



FGR Background Primer

October 2026

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Transforming Care for Preeclampsia, Fetal Growth Restriction and Stroke

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About This Primer

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Purpose

Provide disease/indication background ahead of a key opinion leader (KOL) call on fetal growth restriction (FGR) covering what FGR is, what it means for mother and baby, how it is currently managed, and why it is a significant unmet medical need.

What it contains

Information drawn from published, peer-reviewed literature and DiaMedica's previously public disclosures. Every data point is cited to its public source.

What it does not contain

No confidential information, no material non-public information and no unreported data from DiaMedica clinical trials.

Forward-looking statements

Statements about DM199 describe hypotheses or previously disclosed plans, not demonstrated results. Actual results may differ; see DiaMedica's SEC filings for risk factors.

DM199 Phase 2 Early Onset Severe Fetal Growth Restriction (FGR)

Investigator Sponsored Trial (IST) - Phase 2 in South Africa: ongoing

FGR Participants:

- 27+0 to 32+6 weeks GA
- Less than **3rd centile** on fetal growth charts

IST Cape Town

30 early-onset fetal growth restriction participants
SC: 5, 10 and 1-15 µg/kg (3x6 plus 12)



Inclusion Criteria (additional)

- › No evidence of fetal compromise that warrants immediate delivery
- › Co-existing diagnosis of preeclampsia permitted, not required

Treatment

- › DM199 SC dose every 3 days until delivery
- › 3 dose levels: 5, 10 and 1-15 µg/kg (3rd cohort based on results of first two)
- › 12 patient confirmation cohort at identified optimal dose level

Endpoints

Primary:

- › Safety:
 - Incidence of treatment emergent adverse events
 - Umbilical cord blood levels of DM199 after birth
- › Efficacy:
 - Changes in uterine artery and umbilical artery Doppler flow
 - Changes in fetal Doppler parameters
 - Birthweight centile

Secondary outcomes:

- › Prolongation of gestation
- › Fetal growth trajectory
- › Changes in maternal blood pressure
- › Use of antihypertensives

Exploratory outcomes:

- › PK profiling
- › Changes in plasma biomarkers
- › AE monitoring

What is Fetal Growth Restriction (FGR) & How Common Is It?

- › FGR is a condition where a failing placenta cannot meet the oxygen and nutritional needs of the growing fetus, causing it to fall short of its genetically predetermined size. It most commonly results from poor placental function (placental insufficiency)¹
 - › The fetus redirects its limited supply of oxygen and nutrients away from growth and toward survival, prioritizing blood flow to the brain and heart and slowing growth trajectory¹
 - › Clinically, most cases are identified among fetuses under the 10th centile on fetal growth charts; **fetuses under the 3rd centile are at the greatest risk and represent the clearest cases of true FGR³**
- › *FGR is one of obstetrics' “big four” complications alongside preeclampsia, spontaneous preterm birth, and diabetes in pregnancy³*

Up to ~10%

of all pregnancies are complicated by FGR

3.6M

Births per year in the US²

Source(s): (1) Lees CC, Romero R, Stampalija T, et al. Clinical Opinion: The diagnosis and management of suspected fetal growth restriction: an evidence-based approach. Am J Obstet Gynecol 2022; 226(3): 366-78. (2) [FastStats - Births and Natality](#). (3) Tong S, et al. The Potential of DM199 to Treat Fetal Growth Restriction (white paper), Sept. 2026, and references therein.

Clinical Concern: FGR Is the Single Greatest Risk Factor For Stillbirth¹

- › Stillbirth ends 1 in 150 births, and impacts roughly 21,000 families a year in the US, far more common than widely believed²
- › It disproportionately affects minorities and those with the lowest incomes²
- › Risk rises sharply as birthweight centile falls, and is greatest for fetuses under the 3rd centile³

1 in 150

births end in stillbirth (~21,000 families/year in the US)²

3 to 4x

increased perinatal mortality for babies between the 3rd and 10th centile³

~10x

increased perinatal mortality for babies under the 3rd centile (15x under the 1st at term)³

Sources: (1) Malhotra A, et al. Front Endocrinol (Lausanne) 2019; 10: 55. (2) Sullivan HK et al., Stillbirths in the United States. JAMA 2025;334(22):2033-5. (3) Francis JH et al., ANZJOG 2014;54(4):354-9.

Long Term Impact Includes A Lifetime of Increased Risk

› Most growth restricted fetuses are born alive, but weeks of in utero starvation rewire their physiology¹

Neonatal Period

Perinatal asphyxia and brain injury, feeding difficulties, hypoglycemia, and other complications²

Childhood

Early cardiovascular changes, and poorer neurodevelopmental and educational outcomes^{2,3}

Adulthood

Increased risk of stroke, coronary artery disease, diabetes, and obesity, as described in the field of Developmental Origins of Health and Disease (DOHaD)¹

A drug that rescues placental function may not just reduce stillbirth. It may reduce disease risk across an entire lifetime

Sources: (1) Tong S, et al. The Potential of DM199 to Treat Fetal Growth Restriction (white paper), Sept. 2026, and references therein. (2) Malhotra A, et al. Front Endocrinol (Lausanne) 2019; 10: 55. (3) Adanikin A, et al. PLoS Med 2022; 19(10): e1004108.

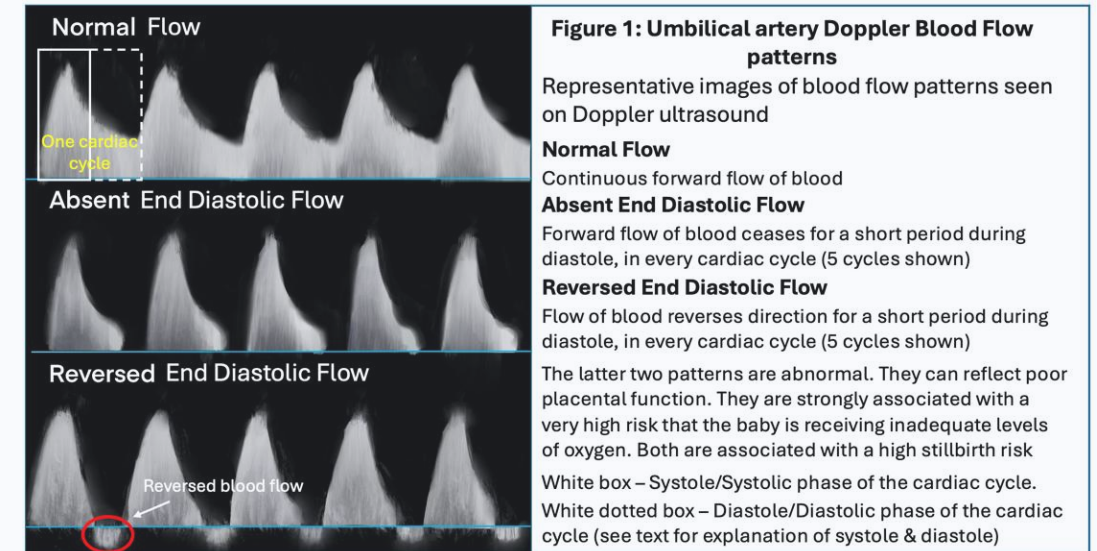
Clinicians Can Monitor FGR, but Cannot Treat It

Monitoring

- › Umbilical artery Doppler tracks the degree of blood flow resistance in the umbilical artery, which typically worsens in a stepwise pattern
 - › For example, increased diastolic resistance → absent end-diastolic flow (AEDF) → reversed end-diastolic flow (REDF)
- › In REDF, resistance is so high that blood flows backwards during diastole, a sign strongly associated with imminent stillbirth
- › Uterine artery Doppler reflects the maternal side, and may be an excellent way to monitor a therapy aiming to increase blood supply to the placenta

No Treatment: Watch and Deliver

- › **There is no disease-modifying therapy for FGR, anywhere in the world**
- › Once diagnosed, management is close surveillance and timed birth: as late as possible, but before a stillbirth happens
- › At term (≥ 37 weeks), the call is straightforward: deliver soon
- › Preterm, it is a genuine dilemma: very preterm birth carries serious risk of cerebral palsy, intellectual deficit, blindness, deafness, and death
- › Clinicians must balance two competing risks: continued placental insufficiency in utero versus the risks of an early birth



Content and figure adapted from Tong S, Walker SP, Cluver CA white paper, Sept 2026. (Figure 1: Umbilical artery Doppler blood flow patterns).

Severe Early-onset FGR: Stage-by-stage Doppler Deterioration

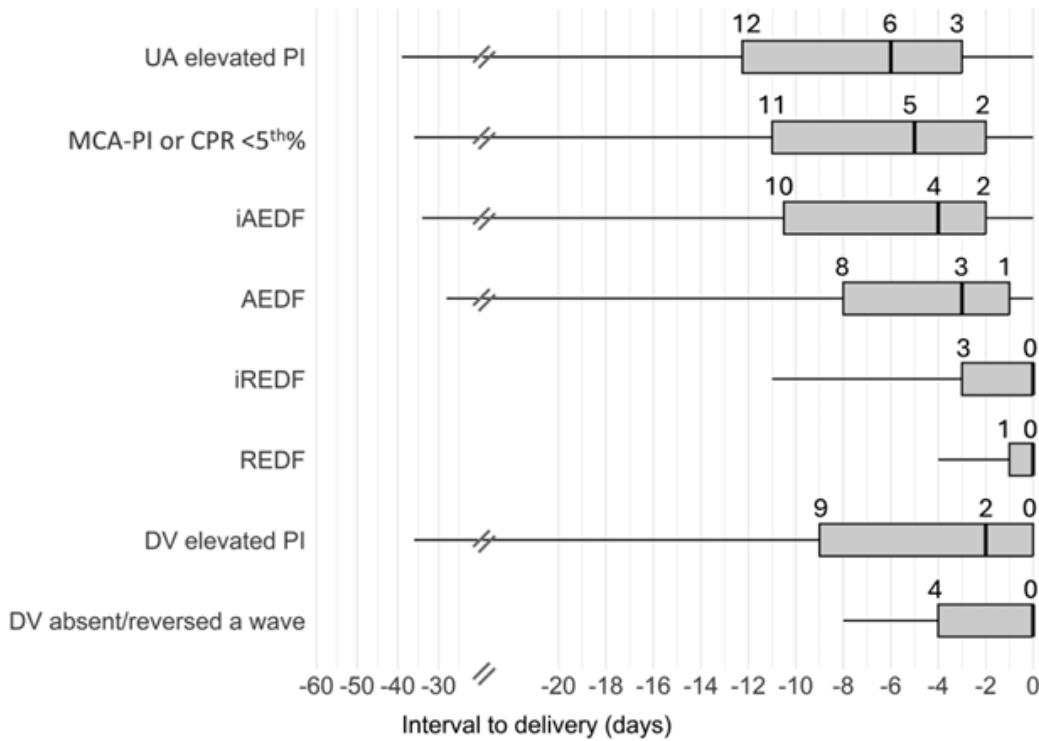
Deterioration is rapid

Each Doppler stage typically gives way to the next in 4 to 7 days. In the fastest cases, fetuses moved through several stages between scans, going from elevated UA-PI to reversed end-diastolic flow in a median of just 5 days.

Why it doesn't reach 34 weeks

Worsening Doppler findings force early delivery. Mean GA at birth was 28.6 ± 3.1 weeks, and 95% of babies were born before 34 weeks, well short of protocol targets of 30–32 weeks for REDF and 32–34 weeks for AEDF¹

Time to Delivery by Fetal Doppler Stage in Early-Onset FGR



Distribution of time from initial diagnosis of each specific Doppler abnormality until delivery within the cohort of 241 severe early-onset FGR singleton pregnancies, with the day of delivery designated as time zero. Vertical line = median number of days to delivery. AEDF, absent end diastolic flow; CPR, cerebroplacental ratio; DV, ductus venosus; iAEDF, intermittent absent end diastolic flow; iREDF, intermittent reversed end diastolic flow; MCA, middle cerebral artery; PI, pulsatility index; REDF, reversed end diastolic flow; UA, umbilical artery.

Source(s): (1) Pardo N, et al. Umbilical artery Doppler deterioration, time to delivery, and risk of fetal death in early-onset severe fetal growth restriction progressing to absent or reversed end-diastolic flow. Am J Obstet Gynecol. 2026;235(2):395-408.

Impact of FGR on Latency in the Setting of Expectant Management of PE

CAOG Papers

ajog.org

The impact of fetal growth restriction on latency in the setting of expectant management of preeclampsia

David McKinney, MD; Heather Boyd, MD; Amanda Langager, MD; Michael Oswald, BS; Abbey Pfister, BS; Carri R. Warshak, MD

BACKGROUND: Fetal growth restriction is a common complication of preeclampsia. Expectant management for qualifying patients has been found to have acceptable maternal safety while improving neonatal outcomes. Whether fetal growth restriction influences the duration of latency during expectant management of preeclampsia is unknown.

OBJECTIVE: The objective of the study was to determine whether fetal growth restriction is associated with a reduced interval to delivery in women with preeclampsia being expectantly managed prior to 34 weeks.

STUDY DESIGN: We performed a retrospective cohort of singleton, live-born, nonanomalous deliveries at the University of Cincinnati Medical Center between 2008 and 2013. Patients were included in our analysis if they were diagnosed with preeclampsia prior to 34 completed weeks and if the initial management plan was to pursue expectant management beyond administration of steroids for fetal lung maturity. Two study groups were determined based on the presence or absence of fetal growth restriction. Patients were delivered when they developed persistent neurological symptoms, severe hypertension refractory to medical therapy, renal insufficiency, nonreassuring fetal status, pulmonary edema, or hemolysis elevated liver low platelet syndrome or when they reached 37 weeks if they remained stable without any other indication for delivery. Our primary outcome was the interval from diagnosis of preeclampsia to delivery, measured in days. Secondary outcomes included indications for delivery, rates of induction and cesarean delivery, development of severe morbidities of preeclampsia, and select neonatal outcomes. We performed a multivariate logistic regression analysis comparing those with fetal growth restriction with those with normally grown fetuses to determine whether there is an association between fetal growth restriction and a shortened interval to delivery, neonatal intensive care unit admission, prolonged neonatal stay, and neonatal mortality.

RESULTS: A total of 851 patients met the criteria for preeclampsia, of which 199 met inclusion criteria, 139 (69%) with normal growth, and 60 (31%) with fetal growth restriction. Interval to delivery was significantly shorter in women with fetal growth restriction, median (interquartile range) of 3 (1.6) days vs normal growth, 5 (2.12) days, $P < .001$. The association between fetal growth restriction and latency less than 7 days remained significant, even after post hoc analysis controlling for confounding variables (adjusted odds ratio, 1.66 [95% confidence interval, 1.12–2.47]). There were no differences in the development of severe disease (85.9 vs 91.7%, $P = .26$), need for intravenous antihypertensive medications (47.1 vs 46.7%, $P = .96$), and the development of severe complications of preeclampsia (51.1 vs 42.9%, $P = .30$) in normally grown and growth-restricted fetuses, respectively. Fewer women with fetal growth restriction attained their scheduled delivery date, 3 of 60 (5.0%), compared with normally grown fetuses, 12 of 139 (15.7%), $P = .03$. Admission to the neonatal intensive care unit, neonatal length of stay, and neonatal mortality were higher when there was fetal growth restriction; however, after a logistic regression analysis, these associations were no longer significant.

CONCLUSION: Fetal growth restriction is associated with a shortened interval to delivery in women undergoing expectant management of preeclampsia when disease is diagnosed prior to 34 weeks. These data may be helpful in counseling patients regarding the expected duration of pregnancy, guiding decision making regarding administration of steroids and determining the need for maternal transport.

Key words: expectant management of preeclampsia, fetal growth restriction, preeclampsia

Source(s): (1) McKinney D, et al. The impact of fetal growth restriction on latency in the setting of expectant management of preeclampsia. American Journal of Obstetrics & Gynecology, 2016; 214, 395.e1-395.e7

FGR Pulsatility Index Natural History

Early-onset FGR

- Placenta-mediated FGR/preeclampsia is a structural, progressive disease. The primary lesion is failed maternal spiral artery remodeling, causing maternal vascular malperfusion. Secondary fetal villous vascular changes follow, e.g., dedifferentiation of stem villous smooth muscle, which correlates with absent/reversed umbilical artery end-diastolic flow. Progressive infarction and villous loss further reduce the functional exchange surface. It is not self-correcting.¹
- Absent an intervention that improves placental perfusion, resistance (and PI, until flow becomes discontinuous) is expected to trend upward over time, with progressive Doppler deterioration^{2,3}.

Expected without treatment

Continued Doppler worsening

Evidence of biologically relevant effect

Stabilization

PI holds steady;
no progression to the next stage

PI reduction

Measured decrease in PI;
a more profound effect

Source(s): (1) Burton GJ, et al. Am J Obstet Gynecol. 2018 Feb;218(2S):S745-S761. doi: 10.1016/j.ajog.2017.11.577. (2) Damhuis SE, et al. Obstet Gynecol Clin North Am. 2021;48(2):267-279. doi:10.1016/j.ogc.2021.02.002. (3) Pardo N, et al. Am J Obstet Gynecol. 2026;235(2):395-408.

DiaMedica White Paper: The Potential of DM199 to Treat Fetal Growth Restriction



Background Reading

All papers are published and publicly available. Deck slide numbers refer to this primer.

#	Paper	Key takeaway	Slide
1	Lees CC, Romero R, Stampalija T, et al. The diagnosis and management of suspected fetal growth restriction: an evidence-based approach. Am J Obstet Gynecol. 2022;226(3):366-78. doi:10.1016/j.ajog.2021.11.1357	Expert consensus review: SGA vs. FGR definitions, early- vs. late-onset FGR (32-week cut-off), Doppler surveillance and timing of delivery.	5
2	Sullivan HK, et al. Stillbirths in the United States. JAMA. 2025;334(22):2033-5. doi:10.1001/jama.2025.17392	2.8M US commercially insured births (2016-22): stillbirth ~6.8 per 1,000 (~21,000 families/yr), higher in lower-income and minority communities.	6
3	Francis JH, Permezel M, Davey MA. Perinatal mortality by birthweight centile. Aust N Z J Obstet Gynaecol. 2014;54(4):354-9. doi:10.1111/ajo.12205	Population data (Victoria, 1999-2008): perinatal death rises as birthweight centile falls; ~3-4x risk at 3rd-10th centile, ~10x below the 3rd.	6
4	Malhotra A, Allison BJ, Castillo-Melendez M, et al. Neonatal morbidities of fetal growth restriction: pathophysiology and impact. Front Endocrinol. 2019;10:55. doi:10.3389/fendo.2019.00055	Review of how placental insufficiency damages the newborn brain, heart, lungs, gut and metabolism.	6,7
5	Pardo N, Kingdom J, Nevo O, Pardo A, Melamed N. Umbilical artery Doppler deterioration, time to delivery, and risk of fetal death in early-onset severe FGR progressing to absent or reversed end-diastolic flow. Am J Obstet Gynecol. 2026;235(2):395-408. doi:10.1016/j.ajog.2026.03.003	241 severe early-onset FGR pregnancies: each Doppler stage progresses in ~4-7 days; mean birth at 28.6 weeks; fetal death risk rises to 11.5% with reversed flow.	9,11
6	McKinney D, Boyd H, Langager A, et al. The impact of fetal growth restriction on latency in the setting of expectant management of preeclampsia. Am J Obstet Gynecol. 2016;214:395.e1-7. doi:10.1016/j.ajog.2015.12.050	In preeclampsia before 34 weeks, co-existing FGR shortened time to delivery (median 3 vs. 5 days).	10

Also cited in the deck: Adanikin A, PLoS Med 2022; Damhuis SE, Obstet Gynecol Clin North Am 2021; Tong S, et al., DM199 white paper, Sept 2026.; FastStats - Births and Natality; Burton GJ, et al. Am J Obstet Gynecol. 2018 Feb;218(2S):S745-S761. doi: 10.1016/j.ajog.2017.11.577.