SOGC Guideline 2023
Fetal Growth Restriction: Screening, Diagnosis, and Management in Singleton Pregnancies

What the Sonographer & Radiologist need to know

Presented on behalf of all authors by:

John Kingdom

MFM Division
Department of Obstetrics and Gynaecology
Mount Sinai Hospital
University of Toronto

1. Definitions: Established by ISUOG Delphi Consensus

- *"It is important for clinicians to understand the difference between fetal growth restriction and small for gestational age because fetal growth restriction is a risk factor for perinatal morbidity and mortality, while small for gestational age is not"*
- *"Fetal growth restriction is broadly categorized as a rare early-onset disease (prevalence 0.5%–1%) prior to 32 weeks' gestation, and a more common late-onset disease (prevalence 5%–10%) when diagnosed at 32 weeks and beyond"*

Early-Onset FGR – a rare condition

"Diagnosis at <32+0 weeks' gestation with at least one of 3 criteria:"

- *EFW or AC <3rd centile alone*
- *Abnormal umbilical artery Doppler (PI >95th centile, AEDFV, REDFV)*
- *EFW or AC < 10th centile with:*
  - *Abnormal uterine artery Doppler (mean PI >95th percentile)*
  - *Abnormal umbilical artery Doppler (PI > 95th percentile)*

- Implications
  - Obstetric sonographers should be comfortable obtaining uterine artery Doppler waveforms
  - Obstetric ultrasound units should use gestational age-specific reporting of all Doppler waveforms

Late-onset FGR – a common condition

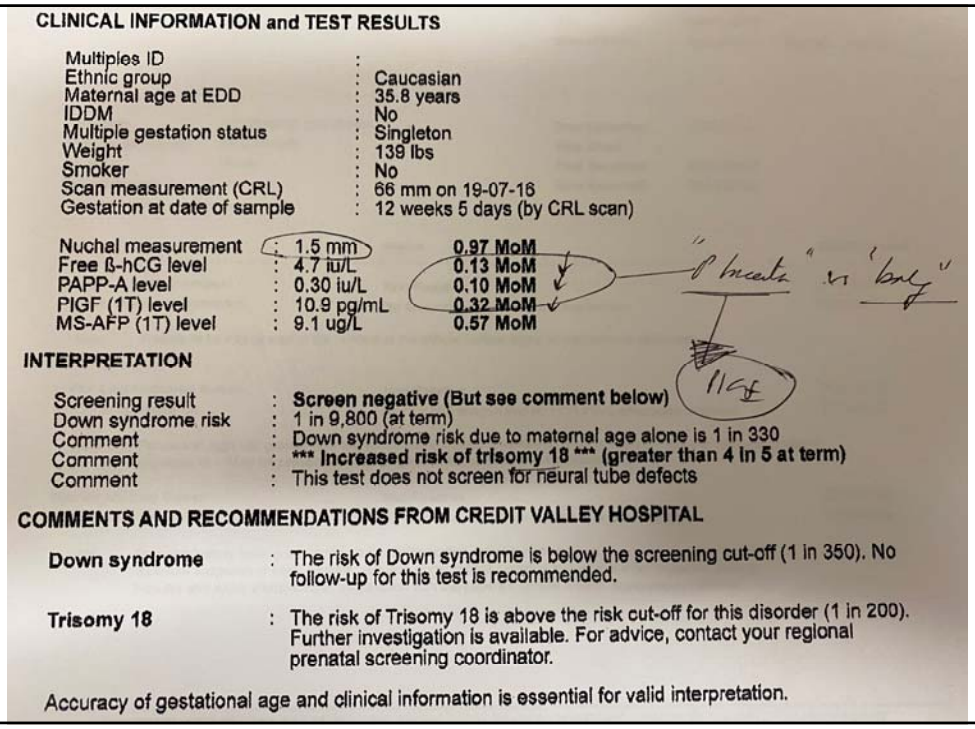
"Diagnosis at ≥32 weeks' gestation and requires either:"

- *EFW or AC < 3rd percentile alone, or*
- *2 of the following*
  - *EFW or AC <10th percentile*
  - *EFW or AC crossing 2 quartiles*
  - *Abnormal Doppler finding of either*
    - *Umbilical artery Doppler (PI >95th centile, or A/REDFV)*
    - *Cerebro-placental ratio <5th percentile*

- Implications
  - Obstetric sonographers should be comfortable obtaining middle cerebral artery Doppler waveforms
  - Obstetric ultrasound units should use gestational age-specific reporting of all Doppler waveforms

Prediction of FGR: First Trimester

- *"In the first trimester, multimodal screening for fetal growth restriction is substantially more effective than clinical risk factor-based screening, however multimodal screening is not presently recommended because of the logistical challenges to implementation in Canada"*
- Implication
  - It is unlikely that Canadian sonographers will be asked to re-organize and perform large-scale uterine artery Doppler screening during standard NT examinations



CLINICAL INFORMATION and TEST RESULTS

Multiples ID	:	
Ethnic group	:	Caucasian
Maternal age at EDD	:	35.8 years
IDDM	:	No
Multiple gestation status	:	Singleton
Weight	:	139 lbs
Smoker	:	No
Scan measurement (CRL)	:	66 mm on 19-07-16
Gestation at date of sample	:	12 weeks 5 days (by CRL scan)

Nuchal measurement	:	1.5 mm	0.97 MoM
Free ß-hCG level	:	4.7 iu/L	0.13 MoM
PAPP-A level	:	0.30 iu/L	0.10 MoM
PIGF (1T) level	:	10.9 pg/mL	0.32 MoM
MS-AFP (1T) level	:	9.1 ug/L	0.57 MoM

INTERPRETATION

Screening result	:	**Screen negative (But see comment below)**
Down syndrome risk	:	1 in 9,800 (at term)
Comment	:	Down syndrome risk due to maternal age alone is 1 in 330
Comment	:	***** Increased risk of trisomy 18 *** (greater than 4 in 5 at term)**
Comment	:	This test does not screen for neural tube defects

COMMENTS AND RECOMMENDATIONS FROM CREDIT VALLEY HOSPITAL

Down syndrome	:	The risk of Down syndrome is below the screening cut-off (1 in 350). No follow-up for this test is recommended.
Trisomy 18	:	The risk of Trisomy 18 is above the risk cut-off for this disorder (1 in 200). Further investigation is available. For advice, contact your regional prenatal screening coordinator.

Accuracy of gestational age and clinical information is essential for valid interpretation.

Prediction of FGR in the Second Trimester Abnormal FTS or MSS Biomarkers

- *"Pregnant patients with abnormal first or second trimester maternal serum screening analytes may be at risk for fetal growth restriction and other placenta-mediated complications"*

Prediction of FGR in the Second Trimester: Ultrasound

- *"a combination of ultrasound observations (made at the fetal anatomical ultrasound) may be useful for identifying pregnancies at risk of developing fetal growth restriction"*
  - *fetal biometry measurements >1 week behind gestational age*
  - *short femurs*
  - *echogenic fetal bowel*
  - *Umbilical cord abnormalities*
    - *a 2-vessel cord, or a marginal or velamentous placental cord insertion*
  - *Placental morphologic abnormalities*
    - *Grossly abnormal shape, size or texture*

The 18-20 week anatomy examination:

Increasing recognition that this is a risk-assessment opportunity

- Risk factors may be evident to sonographer and/or radiologist
  - Disclosure of abnormal eFTS / MSS data
  - "False positive" testing for Down's syndrome / normal NIPT
  - OB and/or medical Hx outlined on requisition
- Risk factors may be discovered during the US examination

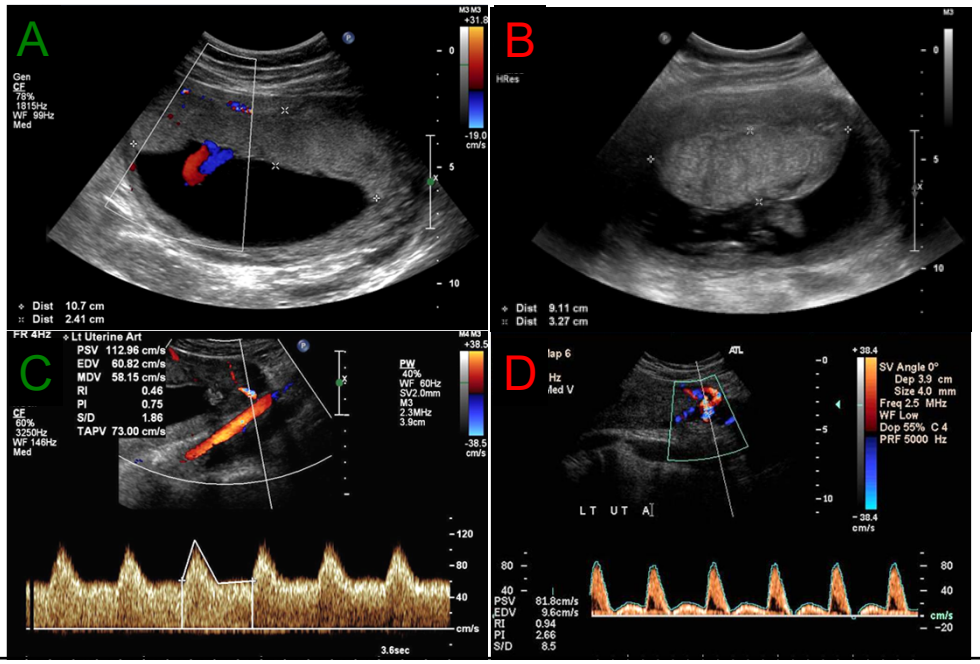
Risk Assessment for FGR: Second Trimester

(The Placental ultrasound examination)

- *"Health care providers should use uterine artery Doppler assessment (where available) to identify individuals those at greatest risk of fetal growth restriction"*

Normal Placental Ultrasound

MVM Placental Disease



Original Research

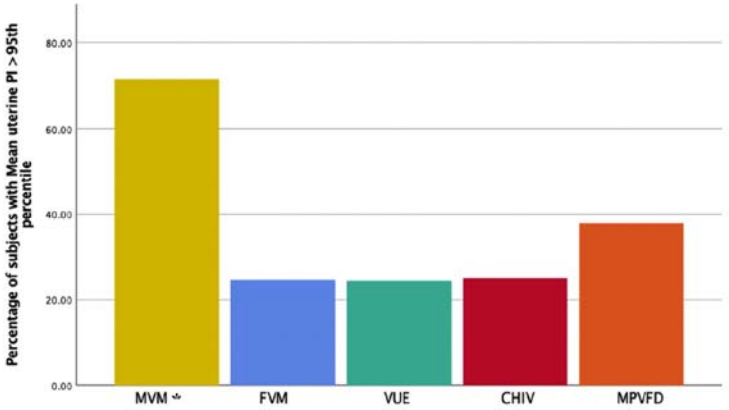
ajog.org

OBSTETRICS

Diagnostic utility of serial circulating placental growth factor levels and uterine artery Doppler waveforms in diagnosing underlying placental diseases in pregnancies at high risk of placental dysfunction

Swati Agrawal, MBBS, MSc; W. Tony Parks, MD; Helen Dehui Zeng, BSc; Anjana Ravichandran, BHSc; Eran Ashwal, MD; Rory C. Windrim, MB, MSc; Sebastian R. Hobson, MBBS, PhD; Nir Melamed, MD; John C. Kingdom, MD

FIGURE 1
Abnormal mean uterine artery Doppler stratified by placental pathology diagnosis



The *(asterisk)* denotes significantly elevated mean PI in the MVM group compared with all other groups (*P* value <.001 between MVM and other groups; no significant difference among other groups).

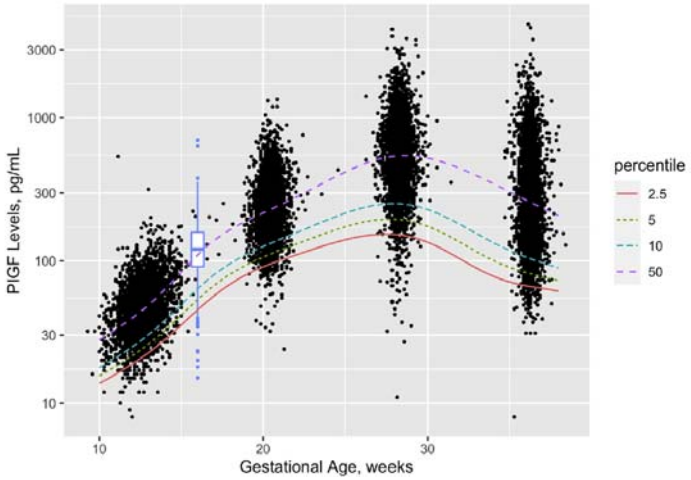
MVM, maternal vascular malperfusion; *PI*, pulsatility index.

Agrawal. Placental growth factor and placental pathology. Am J Obstet Gynecol 2022.

Risk Assessment for FGR: Second Trimester

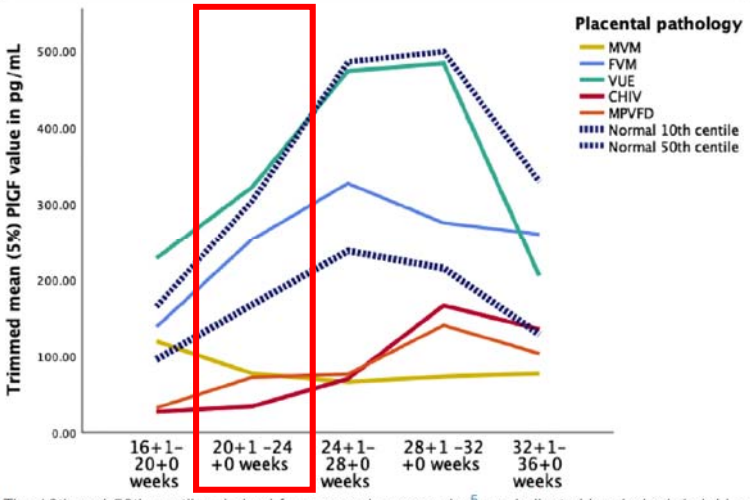
- *"Measurement of maternal placental growth factor (where available) may aid the health care provider to recognize the at-risk pregnant patient"*

FIGURE 2
Gestational age-specific distribution of circulating maternal PIGF levels



McLaughlin et al., AJOG, 2021

FIGURE 2
Trends in circulating placental growth factor stratified by placental pathology



The 10th and 50th centiles derived from normal pregnancies[5] are indicated by *dashed dark blue lines.*

Agrawal. Placental growth factor and placental pathology. Am J Obstet Gynecol 2022.

Reporting implications in the US Department

- "No fetal abnormality was detected in this examination, however some additional findings (summarize) indicate an increased risk of developing FGR"
  - "patient rebooked for a placental ultrasound assessment in 2 weeks"
  - "consider maternal Placental Growth factor (PlGF) blood test"
- Uterine artery Doppler should be reported/interpreted as mean PI for gestational age
- Obstetric ultrasound units must have ready access to gestational age-specific PULSATILITY INDEX reference ranges – <u>for all arterial Doppler studies</u>

Primary Screening approaches in the 2nd and 3rd trimesters

- *"Uterine artery and umbilical artery Doppler waveform assessments in the second or third trimesters are not effective primary screening tools for the prediction of fetal growth restriction in low-risk pregnancies"*
- *"Measurement of circulating maternal placental growth factor in either the second or the third trimesters is not effective in the prediction of fetal growth restriction in low-risk pregnancies"*

Detection of SGA size and FGR

- *"Health care providers can use serial symphysis–fundal height measurements to detect fetal growth restriction in clinically low-risk patients with a normal body mass index (18.5-24.9 kg/m^2)"*
- *For patients with an elevated body mass index (especially when >40 kg/m^2), polyhydramnios, or large fibroids, health care providers should use ultrasound to detect fetal growth restriction instead of symphysis–fundal height measurements"*

Routine 3rd trimester US ?

- *"Routine third trimester ultrasound examinations improve the detection of SGA fetuses in comparison with symphysis fundal height (SFH) measurements and selective use of ultrasound"*
- *"Routine third trimester ultrasound does not reduce the risk of either stillbirth or adverse perinatal outcomes but confers additional benefits such as the detection of breech presentation and major fetal abnormalities"*

EFW and EFW Centile: Methods

- *"Sonographers should calculate the estimated fetal weight using the Hadlock-3 formula applied to ultrasound measurements of the head circumference, the abdominal circumference and femur length"*
- *"Health care providers should interpret fetal growth by plotting estimated estimated fetal weight on an ultrasound-based fetal growth chart derived from uncomplicated pregnancies"*

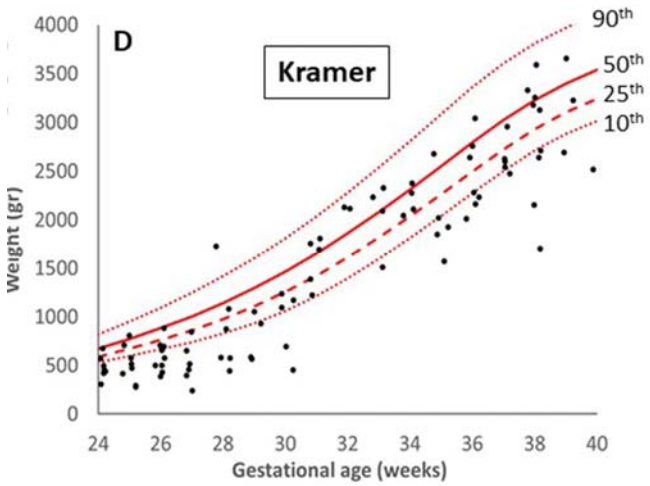
Archives of Gynecology and Obstetrics (2021) 303:381–390
https://doi.org/10.1007/s00404-020-05747-4

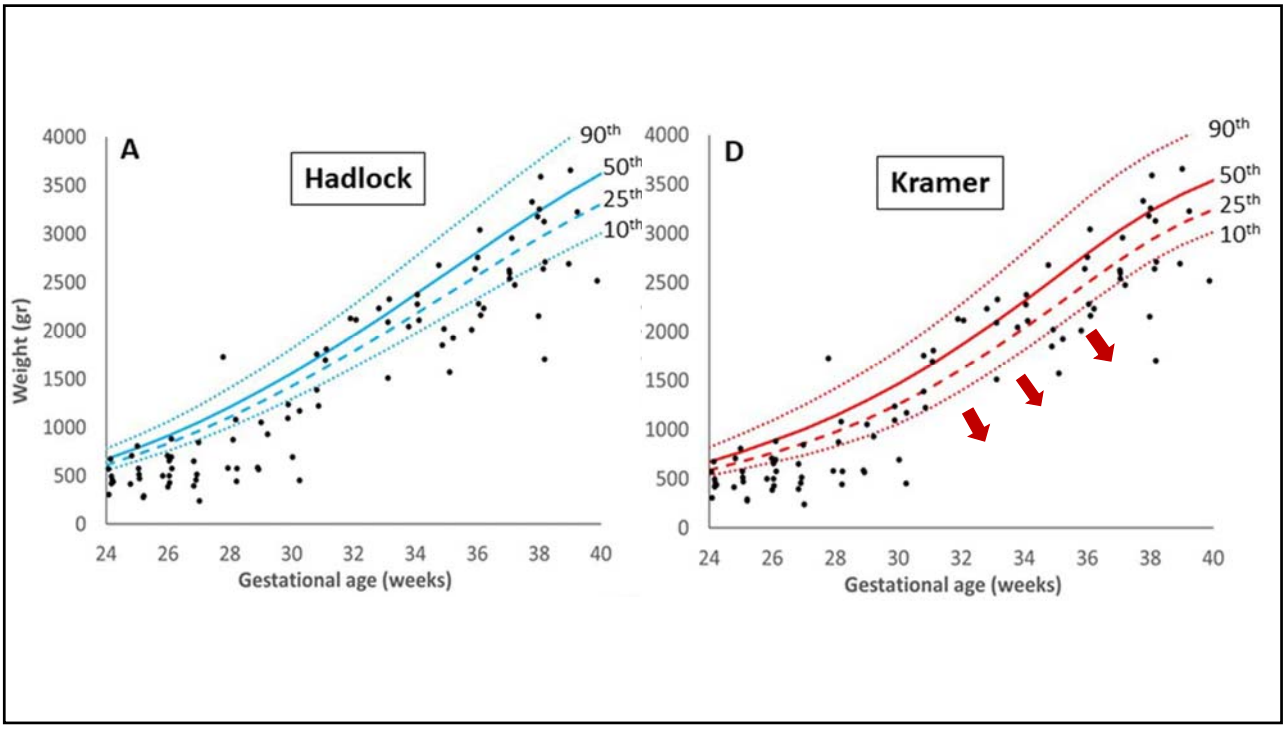
MATERNAL-FETAL MEDICINE

Check for updates

Identification of the optimal growth chart and threshold for the prediction of antepartum stillbirth

Liran Hiersch[1,2,3] · Hayley Lipworth[1] · John Kingdom[2,4] · Jon Barrett[1,2] · Nir Melamed[1,2]


D
Kramer
90th
50th
25th
10th
Weight (gr)
Gestational age (weeks)


A
Hadlock
D
Kramer
90th
50th
25th
10th
Weight (gr)
Gestational age (weeks)

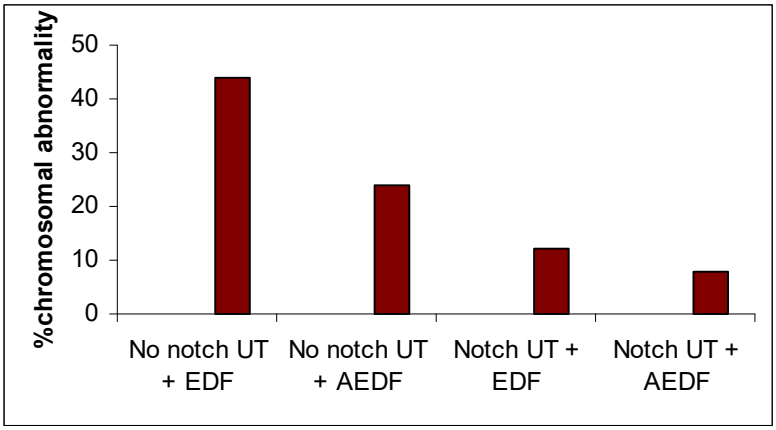
US evaluation of the FGR fetus

- *"Suspected fetal growth restriction should be systematically assessed by….. obtaining a detailed sonographic assessment to establish the diagnosis and underlying cause, differentiating"*
  - *a healthy small for gestational age fetus*
  - *from a fetus with placenta-mediated fetal growth restriction*
  - *or a fetus with impaired growth potential caused by an underlying genetic disorder, malformation, or infection*

Diagnostic role of umbilical artery Doppler

- *"Umbilical artery Doppler waveforms are typically abnormal in placenta-mediated early-onset fetal growth restriction, and typically normal in placenta-mediated late-onset fetal growth restriction"*
- *"Umbilical artery Doppler may be abnormal when fetal growth restriction is due to aneuploidy (trisomy 18, trisomy 21 and triploidy) or other intrinsic fetal diagnoses"*

Risk of aneuploidy in SGA fetuses by Uterine and Umbilical Artery Doppler (n=497)



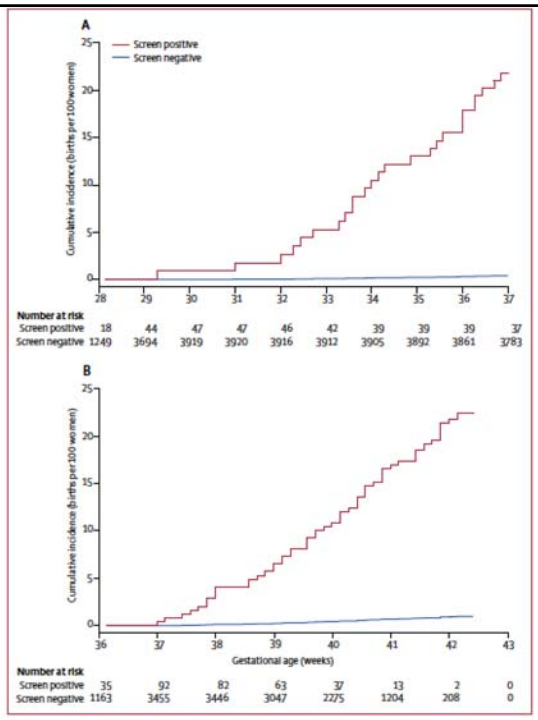
Snijders et al. 1993 AJOG

PlGF (or the sFLT1/PlGF ratio test

- *"When fetal growth restriction is suspected from viability to 36 weeks, the measurement of either placental growth factor (PlGF) alone, or the ratio of soluble fms-like tyrosine kinase-1 to PlGF (where either is available), may help clinicians to identify growth-restricted fetuses affected by underlying placental pathology disorders"*

Screening for fetal growth restriction using ultrasound and the sFLT1/PlGF ratio in nulliparous women: a prospective cohort study

Francesca Gaccioli*, Ulla Sovio*, Emma Cook, Martin Hund, D Stephen Charnock-Jones†, Gordon C S Smith†



Cumulative probability of SGA preterm birth <37 weeks
screen-positive (red)
screen-negative (blue)

Cumulative probability of SGA birth with FGR-related morbidity/mortality or pre-eclampsia >36 weeks
screen-positive (red)
screen-negative (blue)

Combined screening increases screening test precision

	True positive/false positive	True negative/false negative	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Ultrasonic estimated fetal weight below the tenth percentile	39/482	3207/19	5·1 (4·2-6·3)	0·38 (0·26-0·54)	67·2% (53·8-78·3)	86·9% (85·8-88·0)	7·5% (5·5-10·1)	99·4% (99·1-99·6)
sFLT1/PlGF ratio >38	31/532	3157/27	3·7 (2·9-4·8)	0·54 (0·41-0·72)	53·4% (40·3-66·1)	85·6% (84·4-86·7)	5·5% (3·9-7·7)	99·2% (98·8-99·4)
Ultrasonic estimated fetal weight below the tenth percentile and sFLT1/PlGF ratio >38	22/80	3609/36	17·5 (11·8-25·9)	0·63 (0·52-0·78)	37·9% (26·1-51·4)	97·8% (97·3-98·3)	21·6% (14·5-30·8)	99·0% (98·6-99·3)
Ultrasonic estimated fetal weight below the tenth percentile and lowest decile of abdominal circumference growth velocity*	18/143	3532/40	8·0 (5·3-12·1)	0·72 (0·60-0·85)	31·0% (20·2-44·4)	96·1% (95·4-96·7)	11·2% (7·1-17·1)	98·9% (98·5-99·2)
Delphi procedure definition of late fetal growth restriction*	35/377	3257/22	5·9 (4·7-7·4)	0·43 (0·31-0·60)	61·4% (47·9-73·4)	89·6% (88·6-90·6)	8·5% (6·2-11·6)	99·3% (99·0-99·6)

Small for gestational age was defined using a non-customised birthweight standard (see Methods). sFLT1=soluble fms-like tyrosine kinase 1. PlGF=placental growth factor. *See appendix for definitions.

Table 3: **Ultrasonic and biochemical screening test diagnostic effectiveness at 36 weeks of gestational age for subsequent delivery of a small for gestational age infant associated with either maternal pre-eclampsia or perinatal morbidity or mortality (n=3747)**

Savings from much lower false-positive interventions
(US screening alone 482 vs. 80 combined screening)
greatly outweighs the incremental cost of angiogenic growth factor testing

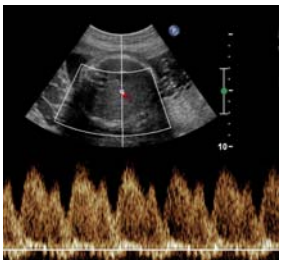
Hypertension

ORIGINAL ARTICLE

Increased Placental sFLT1 (Soluble fms-Like Tyrosine Kinase Receptor-1) Drives the Antiangiogenic Profile of Maternal Serum Preceding Preeclampsia but Not Fetal Growth Restriction

Francesca Gaccioli, Ulla Sovio, Sungsam Gong, Emma Cook, D. Stephen Charnock-Jones, Gordon C.S. Smith

Early-onset FGR: Surveillance

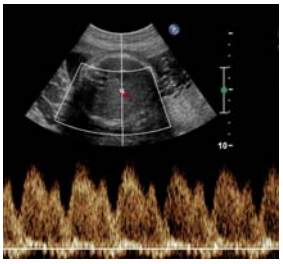


- *"Clinicians should primarily use a combination Doppler studies (uterine artery, umbilical artery, middle cerebral artery, cerebroplacental ratio and ductus venosus Doppler) to identify early-onset (<32 weeks) fetal growth restriction"*
- *Biophysical profile, modified biophysical profile and visual non-stress test interpretation should not be used in isolation to monitor the early-onset fetal growth restriction fetus"*

Early-onset FGR: Surveillance

- *"Weekly outpatient assessments are indicated when Doppler studies of the umbilical artery are abnormal, and should comprise middle cerebral artery Doppler and ductus venosus Doppler. Outpatient assessments are appropriate so long as these fetal Doppler studies are normal"*
- *"Daily inpatient surveillance is indicated when highly-abnormal umbilical Doppler waveforms (reversed end-diastolic flow velocities [REDF]) are observed, and when absent end-diastolic flow velocities (AEDF) in the umbilical artery are accompanied by abnormal middle cerebral artery or ductus venosus Doppler studies"*

Early-onset FGR: Surveillance
Key role now for DV Doppler

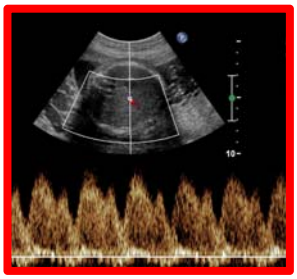


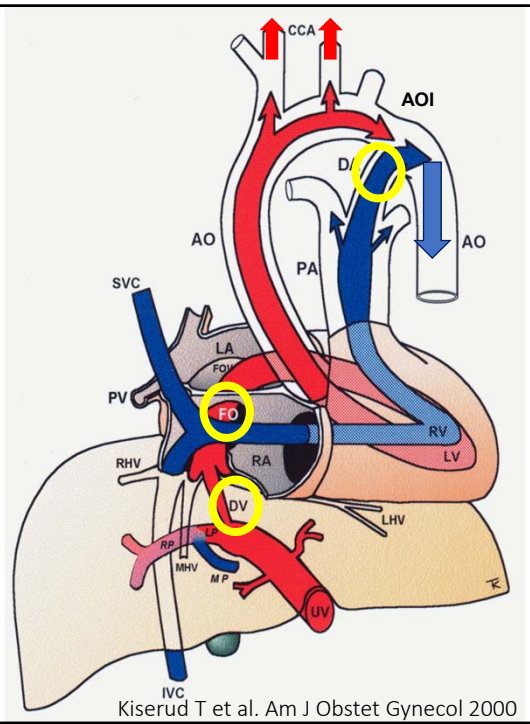
- *"Clinicians may safely defer delivery until 30-32 weeks when reversed end-diastolic flow (REDF) velocity is found in the umbilical arteries, and to 32-34 weeks when absent end-diastolic flow (AEDF) velocity is found, so long as ductus venosus Doppler and non-stress tests are normal"*
- IMPLICATION for practice
  - Understand venous anatomy within the liver
  - Avoid false-positive test (Doppler on the wrong intra-hepatic vein)

The Fetal circulation has

3 Physiologic shunts

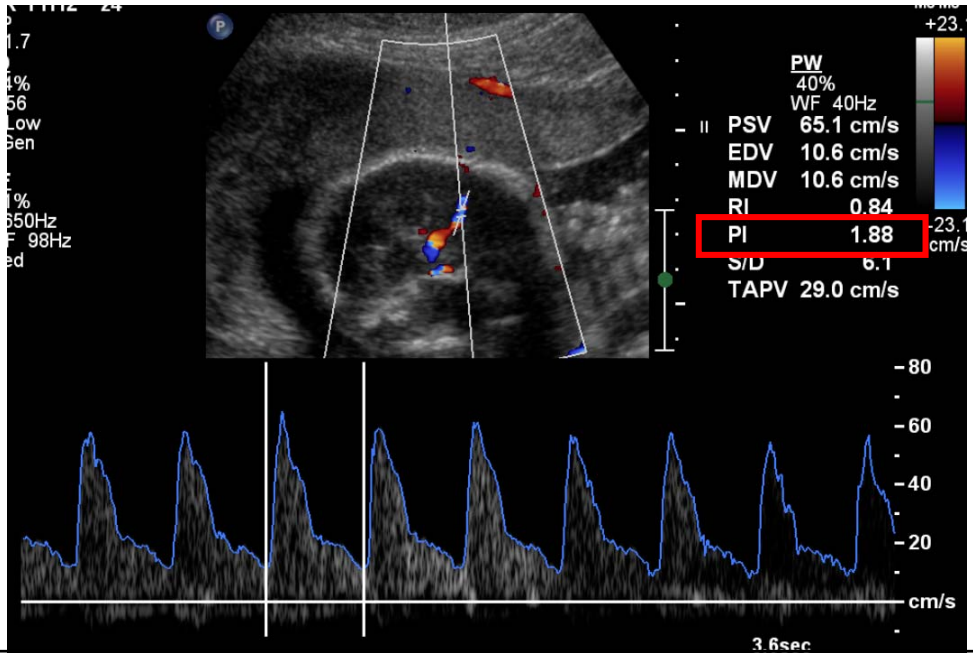
Oxygenated blood from the placenta traverses at high speed from the IHV to the R atrium and on into the L atrium to get to the brain

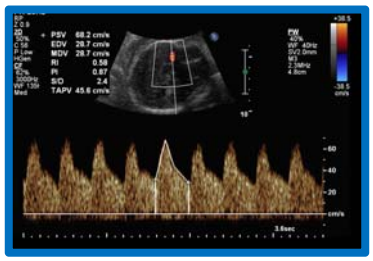




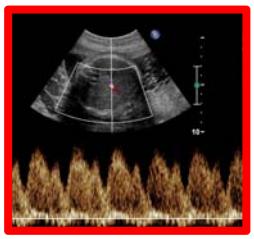
Kiserud T et al. Am J Obstet Gynecol 2000

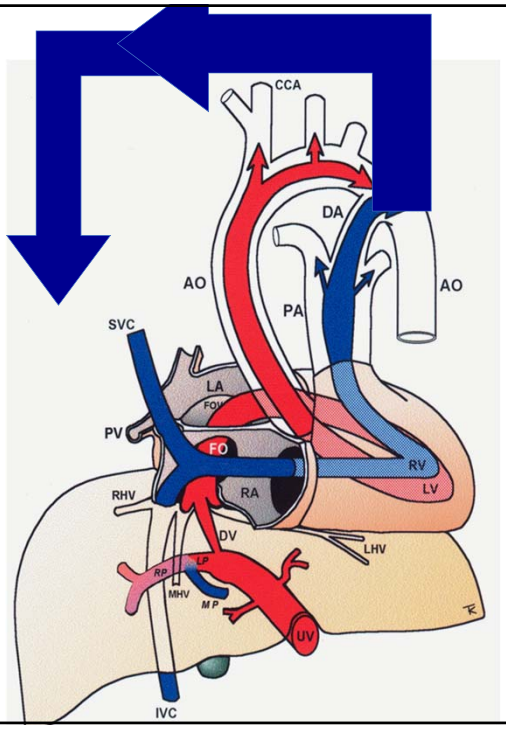
Normal Middle Cerebral Artery Doppler

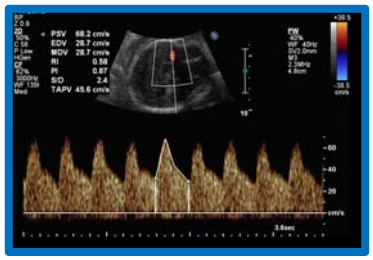


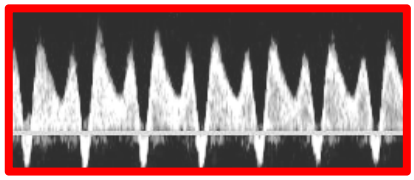


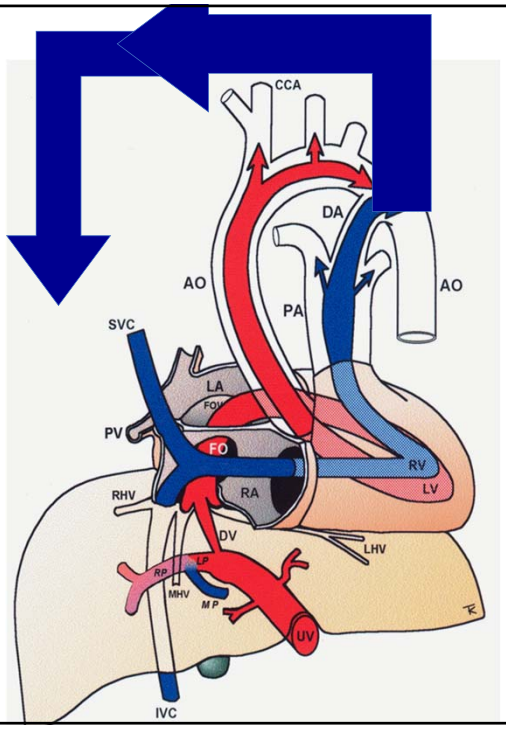
MCA Redistribution is advantageous to the early-onset FGR fetus:
therefore it is not an indication for delivery



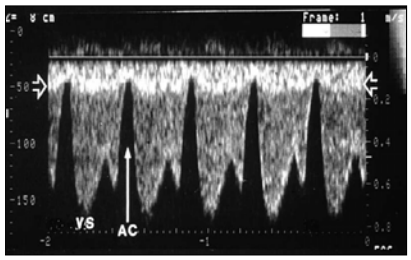


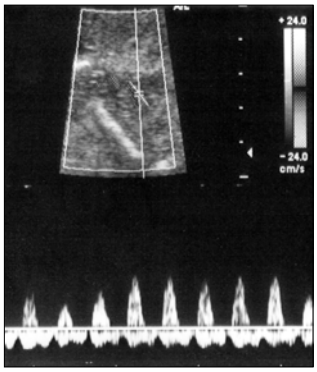






Abnormal DV Causes IHV and UV Pulsations Indicates Right Heart Failure and Acidosis





Late-Onset FGR: Diagnosis

- *"Clinicians may use a variety of tools to monitor the fetus with suspected late-onset fetal growth restriction. Standard of care methods comprise fetal movement counting, full or modified biophysical profile scoring, and non-stress testing"*
- *"Umbilical artery Doppler should not be used as a monitoring tool in isolation"*

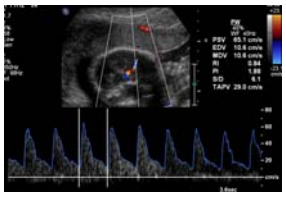
Late-onset FGR: WHAT IS NEW?

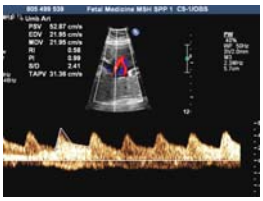
Late-onset FGR: MCA Doppler

- *"Middle cerebral artery Doppler may be used as a monitoring tool, but should ideally be combined with umbilical artery Doppler and interpreted by deriving the cerebro-placental Doppler ratio (middle cerebral artery pulsatility index / umbilical artery pulsatility index)"*
- *"Middle cerebral artery Doppler should be performed during fetal quiescence to avoid false-positive test results"*
- *"An abnormal cerebro-placental ratio test is interpreted as <5th percentile for gestational age and indicates, depending on gestational age, the need for either enhanced surveillance or delivery"*

Cerebro-placental Ratio (CPR)

- Middle cerebral artery PI / Umbilical artery PI





- 1.88 / 0.99 = 1.9 which is reassuring
- Abnormal when the waveforms are similar ie ratio approaches 1

Ultrasound Obstet Gynecol 2019; **53**: 465–472
Published online 13 February 2019 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.20157

Fetal Medicine Foundation reference ranges for umbilical artery and middle cerebral artery pulsatility index and cerebroplacental ratio

A. CIOBANU[1], A. WRIGHT[2], A. SYNGELAKI[1], D. WRIGHT[2], R. AKOLEKAR[3] and K. H. NICOLAIDES[1]

[1]*Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK;* [2]*Institute of Health Research, University of Exeter, Exeter, UK;* [3]*Fetal Medicine Unit, Medway Maritime Hospital, Gillingham, UK*

KEYWORDS: cerebroplacental ratio; Doppler ultrasound; fetal middle cerebral artery pulsatility index; reference range; umbilical artery pulsatility index

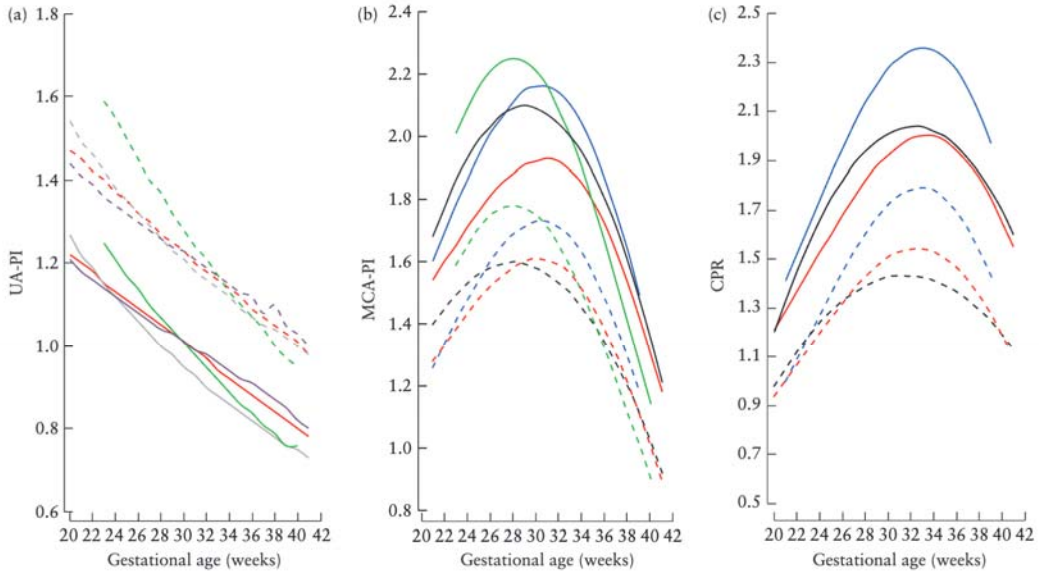


Figure 2 Comparison of 50th (solid lines) and 90th (dashed lines) percentiles of umbilical artery (UA) pulsatility index (PI) (a) and 50th (solid lines) and 10th (dashed lines) percentiles of middle cerebral artery (MCA) PI (b) and cerebroplacental ratio (CPR) (c), according to gestational age, between Fetal Medicine Foundation chart (——) and previous charts: Acharya *et al.*[17] (——); Ebbing *et al.*[20] (——); Parra-Cordero *et al.*[21] (——); Bahlmann *et al.*[22] (——); and Morales-Roselló *et al.*[23] (——).

Late-onset FGR: Frequency of assessment

- *"Weekly assessments are appropriate when"*
  - *umbilical artery and middle cerebral Doppler are normal*
  - *the pregnancy is otherwise stable, including normal fetal movements*
  - *The estimated fetal weight or fetal abdominal circumference are in the 3rd-10th percentile range*
- *"Twice-weekly surveillance or delivery is indicated when"*
  - *estimated fetal weight or abdominal circumference are <3rd centile and additional observations suggest true fetal growth restriction.*
    - *abnormal uterine artery Doppler (mean pulsatility index >95th percentile)*
    - *abnormal umbilical artery Doppler (pulsatility index >95th percentile)*
    - *abnormal middle cerebral artery Doppler (pulsatility index < 5th percentile or cerebro-placental ratio < 5th percentile [approx. 1.0])*
    - *low amniotic fluid (maximum vertical cord-free pocket <2cm or amniotic fluid index <5cm);*

Late-onset FGR: Timing of delivery

- *"When healthy SGA (estimated fetal weight and abdominal circumference at 3rd-10th percentile) is observed with serial normal Doppler studies, and additional fetal surveillance tests), clinicians should consider delivery by 39 weeks' gestation"*
- *"Clinicians managing uncomplicated late-onset FGR (estimated fetal weight or abdominal circumference at <3rd percentile with normal Doppler studies and normal additional fetal surveillance tests), should consider delivery by 37 weeks' gestation"*

Late-onset FGR: Timing of delivery

- *"Clinicians should recommend delivery by 37 weeks in late-onset FGR when any of the following are present"*
  - *abnormal umbilical artery Doppler (pulsatility index >95th percentile)*
  - *abnormal cerebro-placental Doppler (ratio <5th percentile)*
  - *abnormal full or modified biophysical profile*
  - *oligohydramnios*

Summary of Key Changes

- Adoption of Hadlock formula and ultrasound-derived fetal growth charts to interpret fetal growth
- Role of uterine artery Doppler and PlGF to define the risk of FGR
  - at >20 weeks' gestation
- No role for routine 3rd trimester US
  - Combined screening with PlGF under RCT evaluation
- Increased emphasis on Doppler-based diagnosis and surveillance
  - DV Doppler in early-onset FGR
  - Cerebro-placental Doppler ratio in late-onset FGR
- Importance of using gestational age-specific references ranges for interpretation of all arterial Doppler waveforms

John C. Kingdom, MD FRCSC, Toronto, ON
Eran Ashwal, MD FRCSC, Hamilton, ON
Andrea Lausman, MD FRCSC, Toronto, ON
Jessica Liauw, MD FRCSC, Vancouver, BC
Nancy Soliman, MD FRCSC, Calgary, AB
Ernesto Figueiro Filho, MD PhD FRCSC, Regina, SK
Christopher Nash, MD FRCSC, Halifax, NS
Emmanuel Bujold, MD FRCSC, Laval, QC
Nir Melamed, MD MSc, Toronto, ON