Placenta Growth Factor: Diagnostic and Management Implications in High-Risk Obstetrics

John Kingdom, MD

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

Talk Objectives:

Sinai Health System

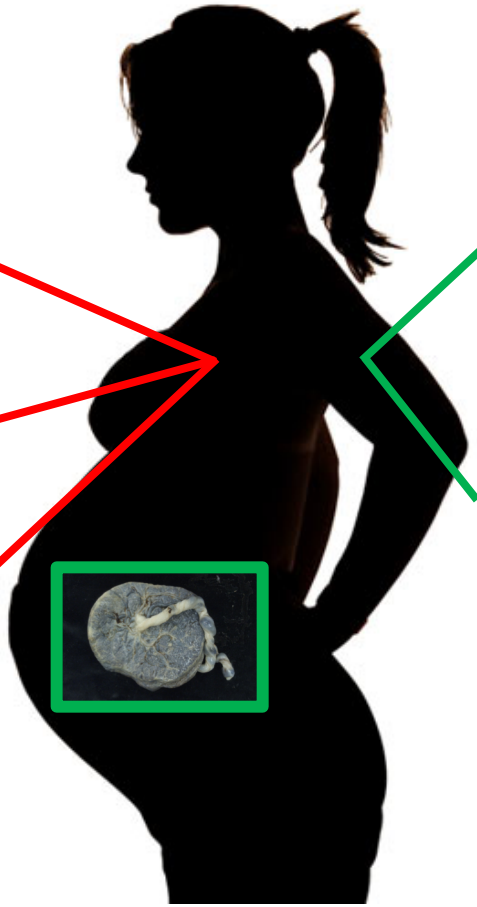
Relationship between abnormal placental development, circulating angiogenic growth factors and the origins of preeclampsia

Role of angiogenic growth factors in the diagnosis and management of preeclampsia.

Screening utility of angiogenic growth factors in the prevention of severe preeclampsia / fetal growth restriction.

Cardiovascular Function in Normal Pregnancy

The maternal cardiovascular system undergoes important modifications to promote fetal growth / build blood reserve



Cardiac Output ↑ 40%

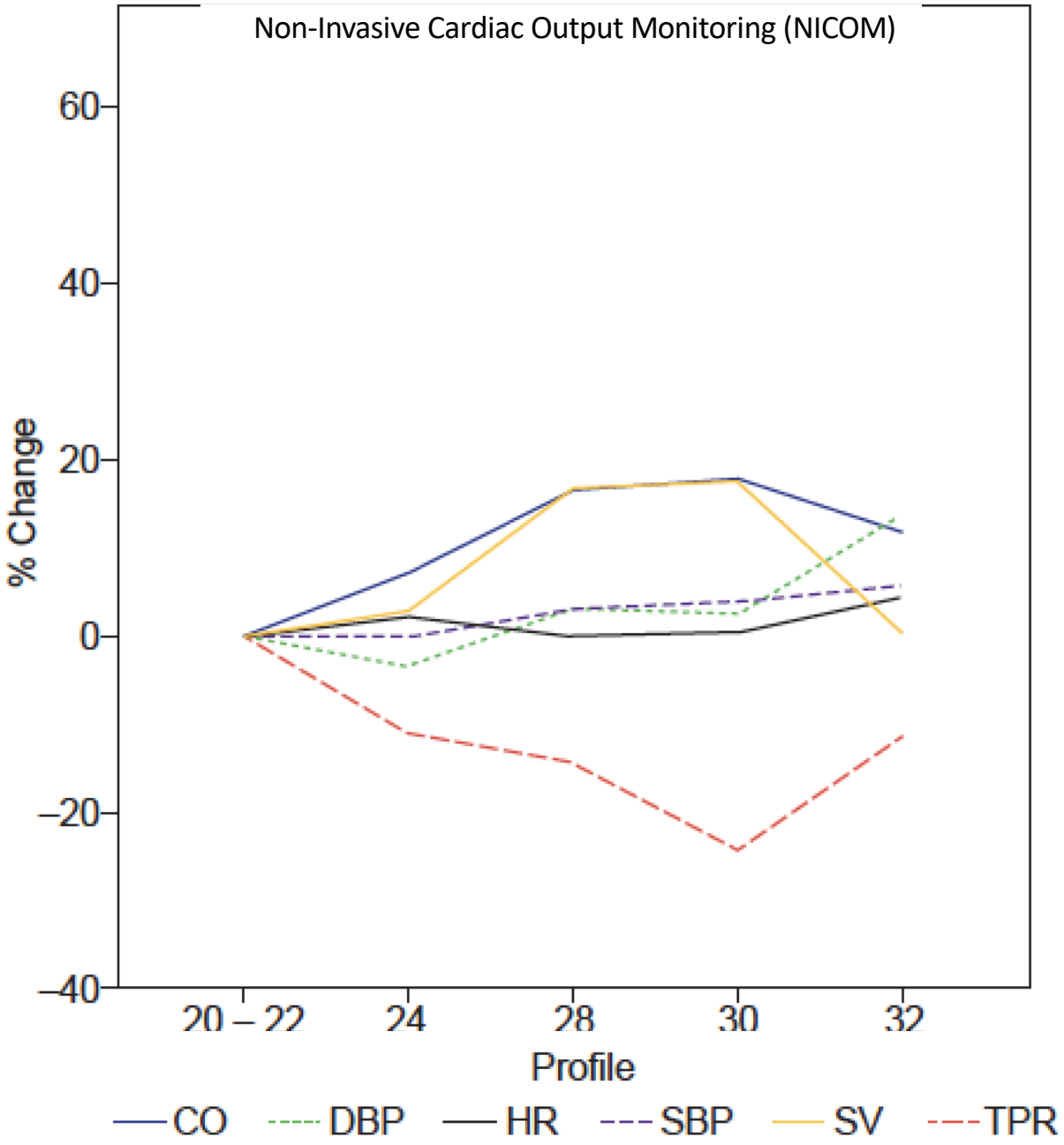
Stroke Volume ↑ 30%

Heart Rate ↑ 15%

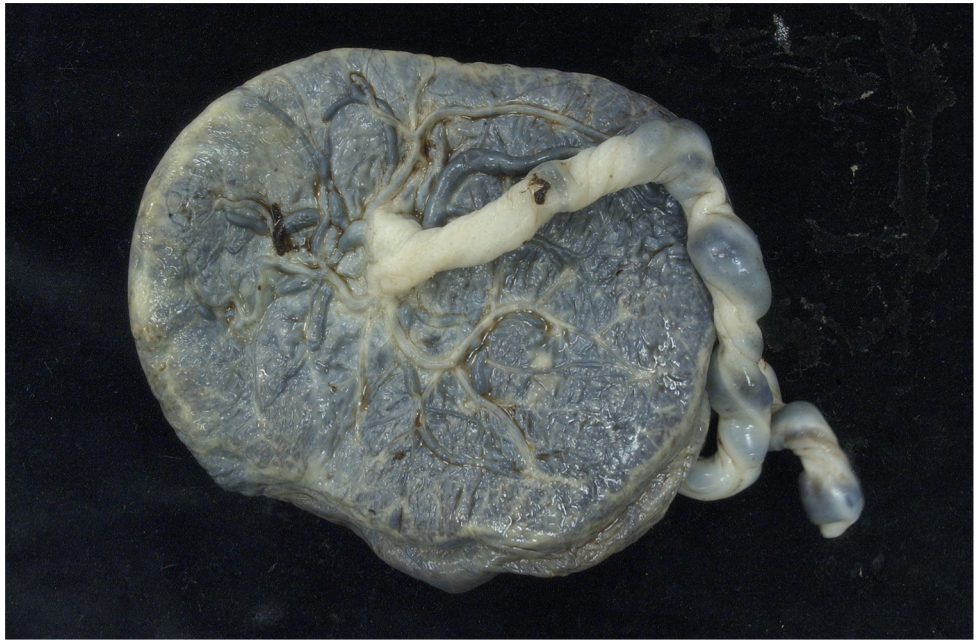
Vascular Resistance ↓ 40%

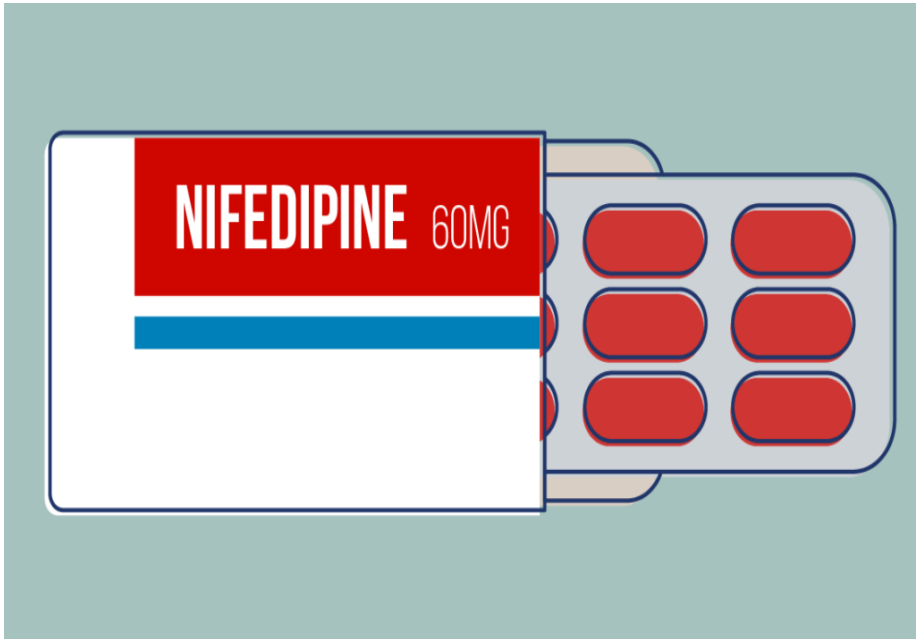
Mean Arterial Pressure ≠

Abbas (2005) *International Journal of Cardiology*

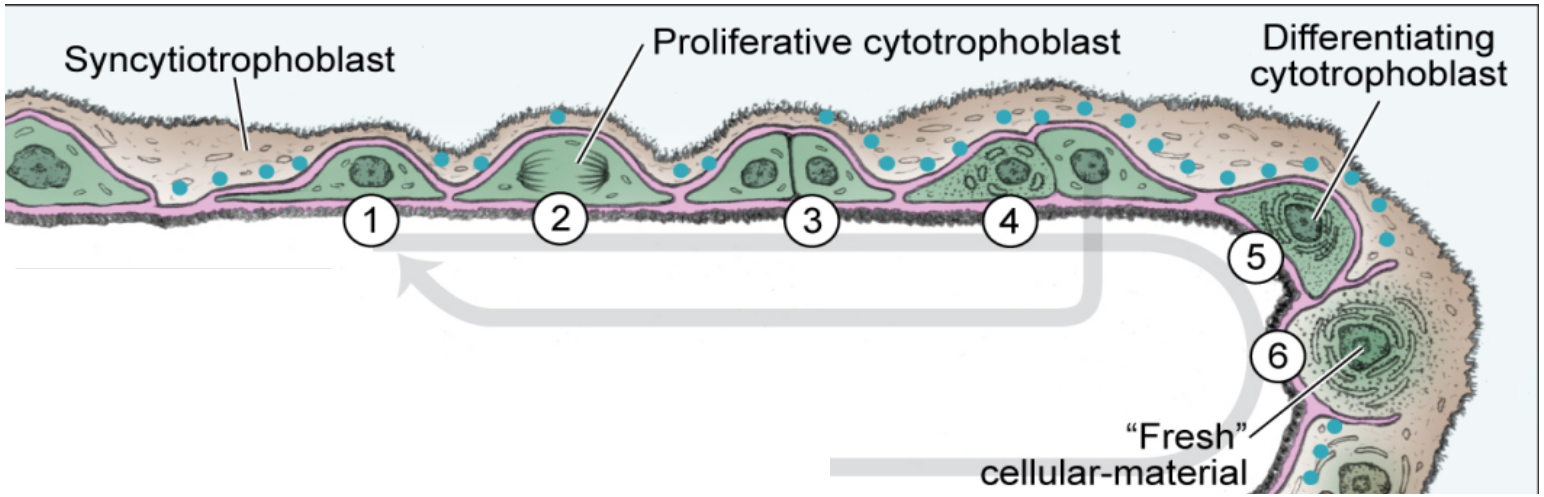

Non-Invasive Cardiac Output Monitoring (NICOM)
60
40
20
0
–20
–40
% Change
20 – 22
24
28
30
32
Profile
CO
DBP
HR
SBP
SV
TPR

Systemic Vasodilation: the Key to Pregnancy Success



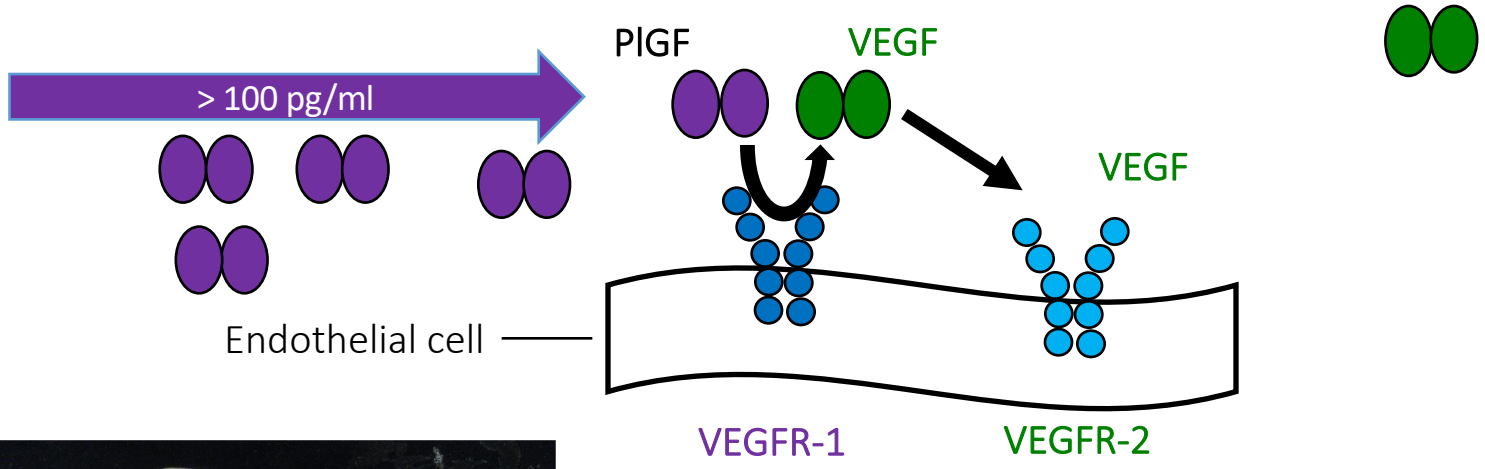


The surface of Healthy Placental Villi Secretes Increasing amounts of PlGF



Kingdom & Drewlo, Blood, 2011

In the normal "high circulating PlGF" state VEGF is displaced over to it's potent VEGFR-2 receptor to stimulate angiogenesis and vaso-relaxation



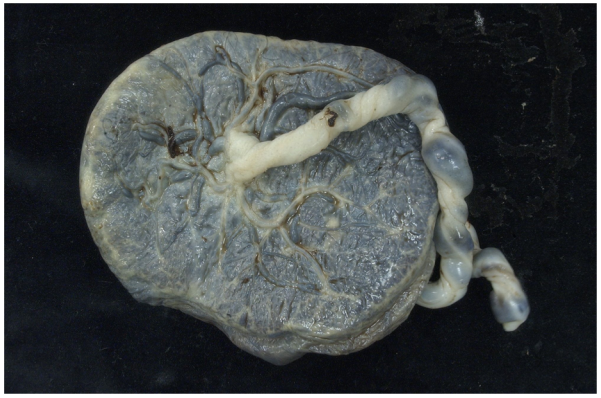
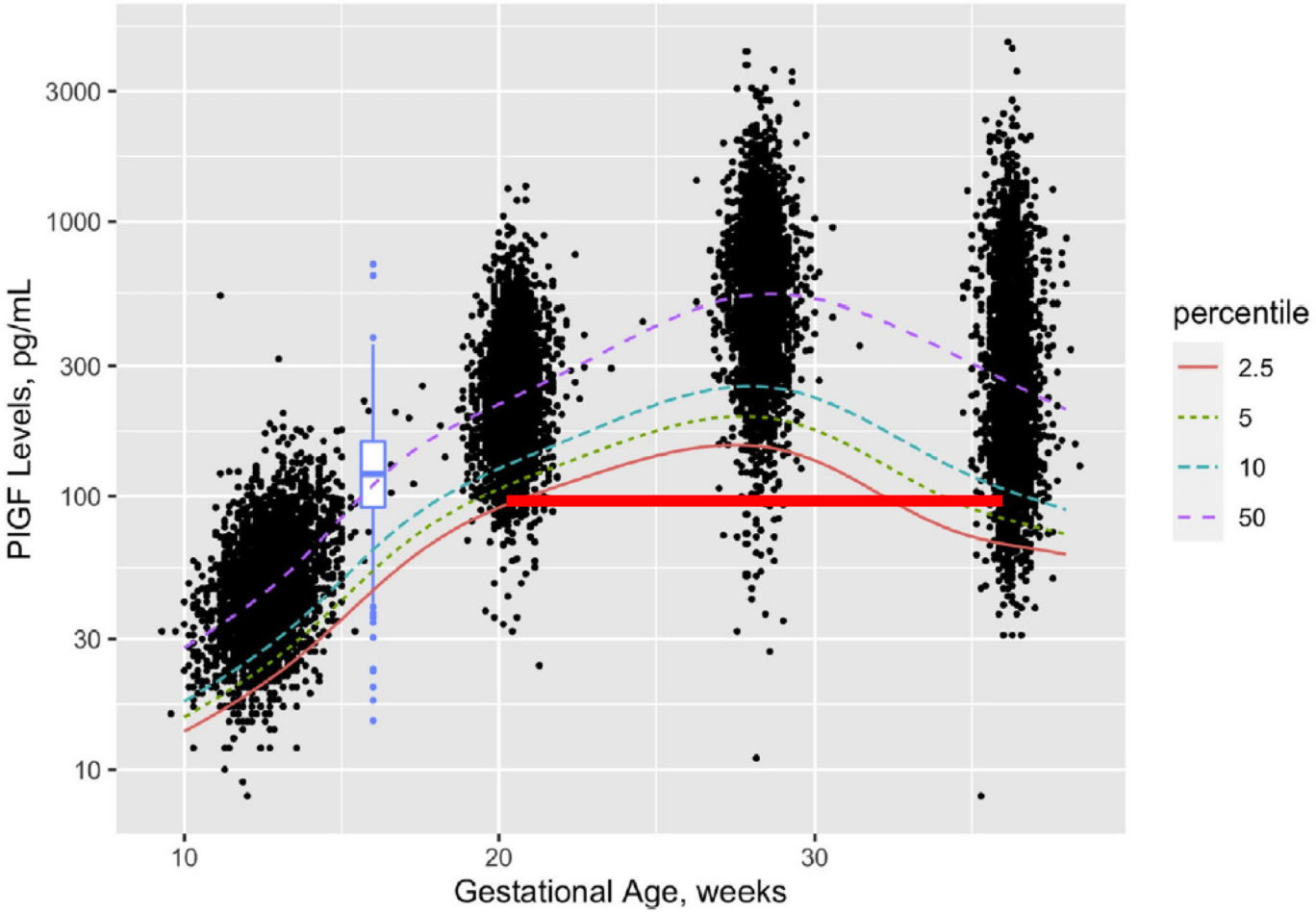


FIGURE 2

Gestational age-specific distribution of circulating maternal PIGF levels

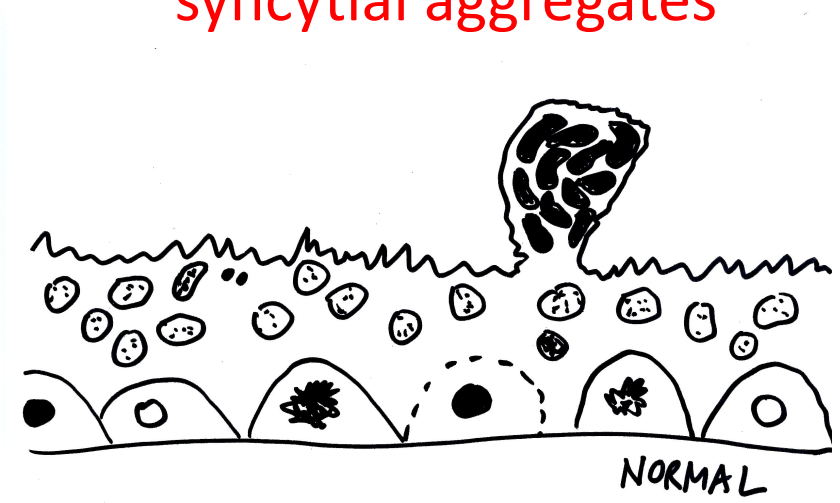


McLaughlin & Kingdom, AJOG 2021 (Sept)

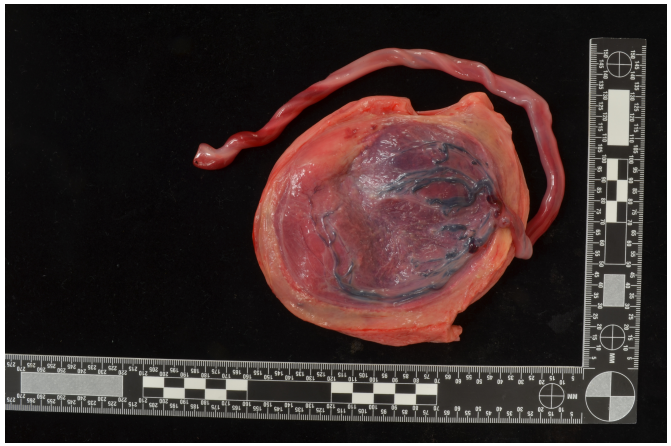
In normal placental development the villi secrete high amounts of PlGF and suppress synthesis and release of sFlt-1 from syncytial aggregates

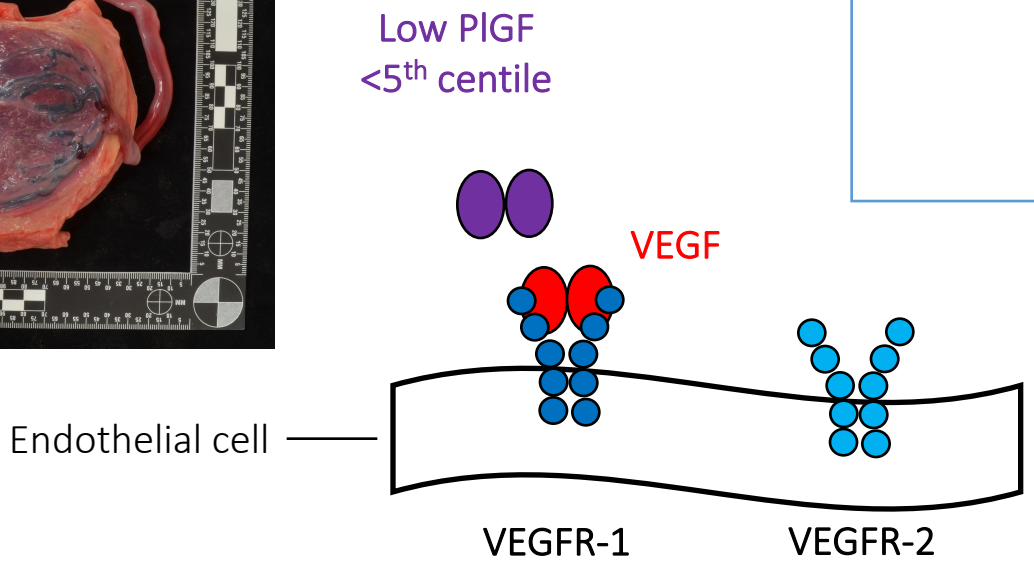
PlGF ↑

sFlt-1 ↓



In a pathologic "low circulating PlGF" state VEGF remains mostly on it's non-functional VEGFR-1 receptor





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JOGC
Journal of Obstetrics and Gynaecology Canada
Journal d'obstétrique et gynécologie du Canada

Altered Hemodynamics and Hyperuricemia Accompany an Elevated sFlt-1/PlGF Ratio Before the Onset of Early Severe Preeclampsia

Anne Doherty, MB,[1] Jose C.A. Carvalho, MD, PhD,[1,2] Sascha Drewlo, PhD,[2,4] Afif EL-Khuffash, MD,[3] Kristi Downey, MSc,[1] Madelaine Dodds,[2] John Kingdom, MD[2,4]

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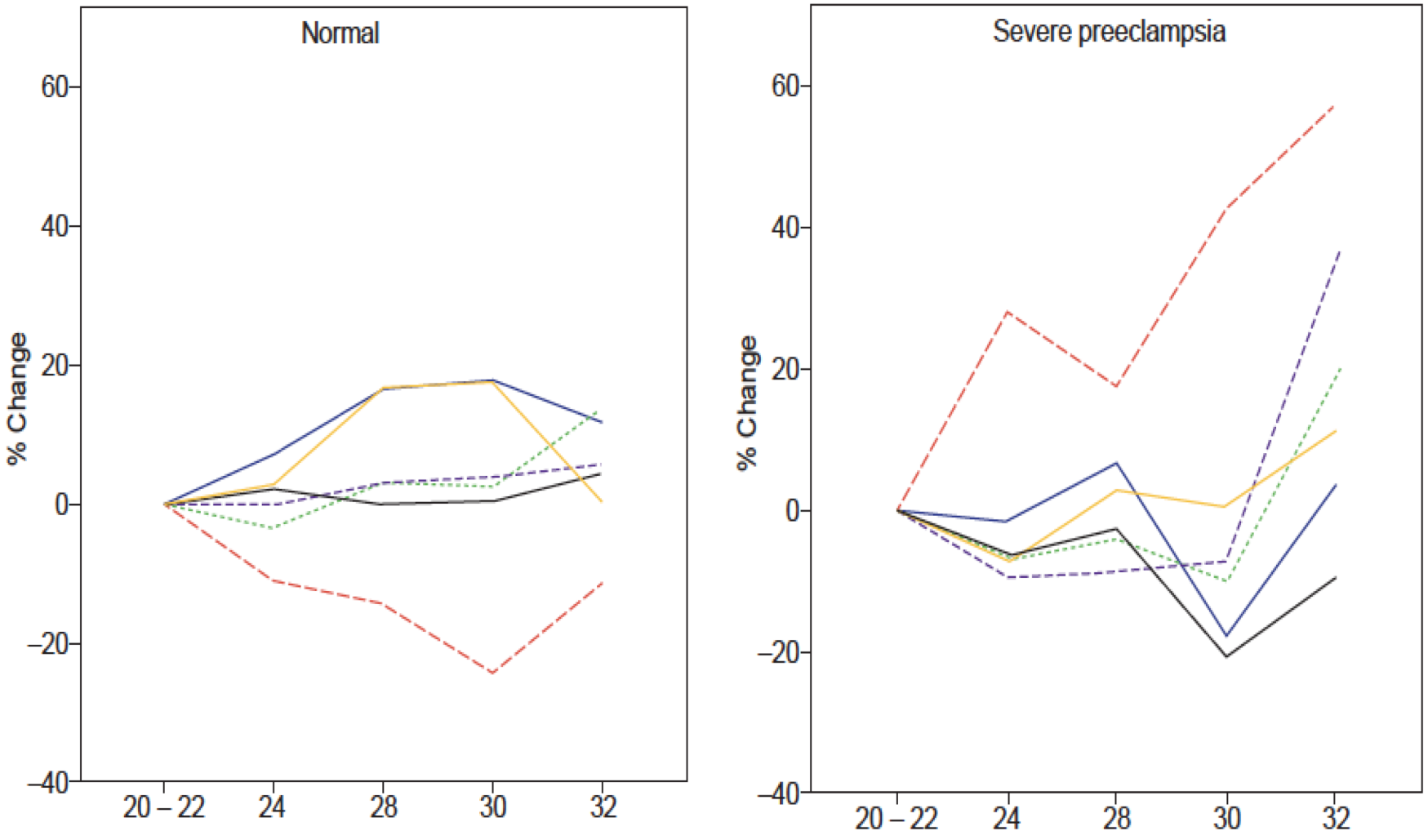
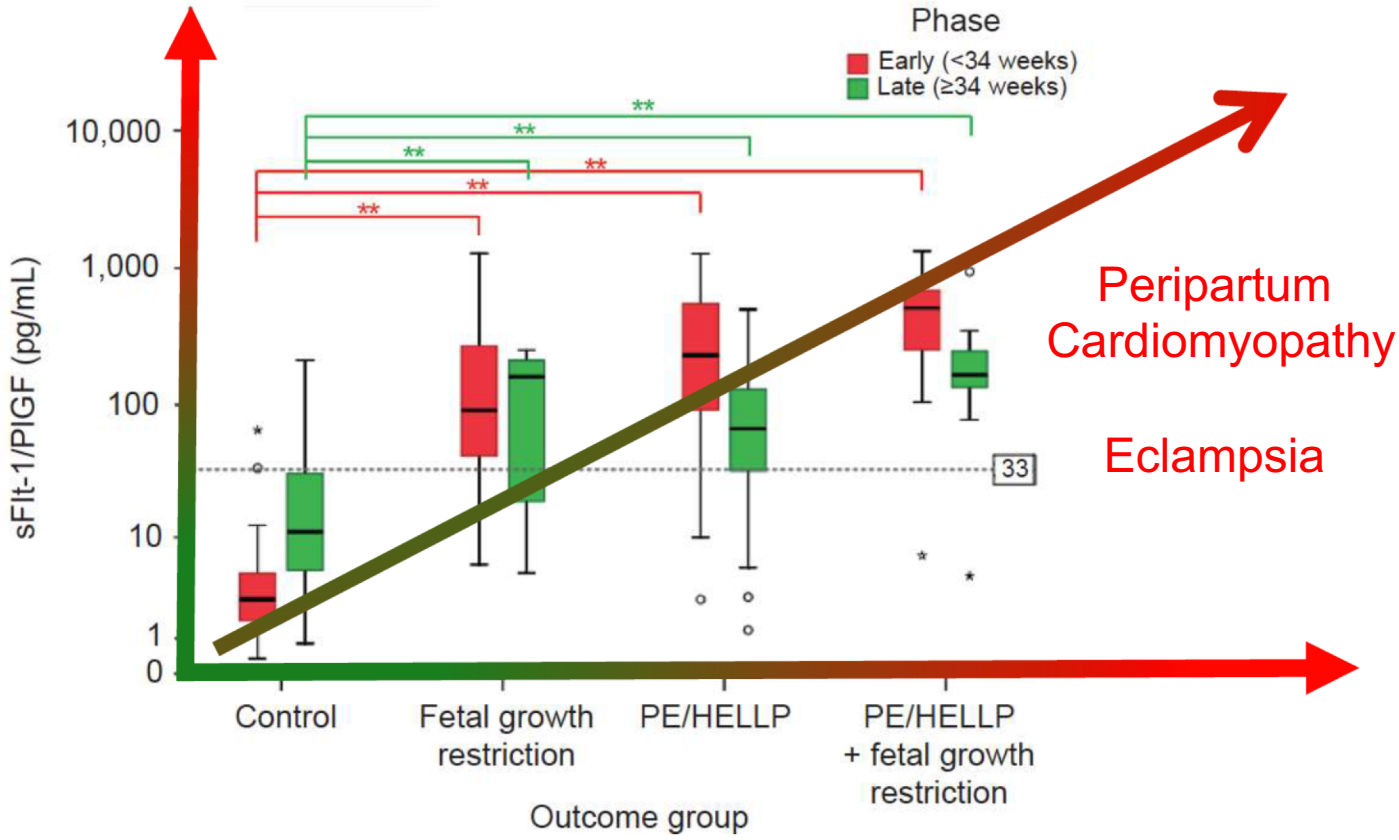
[2]Department of Obstetrics and Gynaecology, Mount Sinai Hospital, University of Toronto, Toronto ON

[3]Department of Neonatology, Mount Sinai Hospital, University of Toronto ON

[4]The Lunenfeld-Tannenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto ON


Normal
Severe preeclampsia
% Change
60
40
20
0
–20
–40
20 – 22
24
28
30
32


Phase
Early (<34 weeks)
Late (≥34 weeks)
sFlt-1/PlGF (pg/mL)
10,000
1,000
100
10
1
0
33
**
Control
Fetal growth restriction
PE/HELLP
PE/HELLP + fetal growth restriction
Outcome group
Peripartum Cardiomyopathy
Eclampsia

Talk Objectives:

Relationship between abnormal placental development, circulating angiogenic growth factors and the origins of preeclampsia

Role of angiogenic growth factors in the diagnosis and management of preeclampsia.

Screening utility of angiogenic growth factors in the prevention of severe preeclampsia / fetal growth restriction.

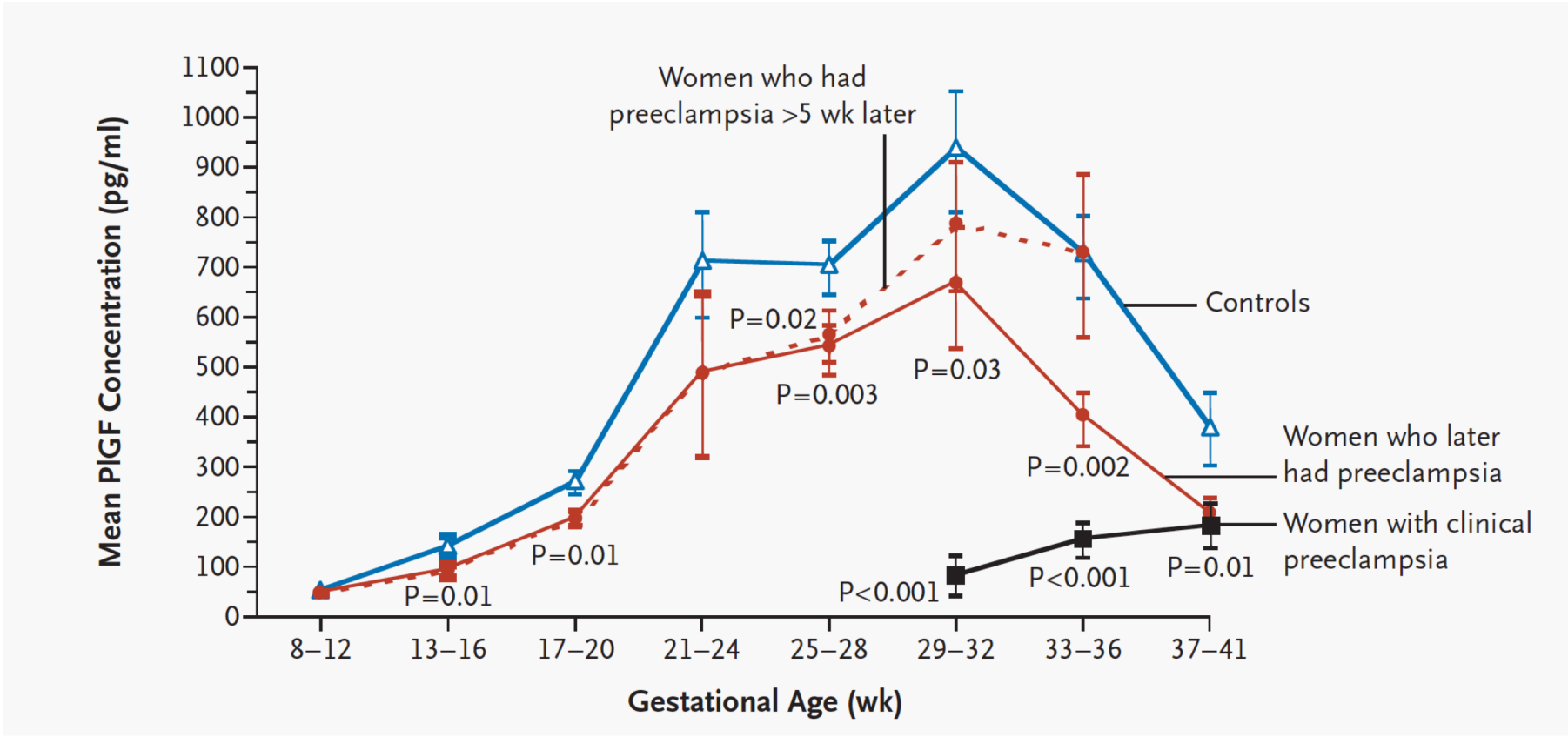
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Circulating Angiogenic Factors and the Risk of Preeclampsia

Richard J. Levine, M.D., M.P.H., Sharon E. Maynard, M.D., Cong Qian, M.S., Kee-Hak Lim, M.D., Lucinda J. England, M.D., M.S.P.H., Kai F. Yu, Ph.D., Enrique F. Schisterman, Ph.D., Ravi Thadhani, M.D., M.P.H., Benjamin P. Sachs, M.B., B.S., D.P.H., Franklin H. Epstein, M.D., Baha M. Sibai, M.D., Vikas P. Sukhatme, M.D., Ph.D., and S. Ananth Karumanchi, M.D.

Placental Growth Factor (PlGF) Trajectories in Preeclampsia



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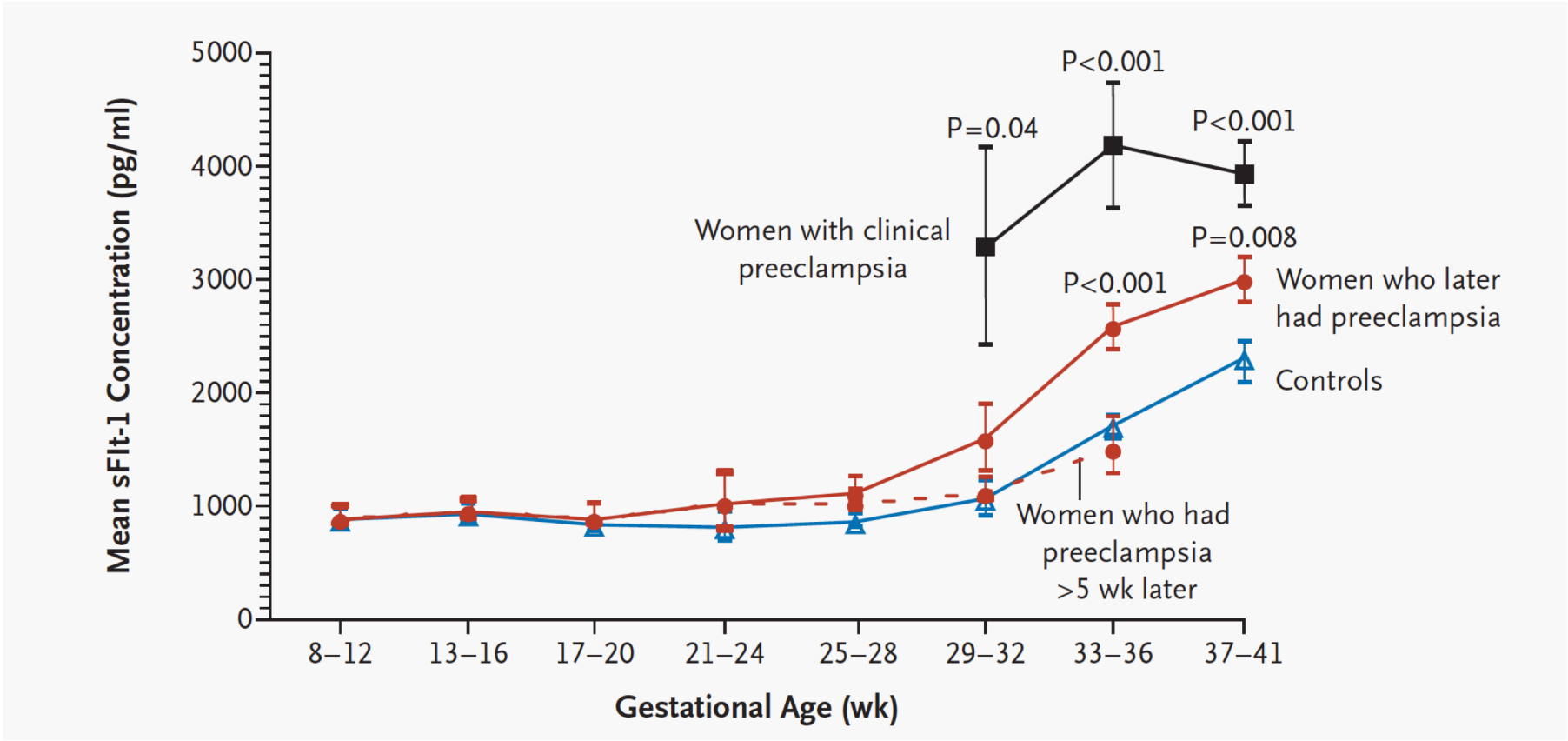
Levine (2004) *NEJM*

Soluble Fms-Like Tyrosine Kinase-1 (sFlt-1) in Preeclampsia



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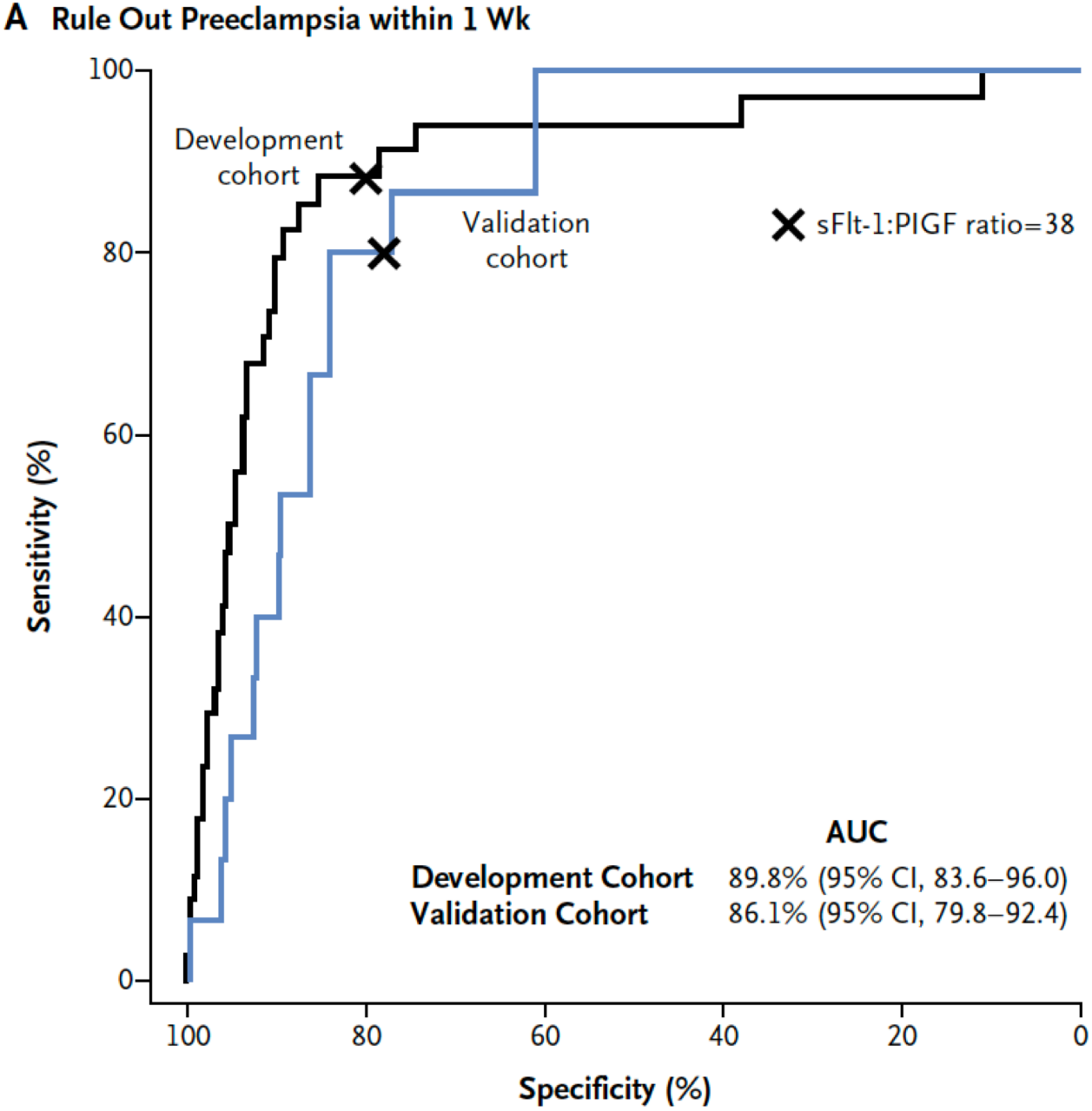
Modified from Levine (2004) *NEJM*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 7, 2016 VOL. 374 NO. 1

Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia

Harald Zeisler, M.D., Elisa Llurba, M.D., Ph.D., Frederic Chantraine, M.D., Ph.D., Manu Vatish, M.B., Ch.B., D.Phil., Anne Cathrine Staff, M.D., Ph.D., Maria Sennström, M.D., Ph.D., Matts Olovsson, M.D., Ph.D., Shaun P. Brennecke, M.B., B.S., D.Phil., Holger Stepan, M.D., Deirdre Allegranza, B.A., Peter Dilba, M.Sc., Maria Schoedl, Ph.D., Martin Hund, Ph.D., and Stefan Verlohren, M.D., Ph.D.


A Rule Out Preeclampsia within 1 Wk
100
80
60
40
20
0
Sensitivity (%)
Development cohort
Validation cohort
sFlt-1:PlGF ratio=38
AUC
Development Cohort 89.8% (95% CI, 83.6–96.0)
Validation Cohort 86.1% (95% CI, 79.8–92.4)
100
80
60
40
20
0
Specificity (%)

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

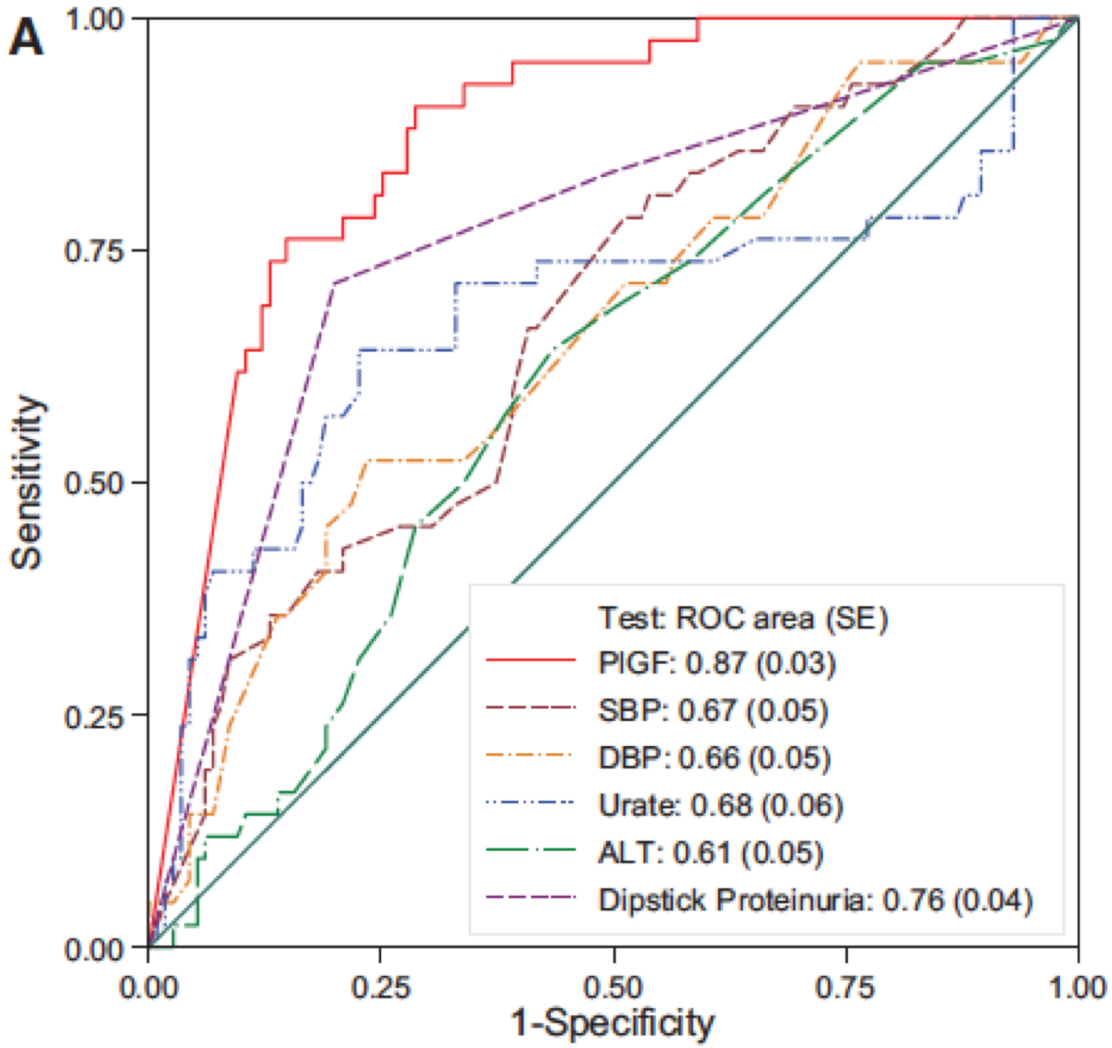
Hypertension

Diagnostic Accuracy of Placental Growth Factor in Women With Suspected Preeclampsia

A Prospective Multicenter Study

Lucy C. Chappell, PhD; Suzy Duckworth, MBBS; Paul T. Seed, CStat;
Melanie Griffin, MBChB; Jenny Myers, PhD; Lucy Mackillop, MA; Nigel Simpson, MBBS;
Jason Waugh, MBBS; Dilly Anumba, MD; Louise C. Kenny, PhD;
Christopher W.G. Redman, MBChir; Andrew H. Shennan, MD

Circulation. 2013;128:2121-2131



Combing other tests with PlGF did not improve diagnostic performance

Normal PlGF excludes Preeclampsia

- Enrolled at <35 weeks, requiring delivery in next 14 days:
  - PlGF <5th centile: NPV 0.98 [0.93 – 0.99]
- Enrolled at <37 weeks, requiring delivery in next 14 days or by 37 weeks
  - PlGF <100pg/ml: NPV 0.98 (0.93–0.995)

Health Economics

DOI: 10.1111/1471-0528.12259
www.bjog.org

Cost and resource implications with serum angiogenic factor estimation in the triage of pre-eclampsia

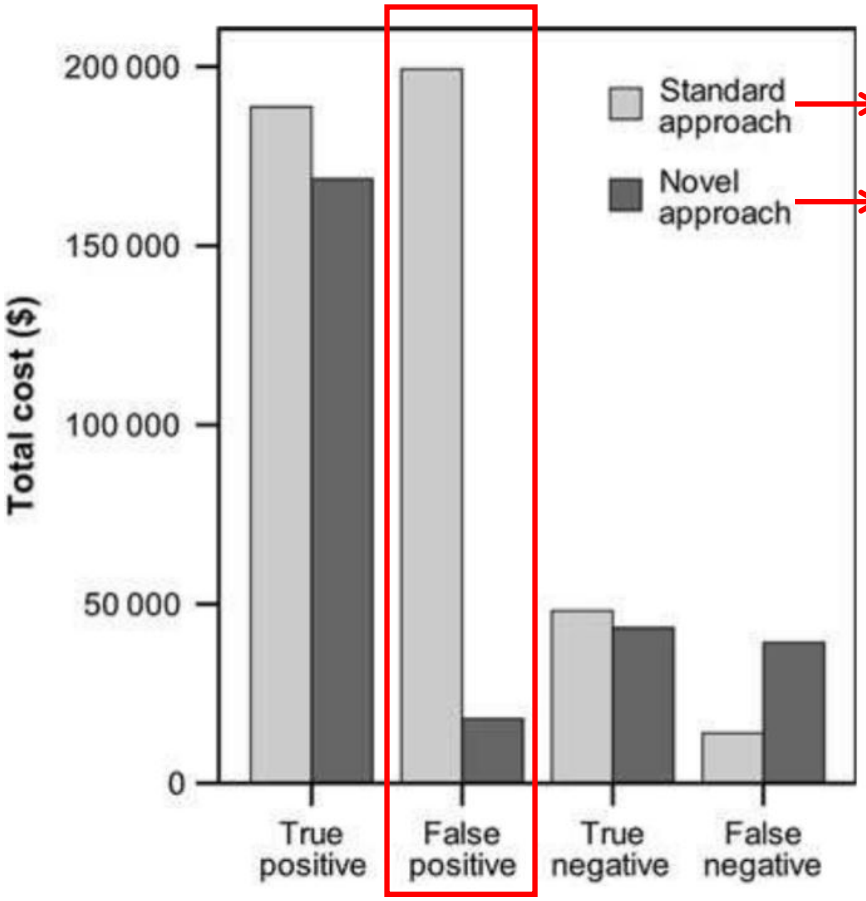
WT Schnettler,[a,b,c] D Dukhovny,[c,d] J Wenger,[c] S Salahuddin,[b,c] SJ Ralston,[a,b,c] S Rana[a,b,c]

[a] Division of Maternal–Fetal Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA [b] Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA, USA [c] Harvard Medical School, Boston, MA, USA [d] Department of Neonatology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Correspondence: Dr S Rana, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Kirstein 382, Boston, MA 02215, USA.
Email srana1@bidmc.harvard.edu

Accepted 7 March 2013. Published Online 7 May 2013.

PlGF Testing for Suspected Preeclampsia is Highly Cost Effective



Blood pressure, proteinuria, liver enzymes, platelets

sFlt-1/PlGF ratio

Average savings of $1215/tested patient.

Schnettler (2013) *BJOG*

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Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial

Kate E Duhig, Jenny Myers, Paul T Seed, Jenie Sparkes, Jessica Lowe, Rachael M Hunter, Andrew H Shennan, Lucy C Chappell*, on behalf of the PARROT trial group†*

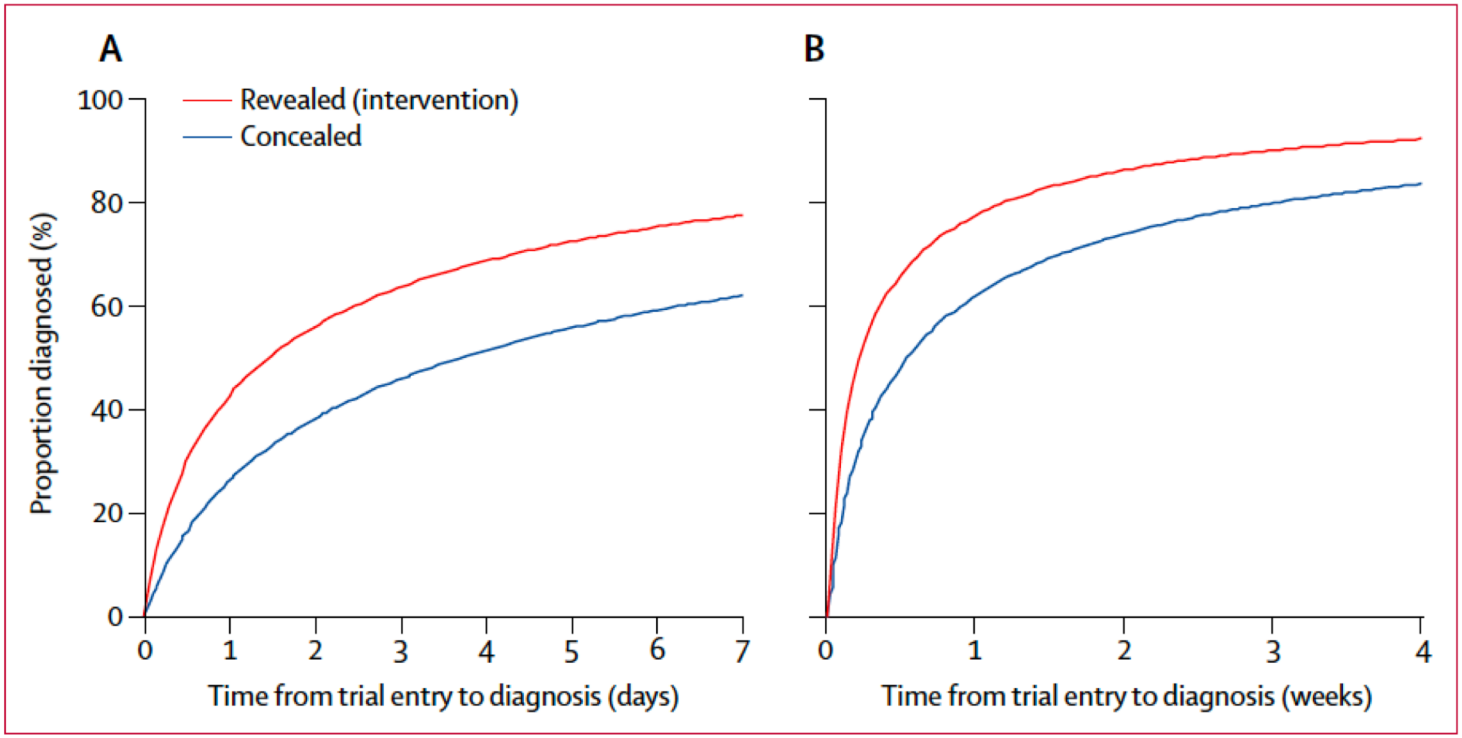

Figure 2: **Proportion of women diagnosed with pre-eclampsia when revealing versus concealing circulating placental growth factor concentrations from clinicians, over days (A) and weeks (B)**
Data are mixed-effects log-normal regression curves.

Hypertension

ORIGINAL ARTICLE

PlGF (Placental Growth Factor) Testing in Clinical Practice

Evidence From a Canadian Tertiary Maternity Referral Center

Kelsey McLaughlin, John W. Snelgrove, Melanie C. Audette, Atif Syed, Sebastian R. Hobson, Rory C. Windrim, Nir Melamed, Sergio Carmona, John C. Kingdom

Maternal, Fetal & Delivery Characteristics

	Normal PlGF Levels N=690	Low PlGF Levels N=289
Age, years	35 [32-38]	35 [31-39]
Pre-pregnancy weight, kg	67 [58-83]	70 [58-83]
Nulliparous, no. (%)	308 (45)	154 (53)
Gestational age at delivery, weeks	37 [36-38]	31 [28-34]
Birthweight, kg	2.8 [2.3-3.3]	1.2 [0.8-1.7]
Intergrowth centile, %	47 [16-72]	7 [2-19]

Data are presented as median [interquartile range] or n (%).

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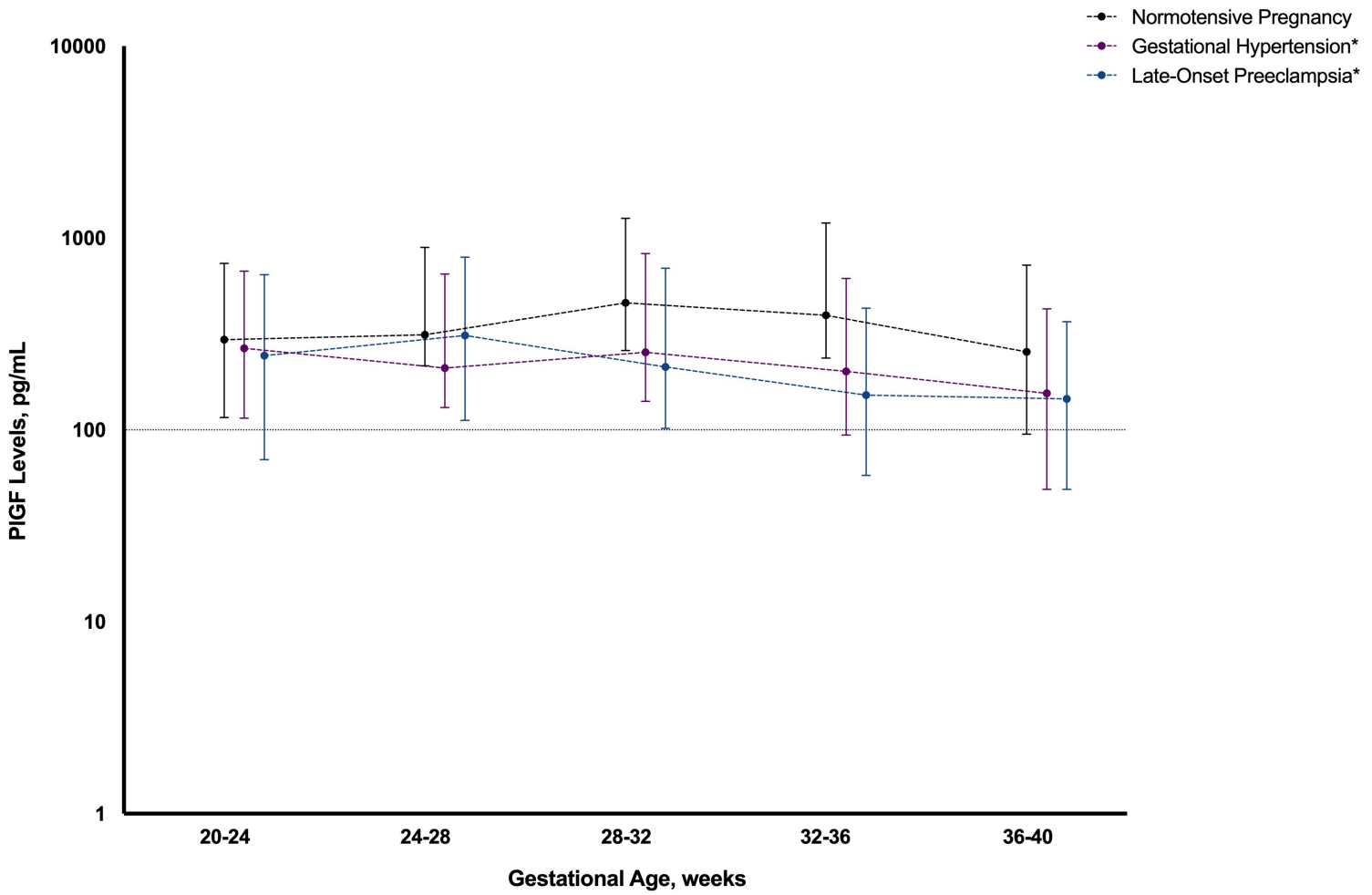
McLaughlin (2021) *Hypertension*

PlGF Patterns Across Pregnancy



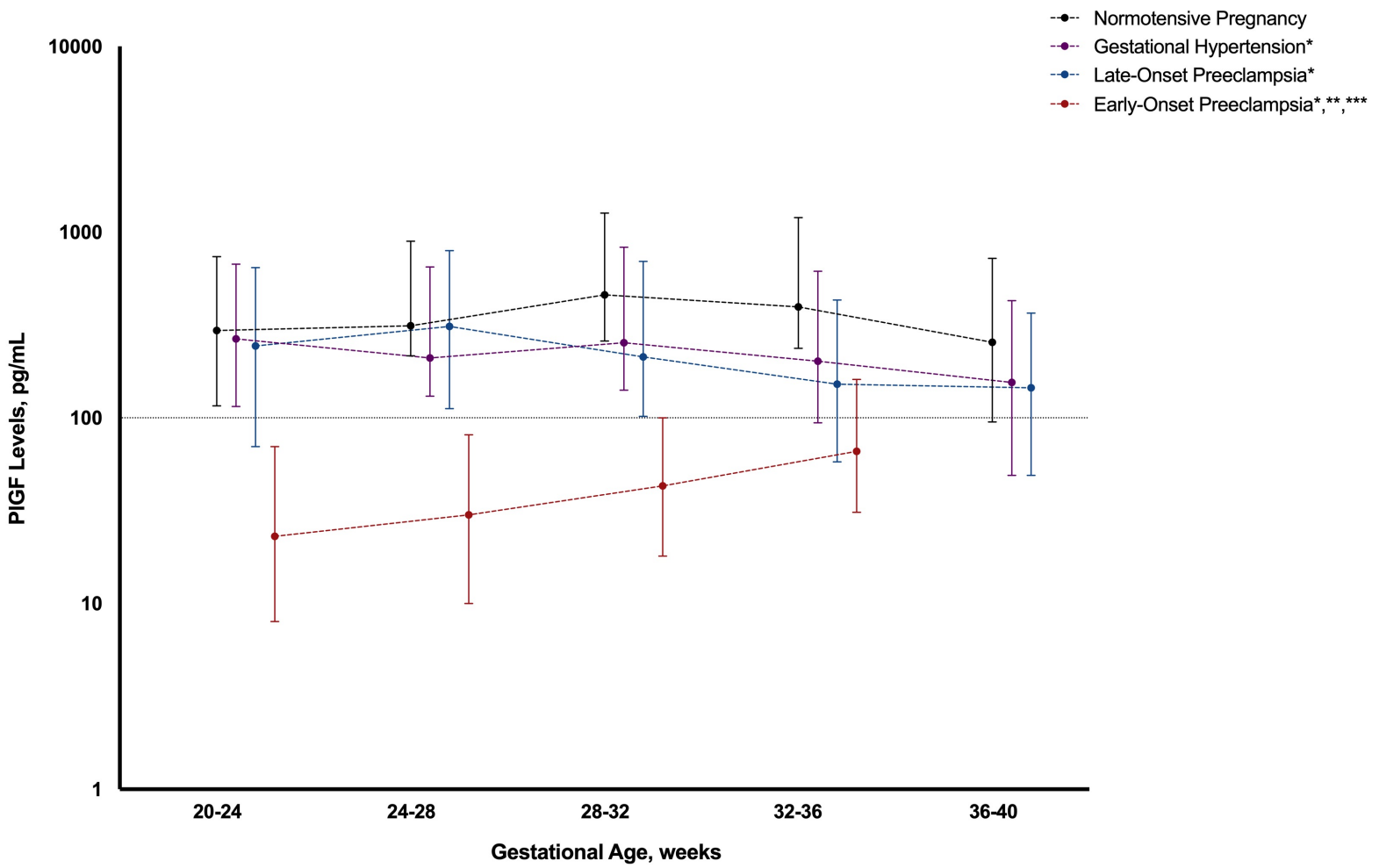
Data are presented as median [interquartile range]

Note log10 scale for PlGF values

.

McLaughlin (2021) *Hypertension*

PlGF Patterns Across Pregnancy



Data are presented as median [interquartile range].

*Indicates P < 0.0001, compared to normal pregnancy, ** Indicates P < 0.0001, compared to gestational hypertension, ***Indicates P < 0.0001, compared to late-onset preeclampsia.

McLaughlin (2021) *Hypertension*

Low PlGF Levels Strongly Associated with Early-Onset Preeclampsia

Maternal Outcomes	Normal PlGF Levels N=690	Low PlGF Levels N=289	Adj. Odds Ratio (95% CI)
Normotensive pregnancy	327 (47%)	47 (16%)	-
Gestational hypertension	197 (29%)	47 (16%)	
Late-onset preeclampsia	147 (21%)	42 (15%)	
Early-onset preeclampsia	19 (3%)	153 (53%)	58.2 (32.1-105.4)

Data are presented as n (% of row). OR adjusted for maternal age, ethnicity and parity.

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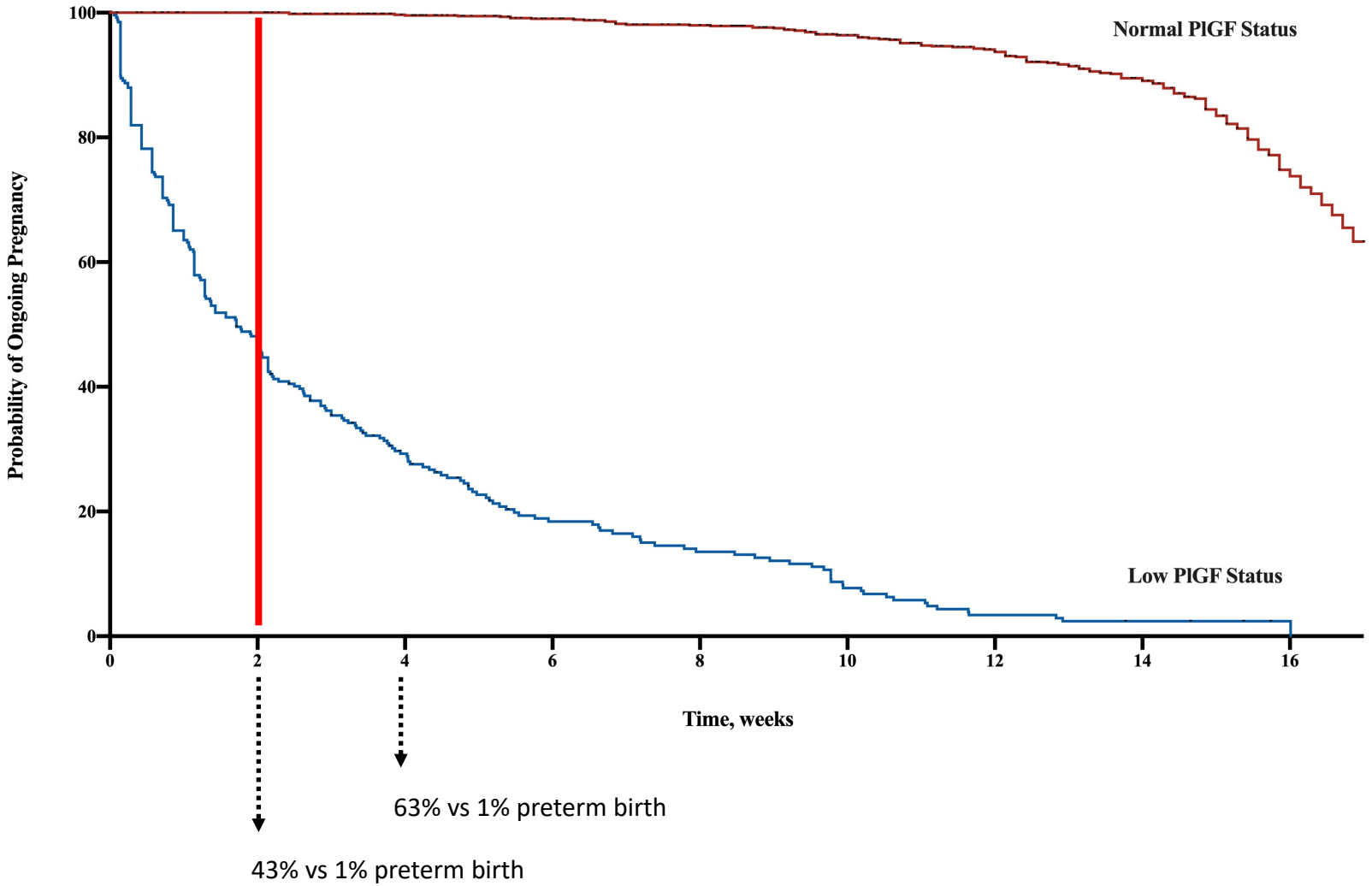
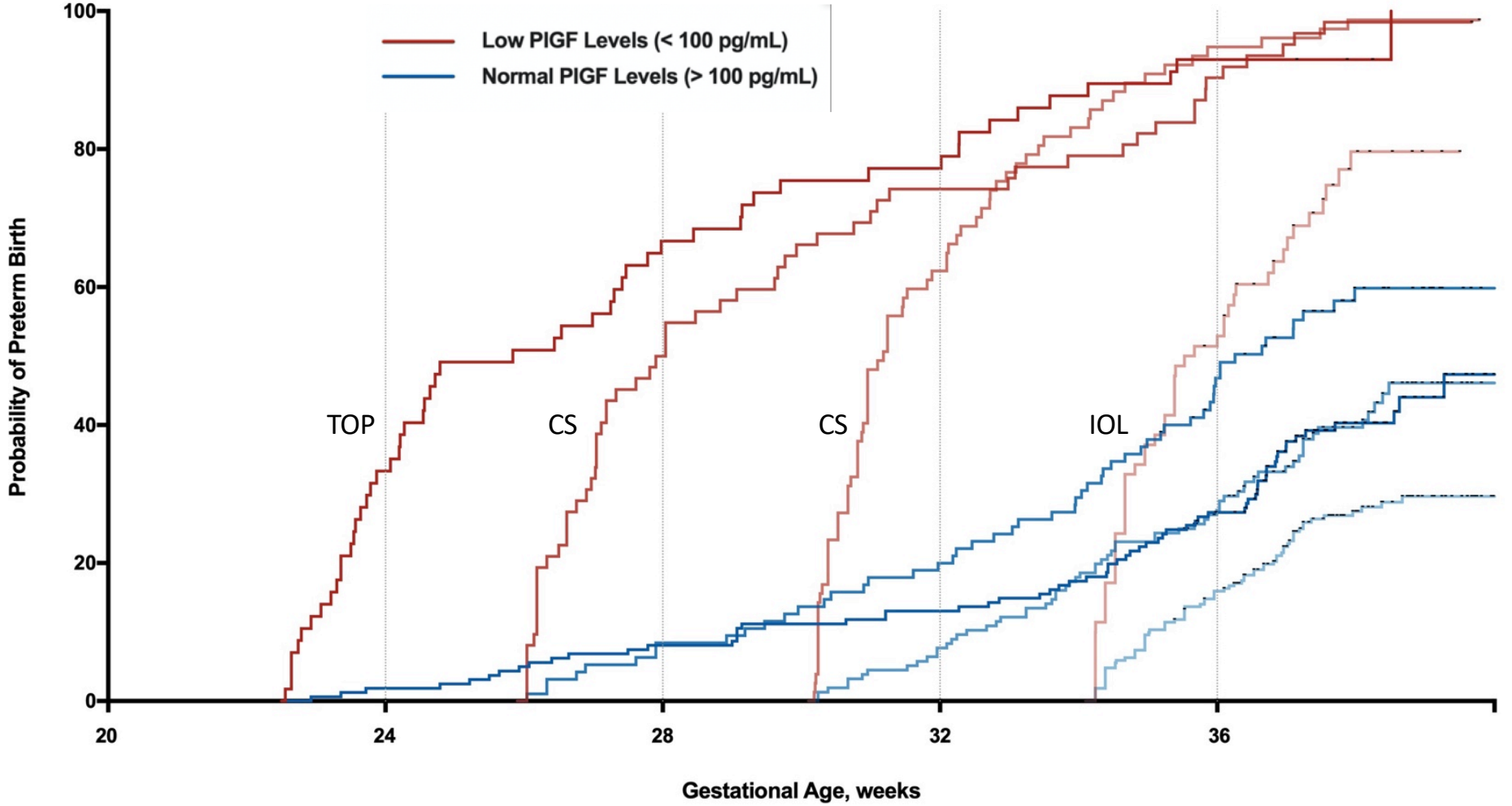
McLaughlin (2021) *Hypertension*

Probability of Preterm Birth < 37 Week's Gestation: Survival analysis from time of sampling



McLaughlin (2021) *Hypertension*

Clinical Implications Stratified by Gestational Age



PlGF Rapidly Differentiates between Causes of Early-Onset FGR

Stillbirth/TOP Outcomes	PlGF >100pg/ml N=10	PlGF <100pg/ml N=48
Anticipated stillbirth, no. (%)	7 (70%)	43 (89%)
Pathogenesis		
Severe placental disease, no. (%)	0 (0%)	41 (85%)
Fetal abnormality, no. (%)	8 (80%)	3 (6%)
Major Placental Pathology Findings		
Maternal vascular malperfusion, no. (%)	0 (0)	37 (77)
Fetal thrombotic vasculopathy, no. (%)	1 (10)	12 (25)

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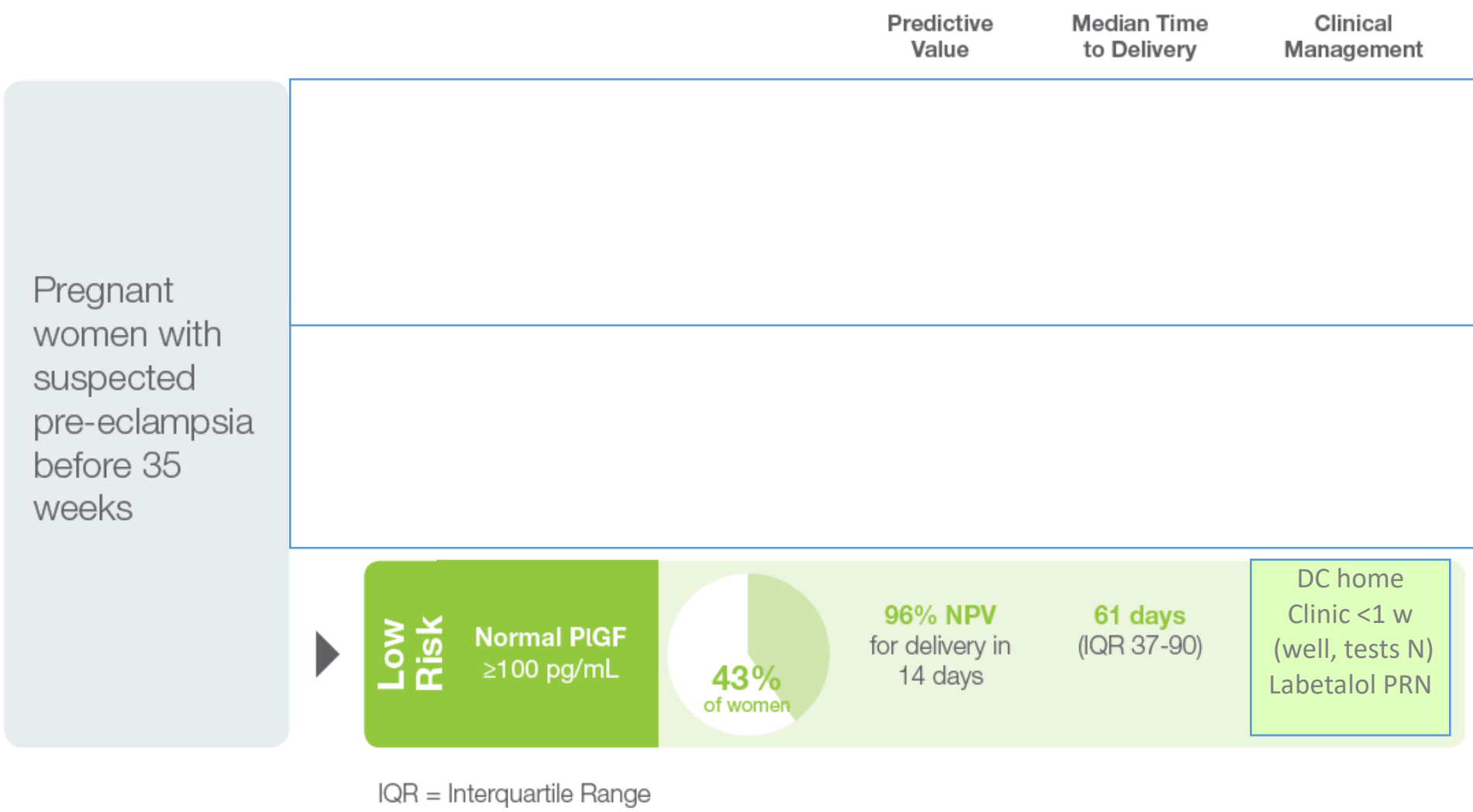
McLaughlin (2021) Hypertension

PlGF Triage Algorithm Mount Sinai Toronto



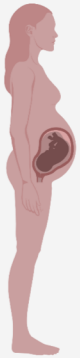
IQR = Interquartile Range

Adapted with permission from Lucy Chappell & Jenny Myers

Real-Time PlGF Testing can Profoundly Change Perinatal Care

High-risk of placental dysfunction, hypertensive disorder of pregnancy, fetal growth restriction

20^0 - 35^6 weeks of gestation

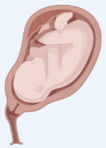


Normal PlGF Levels

Low risk of preeclampsia, stillbirth due to placental disease and imminent preterm birth

Avoid unnecessary clinical intervention & maternal morbidity

Low PlGF Levels



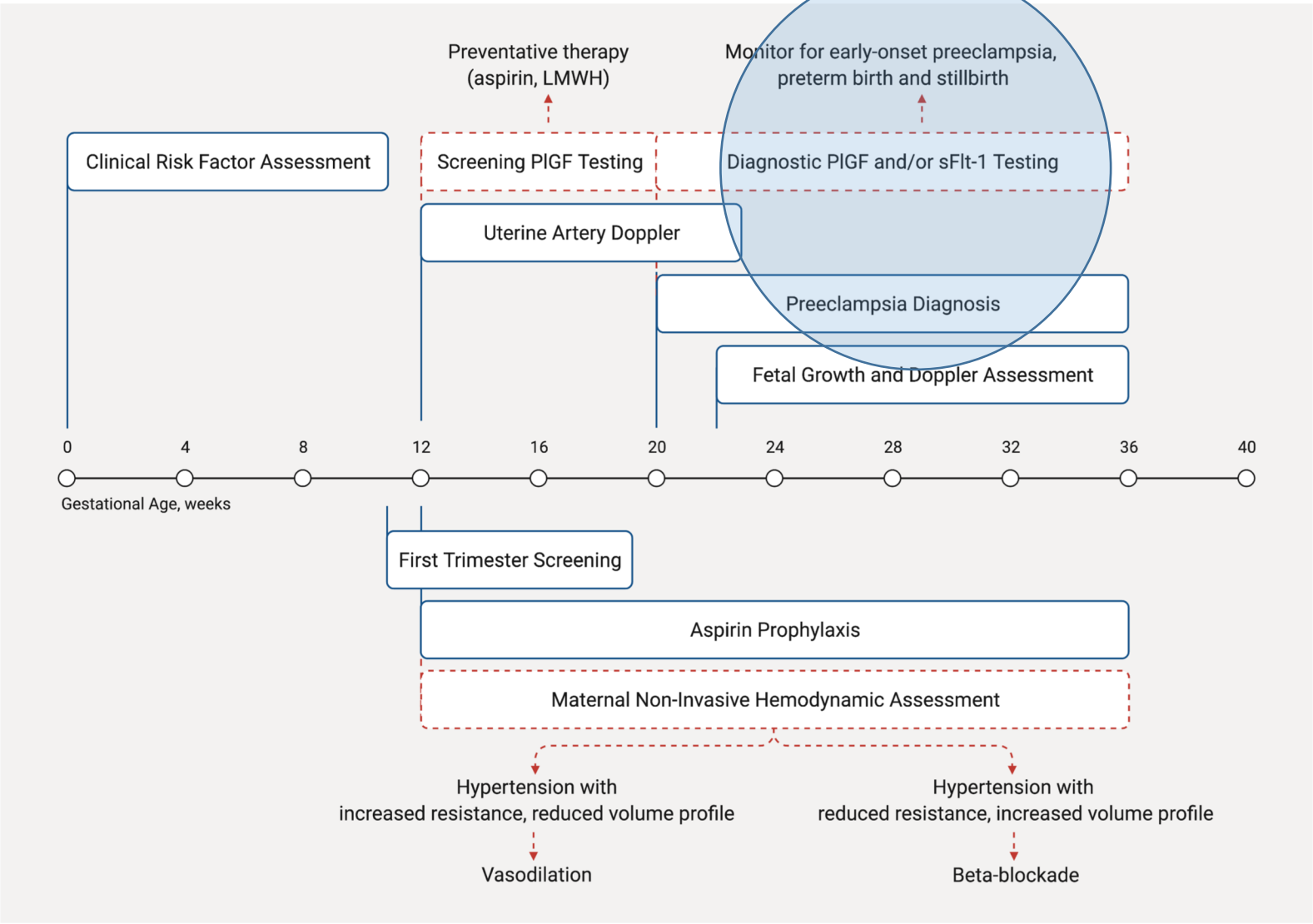
Increased rates of imminent preterm birth

Increased risk of preeclampsia and stillbirth due to placental disease

Justify the deployment of higher-level maternal-fetal care and additional clinical interventions

McLaughlin (2021) *Hypertension*

Improving Outcomes for women at risk of preeclampsia: Overall Strategy



Can we anticipate and prevent this life-threatening emergency?

Extreme
Vasoconstriction and
low CO in
Severe Early-Onset
Pre-eclampsia

Hemodynamic Phenotypes in Women who subsequent develop Preeclampsia

Parameter	Controls n=1119	Early PE n=75	Late PE n=32
24 weeks gestation			
Heart rate	80±11	75±14*	89±13*†
Systolic blood pressure, mm Hg	115±11	121±10*	115±13†
Diastolic blood pressure, mm Hg	62±11	70±10*	60±12†
Mean blood pressure, mm Hg	80±8	87±8*	79±9†
Total vascular resistance, dyn · s · cm^{-5}	990±179	1605±248*	739±244*†
Stroke volume, mL	83±11	61±13*	102±19*†
Cardiac output, L	6.61±1.10	4.49±1.09*	8.96±1.83*†

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Data are presented as means ± SD.
*P<0.05 vs controls.
†P<0.05 vs early PE.

Valensise (2008) *Hypertension*

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ISSN 0194-911X
http://hyper.ahajournals.org

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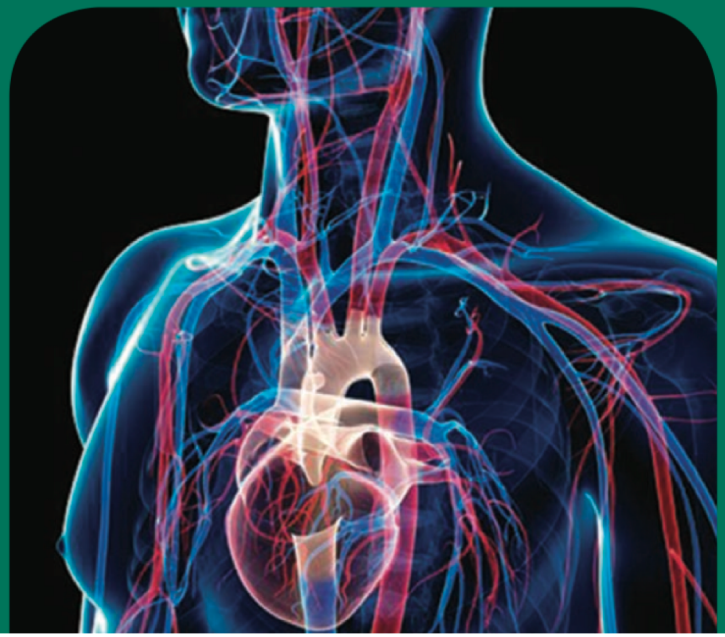
Hypertension



Featured Articles

Antihypertensive Therapy in Preeclampsia

Socioeconomic Status and Hypertension in Africa

Long-Term Primary Aldosteronism Outcome

Brief Review

Should Maternal Hemodynamics Guide Antihypertensive Therapy in Preeclampsia?

Kelsey McLaughlin, Ralph R. Scholten, John C. Kingdom, John S. Floras, John D. Parker

Hypertension in pregnancy impacts ≈10% of all pregnancies.[1] Hypertensive disorders of pregnancy include chronic hypertension, gestational hypertension (new-onset hypertension with blood pressure <140/90 after 20 weeks gestation), or preeclampsia (new-onset hypertension with blood pressure <140/90 after 20 weeks gestation with proteinuria or thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral/visual symptoms). On the basis of the timing of clinical presentation or delivery, preeclampsia may be further classified into either early-onset preeclampsia (<34 weeks) or late-onset preeclampsia (34 weeks and beyond).

Hypertensive disorders of pregnancy are a leading cause of maternal morbidity and mortality, accounting for 14% of all maternal deaths worldwide.[2] Gestational hypertension is typically benign; however, 46% of women with gestational hypertension will progress to preeclampsia.[3,4] Although less common, preeclampsia is considered a more severe disease that progresses rapidly and is associated with increased risk of subsequently develop early-onset or late-onset preeclampsia exhibit distinct hemodynamic profiles early in pregnancy before the development of clinical hypertension, hemodynamic-guided therapy may improve blood pressure management in women with preeclampsia.[11]

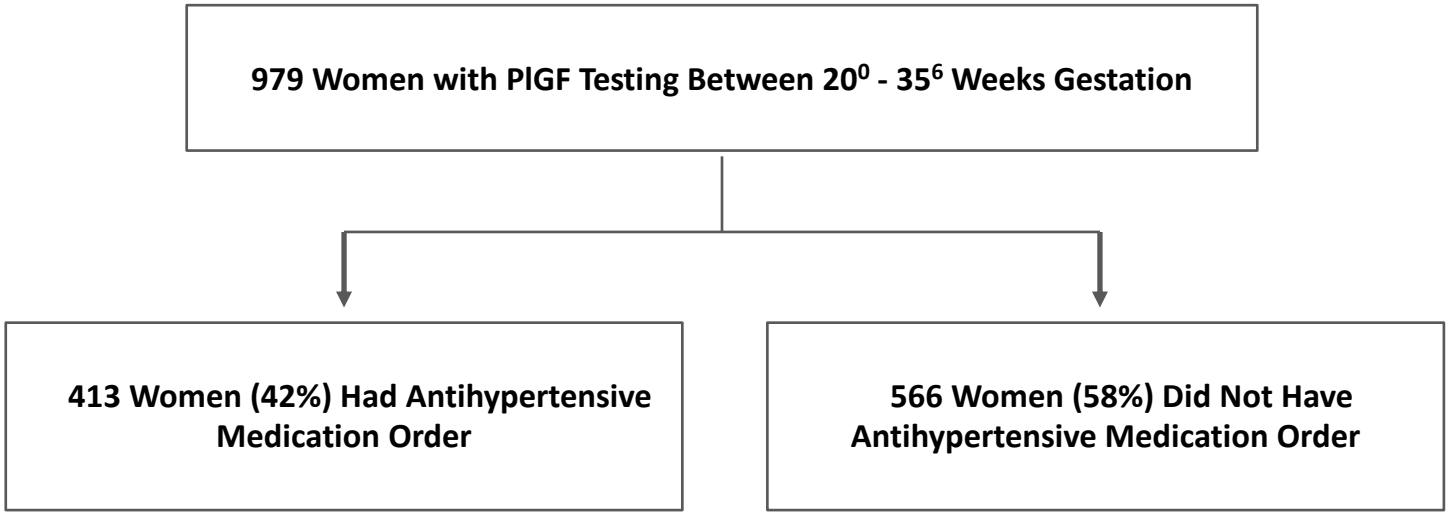
This review will focus specifically on the potential use of maternal hemodynamic-guided therapy for pregnant women with preeclampsia, the more severe hypertensive disorder of pregnancy that has been the subject of intense research in recent years. Hemodynamic-guided therapy for pregnant women with chronic hypertension, gestational hypertension, and preeclampsia superimposed on preexisting hypertension is beyond the scope of this review, as these hypertensive disorders have not been as thoroughly investigated as preeclampsia and there is currently not enough information on maternal hemodynamics in these diseases.

Pathophysiology of Preeclampsia

Sinai Health System

McLaughlin (2018) *Hypertension*

Response to Antihypertensive Therapy by Initial PlGF Test Result

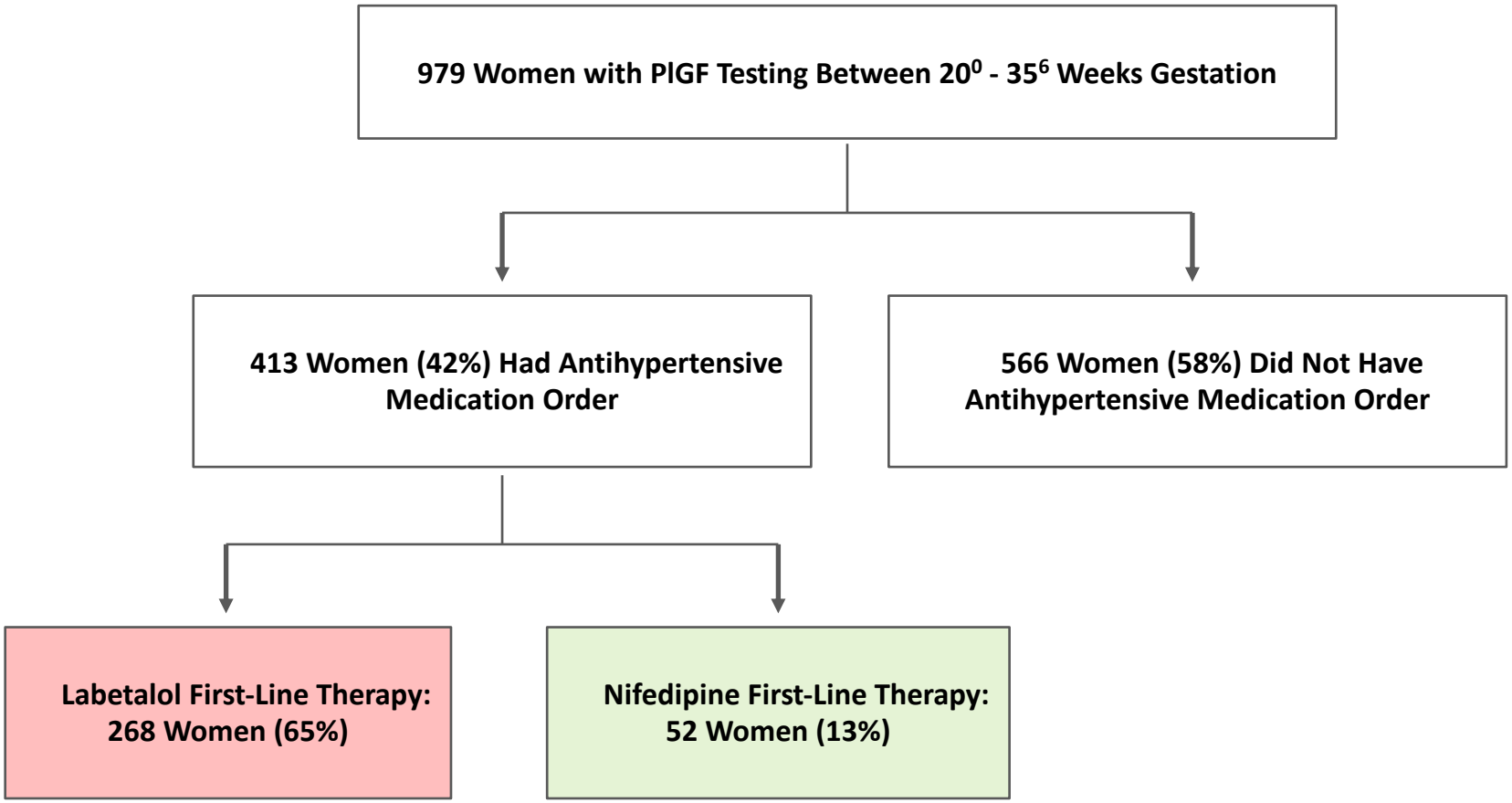


Low PlGF status was associated with increased use of antihypertension medication order/s prior to birth
relative to women with normal PlGF levels

(odds ratio 4.7 [3.5 – 6.5])

Sinai Health System

Response to Antihypertensive Therapy by Initial PlGF Test Result



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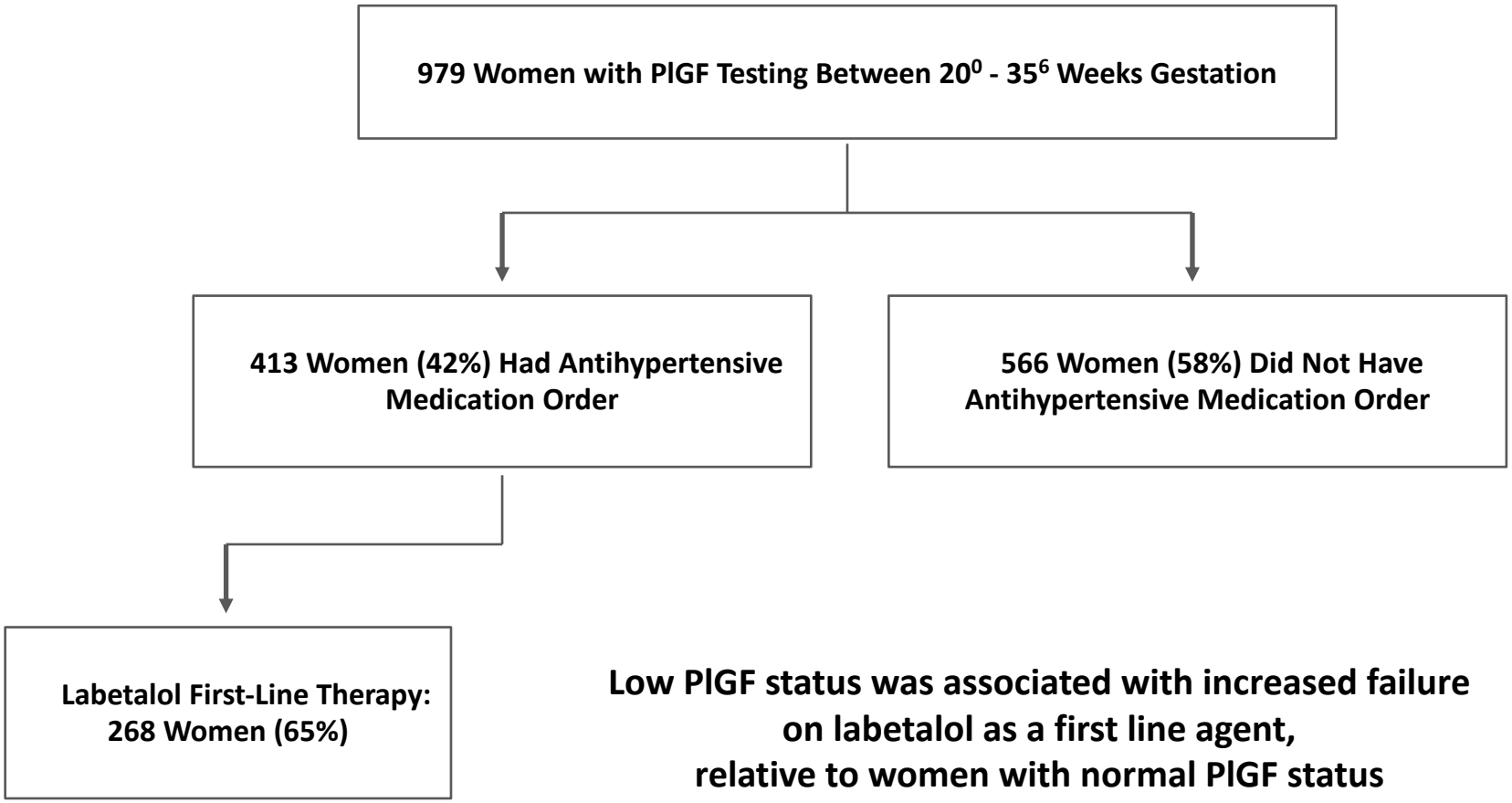
Antihypertensive Therapy in Pregnant Women with PlGF Testing



Low PlGF status was associated with increased failure on labetalol as a first line agent, relative to women with normal PlGF status (odds ratio 3.5 [2.1 – 5.7])

Sinai Health System

PHENOTYPE-DIRECTED MANAGEMENT OF HYPERTENSION IN PREGNANCY

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Laura E. Sienas MD[3]

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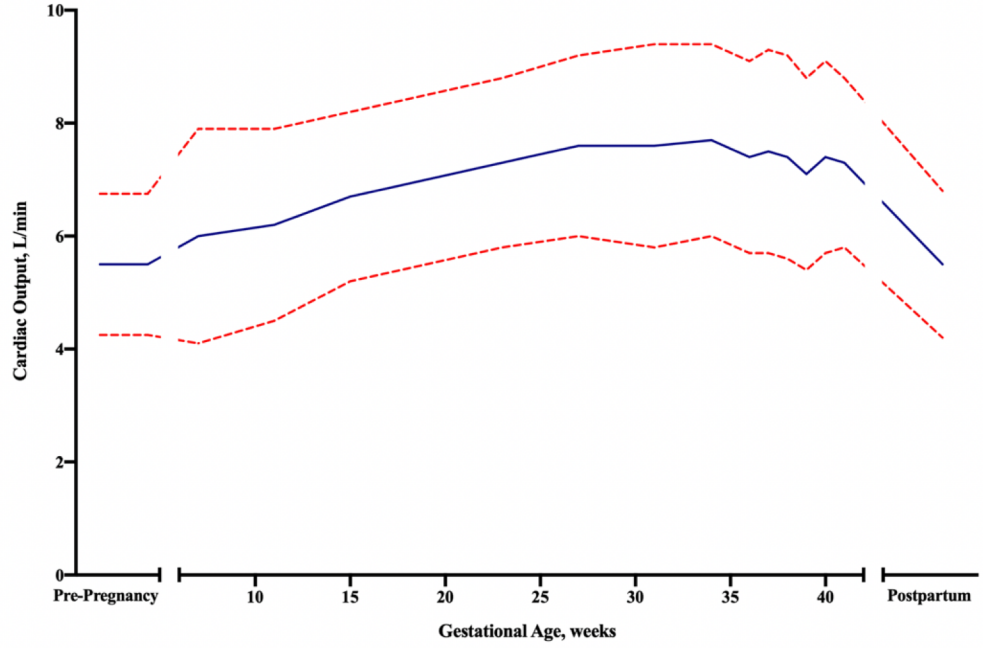
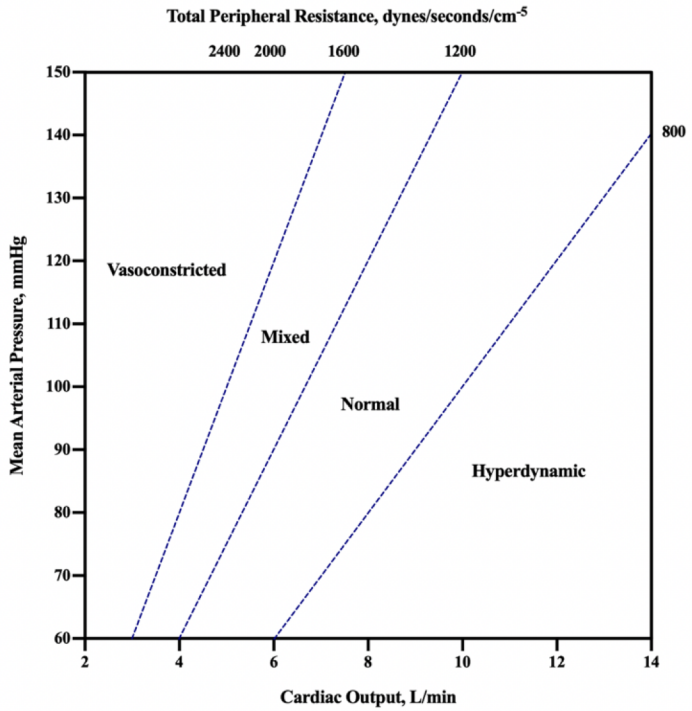
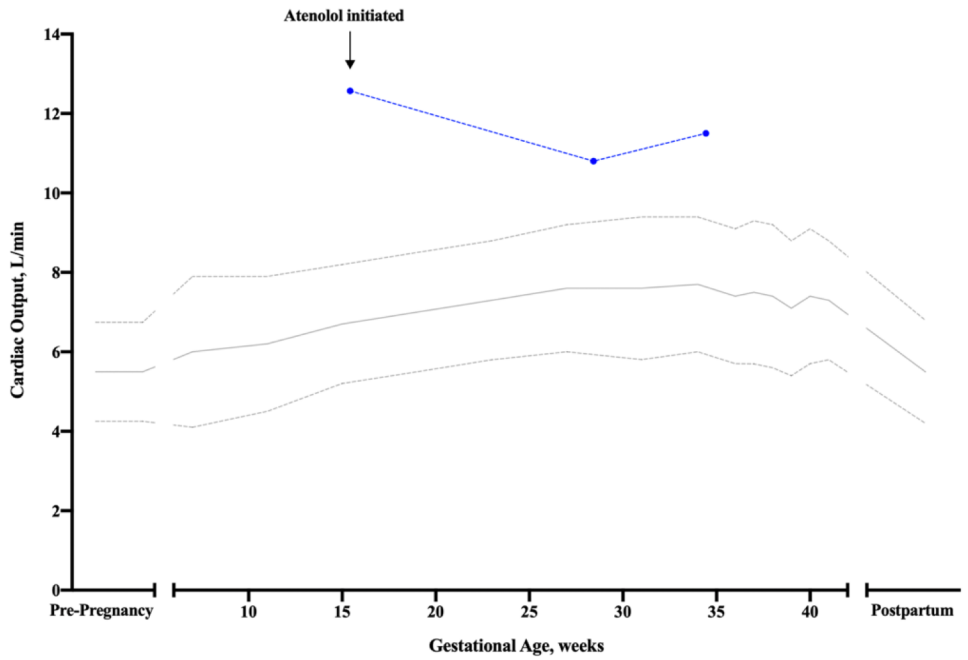
A


Cardiac Output, L/min
10
8
6
4
2
0
Pre-Pregnancy
10
15
20
25
30
35
40
Postpartum
Gestational Age, weeks

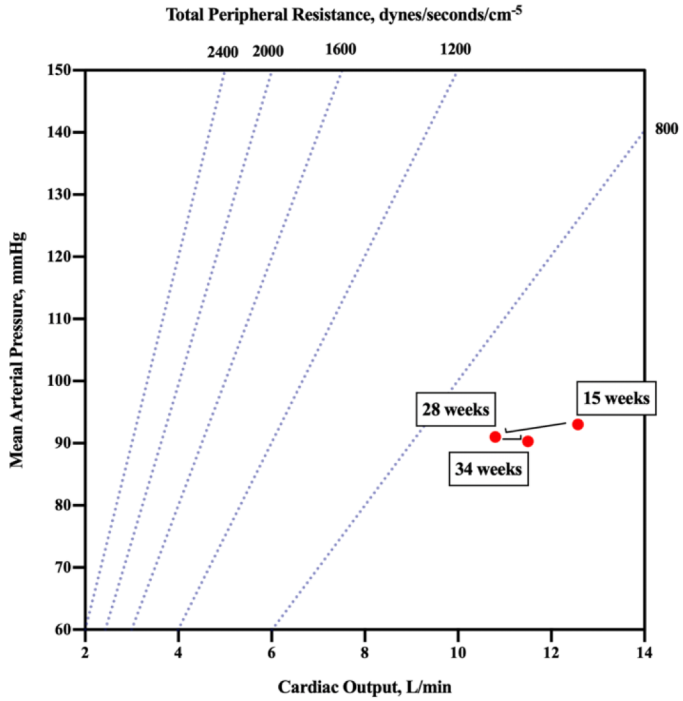
B


Total Peripheral Resistance, dynes/seconds/cm-5
2400
2000
1600
1200
800
Mean Arterial Pressure, mmHg
150
140
130
120
110
100
90
80
70
60
Vasoconstricted
Mixed
Normal
Hyperdynamic
2
4
6
8
10
12
14
Cardiac Output, L/min

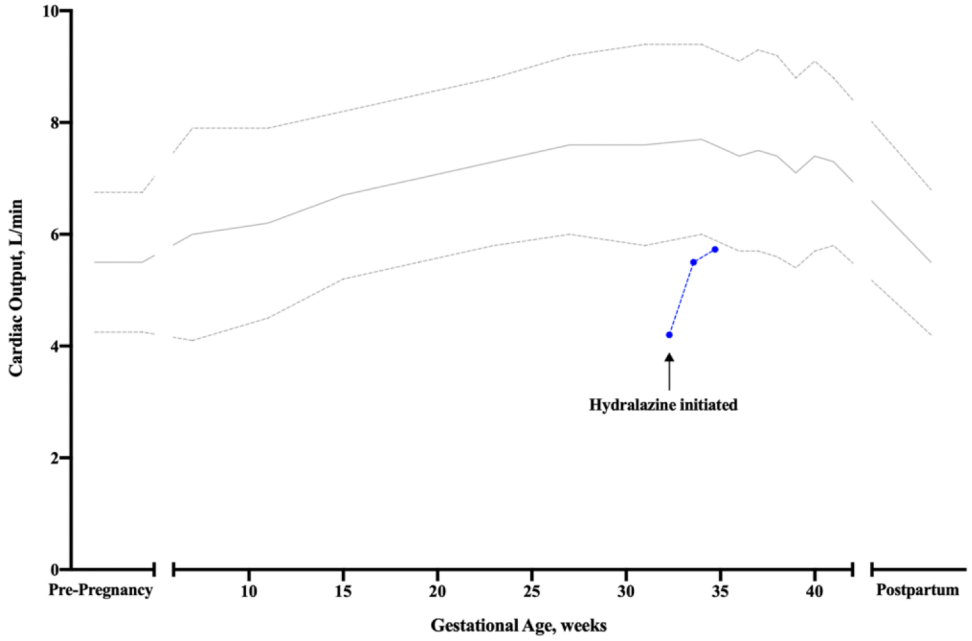
A


Atenolol initiated
Cardiac Output, L/min
0
2
4
6
8
10
12
14
Pre-Pregnancy
10
15
20
25
30
35
40
Postpartum
Gestational Age, weeks

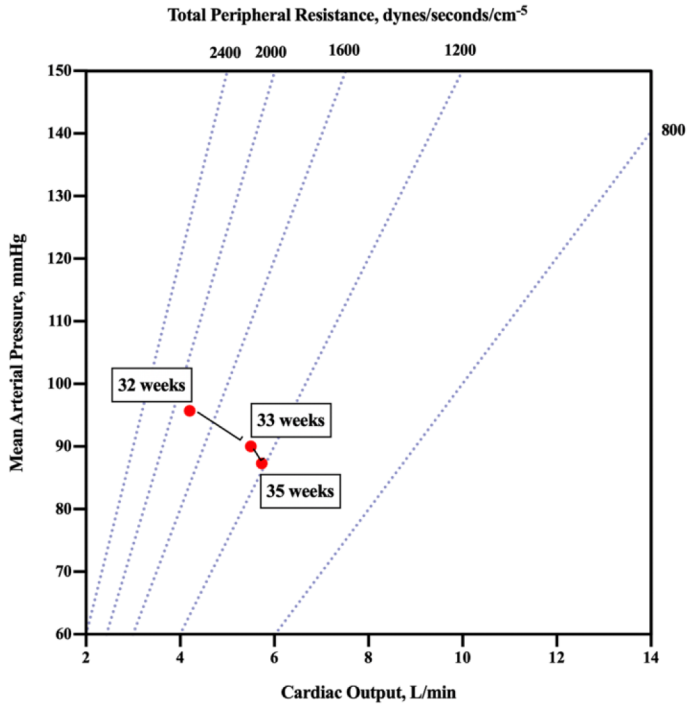
B


Total Peripheral Resistance, dynes/seconds/cm-5
2400
2000
1600
1200
800
Mean Arterial Pressure, mmHg
60
70
80
90
100
110
120
130
140
150
2
4
6
8
10
12
14
Cardiac Output, L/min
28 weeks
15 weeks
34 weeks

A


Cardiac Output, L/min
10
8
6
4
2
0
Pre-Pregnancy
10
15
20
25
30
35
40
Postpartum
Gestational Age, weeks
Hydralazine initiated

B


Total Peripheral Resistance, dynes/seconds/cm-5
2400
2000
1600
1200
800
Mean Arterial Pressure, mmHg
150
140
130
120
110
100
90
80
70
60
2
4
6
8
10
12
14
Cardiac Output, L/min
32 weeks
33 weeks
35 weeks

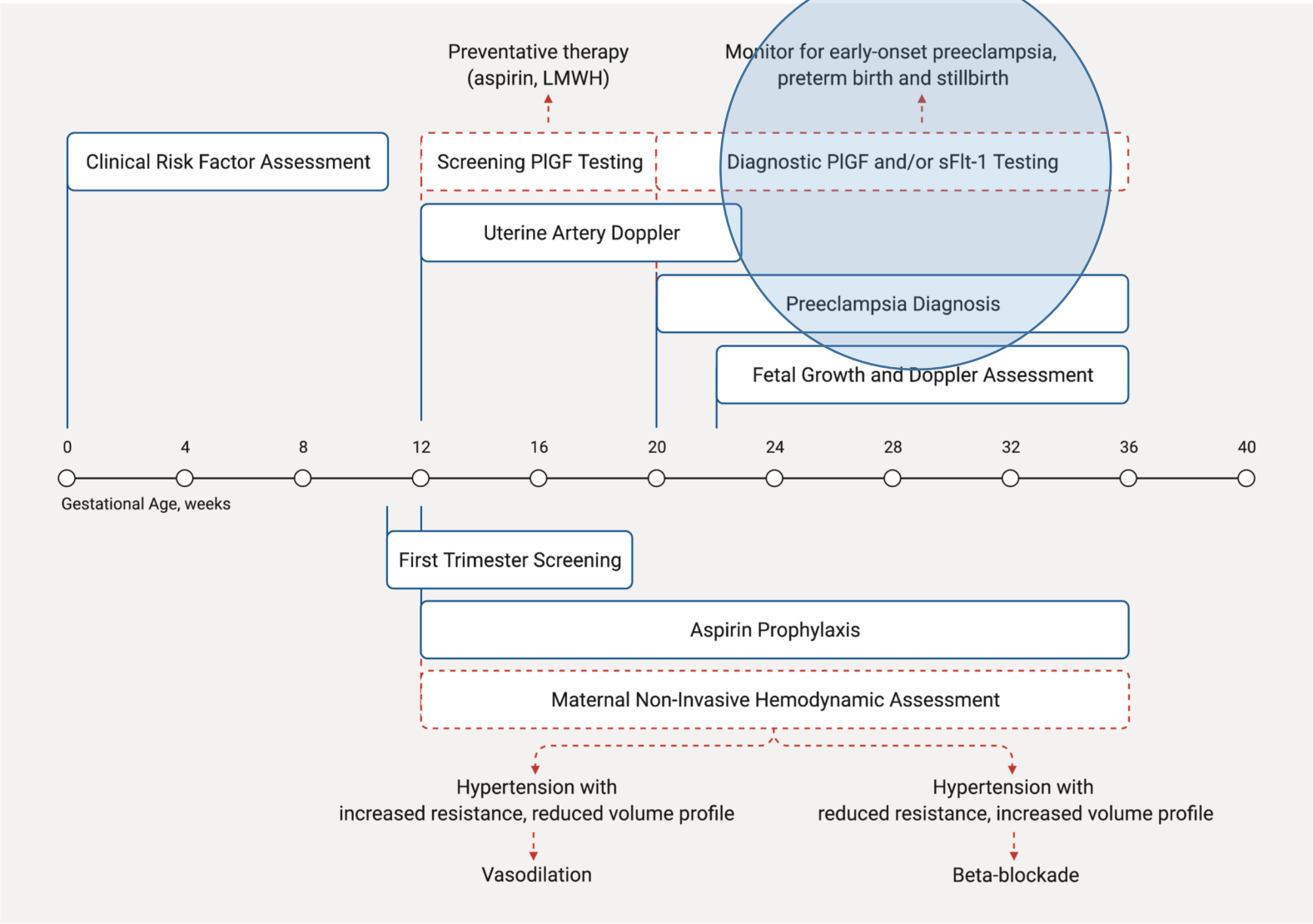
Talk Objectives:

Relationship between abnormal placental development, circulating angiogenic growth factors and the origins of preeclampsia

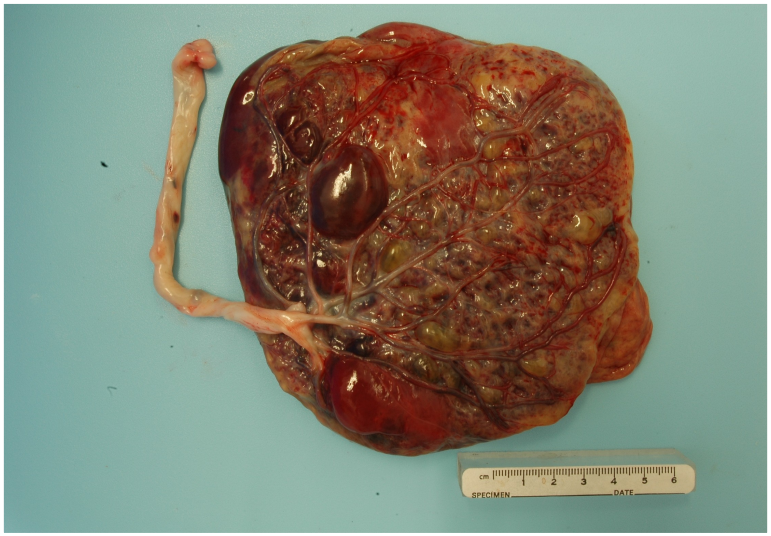
Role of angiogenic growth factors in the diagnosis and management of preeclampsia.

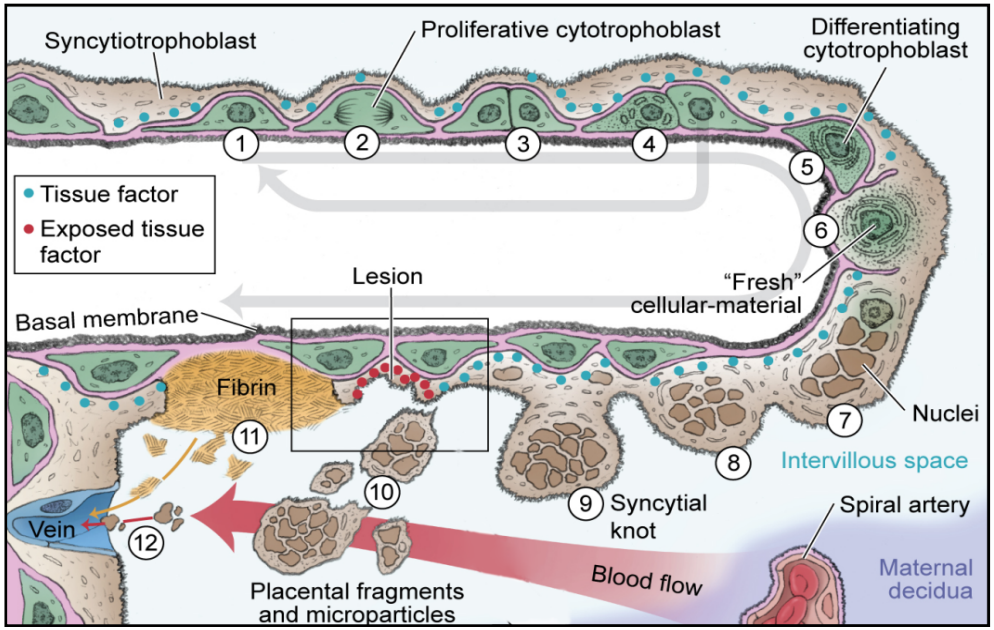
Screening utility of angiogenic growth factors in the prevention of severe preeclampsia / fetal growth restriction.

Improving Outcomes for women at risk of preeclampsia: Overall Strategy



It is counter-intuitive to believe that low-dose ASA effectively prevents severe early-onset preeclampsia





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Dalteparin for the prevention of recurrence of placental-mediated complications of pregnancy in women without thrombophilia: a pilot randomized controlled trial

E. REY, P. GARNEAU, M. DAVID, R. GAUTHIER, L. LEDUC, N. MICHON, F. MORIN, C. DEMERS, S. R. KAHN, L. A. MAGEE, M. RODGER,

First published: 15 December 2008 |
https://doi-org.myaccess.library.utoronto.ca/10.1111/j.1538-7836.2008.03230.x |
Citations: 146

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Low-molecular-weight heparin for prevention of preeclampsia and other placenta-mediated complications: a systematic review and meta-analysis

Monica Cruz-Lemini, MD, PhD; Juan Carlos Vázquez, MD, MSc; Johana Ullmo, MD; Elisa Llurba, MD, PhD

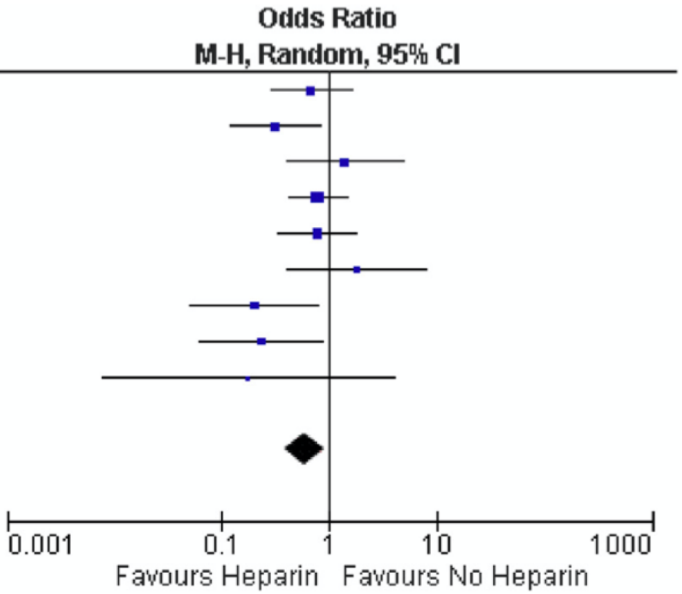
FIGURE 5

Effect of low-molecular-weight heparin on prevention of preeclampsia in studies with history of preeclampsia as inclusion criteria and treatment started before 16 weeks' gestation

	Heparin		No heparin			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
de Vries 2012	11	70	15	69	15,3%	0,67 [0,28, 1,59]
Gris 2011	6	112	17	112	13,1%	0,32 [0,12, 0,84]
Groom 2017	6	73	5	83	9,4%	1,40 [0,41, 4,78]
Haddad 2016	22	124	27	125	21,1%	0,78 [0,42, 1,47]
Llurba 2020	11	146	13	137	15,7%	0,78 [0,34, 1,80]
Martinelli 2012	5	63	3	65	7,1%	1,78 [0,41, 7,79]
Mello 2005	3	41	11	39	8,0%	0,20 [0,05, 0,79]
Rey 2009	3	57	11	57	8,3%	0,23 [0,06, 0,88]
van Hoorn 2016	0	16	2	16	1,9%	0,18 [0,01, 3,97]
Total (95% CI)		**702**		**703**	**100,0%**	**0,60 [0,39, 0,93]**
Total events	67		104			

Heterogeneity: Tau² = 0,13; Chi² = 11,68, df = 8 (P = 0,17); I² = 31%

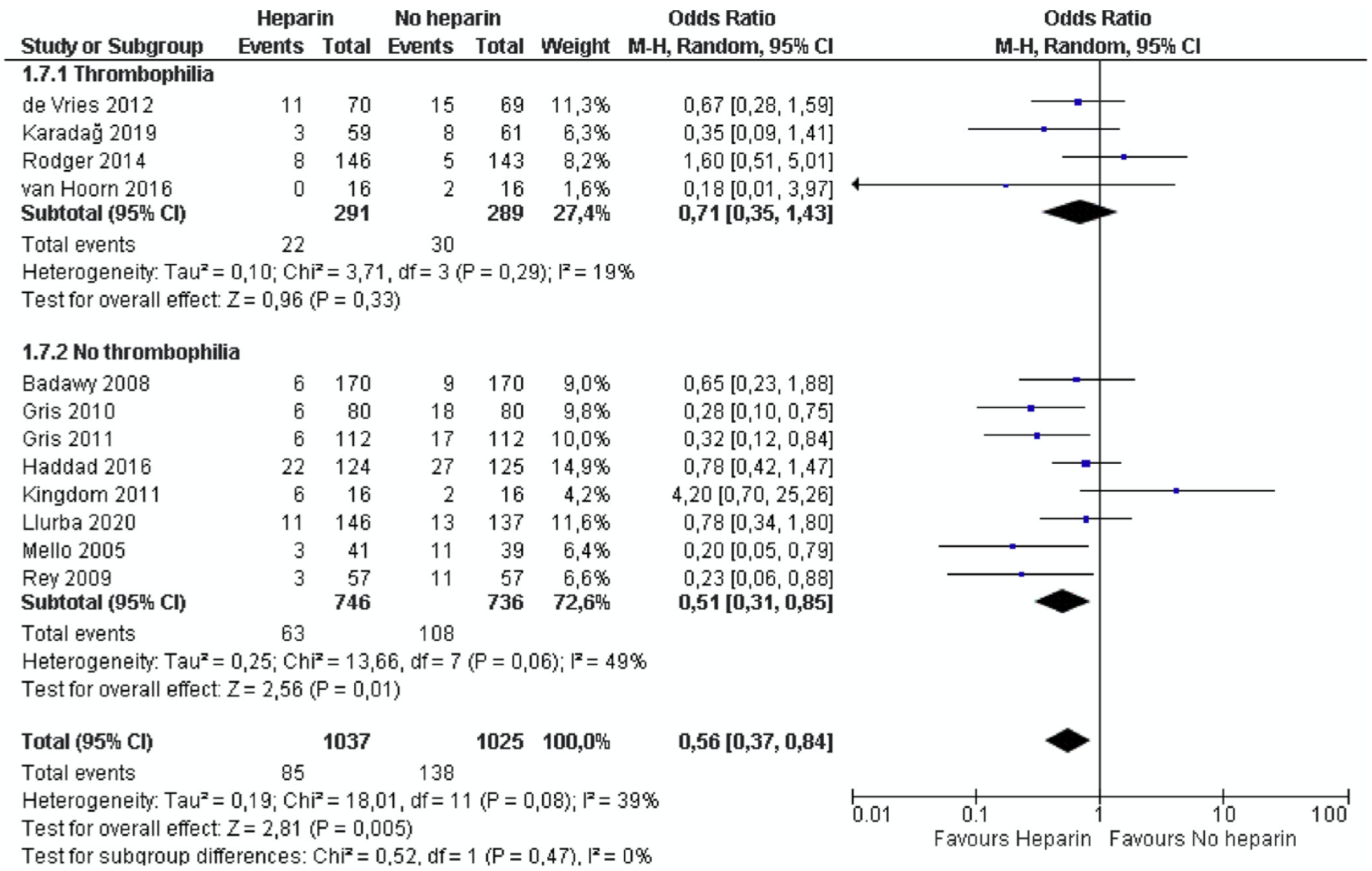
Test for overall effect: Z = 2,30 (P = 0,02)



Cruz-Lemini. Low-molecular-weight heparin for prevention of preeclampsia. Am J Obstet Gynecol 2020.

FIGURE 6

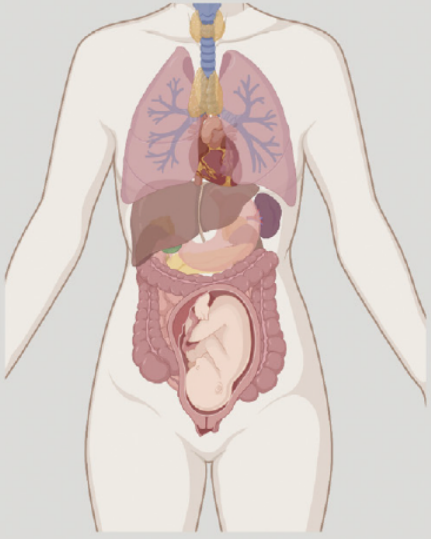
Effect of low-molecular-weight heparin on the prevention of preeclampsia in studies with and without thrombophilia



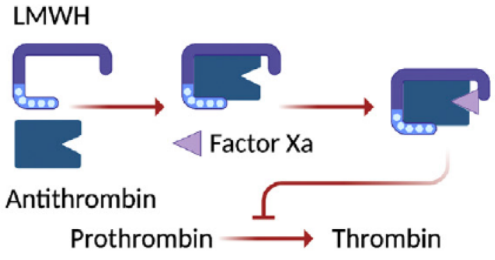
Cruz-Lemini. Low-molecular-weight heparin for prevention of preeclampsia. Am J Obstet Gynecol 2020.

FIGURE 1
Systemic effects of LMWH in pregnancy[1,17–24]

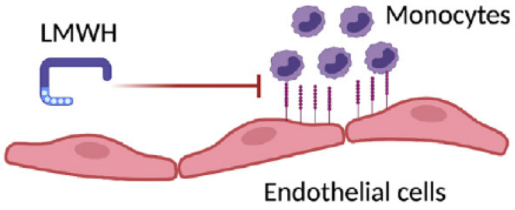
Systemic Effects of Low Molecular Weight Heparin in Pregnancy



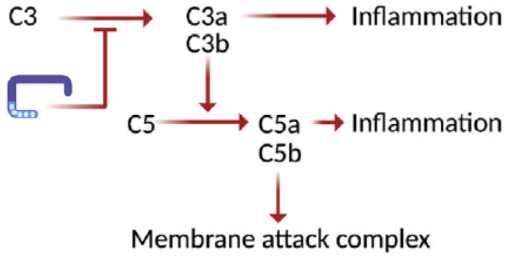
Inhibit thrombin formation



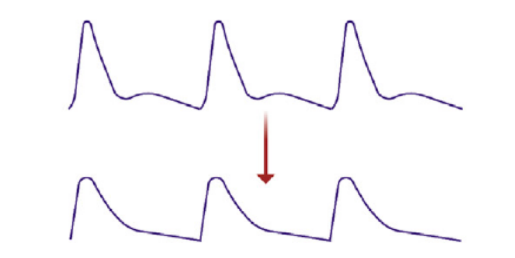
Prevent monocyte adhesion



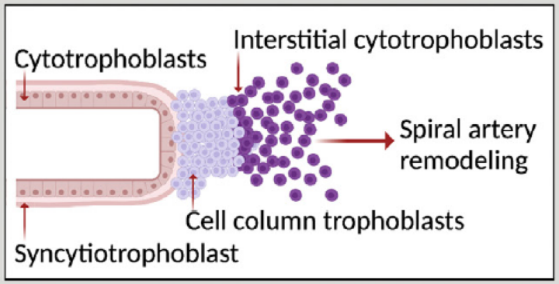
Suppress complement activation



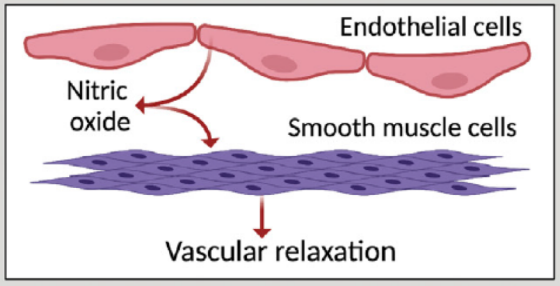
Decrease uterine artery pulsatility index



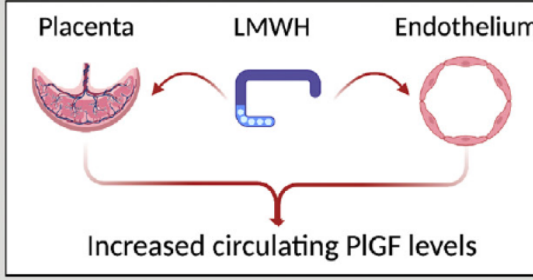
Promote differentiation and invasion of trophoblasts



Improve systemic vascular function



Increase circulating PlGF levels



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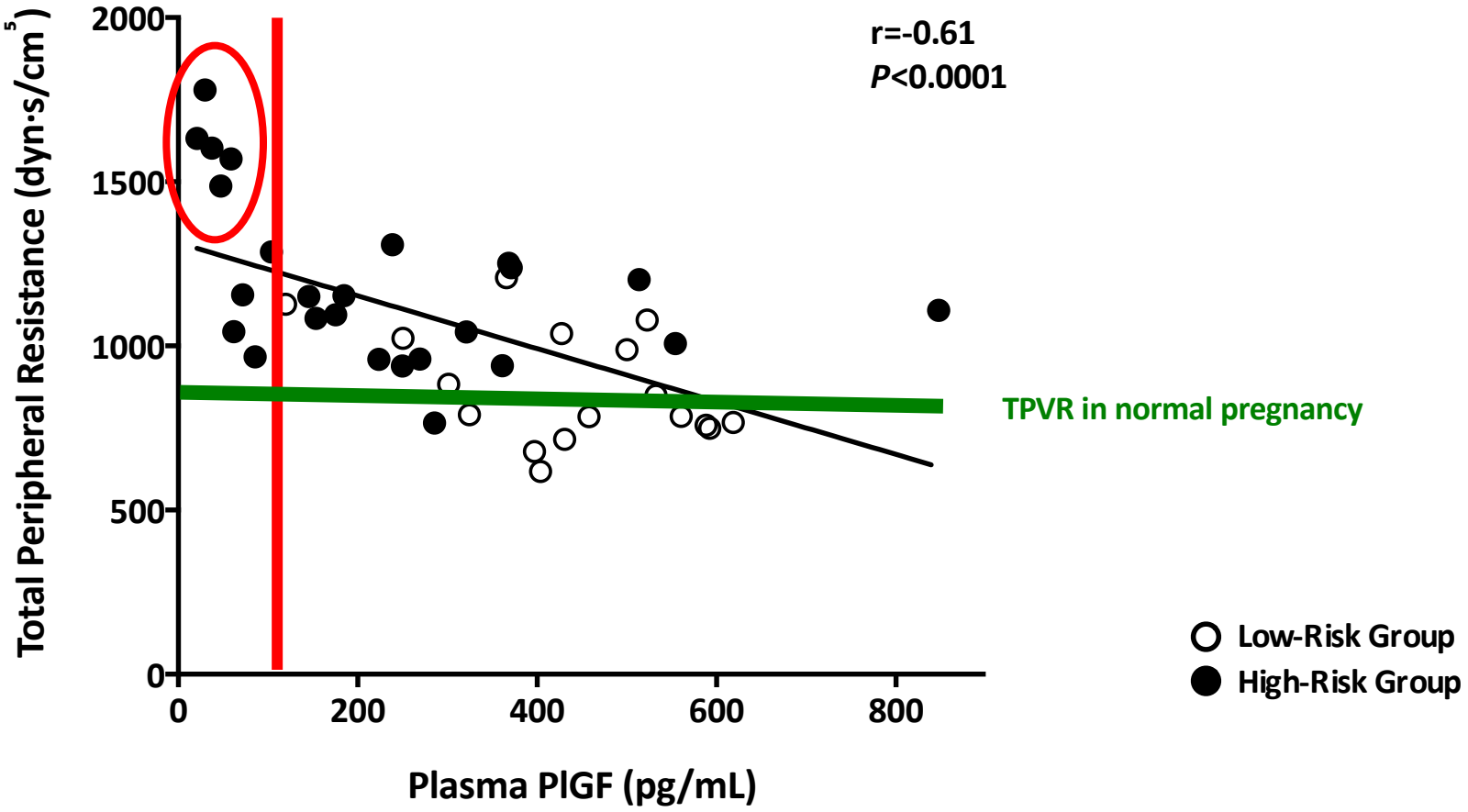
Original Article

Low Molecular Weight Heparin Improves Endothelial Function in Pregnant Women at High Risk of Preeclampsia

Kelsey McLaughlin, Dora Baczyk, Audrey Potts, Michelle Hladunewich, John D. Parker, John C.P. Kingdom

2017, Hypertension

Circulating PlGF & Systemic Vascular Resistance at 20-24 weeks



McLaughlin (2017) *Hypertension*

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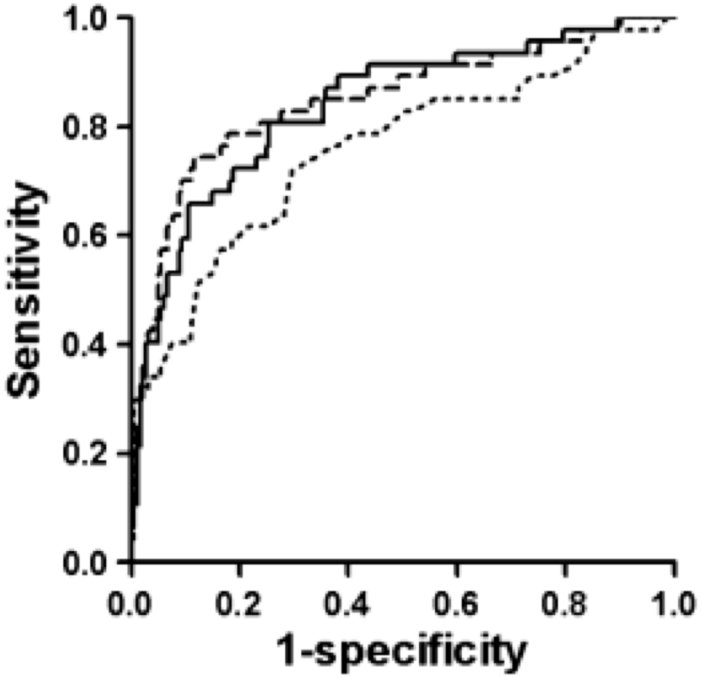
DOI: 10.1111/1471-0528.12195
www.bjog.org

Angiogenic factors combined with clinical risk factors to predict preterm pre-eclampsia in nulliparous women: a predictive test accuracy study

JE Myers,[a] LC Kenny,[b] LME McCowan,[c] EHY Chan,[c] GA Dekker,[d] L Poston,[e] NAB Simpson,[f] RA North,[e] on behalf of the SCOPE consortium

Table 3. Comparison of plasma angiogenic markers in preterm pre-eclampsia with controls

	No preterm pre-eclampsia (n = 188)		Preterm pre-eclampsia (n = 47)		*P*-valu
14–16 weeks					
PlGF* (pg/ml)	55	(33–90)	25	(17–48)	<0.000
sEng (ng/ml)	62	(54–72)	71	(56–83)	0.005
sFlt1 (pg/ml)	450	(223–848)	543	(253–1134)	0.20
19–21 weeks					
PlGF* (pg/ml)	134	(82–217)	73	(40–137)	<0.000
sEng (ng/ml)	61	(51–69)	74	(59–87)	<0.000
sFlt-1 (pg/ml)	426	(227–732)	371	(202–749)	0.92



Original Research ajog.org

OBSTETRICS

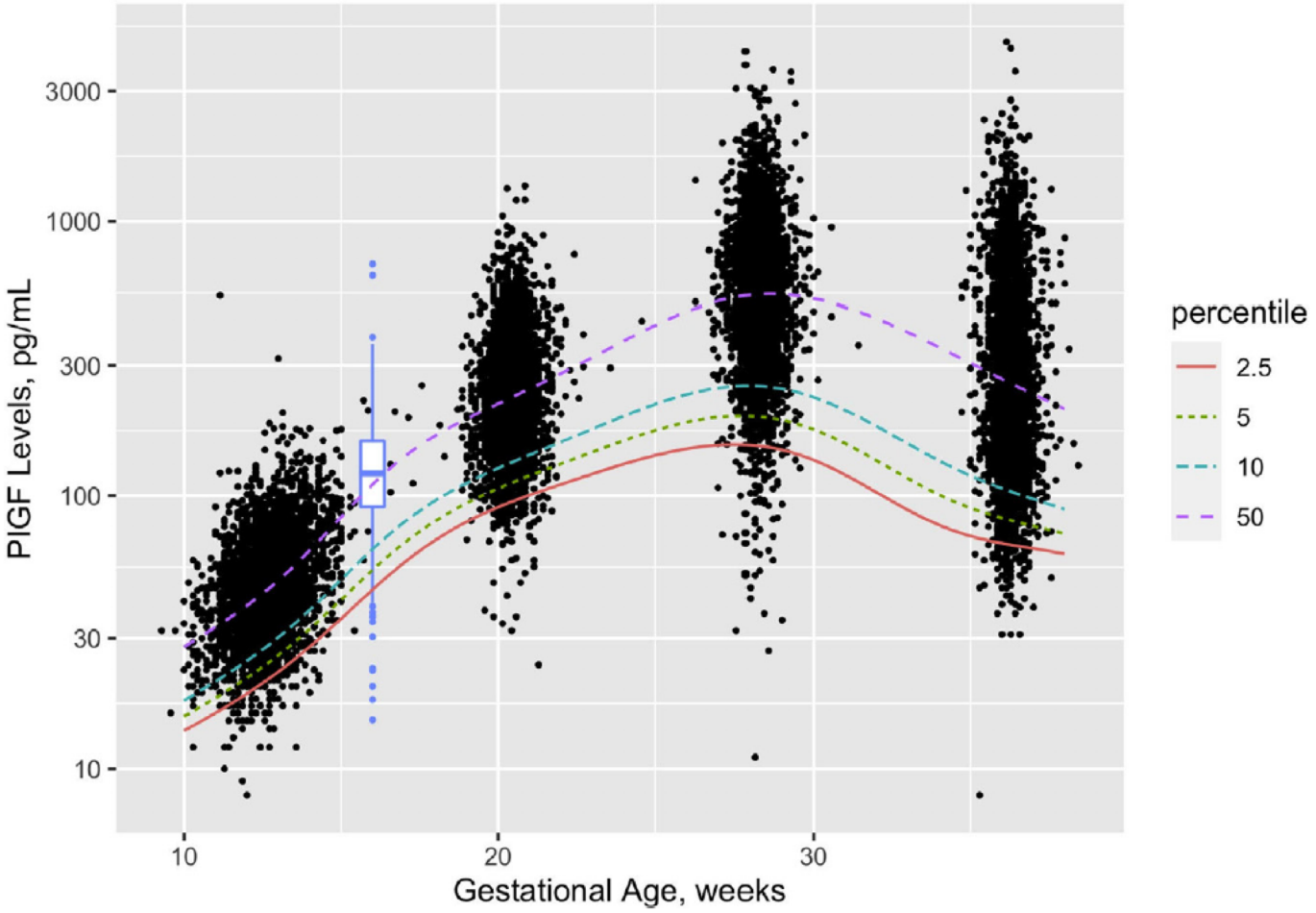
Circulating maternal placental growth factor responses to low-molecular-weight heparin in pregnant patients at risk of placental dysfunction

Kelsey McLaughlin, PhD; Sebastian R. Hobson, MBBS, PhD; Anjana Ravi Chandran, BHSc; Swati Agrawal, MBBS, MSc; Rory C. Windrim, MB, MSc; W. Tony Parks, MD; Adrian W. Bowman, PhD; Ulla Sovio, PhD; Gordon C. Smith, MD, PhD; John C. Kingdom, MD

McLaughlin et al., 2021

FIGURE 2

Gestational age-specific distribution of circulating maternal PIGF levels

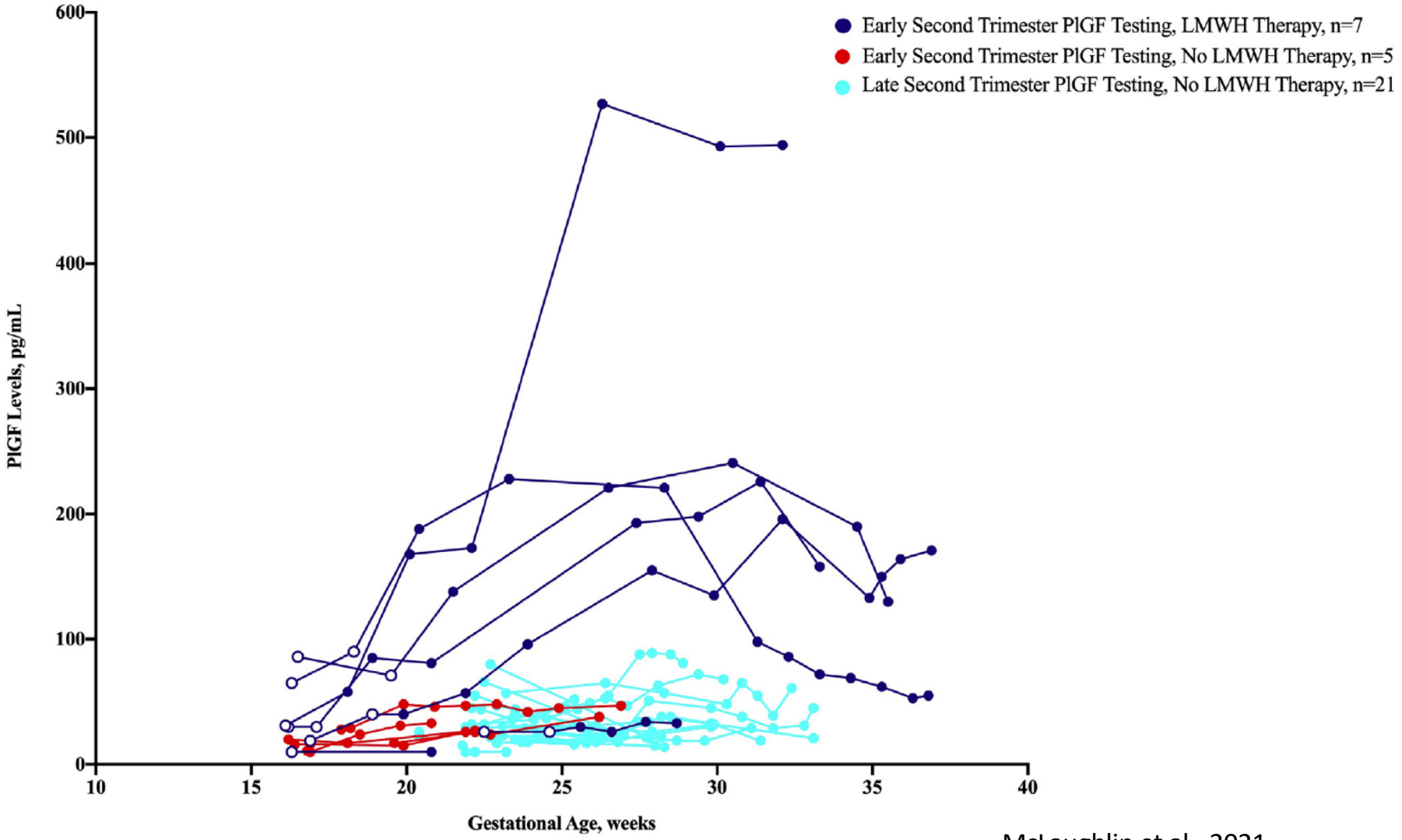


McLaughlin et al., 2021

Gestational Age	5th Centile	10th Centile	50th Centile
12	22	25	40
13	26	30	48
14	32	38	62
15	43	51	85
16	58	69	118
17	72	86	149
18	83	99	170
19	93	111	189
20	106	125	216
21	118	141	245
22	126	151	267
23	135	164	296
24	150	184	342
25	167	207	399
26	182	229	458
27	193	246	510
28	196	253	541
29	188	245	540
30	172	226	516
31	154	204	485
32	136	181	447
33	118	158	402
34	103	137	355
35	91	120	307
36	83	106	266

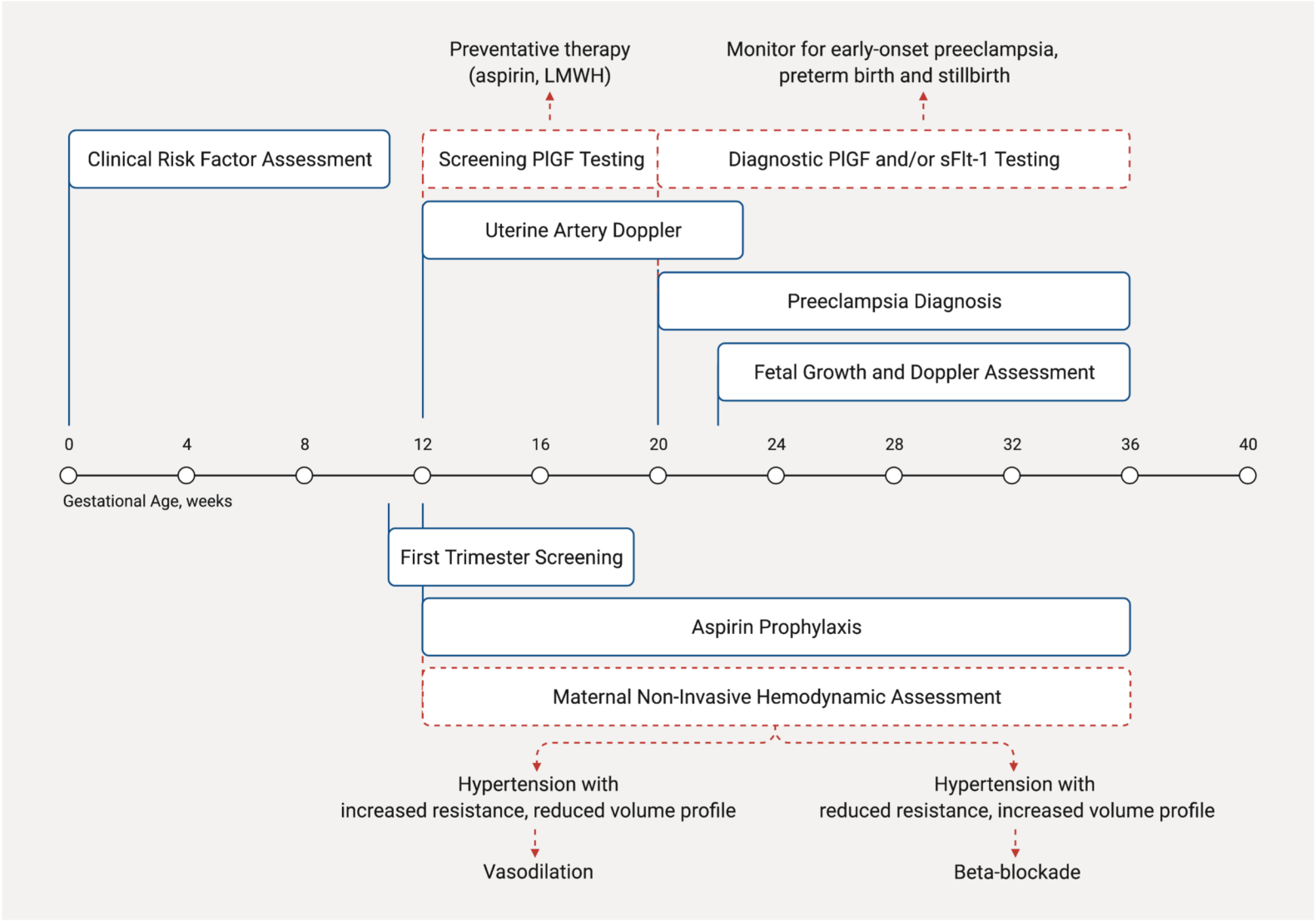
FIGURE 3

PlGF levels in pregnant patients at risk of placental dysfunction



McLaughlin et al., 2021

Improving Outcomes for women at risk of preeclampsia: A Multi-Pronged Strategy



THE LANCET

Seminar

Pre-eclampsia

Lucy C Chappell, Catherine A Cluver, John Kingdom, Stephen Tong

Pre-eclampsia is a multisystem pregnancy disorder characterised by variable degrees of placental malperfusion, with release of soluble factors into the circulation. These factors cause maternal vascular endothelial injury, which leads to hypertension and multi-organ injury. The placental disease can cause fetal growth restriction and stillbirth. Pre-eclampsia is a major cause of maternal and perinatal mortality and morbidity, especially in low-income and middle-income countries. Prophylactic low-dose aspirin can reduce the risk of preterm pre-eclampsia, but once pre-eclampsia has been diagnosed there are no curative treatments except for delivery, and no drugs have been shown to influence disease progression. Timing of delivery is planned to optimise fetal and maternal outcomes. Clinical trials have reported diagnostic and prognostic strategies that could improve fetal and maternal outcomes and have evaluated the optimal timing of birth in women with late preterm pre-eclampsia. Ongoing studies are evaluating the efficacy, dose, and timing of aspirin and calcium to prevent pre-eclampsia and are evaluating other drugs to control hypertension or ameliorate disease progression.

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S0140-6736(20)32335-7

Department of Women and Children's Health, School of Life Course Sciences, Kings' College London, London, UK (Prof L C Chappell PhD); Department of Obstetrics and Gynaecology, Stellenbosch University, Stellenbosch, South Africa (C A Cluver PhD); Tygerberg Hospital, Cape Town, South Africa (C A Cluver); Department of Obstetrics and Gynaecology, University of Toronto, Toronto, ON, Canada (Prof J Kingdom MD); Department of Obstetrics and Gynaecology, University of Melbourne, Melbourne, VIC, Australia (Prof S Tong PhD); Mercy Hospital for Women, Heidelberg, VIC, Australia (Prof S Tong)

Introduction

Pre-eclampsia complicates about 3–5% of all pregnancies and is estimated to cause at least 42 000 maternal deaths annually.[1–3] For every loss related to pre-eclampsia, at least 50–100 women have substantial morbidity.[2,4,5] Low-income and middle-income countries (LMIC) have the highest burden of major complications because of scarce resources and poorer access to adequate obstetric care and family planning services than high-income countries.[6,7]

pressure sustained at ≥90 mm Hg, or both) with proteinuria, or end organ dysfunction after 20 weeks' gestation (panel), or both; appendix p 1 summarises how major international guidelines define pre-eclampsia.[8–12] Organs affected by pre-eclampsia include the brain, causing severe headache, visual disturbances, or eclamptic seizures; the liver, causing epigastric pain or abnormal liver function tests; the kidneys, causing abnormal renal function tests or proteinuria; the haematological system, causing haemolysis, thrombo-

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Dr. Nir Melamed

Dr. Gordon Smith
Dr. Adrian Bowman

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