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Review article

Practice variation in diagnosis, monitoring and management of fetal growth restriction in the Netherlands

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ABSTRACT

Objectives: Fetal growth restriction (FGR) is a condition characterized by its complexity in diagnosis and management. There is a need for early accurate diagnosis, evidence-based monitoring and management of FGR to improve neonatal outcomes. This study evaluated differences and similarities in protocols of Dutch hospitals in the approach of (suspected) FGR in the context of the national guideline.

Study design: FGR protocols were collected from Dutch hospitals between November 2019 and June 2020. Collected data were coded for further analysis and categorized in eight predetermined key domains of definition, preventive measures, testing, referral, monitoring strategies, interventions, mode of delivery and pathologic placenta examination.

Results: 55 of 71 approached hospitals (78 %) responded to the request and 54 protocols (76 %) were obtained. Protocols used variable definitions of FGR, and management was mostly based on fetal biometry results in combination with Doppler results (n = 47, 87 %). In pregnancies with an abdominal circumference (AC) or an estimated fetal weight (EFW) <10th percentile with normal Doppler results, induction of labour was recommended ≥37 weeks (n = 1, 2 %), ≥38-40 weeks (n = 23, 43 %); ≥41 weeks (n = 1, 2 %) or not specified (n = 29, 54 %). In case of an umbilical artery (UA) Doppler pulsatility index >95th percentile, (preterm) labour induction was recommended in the majority of the protocols regardless of fetal size (≥36 weeks: n = 2, 4 %; ≥37 weeks: n = 41, 76 %, not stated: n = 11, 20 %).

Conclusion: This study found practice variation in all predetermined domains of FGR protocols of Dutch hospitals, underscoring the complexity of the condition. The differences found in this study feed the research agenda that informs the process of improving obstetric care by better identification of the fetus at risk for consequences of FGR, improving evidence-based monitoring strategies to identify (imminent) fetal hypoxia, and more accurate timing of delivery.

Introduction

Fetal growth restriction (FGR) is commonly defined as a condition in which the fetus does not reach its intrinsic growth potential [1–3]. Placental insufficiency, due to a variety of placental lesions, is the common underlying pathophysiologic mechanism [4]. Ongoing malnutrition and perinatal chronic and acute hypoxia put fetuses at an imminent increased risk of perinatal mortality and morbidity [5,6]. In the long term it has been associated with poor neurodevelopmental outcome. Furthermore, infants born with FGR are at higher risk to develop cardiovascular disease in adult life [5,7–9].

Traditionally, FGR was defined as fetuses being too small for their gestational age (SGA) according to a reference chart, which often took the 10th percentile as the cut-off value for (ab)normality [10]. However,

FGR is a condition that cannot easily be captured in a single definition. Although SGA (a statistical deviation of size in relation to the reference) has overlap with FGR (a pathological condition), it is not synonymous [2,11]. In 2016 an international consensus definition was established through a Delphi procedure that incorporates functional parameters of placental function [2]. The 2017 Dutch national guideline, as well as the 2020 International Society of Ultrasound in Obstetrics and Gynecology practice guideline of FGR, describe approaches for early diagnosis, close follow-up, and timely delivery of pregnancies with FGR to improve outcomes [12,13].

This paper studies the current practice variation in the Netherlands by comparing FGR hospital protocols with the aim of identifying how knowledge is currently implemented and which apparent knowledge gaps may exist.

Methods

Protocol collection

All 71 Dutch hospitals with an obstetrics department were contacted by telephone or email to share their protocol on FGR between November 2019 and June 2020. A reminder was sent by e-mail if a hospital did not respond to the initial request within four months.

Year of publication

The year of publication or last update of the FGR protocol was categorized in predetermined subgroups: $2014 \leq 2016$, ≥ 2017–2020 or date not stated. These subgroups were based on the year of publication of the consensus definition [2] and the latest national Dutch guideline from the Dutch Society of Obstetrics and Gynecology 'Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG)' [13].

Data extraction

All collected protocols were thoroughly reviewed and (baseline) characteristics of each protocol were systematically extracted. The characteristics were categorized in the key domains of definition, preventive measures, testing, referral, monitoring, intervention, mode of delivery, and pathologic examination of the placenta (Appendix, Table S1). For each of the domains only one answer was possible. Any uncertainties in the interpretation of the protocols were discussed within the steering group. All collected data were coded for further analysis through a prespecified legend. Missing variables were listed as 'not stated'. Variables were checked for overlap by the steering group and, where applicable, merged into a single variable.

Data analysis

Descriptive statistics (count and percentages) were used to analyze the protocols. Tables were made for testing (genetic diagnostic testing, cytomegalovirus (CMV), advanced ultrasound examination) and referral to a tertiary-care hospital. Histograms were made for monitoring (umbilical artery (UA) Doppler, middle cerebral artery (MCA) Doppler, reduced fetal movements (RFM)), referral back to routine and/or primary care, and indication for expedited delivery based on biometry and based on Doppler velocimetry results.

Ethical approval

Ethics approval was not required for this study since it did not involve any human test subjects.

Results

Protocol collection

71 Dutch hospitals were approached to share their protocol, of which ten (14 %) were tertiary-care centers and 61 (86 %) were secondary-care centers (Appendix, Fig. S1). 55 out of 71 (78 %) hospitals responded to the request. One hospital was not able to send the protocol as it was still under review. Ten out of ten (100 %) tertiary-care centers shared their protocol and 44 out of 61 (72 %) secondary-care centers shared their protocol. Out of the 54 remaining hospitals, 50 hospitals (93 %) used self-written FGR protocols, and four hospitals (7 %) used the 2017 national guideline of the Dutch Society of Obstetrics and Gynecology (NVOG) [13]. Ten of the 54 protocols (19 %) were from tertiary-care hospitals and 44 (81 %) from secondary-care hospitals. Of the ten tertiary-care hospitals, one hospital (10 %) used the guideline of the Dutch Society of Obstetrics and Gynecology. Of the 44 secondary-care hospitals, three hospitals (7 %) used this national guideline (Appendix, Fig. S1) [13].

Year of publication

17 Protocols (32 %) did not state the year of publication. Five protocols (9 %) were last updated between 2014 and 2016, and 32 protocols (59 %) were published or updated from 2017 up and until 2020 (Appendix, Table S2). 25 out of 32 (78 %) of these protocols were, to a varying extent, based on the 2017 national guideline [13].

Definition of FGR

Two protocols (4 %) defined FGR according to the Delphi consensus definition [2], 43 protocols (80 %) used the definition of the Dutch Society of Obstetrics and Gynecology (NVOG) national guideline [13], three protocols (6 %) used the definition of a fetal growth (abdominal circumference (AC) and/or estimated fetal weight (EFW)) < 10th percentile and two protocols (4 %) an AC and/or EFW < 5th percentile. Four protocols (7 %) used other definitions (Appendix, Table S3). Eight protocols (15 %) made a distinction between early-onset (<32 weeks) and late-onset (>32 weeks) in the definition of FGR. None of the included hospitals used separate protocols for early versus late-onset FGR.

Fetal growth references

The 2017 national guideline recommended to use the Hadlock3 or Hadlock4 formula to calculate EFW [13]. 27 protocols (50 %) did not mention which method was used to calculate EFW. 27 protocols (50 %) prescribed the Hadlock3 or Hadlock4 formula to calculate EFW [14]. As a reference for EFW, 31 protocols (57 %) did not state the use of reference growth curves, 21 protocols (39 %) used Verburg growth curves, in accordance with the 2017 national guideline, to evaluate fetal growth, and two protocols (4 %) used the Perined Hoftiezer standards for birth weight [13,15,16].

Prevention

40 protocols (74 %) recommended a daily dose of 80–100 mg prophylactic low-dose aspirin (LDA) to decrease the risk of developing placental insufficiency in women at high risk of FGR, in line with the 2017 national guideline [13].

Testing

The details regarding genetic diagnostic testing, CMV, and advanced ultrasound examination in identifying the cause of FGR, were summarized and compared with the 2017 national guideline, respectively, in

Appendix, Tables S4, S5 and S6 [13].

In 43 protocols (80 %) no recommendations were given regarding uterine artery (UtA) Doppler measurements, in line with the 2017 national guideline [13]. Seven protocols (13 %) advised not to monitor the UtA Doppler. Three protocols (6 %) advised to measure the UtA Doppler in case of an EFW < 3rd percentile and one protocol (2 %) advised to measure the UtA Doppler around 18–20 weeks in case of a high risk of developing FGR.

Referral to or consultation at a tertiary-care hospital

A lot of variation was observed between protocols regarding the indication of referral, ranging from referral when FGR is diagnosed < 24 weeks (n = 2, 4 %); referral when FGR is diagnosed < 32 weeks (n = 1, 2 %); and referral in case of FGR diagnosis < 32 weeks and/or EFW < 1250 g (n = 5, 9 %), to consultation of a tertiary-care hospital in case of FGR < 32 weeks (n = 12, 22 %), in line with the 2017 national guideline [13]; or consultation of a tertiary-care hospital in case of FGR < 32 weeks and/or EFW < 1250 g (n = 3, 6 %). Referral to a tertiary-care center was not applicable for the protocols received from tertiary-care centers (n = 10, 19 %). All reported referral indications are summarized in Appendix, Table S7.

Biometry

One protocol (2 %) did not indicate the recommended frequency of biometry. 52 protocols (96 %) indicated to perform biometry every 10 to 14 days, in accordance with the 2017 national guideline [13]. One protocol (2 %) indicated to perform biometry every other week and to increase to a weekly frequency in case the UA pulsatility index gets > 95th percentile (from 26 weeks gestational age onwards).

Amniotic fluid (AF)

Most protocols (n = 35, 65 %) did not indicate to monitor AF. Indication to monitor AF and the monitoring frequency was given in 19 protocols (35 %). Ten protocols (19 %) indicated to monitor AF once a week; two protocols (4 %) indicated to monitor AF once every-two weeks; one protocol (2 %) indicated every-two weeks, or twice a week in case of oligohydramnios or anhydramnios; one protocol (2 %) indicated to monitor AF once or twice a week; one protocol (2 %) indicated to monitor AF once a week in case of normal Doppler results or a pulsatility index of the UA > 95th percentile and twice a week in case of absent or reversed end-diastolic flow (ARED flow); one protocol (2 %) indicated to monitor AF twice a week when a patient is admitted to the hospital with ARED flow; one protocol (2 %) indicated once per two weeks in case of normal Doppler results and twice a week in case of abnormal Doppler results. No management decisions were solely based on AF, in line with the 2017 national guideline [13].

UA Doppler and MCA Doppler

The recommended monitoring frequency of the UA pulsatility index and MCA pulsatility index are displayed in Figs. 1 and 2, respectively. In summary, most protocols, 32 out of 54 (59 %) recommended to perform Doppler measurements of the UA once a week and more often when abnormal. Most protocols, 21 out of 54 (39 %), recommended to perform Doppler measurements of the MCA once a week if the pulsatility index of the UA is normal or when there is an abnormal CPR and twice a week in case of ARED flow or RED flow of the UA. These recommendations were in accordance with the 2017 national guideline [13].

Ductus venosus (DV)

Most protocols (n = 46, 85 %) did not include recommendations about DV measurements. Three protocols (6 %) mentioned that DV
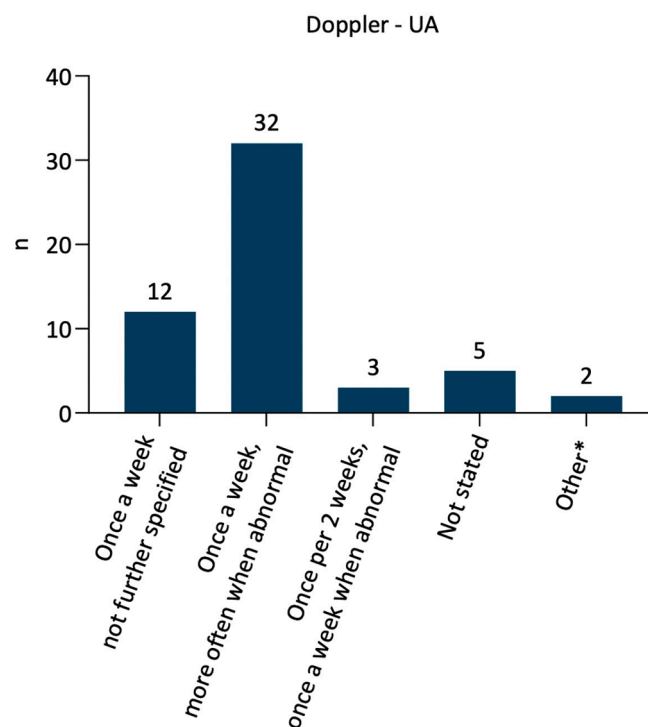

Fig. 1. Recommended monitoring frequencies of the umbilical artery (UA) Doppler in Dutch hospital protocols. *1/2 wks when normal, 1/wk when > p95 with positive EDF, 2/wk in case of brainsparing; 1/2 wks when normal, 2/wk when > p95 with positive EDF and also 2/wk when ARED flow.

measurements should not be used to manage FGR, but these protocols did not specifically state an indication regarding measuring DV. Five protocols (9 %) stated a specific indication: one protocol indicated to assess DV flow once a week in case of FGR < 32 weeks; one protocol indicated to monitor DV twice a week in case of FGR < 32 weeks; one protocol indicated to monitor DV twice a week in case of ARED flow; one protocol indicated to measure it in case of FGR < 32 weeks and a UA pulsatility index > p95; one protocol stated to monitor DV only on a specific indication, not further specified. In none of the protocols management decisions were exclusively based on DV measurements, in line with the 2017 national guideline [13].

Cardiotocography (CTG)

Four protocols (7 %) did not include a recommendation regarding CTG monitoring. 16 protocols (30 %) indicated not to perform regular CTG monitoring in case of normal Doppler results, to perform CTG monitoring at least twice a week in case of UA pulsatility index > 95th percentile and daily CTG monitoring in case of ARED flow, in line with the 2017 national guideline [13]. Two protocols (4 %) indicated no CTG monitoring in case of normal Dopplers and daily CTG in case of UA pulsatility > 95th percentile or ARED flow. Three protocols (6 %) indicated no CTG in case of normal Dopplers, twice a week in case of UA pulsatility index > 95th percentile and/or oligohydramnios, twice a day in case of ARED flow or cerebroplacental ratio (CPR) < 1 and/or anhydramnios. Two protocols (4 %) indicated CTG monitoring once a week in case of normal Dopplers, twice a week in case of AU pulsatility index > 95th percentile, once a day in case of ARED flow or MCA pulsatility index < 5th percentile or CPR < 1. Three protocols (6 %) indicated no CTG in case of normal Dopplers, at least twice a week in case of UA pulsatility index > 95th percentile and positive end-diastolic flow (PED flow), ACM > 5th percentile and CPR > 1, once a day in case of UA pulsatility index > 95th percentile and PED flow, ACM < 5th percentile and/or CPR < 1, twice a day in case of ARED flow. Four protocols (7 %)
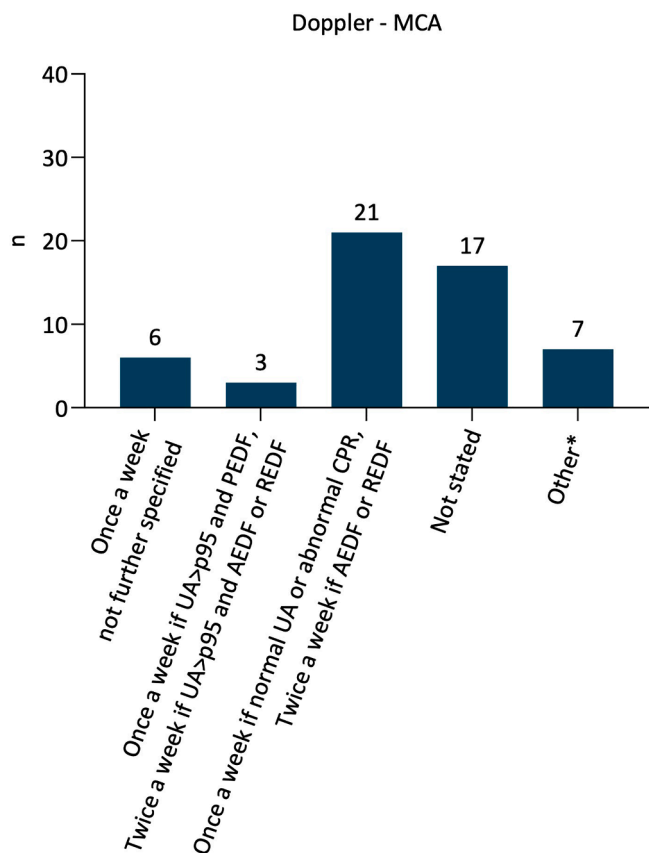
Fig. 2. Recommended monitoring frequencies of the middle cerebral artery (MCA) Doppler in Dutch hospital protocols. *once a week in case of suspected FGR < 32 weeks, not in late FGR; in clinical trials only; 1/wk when normal Dopplers, 1/wk when PI AU > p95 with positive EDF or ARED flow.

indicated no CTG in case of normal Dopplers, at least twice a week in case of UA pulsatility index > 95th percentile and PED flow, and twice a day in case of ARED flow. Ten protocols (19 %) indicated no CTG in case of normal Dopplers, at least twice a week in case of UA pulsatility index > 95th percentile, daily CTG in case of ARED flow, and at least twice a week or daily in case of ACM < 5th percentile (or CPR < 1). Nine protocols (17 %) stated different indications.

Only one protocol (2 %), indicated CTG monitoring not only based on Doppler results but also on fetal size. This protocol recommended not to monitor CTG in case of normal Doppler results, unless fetal growth < 3rd percentile, daily CTG monitoring in case of UA pulsatility index > 95th percentile, two times a day CTG monitoring in case of ARED flow and daily CTG in case of a fetal growth < 3rd percentile. This protocol also indicated to increase CTG frequency in case of RFM.

Computerized CTG is not yet implemented in the Netherlands and standard CTG is currently the standard method being used in the Dutch hospitals. The 2017 national guideline mentioned computerized CTG but did not recommend to use it [13]. Only one of the included protocols, a tertiary-care center, advised to use computerized CTG in case of FGR and doppler abnormalities <32 weeks. In case of ARED flow < 32 weeks, they indicated to measure short term variability by using computerized CTG used as a cut-off for labour (specifically Caesarean section).

RFM

The indications on monitoring and intervention in case of RFM are detailed in Appendix, Fig. S2. In summary, 23 protocols (43 %) did not mention RFM, and 18 protocols (33 %) indicated to increase CTG monitoring frequency and took RFM into consideration for immediate

delivery depending on gestational age, in line with the 2017 national guideline [13].

Referral back to routine and/or primary care

Recommendations on referral back to routine and/or primary care are displayed in Fig. 3. Most protocols (n = 30, 56 %), in line with the 2017 national guideline, indicated return to primary care in case of a normal interval growth AC/EFW between the 5th percentile and 10th percentile, with normal Dopplers and no other pathology (possibly shared care) [13].

Induction of labour based on biometry

The recommendations on timing of expedited delivery based on different biometry results are shown in Fig. 4. In summary, in pregnancies with an AC or an EFW < 10th percentile with normal Doppler results, induction of labour was mostly indicated ≥38–40 weeks (n = 22, 41 %), in line with the national guideline, or it was not stated (n = 29, 54 %), Fig. 4a. In case of an AC or EFW < 3th percentile, 19 (35 %) protocols indicated to induce labour at 37 weeks, in line with the 2017 national guideline [13], or not stated (n = 24, 44 %), Fig. 4b. In case of no fetal growth in 3–4 weeks, 41 (76 %) protocols indicated to induce labour from 34 weeks, in line with the 2017 national guideline [13], Fig. 4c.

Other subgroups in intervention recommendations are mentioned below.

AC and/or EFW < p10 and normal Doppler results

18 protocols (33 %) mentioned this subgroup without any further or more specific lower cut-off for fetal size percentile to distinguish between severe and mild SGA. One protocol (2 %) indicated induction of labour at 37 weeks; 17 protocols (31 %) indicated to induce labour from 38 weeks onwards.

All FGR

Two protocols (4 %) stated an intervention indication for all FGR without further specification of biometry and/or Doppler results: one protocol (2 %) advised to induce labour at 37–38 weeks; one protocol (2
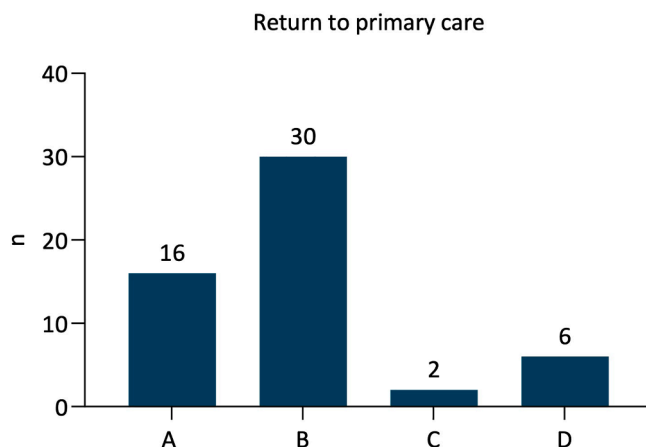
Fig. 3. Recommendations regarding referral back to primary care in Dutch hospital protocols. A: 2x EFW/AC > p10, normal Dopplers and minimum interval between measurements of 10–14 days. B: Normal interval growth AC/EFW p5-10, normal Dopplers, no other pathology (possibly shared care). C: Normal interval growth AC/EFW > p10, normal Dopplers and no other pathology return to standard care; normal interval growth AC/EFW > p5-<p10, normal Dopplers and no other pathology shared care. D: Not stated.

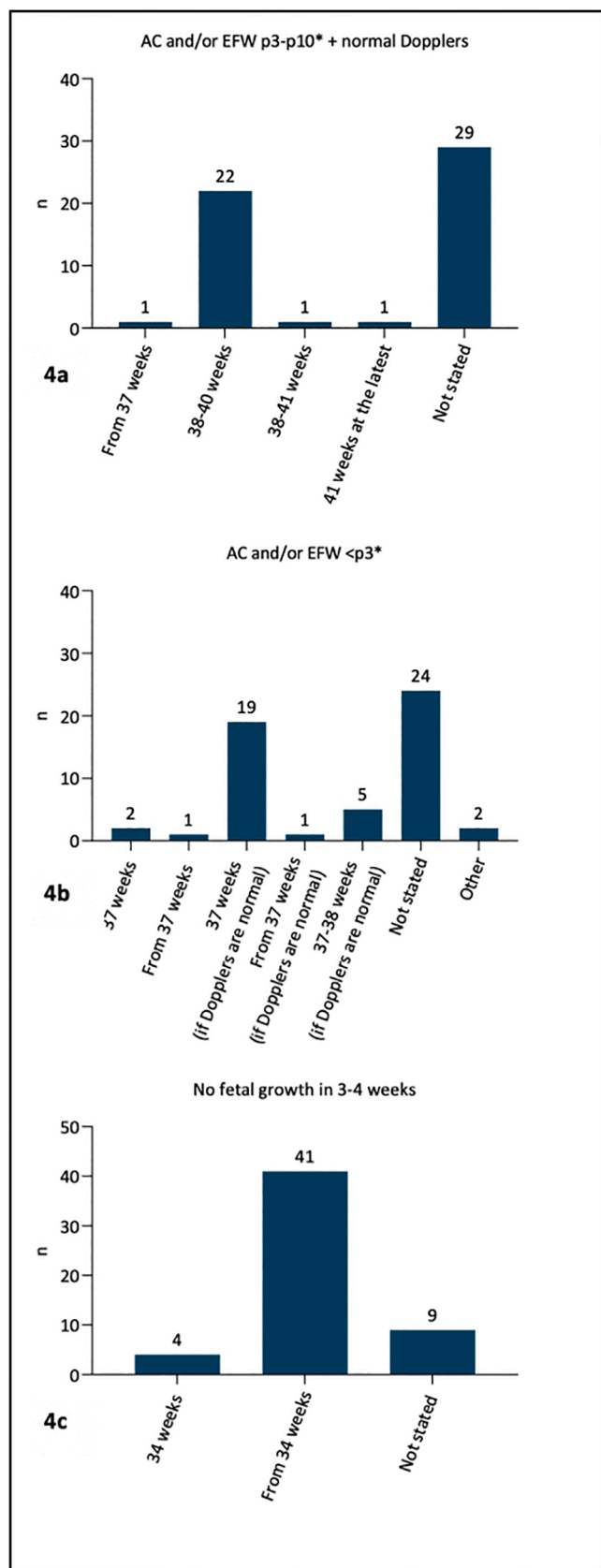**Fig. 4.** Recommendations on induction of labour based on: a. Abdominal circumference (AC) and/or estimated fetal weight (EFW) p3-p10 (*including subgroup p2.3-p10); b. Abdominal circumference (AC) and/or estimated fetal weight (EFW) < p3 (*including subgroup p2.3-p10); c. No fetal growth in 3–4 weeks.

%) advised to induce labour at 38 weeks.

AC and/or EFW p5-p10

Five protocols (9 %) included p5-p10 as a subgroup of FGR. Two (4 %) stated to induce labour from 37 weeks if Doppler results are normal. One of them (2 %) stated to induce labour between 38 and 40 weeks if Doppler results are normal. Two of them (4 %) stated to induce labour at 40 weeks regardless of Doppler results.

AC and/or EFW p3-p5

Four protocols (7 %) mentioned this specific centile group. Two (4 %) indicated to induce labour at 37 weeks in case of AC/EFW p3-p5 and AU pulsatility index p90-p95. Two (4 %) indicated to induce labour at 38 weeks, without mentioning Doppler results.

Induction of labour based on Doppler velocimetry results

Recommendations on induction of labour based on different Doppler velocimetry results are shown in Figs. 5, 6, and 7, respectively. In summary, 41 (76 %) protocols indicated induction of labour at 37 weeks when the UA pulsatility index is > 95th percentile with positive EDF. In case of absent EDF, 37 (69 %) protocols indicated induction of labour at 34 weeks. In case of reversed EDF, 35 (65 %) protocols indicated induction of labour at 34 weeks. The above-mentioned indications for induction of labour based on Doppler results, were all in line with the 2017 national guideline [13].

Mode of delivery

Most protocols (n = 39, 72 %) did not include a recommendation regarding the mode of delivery (vaginal delivery vs caesarean section). Two protocols (4 %) indicated to determine the mode of delivery at an individual patient level. Three protocols (6 %) indicated vaginal delivery, not further specified. Two protocols (4 %) indicated a caesarean section in case of a CTG suspicious for hypoxia. Two protocols (4 %) indicated a caesarean section before 34 weeks and a vaginal delivery after 34 weeks of gestation. Two protocols (4 %) indicated a vaginal delivery in case of a PED flow of the umbilical artery and a caesarean section in case of an ARED flow. One protocol (2 %) indicated a vaginal delivery in case of a PED flow, a vaginal delivery in case of an ARED flow with a favourable Bishop Score and a caesarean section otherwise. One
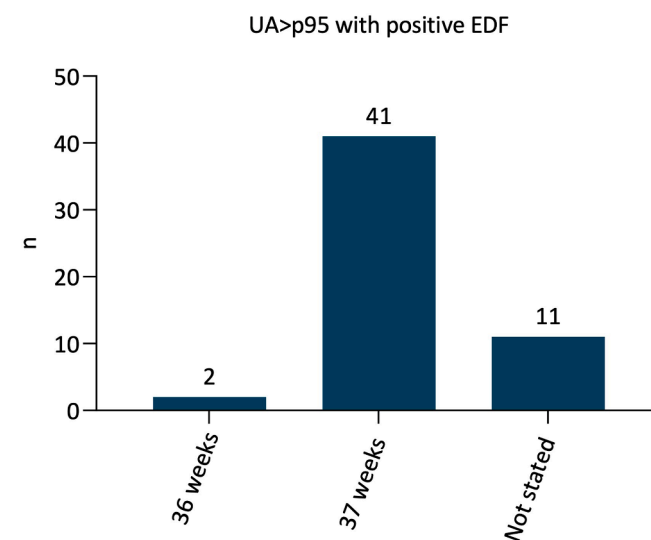

Fig. 5. Recommendations on induction of labour based on umbilical artery (UA) Doppler > 95th percentile with positive end diastolic flow (EDF).
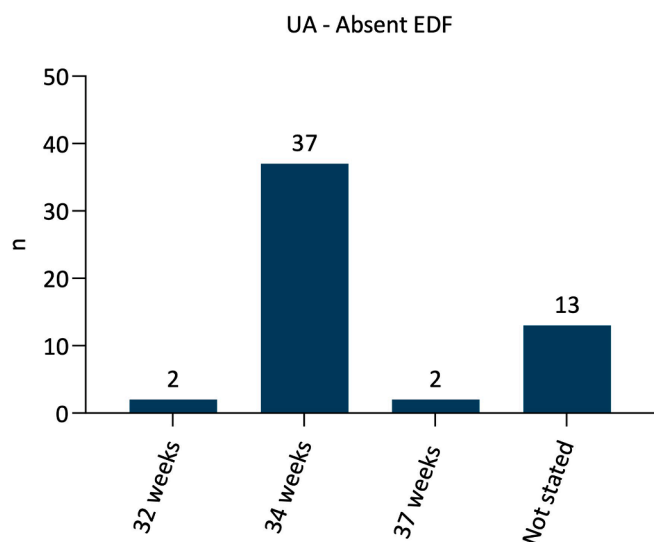
Fig. 6. Recommendations on induction of labour based on umbilical artery (UA) Doppler absent end diastolic flow (EDF).
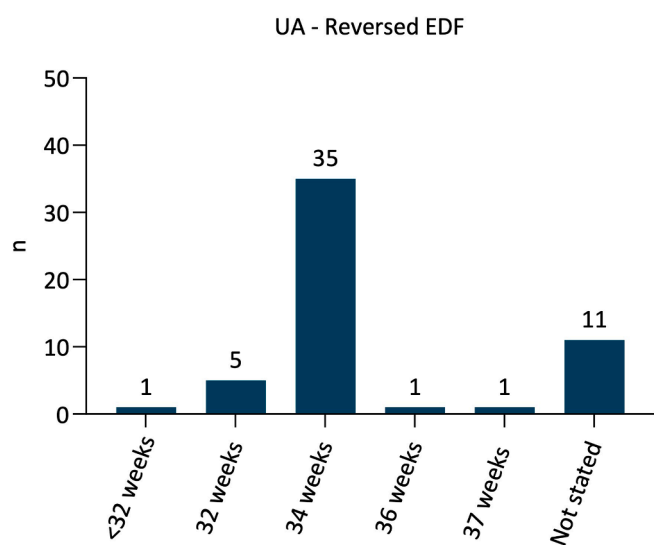

Fig. 7. Recommendations on induction of labour based on umbilical artery (UA) Doppler reversed end diastolic flow (EDF).

protocol (2 %) indicated to decide between vaginal delivery or caesarean section depending on suspected fetal distress in combination with gestational age. One protocol (2 %) indicated vaginal delivery in case of a favourable Bishop score and a caesarean in case of suspected fetal compromise. One protocol (2 %) indicated a vaginal delivery by default but indicated a caesarean section below 34 weeks of gestation with an AC or EFW < 5th percentile or severe Doppler deviations. Mode of delivery was not mentioned in the 2017 national guideline [13].

Pathologic examination of the placenta

Indications to perform pathologic examination of the placenta are described in detail in Appendix, Table S8. In summary, only nine protocols (17 %) indicated to perform pathologic placenta examination in case of FGR. No recommendation was given in the 2017 national guideline [13].

None of the collected protocols suggested the use of serum biomarkers.

Discussion

This study highlights the similarities and large variations between 54 Dutch hospital protocols on FGR. The results of this study are striking, a great variety in both definition and clinical management of FGR was observed between hospital protocols. The Dutch national guideline was last updated in 2017 [13]. 32 (59 %) Protocols were published from 2017 up and until 2020. One would assume that all obstetric units would be aware of this guideline and would more or less follow this guideline. 25 Out of 32 (78 %) of these protocols were, to a varying extent, based on the 2017 national guideline. However, it is possible that hospitals with a non-up-to-date guideline, actually used the 2017 national guideline in daily clinical practice.

A strength of this study is the high response of 76 %. Because 76 % of all the requested protocols were collected, the sample and our associated findings are sufficiently representative for the current situation in the Netherlands. Our observations for the Dutch hospitals might be representative for other countries, although there is no evidence confirming this. To our knowledge, a similar study investigating FGR practice variation in other countries has not been performed yet. A recommendation for future research, would be to investigate this topic in other countries and compare this with the Netherlands. Practice variation might be different in other countries, especially in countries with a significant contribution of private practices. Of note, the current study analyzed hospital protocols and not the monitoring and management strategies in actual clinical practice. These strategies most likely vary even more due to personal expertise and opinions of both healthcare professionals and patients.

Another strength of this study is the exhaustive review of the protocols with predefined domains of definition, preventive measures, testing, referral, monitoring strategies, interventions, mode of delivery and pathologic placenta examination. Any uncertainties in the interpretation of the protocols were discussed within the steering group. This improved the reliability of the data.

Although we think that a 76 % response is quite high, the fact that 24 % of the hospitals did not share their protocol for this study, could also be seen as a limitation. We did not analyze why certain hospitals did not send their protocol despite repeated requests. One could presume that the hospitals that did not have an up-to-date or complete protocol, were the ones that did not respond to the request. This might have led to sampling bias, resulting in a higher sampling probability of hospitals with up-to-date protocols.

We did not perform a statistical analysis on possible collinearity in not incorporating the most up-to-date recommendations by the national guideline. It is arguably true that hospital protocols that did not incorporate the most recent recommendations on one topic, e.g. FGR definition, did also not include the most recent recommendations on another topic, e.g. the frequency of Doppler measurements. We speculate that protocols that followed the 2017 national guideline on certain domains, also did this for the other domains of FGR diagnosis and management.

The International Society of Ultrasound in Obstetrics and Gynecology guideline encourages the use of the international consensus definition of FGR published in 2016 [2,12]. Only two (4 %) protocols used this consensus definition, implicating that at time of protocol collection the widely adopted international consensus definition was not implemented in Dutch hospital protocols. Most protocols used a definition based on fetal size aberration. Fetal size-oriented definition ignores some of the complexity of the overlap and difference between SGA and FGR. On the upside, from the analysis of the protocols it appears that most hospitals manage FGR based on biometry results combined with Doppler velocimetry measurements, reflecting that the SGA-based definition is unsatisfactory in practice. Still the timing of delivery in case of mild FGR with normal Doppler measurements is 38 weeks onwards in most protocols, based on the belief that the long-term neurodevelopmental outcomes for healthy SGA children are better with increasing gestational age.

The collected protocols do not mention the use of risk models to predict the chance of developing FGR and/or preeclampsia (PE) with common shared fundamental pathology, although recommendations for their use may have been included in local protocols on hypertensive disorders of pregnancy. However, most protocols mentioned risk factors for the development of FGR and recommended prophylactic low-dose anti platelet agents to decrease that risk in women at high risk. None of the protocols stated an indication of the use of low-dose aspirin in subsequent pregnancies if the placenta pathology report of the previous pregnancy pointed towards placental insufficiency (regardless of size), and only few protocols indicated to perform pathologic examination of the placenta in case of suspected FGR. The current evidence based on the literature suggests that an integrated risk model of risk factors identifies women at high risk of PE and FGR and that low-dose aspirin is effective in reducing these risks [17–19].

Ductus venosus (DV) Doppler measurements combined with CTG short term variability (STV) have not been applied widely in the monitoring of fetuses with severe preterm FGR. The findings and recommendations from the TRUFFLE study have apparently not been implemented by Dutch clinicians [20–22]. In our opinion, the primary analyses and several post-hoc analyses showed reasonable evidence to consider the ductus venosus as a useful tool in addition to other available monitoring parameters in timing of delivery in early FGR. However, the missing link in the TRUFFLE study is a comparison of computerized STV with traditional visual appreciation of the CTG from a randomized controlled trial [23].

Obviously, there is some consensus among protocols that Doppler measurements of fetal vessels can be useful. The protocol recommendations on the frequency of monitoring of fetal wellbeing by biometry and Doppler velocimetry of the umbilical artery and middle cerebral artery (and their ratio; CPR) are relatively uniform, stating frequencies ranging from once a week to twice weekly. The frequency seems to be Doppler result dependent, but not fetal size dependent, as most hospitals increase Doppler velocimetry measurements from once a week to twice a week in case of UA pulsatility index >95th percentile with a PED flow or an ARED flow. The UtA Doppler has not been implemented as a monitoring tool, although it may be a diagnostic tool at time of diagnosis to identify placental insufficiency as the underlying mechanism [12,24].

Consensus was also observed in the recommendation to induce labour in timely diagnosed late FGR. However, the details of the recommendations show large variations. The International Society of Ultrasound in Obstetrics and Gynecology guideline recommends to consider delivery after 38 weeks of gestation and not to exceed 39 weeks in case of late FGR, in order to reduce the risk of stillbirth [12]. The results of the DIGITAT study also support this recommendation [25], although this study had no information on fetal Doppler abnormalities. These recommendations are therefore open to interpretation for individual cases, which is likely to happen in clinical practice. Currently, there is no randomized evidence for intervention in case of abnormal Dopplers in late FGR. It is unknown if delivery based on Doppler evaluation of the umbilical artery or cerebral blood-flow redistribution improves short- and long-term neurodevelopmental outcomes [12]. The trials that are currently recruiting, DRIGITAT, RATIO37, TRUFFLE2 [26,27], are randomized controlled trials in which expectant management vs induction of labour based upon Doppler velocimetry of the MCA in late FGR is investigated. Hopefully these studies will provide the first guidance for management.

The findings of this study highlight our research agenda. The root cause for the described variation is most likely the lack of a golden standard of the disorder and the lack of evidence-based guidance of management. Most of the available evidence stems from observational studies that are designed to elucidate associations but are not conclusive regarding causation or the effectiveness of interventions. Therefore, the upcoming randomized evidence is highly anticipated.

Conclusion

This study shows both practice variations and similarities between hospital protocols on FGR in the Netherlands and underlines the complexity of diagnosis, monitoring and management of FGR. Randomized evidence is required to inform the appropriateness of options for monitoring and management in FGR.

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.2022.07.021.

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