estimated fetal weight (EFW) / abdominal circumference (AC) EFW/AC $<10^{th}$ percentile, 8.3% (1/12) an EFW/AC $<5^{th}$ percentile while one CPG defined FGR as an arrest of growth or a shift in its rate measured longitudinally. Fifty percent (6/12) of CPGs recommended the use of customized growth charts to assess fetal growth. Regarding the frequency of Doppler assessment, in case of absent or reversed end-diastolic flow (AEDF/REDF) in the umbilical artery (UA) 8.3% (1/12) CPGs recommended assessment every 24-48, 16.7% (2/12) every 48-72 hours, 1 CPG generically recommended assessment 1-2 times per week, while 25% (3/12) did not specifically report the frequency of assessment. Only 3 CPGs reported recommendation on the type of Induction of Labor to adopt. The AGREE II standardized domain scores for the first overall assessment (OA1) had a mean of 50%.

Conclusion: There is significant heterogeneity in major aspects of the management of pregnancies complicated by FGR in published CPGs.

INTRODUCTION

Fetal growth restriction (FGR) is defined as the inability for the fetus to reach its growth potential and represents one of the leading causes of perinatal and neonatal morbidity in developed countries. Identification of pregnancies complicated by FGR is crucial to maximize perinatal outcome as these fetuses are at high risk of short- and long-term complications, including perinatal mortality and morbidity, impaired cardiovascular function, and sub-optimal neuropsychological status. FGR is commonly suspected at ultrasound examination in the third trimester of gestation, although different cut-offs of ultrasound measurements are reported in the published literature. Likewise, several controversies co-exist among the main body societies as regard as crucial aspects of the management of FGR, including frequency and type of prenatal assessment, timing, and mode of delivery [1-4].

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. At present, several clinical practice guidelines (CPGs) on the management of pregnancies complicated by FGR have been released by different societies. The Appraisal of Guidelines for REsearch and Evaluation tool (AGREE II) [5] 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. Despite its clinical relevance, no study has critically evaluated the methodological robustness of CPGs on the management of FGR.

OBJECTIVES

The primary aim of this systematic review was to objectively evaluate the robustness of the published CPGs on the management of pregnancies complicated by FGR using the AGREE II tool. The secondary aim was to assess possible heterogeneity in the clinical management of FGR as recommended by different CPGs.

METHODS

Eligibility criteria, information sources, search strategy

We conducted this research by using the MEDLINE (PubMed), Embase, Google Scholar, Scopus, ISI Web of Science databases to identify national and international guidelines published before October 27th, 2022. Combinations of the following keywords and MESH search terms were used: ("fetal growth restriction" or "fetal growth retardation") OR ("small for gestational age") AND ("guidelines"). No restrictions for geographic location and language were applied.

Study selection

Two reviewers (SA, GC) independently assessed the retrieved titles and abstracts. A third author (FDA) was involved in case of disagreements among authors (AK, GR, RDG, CI). If more versions of the same guideline were available, the most recent and updated one was included. Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-Analysis of Observational Studies in Epidemiology guidelines were followed [6].

Data extraction

The principal variables extracted for the present review included: publication ID (Society), country, year of publication, year of last revision, scope of the CPG and type of methodology adopted. The outcomes were extracted and reported in an online Dropbox sheet for sharing among all authors.

Assessment of risk of bias

"The Appraisal of Guidelines for REsearch and Evaluation (AGREE II)" tool was used to assess the quality and the risk of bias of each eligible guideline.

The AGREE II tool contains 23 items branched into six quality domains and 2 final overall assessment: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, editorial independence. The first domain regards the aim, the health questions covered by the guideline and its target population; the second domain is concerned with the objective of its intended users; the third domain focuses on the method used for the formulation of each recommendation; in the fourth domain is analyzed the language, structure and format of the guideline; the fifth domain evaluates the facilities and/or difficulties on application of the CPG and the sixth domain concerns biases with competing interests.

The last two domains regard a final overall assessment (OA1), which consists of the rating of the overall quality of the CPG and whether the CPG would be recommended for use in practice (OA2).

Each item was evaluated from 2 appraisers on a seven-point scale that ranges from 1 (strongly disagree) to 7 (strongly agree). The reviewers consulted each other after completing the AGREE II assessment to avoid discrepancies. If each appraiser scored 1 for all the items included in this domain the standardized domain score would be 0% (https://www.agreetrust.org/resource-centre/agree-ii). We applied the reaching consensus method to score the items. 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, revised recommended, and not recommended).

Data synthesis

The following clinical points related to the management of pregnancies complicated by fetal growth restriction were analyzed:

1. Diagnostic criteria of FGR;
2. Differentiation between FGR and SGA;
3. Differentiation between early and late FGR (classification);
4. Use of recommended growth charts;
5. Recommendation for detailed anatomical assessment and invasive testing;
6. Screening for fetal infections;
7. Frequency of fetal monitoring (fetal growth scans);
8. Frequency of fetal monitoring (Doppler and CTG) if uncomplicated FGR, if AEDV/REDV, if abnormal DV;
9. Role of MCA Doppler;
10. Criteria for hospital admission;
11. Steroids administration;
12. Magnesium sulphate prophylaxis;
13. Timing at delivery;
14. Indication for Cesarean Section;
15. Indications for induction of labor (IOL);
16. Type of IOL;
17. Prophylactic administration of low-dose aspirin;
18. Postnatal assessment;
19. Placental histopathological assessment.

We performed descriptive statistic to summarize the general characteristics of the guidelines included. Frequencies and raw proportions were carried out to summarize the main recommendations in managing pregnancies with FGR. Moreover, the quality of CPGs was evaluated 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 elicit any advises on how to define scores. To define a CPG as of good quality we adopted the cut-off score according to Amer et al.[7]: if the overall guideline score was >60%, CPGs was recommended; if the overall guideline score was 40% to 60%, CPGs was recommended after modification; and if the guideline score was <40%, it was not recommended. Therefore, the clinical heterogeneity in the CPGs was assessed subjectively and

graphically. The analysis was performed using Excel 16.57 (© 2021 Microsoft Corporation. All rights reserved.) statistical software.

RESULTS

Study selection and characteristics

A total of 73 articles were identified and screened, 20 were assessed with respect to their eligibility for inclusion and 12 CPGs [8-19] were included in the analysis (Table 1, Figure 1). The number of studies excluded and main reasons were summarized in Supplementary Table 1. The CPGs included in this systematic review (SR) consisted of Expert opinion, Review of literature, expert panel consensus. 1/12 [10] was first published in 2012 and revised in 2020, 3/12 [11-16-14] were published in 2013 and one of them were revised in 2014 [14], 1/12 was first published in 2014 and revised in 2017[15], 1/12 was published in 2015[9]. 1/9 was published in 2019 and revised in 2021[13], 1/12 was published in 2020[12]. 1/12 was published in 2021[8], 2/12 were published in 2017 [18,19] and 1 of them revised in 2019[19] and 1/12 [17] was first published in 2011 but revised in 2019. Among the different CPGS included in this systematic review, 8/12 were based upon non-systematic/narrative review of the published literature and expert opinions, while 4 adopted GRADE methodology (Table 1).

Risk of bias of included studies

Table 2 shows a summary of all the AGREE II domains and reports below each column the average AGREE II standardized score for each domain (mean ± SD).

CPGs rated >60% were considered high quality guidelines and were shown in green; medium quality CPGs, rated with 40-59% cut-off, were shown in yellow and low-grade CPGs, rated < 40%, were reported in red.

The AGREE II standardized domain scores for the first overall assessment (OA1) had a mean of 48% Only two CPGs scored more than 60% and revealed a consensus agreement between the reviewers on recommending the use of these CPGs [5].

Synthesis of results

Results were shown in Table 3. There was variability in the definition of FGR reported by the different CPGs included in the present systematic review. Twenty-five percent (3/12) of CPGs adopted the recently published Delphi consensus, 58.3% (7/12) an EFW/AC <10th percentile, 8.3% (1/12) an EFW/AC <5th percentile while one CPG defined FGR as an arrest of growth or a shift in its rate measured longitudinally. Ninety-one-point seven percent (11/12) CPGs differentiate between

FGR and SGA, while only 42% (5/12) between early and late FGR. Fifty percent (6/12) of CPGs recommended the use of customized growth charts to assess fetal growth, 16.7% (2/12) did not suggest the use of a customized growth charts, while 33.3% (4/12) did not specifically report the type of fetal growth charts to use in clinical practice. All CPGs recommended a detailed anatomical assessment in case of FGR in view of its association with fetal structural anomalies and 92% (11/12) also suggested infection screening. There was also heterogeneity in the recommended frequency of growth assessment among the different CPGs; 58.3% (7/12) suggested that fetal growth should be assessed at least every two weeks, 16.7% (2/12) every three weeks while the remaining CPGs generically suggested an ultrasound assessment every 2-3 weeks (1CPG, 8.3%) and every 3-4 weeks (2/12, 16.7%) respectively. Regarding the frequency of Doppler assessment, in case of increased umbilical artery (UA) pulsatility index (PI) but no signs of absent or reversed end-diastolic flow (AEDF/REDF), 16.7% (2/12) CPGs recommended Doppler assessment every two weeks, 50% (6/12) every week, 8.3 % (1/12) CPGs generically recommended assessment 1-2 times per weeks, 8.3 % CPGs (1/12) recommended Doppler assessment twice weekly if PIUA >95th centile, while 16.7 % (2/12) CPGs have not specifically reported the frequency of assessment.

In case of AEDF/REDF 8.3% (1/12) CPGs recommended Doppler assessment every 24-48 h, 33.3% (4/12) every 48-72 hours, 1 CPG generically recommended assessment 1-2 times per week; 16.7% (2/12) CPGs numerous times a week, 1 CPG weekly, while 25 % (3/12) has not specifically reported the frequency of assessment.

Only 6/12 CPGs specifically stated the type of CTG assessment to use, with 33.3 % (4/12) recommending computerized cardiotocography (cCTG). Regarding the frequency of CTG assessment in case of FGR with normal UA Doppler, 16.7% (2/12) of CPG recommended CTG assessment 1-2 times per week, 33.3% (4/12) every week, 8.3 % (1/12) two times per week if PIUA > 95th centile, while 41.7% (5/12) of them did not specifically report the frequency of assessment. Conversely, in case of AEDF/REDF 8.3% (1/12) of CPGs suggested CTG every 2-3 days, 16.7% (2/12) every day, 1 CPG 1-2 times per day, while 66.7% (8/12) did not report the frequency of such assessment. Only 5 CPGs reported the specific criteria for hospital admission: FIGO guideline and Federación Argentina de Sociedades de Ginecología y Obstetricia (FASGO) indicate the presence of AEDV/REDV in the UA or abnormal ductus venosus doppler as criteria for hospital admission. The French College of Gynaecologist and Obstetricians and NZMFMN indicate only the presence of AEDF/REDF in the UA as criteria for hospital admission, while the SMFM recommends hospitalization in case of REDV in the UA.

Only 3/12 CPGs reported the indication to administer steroids according to fetal Doppler status.

Regarding the timing at delivery in case of FGR with mild abnormalities in the UA, middle cerebral artery (MCA) or cerebroplacental ratio (CPR) or presence of FGR without Doppler abnormalities, one CPG recommended delivery at 34-37 weeks, 2 CPGs at 37, 2 CPGs at 36-37 weeks, while 7 CPGs did not report any recommendation. In case of FGR with AEDF in the UA, 41.7% (5/12) recommend delivery by 32 weeks, 41.7% (5/12) by 34 weeks while one CPG generically recommended delivery before 37 weeks of gestation.

In case of REDF 50% (6/12) CPGs suggest considering delivery by 30 weeks, 25% (3/12) by 32 weeks and one CPG by 34 weeks of gestation. Regarding the mode of delivery, 75% (9/12) reported specific indication to perform Cesarean section in case of AEDF flow in the UA, while 25% (3/12) did not report any recommendation. Only 3 CPGs reported recommendation on the type of IOL to adopt in case delivery is needed, with 16.7% (2/12) recommending mechanical induction and 8.3% (1/12) combined mechanical and pharmacological IOL. Finally, there was no specific mention of the type of follow-up infants with a prenatal diagnosis of FGR should undergo.

COMMENT

Main findings

The findings of this systematic review show that there is heterogeneity in several aspects of definition, classification and clinical management of pregnancies complicated by FGR, mainly involving the frequency of fetal monitoring, criteria for hospital admission, timing, and mode of delivery.

Strengths and limitations

This is, to the best of our knowledge, the first systematic review assessing the quality and clinical heterogeneity of CPGs on the management of FGR using the AGREE-II tool. Thorough literature search, evaluation of a multitude of clinical aspects related to the management of pregnancies complicated by FGR and the use of a standardized tool to judge their quality are the main strengths of this systematic review. Furthermore, we could not critically evaluate the different clinical aspects related to the management of SGA fetuses because most of the CPGs included in the present review did not report a precise differentiation between FGR and SGA. Finally, a comprehensive pooled data analysis was not possible for all the observed outcomes in view of the multitude of management options reported by the different CPGs.

Comparison with existing literature

FGR is a multifactorial condition with a significant influence on short- and long-term perinatal outcome [21]. The main issues in the prenatal management of FGR are to identify fetuses at higher risk

of deterioration, utilization of the most appropriate surveillance method and determination of the delivery thresholds. The recently published Truffle Study has shown that a uniform approach to the diagnosis and management of FGR consistently produces better outcome compared to what was previously reported [22].

There is a general agreement among the CPGs on the recommendation for anatomical assessment, screening for fetal infection and invasive prenatal diagnosis in case of FGR diagnosed in the second trimester of pregnancy, especially when there is no ultrasound evidence of placental insufficiency.

However, the findings from this systematic review highlight that there is still significant heterogeneity in the diagnosis and management of FGR and this is likely to reflect on our ability to manage these pregnancies. Diagnostic criteria of FGR vary among the different CPGs and this is likely to affect the ability to identify fetuses at risk of perinatal compromise. Prenatal diagnosis of FGR is based upon a biometric assessment of the fetuses but there is no agreement upon which type of growth charts we should use to accurately identify these fetuses [23].

Ultrasound monitoring represents another area of disagreement among the published CPGs. Although the UA Doppler is universally recommended for monitoring growth restricted fetuses, there is heterogeneity in the frequency of ultrasound monitoring reported by the different CPGs. AEDF/REDF corresponds to malperfusion of 50%–70% of the placental villous vascular tree [24]; in this scenario, most of the CPGs suggest increasing the frequency of ultrasound monitoring to an interval of 48-72 hours, while the frequency of Doppler monitoring is generally reported to be weekly in case of increase UA Doppler PI with positive end diastolic flow.

Likewise, there is still significant heterogeneity among the various CPGs in the indications of cesarean delivery and induction of labor.

Recent studies and systematic reviews have highlighted the role of FGR as one of the major determinants of long-term complications in childhood. FGR children have a higher risk of presenting with sub-optimal cardiovascular and neurophysiological performance later in life [25-26]. It is therefore surprising that none of the CPGs included in the present systematic review extensively reported the type of post-natal follow-up of these children. It may be speculated that pediatric guidelines should report the type and frequency of monitoring of children affected by FGR in utero. However, definitions of growth restriction in pediatrics guidelines are different compared to those reported in the obstetric literature. It is therefore the responsibility of maternal-fetal medicine specialists to identify those fetuses at higher risk of post-natal complications and to stress to the pediatric community the need for long-term cardiovascular and neuropsychological follow-up of these children.

One of the likely explanations for the observed heterogeneity in the recommended management of FGR among the different CPGs could be the lack of adequately powered RCTs on several aspects of the prenatal management. There is no RCT on the frequency of fetal monitoring, criteria for hospitalization and type of IOL in pregnancies complicated by FGR. The lack of a robust evidence extrapolated from RCT does not allow researchers or clinicians to apply an evidence-based management on most aspects of the management of these pregnancies and the current recommendations come mainly from expert opinion based on observational studies. However, this heterogeneity is also dependent on the lack of agreement in the diagnostic criteria of FGR. Using a common nomenclature and homogenous management in medicine is crucial to optimize patients' outcome. In oncology, the use of a standardized staging systems allows to describe the severity of the disease, develop a prognosis, and design a treatment plan for individual patients. More importantly, the use of a common language to define a disease allows us to identify clinical trials that may be appropriate to improve the outcome of the disease. FGR is a multifactorial condition with a well-recognized impact on the short- and long-term outcome of the fetus and newborn. Despite that, there is still significant heterogeneity on how FGR is defined and managed, thus limiting the possibility of developing large trials to specifically address different clinical aspects of the management of FGR.

Conclusions and Implications

There is a significant heterogeneity in some of the main aspects of the clinical management of FGR in the published CPGs. The findings from this systematic review highlight the need for developing guidelines by the national and international societies to standardize the management of FGR and to inform the design of large trials aimed at specifically assessing the various aspects of the management of FGR.

298 **References**

299

300 1. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth
301 restriction: a Delphi procedure. Ultrasound in obstetrics & gynecology: the official journal of
302 the International Society of Ultrasound in Obstetrics and Gynecology. 2016;48(3):333-339.
303 doi:10.1002/uog.15884

304 2. Villalain C, Galindo A, Di Mascio D, et al. J Matern Fetal Neonatal Med. 2021 Jun 8:1-7.
305 doi: 10.1080/14767058.2021.1926977. Epub ahead of print.

306 3. Di Mascio D, Villalain C, Rizzo G, et al. Acta Obstet Gynecol Scand. 2021 Jul;100(7):1313-
307 1321. doi: 10.1111/aogs.14135. Epub 2021 Apr 1. PMID: 33792924.

308 4. Di Mascio D, Herraiz I, Villalain C, et al. Comparison between Cerebroplacental Ratio and
309 Umbilicocerebral Ratio in Predicting Adverse Perinatal Outcome in Pregnancies Complicated
310 by Late Fetal Growth Restriction: A Multicenter, Retrospective Study. Fetal Diagn Ther.
311 2021;48(6):448-456. doi: 10.1159/000516443. Epub 2021 Jun 15. Erratum in: Fetal Diagn
312 Ther. 2021;48(8):640.

313 5. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: Advancing guideline
314 development, reporting and evaluation in health care. CMAJ. 2010;182(18).
315 doi:10.1503/cmaj.090449

316 6. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting
317 systematic reviews and meta-analyses of studies that evaluate healthcare interventions:
318 explanation and elaboration. BMJ (Clinical research ed). 2009;339. doi:10.1136/bmj.b2700

319 7. Amer YS, Titi MA, Godah MW, et al. International alliance and AGREE-ment of 71
320 clinical practice guidelines on the management of critical care patients with COVID-19: a
321 living systematic review. Journal of Clinical Epidemiology. 2022;142:333-370.
322 doi:10.1016/j.jclinepi.2021.11.010

8. Melamed N, Baschat A, Yinon Y, et al. FIGO (international Federation of Gynecology and obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. International Journal of Gynecology and Obstetrics. 2021;152(S1):3-57. doi:10.1002/ijgo.13522

9. Vayssière C, Sentilhes L, Ego A, et al. Fetal growth restriction and intra-uterine growth restriction: Guidelines for clinical practice from the French College of Gynaecologists and Obstetricians. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2015;193:10-18. doi:10.1016/j.ejogrb.2015.06.021

10. Martins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction: (Replaces Clinical Guideline Number 3, April 2012). American Journal of Obstetrics and Gynecology. 2020;223(4):B2-B17. doi:10.1016/j.ajog.2020.05.010

11. Lausman A, Kingdom J, Gagnon R, et al. Intrauterine Growth Restriction: Screening, Diagnosis, And Management. Journal of Obstetrics and Gynaecology Canada. 2013;35(8):741-748. doi:10.1016/S1701-2163(15)30865-3

12. Lees CC, Stampalija T, Baschat A, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound in Obstetrics and Gynecology. 2020;56(2):298-312. doi:10.1002/uog.22134

13. ACOG PRACTICE BULLETIN Clinical Management Guidelines for Obstetrician-Gynecologists.; 2020. http://journals.lww.com/greenjournal

14. GUIDELINE FOR THE MANAGEMENT OF SUSPECTED SMALL FOR GESTATIONAL AGE SINGLETON PREGNANCIES AND INFANTS AFTER 34 WEEKS' GESTATION, revised November 2014.

15. Institute of Obstetricians and Gynaecologists Royal College of Physicians of Ireland. CLINICAL PRACTICE GUIDELINE FETAL GROWTH RESTRICTION.

16. RCOG. The Investigation and Management of the Small-for-Gestational-Age Fetus.; 2013.

17.http://www.fasgo.org.ar/archivos/consensos/Actualizacion_consenso_RCIU_FASGO_2017.pdf [last update 24th of May, 2022]

18. http://www.clap.ops-oms.org/publicaciones/clap1586.pdf [last update 24th of May, 2022]

19. Kehl S, Dötsch J, Hecher K, et al. Intrauterine Growth Restriction. Guideline of the German Society of Gynecology and Obstetrics (S2k-Level, AWMF Registry No. 015/080, October 2016). Geburtshilfe Frauenheilkd. 2017;77(11):1157-1173. doi:10.1055/s-0043-118908

20. Guyatt GH OAVGKRFYYACPSHGWGroup. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26;336(7650):924-6. doi: 10.1136/bmj.39489.470347.AD. PMID: 18436948; PMCID: PMC2335261.

21. Miller SL, Huppi PS, Mallard C. THE CONSEQUENCE OF FETAL GROWTH RESTRICTION ON BRAIN STRUCTURE AND NEURODEVELOPMENTAL OUTCOME J Physiol 2016 Feb 15;594(4):807-23. doi: 10.1113/JP271402. Epub 2016 Jan 5.

22. B Mylrea-Foley, A Bhide, E Mullins, J Thornton, N Marlow , T Stampalija , R Napolitano , C C Lees , Building consensus: thresholds for delivery in TRUFFLE-2 randomized intervention study

Ultrasound Obstet Gynecol. 2020 Aug;56(2):285-287. doi: 10.1002/uog.22124

23. Visser GHA, Nicholson WK, Barnea ER, et al. FIGO position paper on reference charts for fetal growth and size at birth: Which one to use?, Int J Gynaecol Obstet. 2021 Feb;152(2):148-151. doi: 10.1002/ijgo.13500. Epub 2020 Dec 29.

24. Morrow RJ, Adamson SL, Bull SB, Ritchie JW. Effect of placental embolization on the umbilical arterial velocity waveform in fetal sheep. Am J Obstet Gynecol. 1989 Oct;161(4):1055-60. doi: 10.1016/0002-9378(89)90783-7

25. Sharma D, Shastri S, Sharma P. Intrauterine growth restriction: antenatal and postnatal aspects. Clin Med Insights Pediatr. 2016 Jul 14;10:67-83. doi: 10.4137/CMPed.S40070

26. Valsamakis G, Kanaka-Gantenbein C, Malamitsi-Puchner A, Mastorakos G. Causes of intrauterine growth restriction and the postnatal development of the metabolic syndrome. Ann N Y Acad Sci . 2006 Dec;1092:138-47. doi: 10.1196/annals.1365.012.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3-4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8-9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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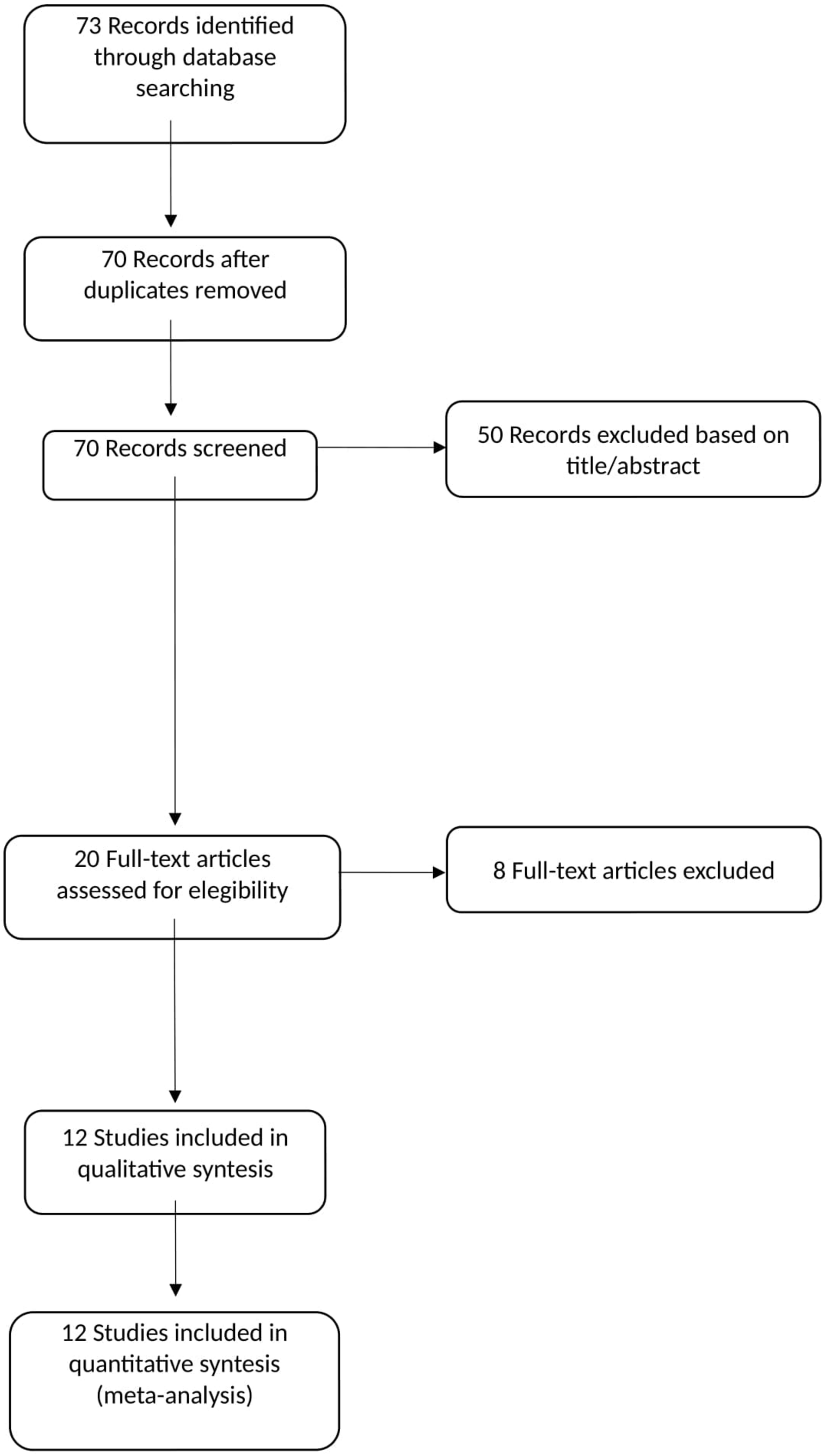
73 Records identified through database searching
70 Records after duplicates removed
70 Records screened
50 Records excluded based on title/abstract
20 Full-text articles assessed for elegibility
8 Full-text articles excluded
12 Studies included in qualitative syntesis
12 Studies included in quantitative syntesis (meta-analysis)

Authors	Year	Title	Reason for the exclusion
Figueras F. et al	2014	Defectos del crescimento fetal	Protocol study from Fetal medicine of Barcelona
Infante L.M.P. et al	2015	Restricciòn del crescimento instrauterino: una aproximaciòn al diagnòstico, siguimiento y manejo	Narrative Review
Arujo M.J.	2012	Restricciòn del crescimento instrauterino	Protocol study from "Obra Social de Empleados de Comercio y Actividades Civiles (Osecac)
Scacchi M.S. et al	2019	GUÍA DE PRÁCTICA CLÍNICA Restricción de Crecimiento Intrauterino Septiembre 2019	c Hospital Ramòn Sardà
Rèmy B.K et al	2019	Indication for Doppler evaluation in the management of intrauterine growth restriction of vascular origin in Sub Saharian Africa	Retrospective cohort study in th Gynaecology and Obstetrics Department of the Yopougon University Hospital
Margaux L.C.	2020	Recommandations du Reseau perinatal Lorrain- retard de Croissance Intra-Utérin	Protocol study from Reseau Perinatal Lorrain
Chamagne M.	2020	Prise en charge du ritard de croissance intra-utérin en France: enquete auprés des centres hospital-universitaires et maternités de type III	Retrospective survey
Rachdi R.	2005	Retard de croissance intra-utérin: etiologie et prise en charge obstetricale	Retrospective study at the Military Hospital of Tunis

AGREE II Score Sheet

Domain	Item	AGREE II Rating						
		1 *Strongly Disagree*	2	3	4	5	6	7 *Strongly Agree*
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.							
	2. The health question(s) covered by the guideline is (are) specifically described.							
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.							
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.							
	5. The views and preferences of the target population (patients, public, etc.) have been sought.							
	6. The target users of the guideline are clearly defined.							
Rigor of development	7. Systematic methods were used to search for evidence.							
	8. The criteria for selecting the evidence are clearly described.							
	9. The strengths and limitations of the body of evidence are clearly described.							
	10. The methods for formulating the recommendations are clearly described.							
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.							
	12. There is an explicit link between the recommendations and the supporting evidence.							
	13. The guideline has been externally reviewed by experts prior to its publication.							
	14. A procedure for updating the guideline is provided.							
Clarity of presentation	15. The recommendations are specific and unambiguous.							
	16. The different options for management of the condition or health issue are clearly presented.							
	17. Key recommendations are easily identifiable.							
Applicability	18. The guideline describes facilitators and barriers to its application.							
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.							
	20. The potential resource implications of applying the recommendations have been considered.							
	21. The guideline presents monitoring and/ or auditing criteria.							
Editorial independence	22. The views of the funding body have not influenced the content of the guideline.							
	23. Competing interests of guideline development group members have been recorded and addressed.							
Overall Guideline Assessment	1. Rate the overall quality of this guideline.	1 *Lowest possible quality*	2	3	4	5	6	7 *Highest possible quality*
Overall Guideline Assessment	2. I would recommend this guideline for use.	*Yes*		*Yes, with modifications*				*No*

Table 1. General characteristics of the CPGs included in the present systematic review.

Guideline	**Country**	**Year**	**Last revision**	**Scope**	
FIGO	Canada	2021	2021	International	Review of literature, expert panel consensus
French College of Gynaecologists and Obstetricians	France	2014	2014	National	Review of literature, expert panel consensus, GRADE method
SMFM	USA	2012	2020	National	Review of literature, expert panel consensus
SOGC	Canada	2013	2013	National	Review of literature, expert panel consensus
ISUOG	UK	2020	2020	National	Review of literature, expert panel consensus
RCOG	UK	2013	2013	National	Review of literature, expert panel consensus, GRADE method
ACOG	USA	2019	2021	National	Review of literature, expert panel consensus
NZMFN	New Zeland	2013	2014	National	Review of literature, expert opinion, GRADE method
Institute of Obstetricians and Gynaecologist	Ireland	2014	2017	Local	Review of literature, expert opinion

"Centro Latinoamericano de Perinatología / Salud de la Mujer y Reproductiva					Review of literature, expert opinion
(CLAP/SMR)"	Sud-America	2011	2019	National	Review of literature, expert panel consensus
Federación Argentina de Sociedades de Ginecología y Obstetricia (FASGO)	Argentina	2017	2017	National	Review of literature, **expert panel consensus GRADE method**
DGGG Germany-SGGG Swiss-OEGGG Austria		2017	2019	National	

Table 2. summary of all the AGREE II domains

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)	OA 1	OA2
FIGO	90%	76%	92%	86%	64%	86%	97%	Y (n=2) YWM (n=0) N (n=0)
French College of Gynaecologist and Obstetricians	43%	43%	36%	29%	26%	64%	0%	Y (n=0) YWM (n=0) N (n=2)
SMFM	90%	38%	63%	76%	39%	86%	57%	Y (n=0) YWM (n=2) N (n=0)
SOGC	86%	48%	52%	62%	46%	86%	29%	Y (n=0) YWM (n=0) N (n=2)
ISUOG	90%	81%	61%	71%	50%	86%	57%	Y (n=0) YWM (n=2) N (n=0)
RCOG	86%	48%	59%	76%	71%	86%	71%	Y (n=1) YWM (n=1) N (n=0)
ACOG	71%	38%	43%	52%	46%	86%	29%	Y (n=0) YWM (n=0) N (n=2)

NZMFN	71%	52%	45%	33%	36%	86%	43%	Y (n=0) YWM (n=1) N (n=1)
Institute of Obstetricians and Gynaecologist	81%	52%	46%	43%	39%	86%	57%	Y (n=0) YWM (n=2) N (n=0)
CLAP/SMR	36%	29%	26%	38%	50%	46%	29%	Y (n=0) YWM (n=0) N (n=2)
FASGO	71%	76%	43%	86%	50%	71%	71%	Y (n=2) YWM (n=0) N (n=0)
DGGG Germany- SGGG Swiss-OEGGG Austria	76%	71%	82%	62%	61%	64%	71%	Y (n=1) YWM (n=1) N (n=0)
Average score for each domain (n%)	**74%**	**51%**	**54%**	**59%**	**48%**	**78%**	**50%**	
SD for each domain (± %)	**18%**	**17%**	**19%**	**20%**	**13%**	**13%**	**26%**	

Table 3. Critical evaluation of the different clinical aspects of the management of pregnancies complicated by FGR among the different CPGs.

Issue (Guidelines tot.=12)	*N (%)*
• **Scope 12/12**	
National	10/12(83,3)
International	1/12(8,3)
Local	1/12 (8,3)
• **Methods of developement 12/12**	
Review of literature, expert panel consensus	7/12(58,3)
Review of literature, expert opinion	2/12(16,7)
Review of literature, expert panel consensus, GRADE method	3/12(25,0)
• **Definition of FGR 12/12**	
Delphi criteria	3/12 (25)
EFW/AC<10th percentile	7/12 (58,3)
Arrest of growth or a shift in its rate measured longitudinally	1/12 (8,3)
AC < 5th centile, discrepancy between HC and AC, customized EFW < 10%, AC or customized EWFcrossing centiles	1/12 (8,3)
• **Differentiation between FGR and SGA (11/12)**	
Yes	11/12 (91,7)
No	1/12 (8,3)
Not stated	0/12(0,0)
Differentiation between early FGR and late FGR (5/12)	
yes(Early < 32w, late >= 32w)	4/12 (33,3)
yes (early < 500 g ± < 24 week, late > 500 g and > 24 weeks)	1/12(8,3)
Not stated	7/12(58,3)
• **Recommended fetal growth charts (8/12)**	
Customized growth chart	6/12(50,0)
Not customized growth chart	2/12(16,7)
Not stated	4/12(33,3)
• **Recommendation for detailed anatomical assessment (12/12)**	
Yes	10/12 (83,3)
yes if early onset SGA	1/12 (8,3)
Yes only with risk factors	1/12(8,3)
Not stated	0/12(0,0)
• **Recommendation for fetal infection screening (11/12)**	
Yes	8/12 (66,7)
Yes if early onset SGA	1/12 (8,3)
Yes only with risk factors	2/12 (16,7)
Not stated	1/12 (8,3)
• **Frequency of fetal growth assessment on ultrasound (12/12)**	
2 weeks	7/12 (58,3)
2-3 weeks	1/12(8,3)
3 weeks	2/12 (16,7)
3-4 weeks	2/12 (16,7)
• **Frequency of Doppler assessment (normal UA Doppler) (10/12)**	

1-2 times per week	1/12(8,3)
Weekly	6/12 (50,0)
Every two weeks	2/12 (16,7)
Twice weekly if PIUA> 95th centile	1/12 (8,3)
Not stated	2/12 (16,7)
• **Frequency of Doppler assessment if PIUA is > + 2 SD for ga and delivery is not indicated (1/12)**	
Twice weekly	1/12 (8,3)
Not stated	11/12(91,7)
• **Frequency of Doppler assessment (AEDF/REDF Doppler) (9/12)**	
Numerous times a week	2/12(16,7)
Every 48-72 hours	2/12(16,7)
Every 24-48 hours	1/12 (8,3)
1-2 times a week	1/12 (8,3)
Weekly	1/12 (8,3)
Twice weekly if AEDF, three times weekly if REDF	2/12 (16,7)
Not stated	3/12(25,0)
• **Frequency of Doppler assessment (AEDF/REDF Doppler) < 34 w if growth plateaus or stops (1/12)**	
Every 48-72 hours	1/12 (8,3)
Not stated	11/12(91,7)
• **Frequency of Doppler assessment (abnormal DV doppler) (2/12)**	
Daily	1/12 (8,3)
Every 12 hours	1/12 (8,3)
Not stated	10/12(83,3)
• **Role of MCA Doppler/PCR at term 9/12**	
Yes	9/12 (75)
No	0/12(0,0)
Not stated	3/12 (25,0)
• **Differentiation beetween cCTG and CTG (6/12)**	
Yes	4/12(33,3)
No	2/12(16,7)
Not stated	6/12(50,0)
• **Frequency of cCTG assessment (normal UA Doppler) (7/12)**	
1-2 times per week	2/12 (16,7)
Weekly	4/12 (33,3)
twice weekly if PIUA> 95th centile	1/12(8,3)
Not stated	5/12(41,7)
• **Frequency of cCTG assessment (normal UA Doppler) < 34w if growth plateaus or stops (1/12)**	
2-3 times per week	1/12 (8,3)
Not stated	11/12(91,7)
• **Frequency cCTG assessment (AEDV/REDV Doppler) (5/12)**	
Increased frequency than weekly	1/12(8,3)
Daily	2/12(16,7)
1-2 times per day	1/12(8,3)
Not stated	8/12(66,7)
• **Frequency cCTG assessment (abnormal DV doppler) (1/12)**	

1-2 times per day	1/12(8,3)
Not specified	11/12(91,7)
• **Criteria for hospital admission according to Doppler anomalies (5/12)**	
Yes	5/12(41,7)
No	0/12 (0,0)
Not stated	7/12 (58,3)
• **Timing for delivery in uncomplicated FGR (11/12)**	
>34 weeks	1/12 (8,3)
36-38 weeks	2/12 (16,7)
37 weeks	3/12(25)
38-39weeks	5/12(41,7)
Not stated	1/12(8,3)
• **Timing for delivery in FGR with mild abnormalities in UA, MCA , CPR or EFW < 3rd centile (5/12)**	
34-37 weeks	1/12(8,3)
37 weeks	2/12(8,3)
36-37 weeks	2/12(8,3)
Not stated	7/12(58,3)
• **Timing for delivery in FGR with AEDF UA (11/12)**	
From 32 weeks	5/12 (41,7)
From 34 weeks	5/12(41,7)
<37 weeks	1/12(8,3)
Not stated	1/12(8,3)
• **Timing for delivery in FGR with REDF UA (11/12)**	
From 30 weeks	6/12 (50,0)
From 32 weeks	3/12 (25,0)
From 34 weeks	1/12 (8,3)
< 37 weeks	1/12 (8,3)
Not stated	1/12 (8,3)
• **Timing for delivery in FGR with abnormal DV Doppler (7/12)**	
From 26 weeks	3/12(25,0)
<32 weeks	2/12 (16,7)
<34 weeks	1/12(8,3)
<37 weeks	1/12(8,3)
Not stated	5/12(41,7)
• **Indication for Cesarean section according to Doppler status (9/12)**	
Yes	9/12 (75,0)
No	0/12(0,0)
Not stated	3/12(25,0)
• **Type of induction of labour (3/12)**	
Mechanical	2/12 (16,7)
Pharmacological	0/12(0,0)
Combined	1/12 (8,3)
Not stated	9/12(75,0)

• **Postnatal assessment 3/12**	
Risk of deficit in postnatal growth, poor neurodevelopmental outcomes, future noncommunicable diseases including obesity, diabetes, hypertension, and cardiovascular disease	3/12 (25,0)
Not stated	9/12 (75,0)
• **Placental histopathological assessment 2/12**	
The most common placental lesions are infarction, decidual arterial disease, syncytial clusters and villous chorangiosis	2/12 (16,7)
Not stated	10/12(83,3)
• **Genetic testing 5/12**	
Yes	5/12(41,7)
No	0/12 (0,0)
Not stated	7/12(58,3)