High Risk Obstetrics Leading to Preterm Birth

Michael J. Paidas, MD,
Professor & Chair, Department of Obstetrics, Gynecology and Reproductive Sciences
University of Miami Miller School of Medicine
2019 Miami-Dade Prematurity Symposium
November 14, 2019, 645pm-730pm and November 15, 2019, 945pm-10-15pm Miami Marriott Dadeland Hotel
9090, S. Dadeland Boulevard, Miami

UHealth University of Miami Health System | University of Miami Miller School of Medicine

Disclosures

Commercial Interest	Relationship	Role
BioIncept, LLC	Grant Stock option	Principal Investigator Scientific Advisory Board
CSL Behring	Grant	Principal Investigator
GestVision	Grant	Principal Investigator
NovoNordisk	Consultant	Consultant
Progenity	Grant	Principal Investigator
rEVO Biologics	Grant, COA Support	Principal Investigator

NIH:
NIAID- Acute Radiation Syndrome
NICHD- Perinatal Brain Injury

Preterm Birth (<37 Weeks)

- Preterm (< 37 w) Delivery Rate (USA): 9.85% pregnancies *(NCHS National Center for Vital Statistics, Natality, 2018)*
- Preterm births account for approximately 70% of neonatal deaths and 36% of infant deaths as well as 25–50% of cases of long-term neurologic impairment in children
- The annual cost of preterm birth in the United States to be $26.2 billion or more than $51,000 per premature infant

BIG NEWS

FDA NEWS

FDA may withdraw approval of drug that manufacturer says prevents preterm birth

November 8, 2019

ADD TOPIC TO EMAIL ALERTS


Sean C. Blackwell

An FDA advisory committee recently voted in favor of withdrawing the agency's approval of Makena, a synthetic progestin, for the prevention of preterm birth in pregnant women who have a history of preterm birth.

According to Amag Pharmaceuticals, which manufactures Makena, the FDA committee came to its decision after a confirmatory trial concluded that the treatment did not decrease the risk for recurrent preterm birth. The findings contradict those that led the FDA to approve an injectable form of the drug in 2011.

Sean C. Blackwell, MD, of the department of obstetrics, gynecology and reproductive sciences at McGovern Medical School-UTHealth in Houston, was an investigator on the confirmatory trial. He explained to Healio Primary Care that the differences in the

BIG NEWS

SMFM Statement: Use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth

Society for Maternal-Fetal Medicine (SMFM) Publications Committee

very high-risk population reported in the Meis trial. For all women at risk of recurrent sPTB, the risk/benefit discussion should incorporate a shared decision-making approach, taking into account the lack of short-term safety concerns but uncertainty regarding benefit. It is important to consider that 17-OHPC is associated with substantial health care costs, injection-site pain, and extra patient visits (15, 16) and that long-term potential maternal and neonatal effects are unknown. The lack of benefit from 17-OHPC seen in the PROLONG trial raises questions regarding the efficacy of 17-OHPC, and additional studies are needed to identify populations in which administration of 17-OHPC may provide needed benefit in the reduction of recurrent sPTB. SMFM will continue to closely follow advances in this area to assure optimal care for women and to provide guidance for maternal-fetal medicine subspecialists.

BIG NEWS

The American College of Obstetricians and Gynecologists — Communications Office
Washington, DC
202-484-3321
communications@acog.org | acog.org

ACOG Statement on 17p Hydroxyprogesterone Caproate

October 25, 2019

Washington, DC — Christopher M. Zahn, MD, vice president, Practice Activities of the American College of Obstetricians and Gynecologists (ACOG), issued the following statement regarding the findings of the PROLONG (Progestin's Role in Optimizing Neonatal Gestation) trial, a randomized, double-blinded, placebo-controlled clinical trial evaluating 17-hydroxyprogesterone caproate (17p):

"ACOG's clinical guidance, 'Prediction and Prevention of Preterm Birth,' details important information for ob-gyns caring for patients at risk for preterm birth, including risk factors, screening modalities, and the evidence around treatment interventions. After reviewing the findings from the PROLONG trial, ACOG finds that its current guidance will remain in effect.

"Consideration for offering 17p to women at risk of recurrent preterm birth should take into account the body of evidence for progesterone supplementation, the values and preferences of the pregnant woman, the resources available, and the setting in which the intervention will be implemented. Additional information from planned meta-analysis and secondary analyses will need to be evaluated to assess the impact this intervention has on women at risk of recurrent preterm birth in the United States.

"ACOG recognizes that the PROLONG clinical trial evaluating 17p in patients with a history of a prior spontaneous singleton preterm delivery, demonstrated no statistical difference in the co-primary outcome of preterm birth less than 35 0/7 weeks of gestation and neonatal composite index. Similarly, the rate of preterm birth less than 37 and less than 32 weeks were not different. No other differences in perinatal or maternal outcomes were detected. ACOG also understands that the authors suggest that the study was underpowered to assess treatment efficacy and that due to previous treatment guidelines, there may have been an unintentional selection bias.

"ACOG's guidance is based on a review of the best available literature. As such, we will continue to monitor this topic, evaluate additional literature and any further analyses as published, and address findings as needed in relevant clinical guidance.

"It is well known that infants born prematurely have increased risks of poor outcomes, including death, and that the risk decreases as gestational age increases. In fact, preterm birth is the leading cause of neonatal mortality in the United States. Preventing preterm birth can help give babies a better chance at a healthy life.

"ACOG remains committed to providing ob-gyns and other women's health care providers with evidence-based guidelines to help ensure the health and well-being of women and their families."

17- alpha-Hydroxyprogesterone (250mg) IM Weekly from 16-20^{6} wk reduces recurrent PTD (RCT Double blind, 2:1 ratio)
Progesterone Group: N= 310 Placebo: N= 153
Meis PJ et al, NEJM 2003; 348: 2379-85

Outcome	Progesterone N= 306	Placebo N= 153	Relative Risk (95% CI)
Del < 37 wks	111 (36.3%)	84 (54.9%)	0.66 (0.54- 0.81)
<37w, Black	64 (35.4%)	47 (52.2%)	0.68 (0.51-0.90)
<37w, non-B	47 (37.6%)	37 (58.7%)	0.64 (0.47-0.87)
Del <35 wks	63 (20.6%)	47 (30.7%)	0.67 (0.48-0.93)
Del < 32 wks	35 (11.4%)	30 (19.6%)	0.58 (0.37- 0.91)

Published online: 25.10.2019
THIEME OPEN ACCESS
Original Article

17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial

Sean C. Blackwell, MD[1] Cynthia Gyamfi-Bannerman, MD, MS[2] Joseph R. Biggio Jr., MD[3] Suneet P. Chauhan, MD[1] Brenna L. Hughes, MD[4] Judette M. Louis, MD[5] Tracy A. Manuck, MD[6] Hugh S. Miller, MD[7] Anita F. Das, PhD[8] George R. Saade, MD[9] Peter Nielsen, MD[10] Jeff Baker, MD[11] Oleksandr M. Yuzko, MD, PhD[12] Galyna I. Reznichenko, MD, PhD[13] Nataliya Y. Reznichenko, MD, PhD[13] Oleg Pekarev, MD, PhD[14] Nina Tatarova, MD, PhD[15] Jennifer Gudeman, PharmD[16] Robert Birch, PhD[17] Michael J. Jozwiakowski, PhD[18] Monique Duncan[16] Laura Williams, MD, MPH[16] Julie Krop, MD[16]

[1] Department of Obstetrics, Gynecology, and Reproductive Sciences, McGovern Medical School-UTHealth, Houston, Texas
[2] Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Columbia University Irving Medical Center, New York, New York
[3] Section of Maternal Fetal Medicine, Women's Services, Ochsner Health Systems, New Orleans, Louisiana
[4] Department of Obstetrics and Gynecology, Duke University, Durham, North Carolina
[5] Department of Obstetrics and Gynecology, University of South Florida, Tampa, Florida
[6] Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, North Carolina
[7] Valley Perinatal Services, Watching Over Mothers and Babies Foundation, Tucson, Arizona
[8] Das Consulting, Guerneville, California
[9] Department of Obstetrics and Gynecology, University of Texas Medical Branch, University of Texas, Galveston, Texas
[10] Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Baylor College of Medicine and The Children's Hospital of San Antonio, San Antonio, Texas
[11] Clinical Research Prime, Idaho Falls, Idaho
[12] Department of Obstetrics and Gynecology, Bukovinian State Medical University, Chernivtsi, Ukraine
[13] Department of Obstetrics and Gynecology, Clinical Maternity Hospital # 4, Zaporizhzhya, Ukraine
[14] Department of Obstetrics and Gynecology, State Government-financed Healthcare Institution of Novosibirsk Region, Novosibirsk, Russia
[15] Department of Obstetrics and Gynecology, Saint-Petersburg Government-financed Healthcare Institution "Maternity Hospital #17," Saint-Petersburg, Russia
[16] AMAG Pharmaceuticals, Inc, Medical Development, Waltham, Massachusetts
[17] Formerly at AMAG Pharmaceuticals, Inc, Medical Development, Waltham, Massachusetts
[18] Jozwiakowski Pharma Consulting LLC, Santa Fe, New Mexico

Address for correspondence Sean C. Blackwell, MD, Department of Obstetrics, Gynecology, and Reproductive Sciences, McGovern Medical School-UTHealth, 6431 Fannin, MSB 3.286, Houston, TX 77030 (e-mail: Sean.blackwell@uth.tmc.edu).

Am J Perinatol

Table 2 Obstetrical outcomes

	17-OHPC $n=1,130$	Placebo $n=578$	RR (95% CI)
Number assessed for outcome, N1	1,113	574	0.95 (0.71–1.26)
PTB < $35^{0/7}$ wk[a]	122 (11.0)	66 (11.5)	
Spontaneous	93 (8.4)	51 (8.9)	0.93 (0.67–1.30)
Indicated	28 (2.5)	14 (2.4)	1.03 (0.55–1.93)
Number assessed for outcome, N1	1,112	572	
PTB < $37^{0/7}$ wk	257 (23.1)	125 (21.9)	1.06 (0.88–1.28)
Spontaneous	209 (18.8)	98 (17.1)	1.10 (0.88–1.36)
Indicated	46 (4.1)	26 (4.5)	0.91 (0.57–1.46)
Number assessed for outcome, N1	1,116	574	0.92 (0.60–1.42)
PTB < $32^{0/7}$ wk	54 (4.8)	30 (5.2)	
Spontaneous	38 (3.4)	22 (3.8)	0.88 (0.52–1.48)
Indicated	15 (1.3)	7 (1.2)	1.11 (0.46–2.63)
Cerclage	6 (0.5)	7 (1.2)	0.44 (0.15–1.32)
Preterm labor[b]	187(16.5)	84 (14.5)	1.14 (0.90–1.44)
Tocolysis	134 (11.9)	63 (10.9)	1.09 (0.82–1.44)
Antenatal corticosteroid therapy	105 (9.3)	61(10.6)	0.88 (0.65–1.20)
Maternal GDM	35 (3.1)	21 (3.6)	0.91 (0.54–1.54)
Preeclampsia	47 (4.2)	30 (5.2)	0.86 (0.51–1.46)
Chorioamnionitis	9 (0.8)	2 (0.3)	2.24 (0.48–10.41)
Abruption	16 (1.4)	4 (0.7)	2.04 (0.69–6.06)
Cesarean delivery	292 (25.8)	140 (24.2)	1.07 (0.90–1.27)

Abbreviations: CI, confidence interval; GDM, gestational diabetes mellitus; OHPC, α-hydroxyprogesterone caproate; PTB, preterm birth; RR, relative risk.
Note: n = number of subjects in the intent to Treat population. N1 = number of subjects with non-missing delivery data or with missing delivery data who were known to be pregnant at the specified gestational age. Relative risk (RR) and confidence interval (CI) adjusted for gestational age at randomization stratum and based on observed data (no imputation for missing data). Data expressed as n (%).Type of delivery (spontaneous and indicated) is not available for women with missing delivery data.
[a]p-Value = 0.72 and is from the Cochran–Mantel–Haenszel test based on the sample sizes within each gestational age at randomization stratum. Missing outcome data were imputed using a multiple imputation analysis.
[b]Not including episode of delivery event.

Table 3 Neonatal outcomes—live-born neonatal population

	17-OHPC $n=1,093$	Placebo $n=559$	RR (95% CI)
Composite neonatal morbidity and mortality index[a]	61 (5.6)	28 (5.0)	1.12 (0.72–1.72)
Neonatal death	6 (0.5)	3 (0.5)	0.98 (0.24–3.91)
Bronchopulmonary dysplasia	6 (0.5)	1 (0.2)	3.02 (0.38–24.1)
Respiratory distress syndrome	54 (4.9)	26 (4.7)	1.06 (0.67–1.68)
Necrotizing enterocolitis	2 (0.2)	2 (0.4)	0.5 (0.07–3.40)
IVH, grade 3 or 4	2 (0.2)	1 (0.2)	0.99 (0.09–10.52)
Proven sepsis	5 (0.5)	3 (0.5)	0.84 (0.20–3.56)
NICU admission	137 (12.5)	58 (10.4)	1.21 (0.90–1.62)
Birth weight (g)	3,076.6 ± 630.0	3,080.1 ± 609.2	NA
TTN	37 (3.4)	11 (2.0)	1.72 (0.89–3.33)
Number of neonates on ventilator support/receiving supplemental oxygen	130 (11.9)	54 (9.7)	1.23 (0.91–1.67)
PDA	4 (0.4)	4 (0.7)	0.53 (0.14–2.06)
ROP	5 (0.5)	7 (1.3)	0.37 (0.12–1.16)
Neonatal LOS (for those admitted to the NICU) (d)	18.6 ± 20.4	23.3 ± 24.5	NA

Abbreviations: CI, confidence interval; IVH, intraventricular hemorrhage; LOS, length of stay; NA, not applicable; NICU, neonatal intensive care unit; OHPC, α-hydroxyprogesterone caproate; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; RR, relative risk; TTN, transient tachypnea of the newborn.
Note: Data expressed as n (%), median (interquartile range), or mean (± standard of deviation). n = number of neonates in the live-born neonatal population. RR and CI are adjusted for gestational age at randomization stratum.
[a]p-Value = 0.62 and is from the Cochran–Mantel–Haenszel test based on the sample sizes within each gestational age at randomization stratum.

Table 4 Pregnancy loss, stillbirth, and neonatal death outcomes

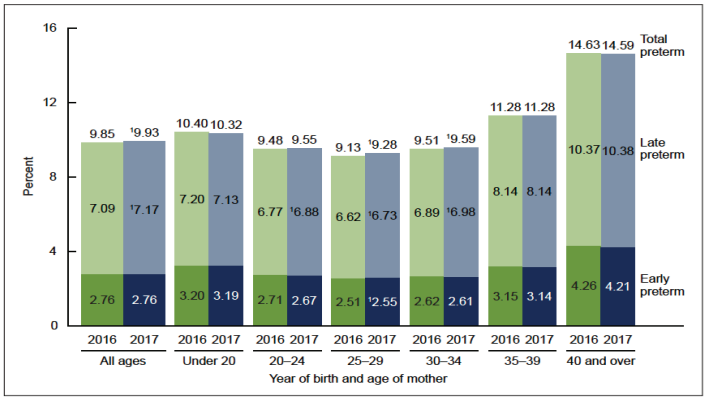
	17-OHPC n/N1 (%)	Placebo n/N1 (%)	RR (95% CI)[a]
Fetal/early infant death[b]	19/1128 (1.7)	11/578 (1.9)	0.87 (0.4–1.81)
Miscarriage[c]	4/866 (0.5)	7/448 (1.3)	0.28 (0.08–0.94)
Stillbirth[d]	12/1124 (1.1)	3/571 (0.5)	2.07 (0.59–7.29)
Early infant death[e]	3/1112 (0.3)	1/568 (0.2)	1.48 (0.14–15.24)

Abbreviations: CI, confidence interval; OHPC, α-hydroxyprogesterone caproate; RR, relative risk.
[a]Relative risk is from the CMH test adjusted for gestational age at randomization stratum.
[b]Denominator is number of patients who received study drug. Fetal/early infant death is defined as a miscarriage, stillbirth, or neonatal death through 28 days of life occurring in a live-born neonate at < 24 weeks of gestation.
[c]Denominator is number of patients who received study drug and were randomized $20^{0/7}$ weeks of GA. Miscarriage is defined as spontaneous delivery from $16^{0/7}$ to $19^{6/7}$ weeks of gestation.
[d]Denominator is number of patients who received study drug and were pregnant beyond ≥ $20^{0/7}$ weeks of GA. Stillbirth is defined as antepartum or intrapartum death from $20^{0/7}$ weeks of gestation through term.
[e]Denominator is number of patients who received study drug and did not have a miscarriage or stillbirth. Patients with missing data are assumed not to have the specified outcome.

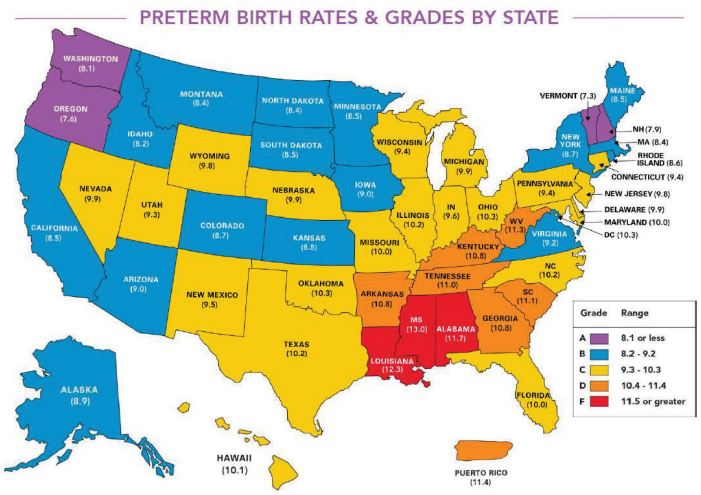
NCHS Data Brief ■ No. 318 ■ August 2018

Green 2016
Blue 2017

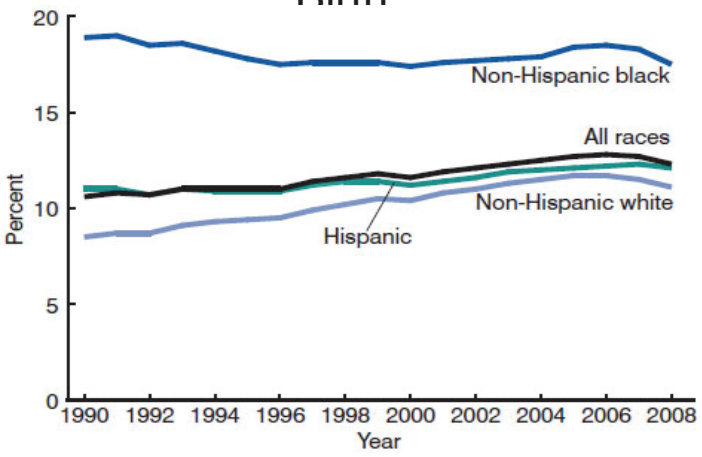
Figure 4. Preterm birth rates, by age of mother: United States, 2016 and 2017



†Significant increase from 2016 (p < 0.05).
NOTE: Figures may not equal totals due to rounding. Preterm is less than 37 completed weeks of gestation, early preterm is less than 34 weeks, and late preterm is 34 to 36 weeks. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db318_table.pdf#4.
SOURCE: NCHS, National Vital Statistics System, Natality.



Racial Disparity & Preterm Birth



Term vs Preterm Birth pathways? Accelerated Parturition: Same Sequence at a Faster Rate

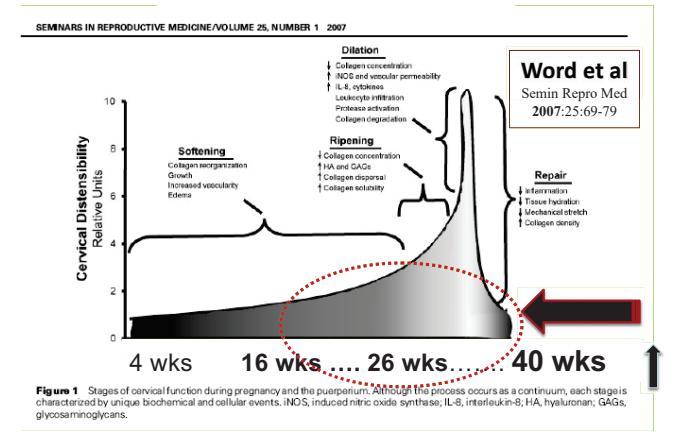
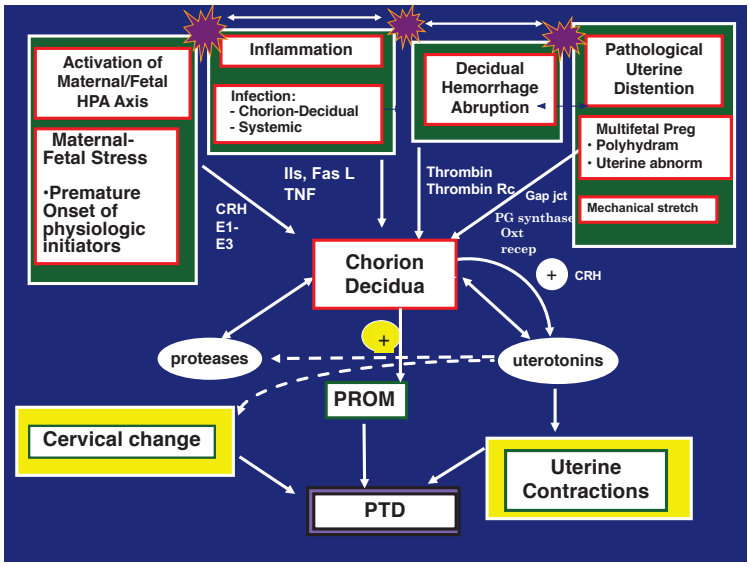
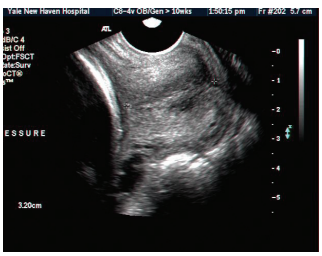


Figure 1 Stages of cervical function during pregnancy and the puerperium. Although the process occurs as a continuum, each stage is characterized by unique biochemical and cellular events. iNOS, induced nitric oxide synthase; IL-8, interleukin-8; HA, hyaluronan; GAGs, glycosaminoglycans.



Cervical Length

- Transvaginal or labial
- Bladder empty
- Image at least 1/2 of the screen
- Internal and external os both visible
- Canal: faint line of echodensity or echolucency



JAMA | Original Investigation

Predictive Accuracy of Serial Transvaginal Cervical Lengths and Quantitative Vaginal Fetal Fibronectin Levels for Spontaneous Preterm Birth Among Nulliparous Women

- 9410 nulliparous women with singleton pregnancies screened with CL and FFN
- 3 study visits: 6- 13 6/7; 16-22 6/7; 22-30 6/7 weeks
- CL at 22 to 30 weeks identified only 23.3% of sPTB < 37weeks.
- CL of 25 mm or less at 16 and 22 weeks identified only 8.0% of sPTB
- Should not be used in routine clinical care in nulliparous women.

Esplin et al, JAMA, 2017

Unproven Technologies in Maternal-Fetal Medicine and the High Cost of US Health Care

Steven L. Bloom, MD; Kenneth J. Leveno, MD

- Health care in the U.S. accounts for 17.8% of the country's total GDP
- Total health care spending—$3.2 trillion—equated to an $10,000 per person
- Universal cervical length screening would incur approximately $175 million in actual health care expenditures per year

JAMA, 2017

Management of Short Cervix During Second Trimester Sonogram

ACOG Practice Bulletin Prediction and Prevention of Preterm Birth 2018

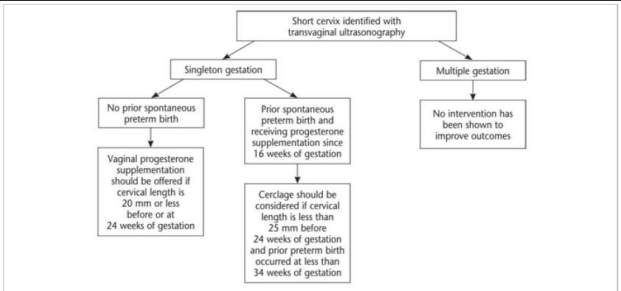
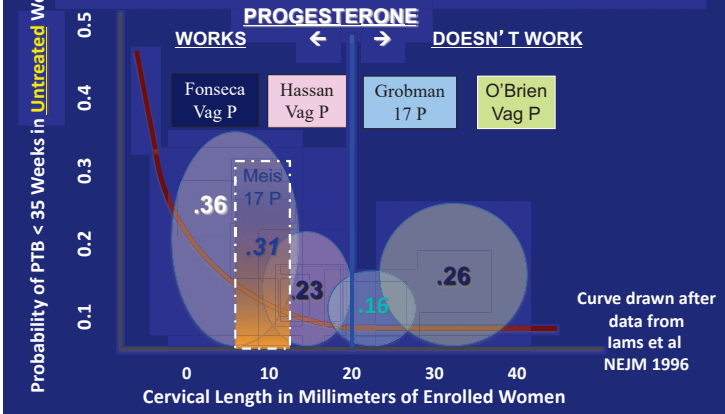


Fig. 1. Algorithm for the management of short cervical length in the second trimester.

- ***Does cerclage placement or progesterone treatment decrease the risk of preterm birth in women with multiple gestations?***

Available data regarding the efficacy of cerclage placement, progesterone supplementation, or both for the reduction of preterm birth risk in women with multiple gestations with a short cervical length with or without a prior preterm birth do not support their use (67). Cerclage may increase the risk of preterm birth in women with a twin pregnancy and ultrasonographically detected cervical length less than 25 mm and is not recommended. In a meta-analysis of randomized trials, cerclage performed in women with a twin pregnancy and a cervical length less than 25 mm was actually associated with a significant twofold increase in the rate of preterm birth (RR, 2.2; 95% CI, 1.2–4) (59). Progesterone treatment does not reduce the incidence of preterm birth in women with twin or triplet gestations and, therefore, is not recommended as an intervention to prevent preterm birth in women with multiple gestations (68–72). Currently, no data are available regarding the efficacy of any other interventions to reduce the risk of preterm birth in women with multiple gestations and a short cervix, and the use of any such alternative measures cannot be recommended outside of formal clinical trials.

Cervical Length in Women Enrolled In Studies of Progestin Prophylaxis of Preterm Birth

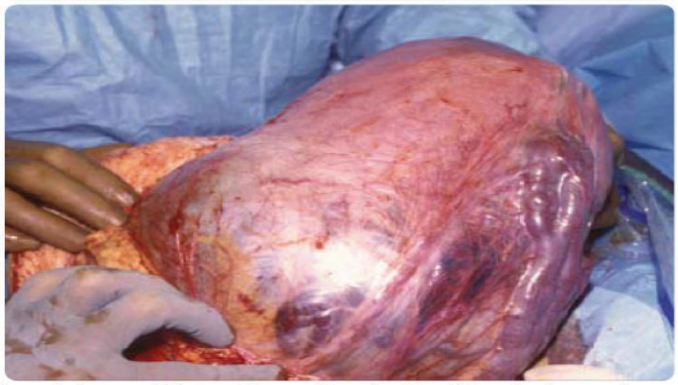


Curve drawn after data from Iams et al NEJM 1996

Preventing Preterm Birth

- Contraception
- Multiple gestations
- Short inter-delivery interval
- Smoking
- Illicit drug use
- Low pre-pregnancy weight
- Poor nutritional status
- Stop unindicated delivery

FIGURE 2
Placenta percreta with bladder invasion at cesarean delivery



Lower uterine segment is bulbous with areas of hemorrhage beneath visceral peritoneum and prominent distended vessels. Fundal and posterior hysterotomy was performed to avoid disruption of placenta before hysterectomy was completed.

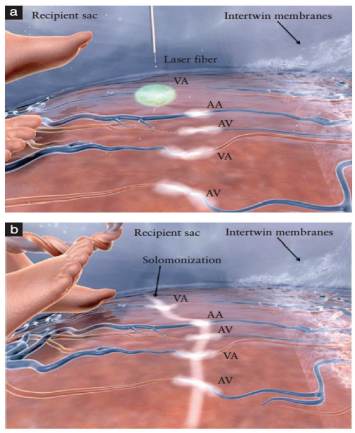
SMFM. Placenta accreta. Am J Obstet Gynecol 2010.

Placenta Accreta

- Reported incidence of abnormal placental attachment has increased from 0.8 per 1000 births (1980s) to 3 per 1000 births in the last decade.
- The increasing rate has been attributed to increases in:
  - Cesarean rate
  - advanced maternal age
  - other prior uterine surgery or curettage
  - irradiation
  - ablation
  - hypertensive disorders of pregnancy
  - maternal smoking

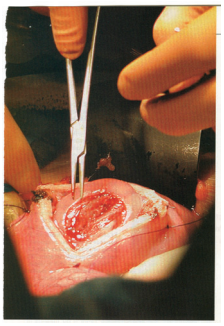
Belfort MA. Am J Obstet Gynecol. 2010 Nov;203(5):430-9. Flood KM et al. Am J Obstet Gynecol 2009;200:632.e1-6. Imudia AN et al. Arch Gynecol Obstet 2009; 280:619-23. Wu S, et al. Am J Obstet Gynecol 2005;192:1458-61. Clark SL, et al. Obstet Gynecol 1985;66:89-92. Read JA, et al. Obstet Gynecol 1980;56:31-4. Silver RM, et al. Obstet Gynecol 2006;107:1226-32.

Laser Ablation of Placenta

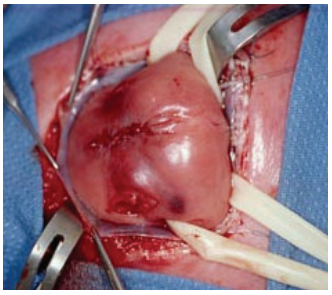


In utero correction of NTD

In utero repair



After NTD repair



Preterm Birth Risk Factors (March of Dimes)

Historical, Genetic, Social, Obstetrical, environmental Risk Factors

- History of preterm birth
- Multiple Gestation
- Uterine or cervical anomalies
- Family history of preterm birth
- Short interval between pregnancy (<18 months)
- No prenatal care
- Poor weight gain
- Fertility treatment
- Birth defects
- Smoking/Alcohol/drugs
- A lot of Stress
- Low socioeconomic status
- Domestic violence
- Pollution/lead/ radiation/paint
- < 17 yrs or >35 yrs

Medical Risk Factors

- Overweight/underweight, eating disorders
- Connective tissue disorders (EDS or vacular EDS)
- Diabetes
- Hypertension/preeclampsia
- Infection, STDs
- Intrahepatic cholestasis of pregnancy
- Thrombophilia

Prediction and Prevention of Recurrent Spontaneous Preterm Birth
Spong CY. Obstet Gynecol 2007; 110:405-15

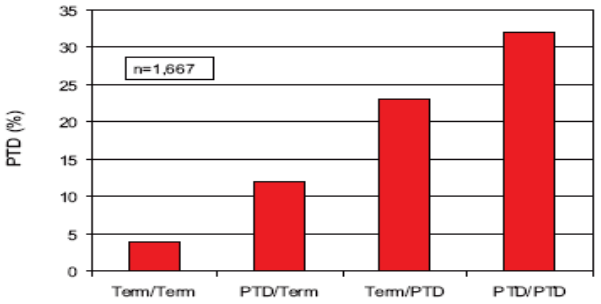


Fig. 4. The risk of subsequent preterm birth is related to the outcome of the prior pregnancy, with the lowest risk occurring when a woman has had two prior term births and the highest risk when she has had two prior preterm births. PTD, preterm delivery. Data from Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. Br J Obstet Gynaecol 1985;92: 921–8.

Recurring Complications in Second Pregnancy*

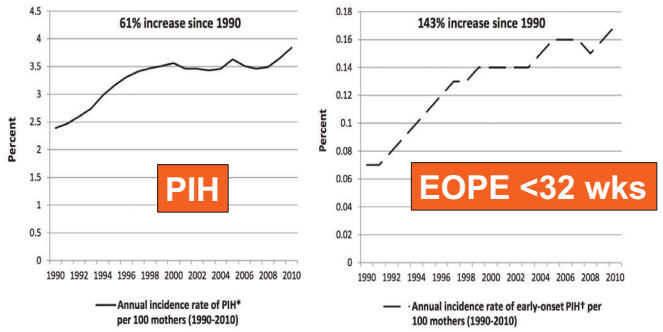
GA	PTD 1st preg %	PTD 2nd preg %	OR	PE 2nd preg %	OR	SGA 2nd preg %	OR	ABR 2nd preg %	OR
≥ 37	96.1	2.7	1	1.1	1	2.1	1	0.7	1
32-36	3.4	14.7	6.12	1.8	1.6	3.2	1.63	1.3	1.84
28-32	0.3	25.4	12.0	2.5	2.18	4.6	2.17	1.9	2.67
20-27	0.1	26.0	13.1	3.2	2.96	4.3	2.23	1.9	2.17

1st preg HTN disorders 5% Preeclampsia 4.1% GHTN 0.9%

Lykke J, Paidas MJ, Langhoff-Roos J. Recurring Complications in Second Pregnancy. *Obstet Gynecol*. 2009 Jun;113(6):1217-24. *p val <.001 OR Stillbirth ns

The Toll of Preeclampsia

- 6 to 8 percent of all pregnancies.
- >200,000 pregnancies in U.S. each year.
- 70 maternal deaths in the U.S. each year
- 50,000 maternal deaths per year worldwide (2nd to VTE)
- Between 0.15 and 0.2 percent of pregnancies in Western countries will be complicated by very early preterm preeclampsia, or 6,000 to 8,000 pregnancies in the US each year.



Note: *Incidence rates measure pregnancy-related hypertension (PIH), excluding renal disease, diabetes, and chronic hypertension. †Early-onset PIH is then restricted to cases with onset at less than 32 weeks GA. Data were obtained from the National Center for Health Statistics Natality dataset.

Fig. 1 Annual incidence rate of all preeclampsia and early-onset preeclampsia (1990–2010). Note: Data were obtained from the National Center for Health Statistics Natality dataset. *Incidence rates measure pregnancy-related hypertension (PIH), excluding renal disease, diabetes, and chronic hypertension. †Early-onset PIH is then restricted to cases with onset at less than 32 weeks gestational age.

Shih T, Peneva D, Xu X, Sutton A, Triche E, Ehrenkranz RA, Paidas M, Stevens W. The Rising Burden of Preeclampsia in the United States Impacts Both Maternal and Child Health. Am J Perinatol. 2015 Oct 19. PMID: 26479171

Table 1 Summary of estimates of relative risk for select risk factors of preeclampsia

Category	Risk factors	Unadjusted relative risk (95% CI)
Pregnancy-specific factors	Nulliparity[2,110]	2.91 (1.28–6.61)
	Partner-related factors (new paternity, limited sperm exposure, e.g., barrier contraception)[2,110,111]	3.10 (1.59–6.73) lack of exposure to sperm cells before contraception via intracytoplasmic sperm with surgically-obtained sperm versus in vitro fertilization with ejaculated sperm
	Multifetal gestation[2]	2.93 (2.04–4.21) twin versus singleton
		2.83 (1.25–6.40) triplet versus twin
Preexisting maternal conditions	Obesity and higher body mass index[2,23,110]	1.55 (1.28–1.88) increased versus normal BMI first antenatal visit
		2.47 (1.66–3.67) increased versus normal BMI before pregnancy
	Pregestational diabetes[2,35]	3.56 (2.54–4.99)
	Chronic hypertension[2,23,110]	3.40 (2.8–4.1)
	Antiphospholipid antibody syndrome[2,112]	9.72 (4.34–21.75)
	Chronic hypertension[113]	1.60 (1.10–2.30) for women with chronic hypertension for at least 4 y
	High blood pressure[110]	2.37 (1.78–3.15) systolic ≥ 130 mm Hg versus < 130 mm Hg at first antenatal visit
	Personal history of preeclampsia[23,35,110]	7.19 (5.85–8.83)
	Family history of preeclampsia[2]	2.90 (1.70–4.93)
	Smoking during pregnancy[2,114–116]	0.68 (0.67–0.69)
Populations with higher risks	Age < 20 y[2,13,20]	1.65 (1.47–1.86)
	Age > 35 y[2,13,20,110]	1.68 (1.23–2.29) primiparas
		1.96(1.34–2.87) multiparas
	Women delivering in Southern US[13]	1.63 (0.96–2.78)

Abbreviations: BMI, body mass index; CI, confidence interval; US, United States.
Note: Table expanded based on Duckitt and Harrington (2005).[10]

Shih T, Peneva D, Xu X, Sutton A, Triche E, Ehrenkranz RA, Paidas M, Stevens W. The Rising Burden of Preeclampsia in the United States Impacts Both Maternal and Child Health. Am J Perinatol. 2015 Oct 19. PMID: 26479171

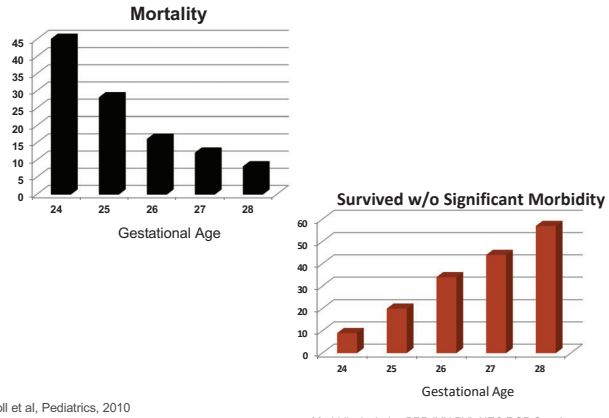
Preeclampsia at < 30 weeks

United States Health Care Burden

- Estimated rate of 0.15-0.2%: 6-8,000 cases/year
- Major cause of maternal and perinatal mortality/morbidity
  - Acute complications
  - Long-term morbidity from serious complications
  - Maternal and fetal programming
- Early Onset PE <32 wks: 143% increase since 1990
- Delivery Indication: Maternal 65.7%; Fetal 19.4%; Both 14.8%

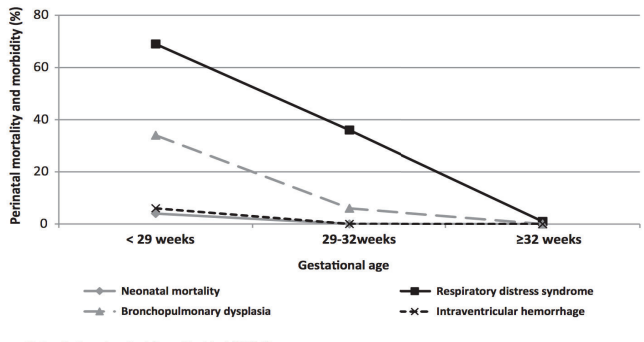
Shih T, Peneva D, Xu X, Sutton A, Triche E, Ehrenkranz RA, Paidas M, Stevens W. The Rising Burden of Preeclampsia in the United States Impacts Both Maternal and Child Health. Am J Perinatol. 2015 Oct 19.

Mooney SS, Lee RM, Tong S, Brownfoot FC. Expectant management of severe preterm preeclampsia: a comparison of maternal and fetal indications for delivery.J Matern Fetal Neonatal Med. 2016 Dec;29(23):3821-6.



Stoll et al, Pediatrics, 2010

Morbidity includes BPD,IVH,PVL,NEC.ROP,Sepsis

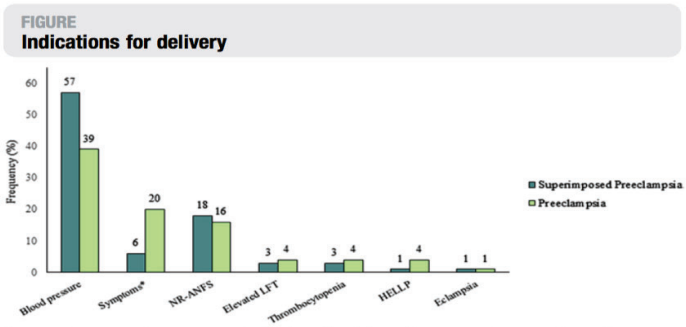


Note: Data extracted from Haddad (2004).

Fig. 2 Perinatal mortality and morbidity according to gestational age for children born to women with preeclampsia (1996–2001). Note: Data extracted from Haddad et al (2004).[80]

Shih T, Peneva D, Xu X, Sutton A, Triche E, Ehrenkranz RA, Paidas M, Stevens W. The Rising Burden of Preeclampsia in the United States Impacts Both Maternal and Child Health. Am J Perinatol. 2015 Oct 19. PMID: 26479171

Preterm Preeclampsia <37 wk



Bar graph representing common indications for delivery in pregnancies complicated by superimposed preeclampsia (*blue*) and preeclampsia (*green*) expectantly managed in hospital setting. The frequencies do not add up to 100% due to missing or other indications for delivery.

LFT, liver function testing; *HELLP*, hemolysis, elevated liver enzymes, and low platelet count; *NR-ANFS*, nonreassuring antenatal fetal surveillance.

*Persistent neurological or gastrointestinal symptoms.

Valent. Expectant management of preeclampsia. Am J Obstet Gynecol 2015.

Valent *et al* 2015 AJOG

Table 3 Summary of infant adverse health outcomes associated with preterm birth

Outcomes category	Examples
Neonatal mortality	65–67,70–72,74,124
Neonatal morbidity	Intraventricular hemorrhaging, bronchopulmonary dysplasia, periventricular leukomalacia, necrotizing enterocolitis, respiratory distress syndrome, retinopathy of prematurity, sepsis, meningitis, pulmonary hemorrhage, neonatal intensive care unit admission, cesarean section, jaundice, hematological abnormalities (polycythemia, neutropenia, thrombocytopenia) 51,80,90,123,124
Neurodevelopmental/behavioral effects	Lower IQ or cognitive impairments in childhood 57,60–62
	Disorders of executive functioning, lower scores of cognitive function, processing speed, and executive functioning in adulthood 63–65,125
	Cerebral palsy 51,126,127
	Depression, hyperactivity, attention problems, anxiety problems, *schizophrenia*, behavioral problems, and other psychiatric problems 67,128–133
Physical effects	Cardiovascular disease, increased blood pressure, stroke, and coronary heart disease 52,53,76,134–136
	Respiratory problems (reduced respiratory health at six years and in adulthood, asthma, chronic lung disease of prematurity) 54,55,58,59
	Lowered bone density in adulthood 137
	Decreased growth at six years 54,55,58,59
Sensory impairment	Blindness, deafness 60,61,63,126,127,138,139
Family and societal effects	Socioemotional delays at 2 y, cognitive delays at 2 y, lower rates of high school completion 140–142

Shih T, Peneva D, Xu X, Sutton A, Triche E, Ehrenkranz RA, Paidas M, Stevens W. The Rising Burden of Preeclampsia in the United States Impacts Both Maternal and Child Health. Am J Perinatol. 2015 Oct 19. PMID: 26479171

Evaluation & Management of Women at Risk of Preeclampsia Recurrence

Preconception
Identify Risk Factors (CHTN, DM, obesity etc)
Review prior pregnancy
Perform baseline metabolic profile & urinalysis
Optimize maternal health
Supplement with folic acid

First Trimester
Perform: US, metabolic profile, CBC, urinalysis
Folic acid supp
Offer First trimester screening
Offer LDA in women with preeclampsia with delivery <34 wks, or occurring in >1 pregnancy & discuss w other women

Second Trimester
Counsel about signs/symptoms of preeclampsia
Monitor for signs/symptoms of preeclampsia
Monitor BP at visits, nursing contacts, or at home
Perform US at 18-22 wks, uterine art Doppler
Hospitalize for severe Gestational HTN, IUGR, or recurrent preeclampsia.

Third Trimester
Monitor for signs/symptoms of preeclampsia
Monitor BP at visits, nursing contacts, or at home
Perform the following as indicated by clinical situation: Lab testing; serial US and amniotic fluid asssessment; umbilical artery Doppler w non stress test, biophysical profile, or both

Hypertension in Pregnancy Task Force 2013

Combined screening for preeclampsia and small for gestational age at 11-13 weeks.

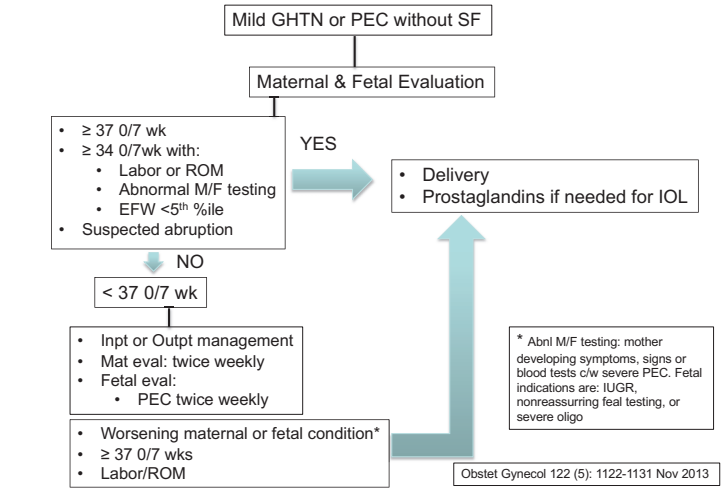
Maternal characteristics, Uterine artery PI, mean arterial pressure, serum pregnancy associated plasma protein-A (PAPP-A, and placental growth factor (PIGF)

Outcome	Detection rate (%)
Early PE	95.3
Late PE	45.6
Preterm SGA	55.5
Term SGA	44.3

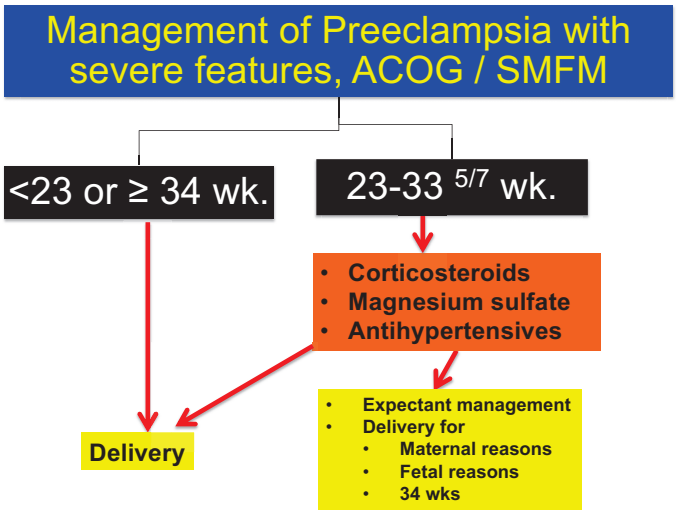
Screen pos: Early PE 1:200 Screen pos: Preterm SGA (del <37w) 1:150 FPS 10.9%
N= 57,458 unaffected; PE n=1,426; SGA =3,168

Poon LC, Syngelaki A, Akolekar R, Lai J, Nicolaides KH.Fetal Diagn Ther. 2013;33(1):16-27.

Management of mild gestational HTN or Preeclampsia without severe features



Management of Preeclampsia with severe features, ACOG / SMFM



Latency: Duration of Expectant Management

- Median latency ranges from 7-14 days (Magee *et al.* 2009 Hypertens Preg)
- Recent cohort (n= 559) restricted to 24-29$^{6/7}$ weeks' (Sutton *et al*. 2016 SMFM):
  - Mean 6.2 days
  - Median 4.0 days
  - Range: 1-58 days

Emerging Therapies for the Treatment & Prevention of Preeclampsia

- Prevention
- Treatment

Low Dose Aspirin Therapy

Low dose aspirin therapy for the prevention of preeclampsia was studied by the US Preventive Services Task Force in a systematic evidence review and published in September 2014. Initiation of therapy is recommended by both USPSTF and ACOG between 12 weeks and 28 weeks of gestation for the following high risk indications:

- History of preeclampsia, especially if accompanied by an adverse outcome
- Multifetal gestation
- Chronic hypertension
- Diabetes (Type 1 and Type 2)
- Renal disease
- Autoimmune disease (such as SLE, antiphospholipid syndrome)

The presence of > 2 moderate risk factors may also be an indication for the use of low dose aspirin.

- Nulliparity
- Obesity (body mass index >30 kg/m2)
- Family history of preeclampsia (mother or sister)
- Sociodemographic characteristics (African American race, low socioeconomic status)
- Age ≥ 35 y
- Personal history factors (e.g., low birthweight or small for gestational age, previous
- adverse pregnancy outcome, >10-y pregnancy interval)

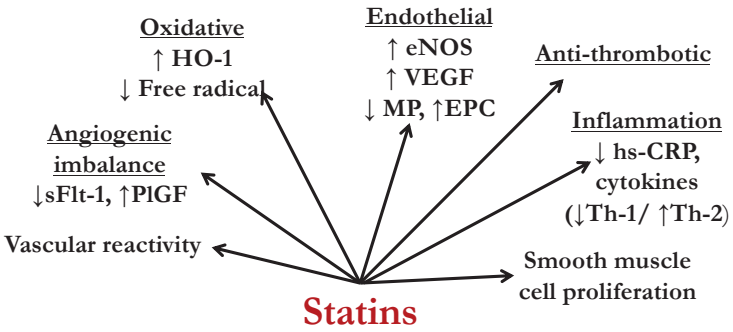
Low Dose Aspirin: Predictions

Outcome	No Aspirin	ACOG	US Preventive Services Task Force	Universal
No. women treated	0	14,000	940,800	4,000,000
Aspirin Cost ($)	0	70,000	4,704,000	20,000,000
Preeclampsia (n)	167,200	166,720	153,160	152,240
Total incremental cost savings ($)^	-	12,909,480	364,495,520	-12,424,360

^ compared to prior approach

Werner EF, Hauspurg AK, Rouse DJ. A Cost-Benefit Analysis of Low-Dose Aspirin Prophylaxis for the Prevention of Preeclampsia in the United States. Obstet Gynecol. 2015 Dec;126(6):1242-50

Statins: Biological Plausibility



Hazuku et al. J Cardiovasc Pharmacol 2008
Laufs et al. PNAS 1998
Endres et al. PNAS 1998
Greenwood et al. Nat Rev Immun. 2006
Shaw et al. Cardiology 2009

Lee at al. circulation 2004
Grosser et al. Free Rad Biol Med 2004
Cudmore et al. Circulation 2007
Ridker et al. N Eng J Med 2008
Marrs CC, Constantine MM Clin Obstet Gynecol 2016

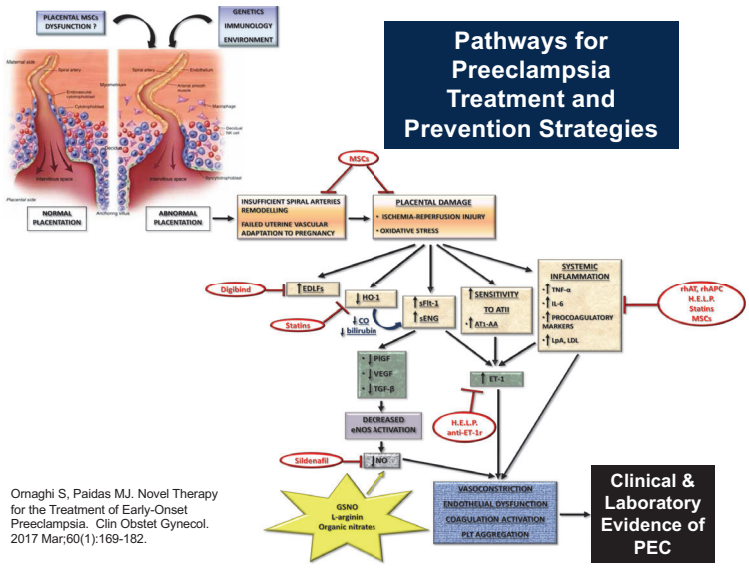
Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial.

Costantine MM, et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Obstetric-Fetal Pharmacology Research Units Network. Am J Obstet Gynecol. 2015 Dec 23.

Intervention: Pravastatin 10mg or placebo daily from 12 0/7- 16 6/7 wks until del

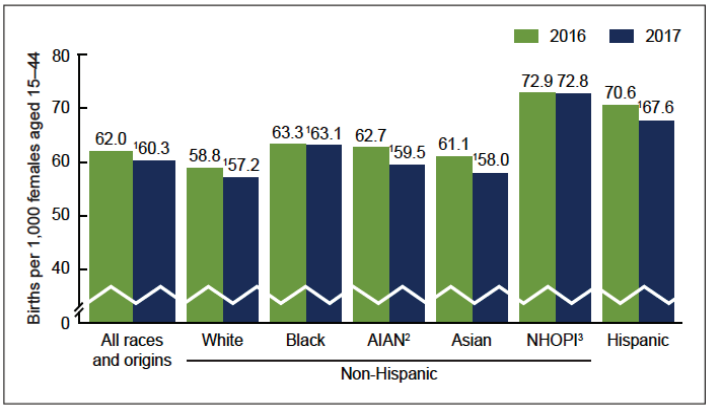
Outcome	Placebo n=10 (%)	Pravastatin n=10 (%)
Preeclampsia	4 (40)	0
Severe Feat	3 (30)	0
GA Del, wks	36.7 +/- 2.1	37.7 +/- 0.9
Ind Del <34wk	1 (10)	0
BW,g	2877 +/-630	3018 +/- 260
NICU LOS ≥ 48 hr	3 (30)	0

Cohort 2: Pravastatin 20mg daily
MFM Network Study under consideration: Pravastatin to Prevent Recurrent PEC <36 wk, n 1760 patients

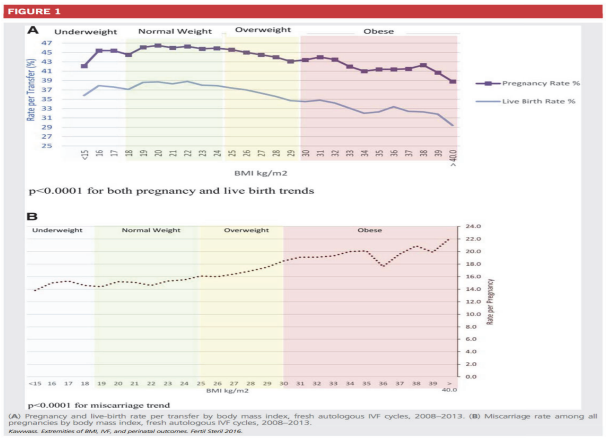


Ornaghi S, Paidas MJ. Novel Therapy for the Treatment of Early-Onset Preeclampsia. Clin Obstet Gynecol. 2017 Mar;60(1):169-182.

Figure 1. General fertility rates, by race and Hispanic origin of mother: United States, 2016 and 2017



IVF and BMI, Fert Sterility 2016



Kawwass JF et al. Fert Steril 2016

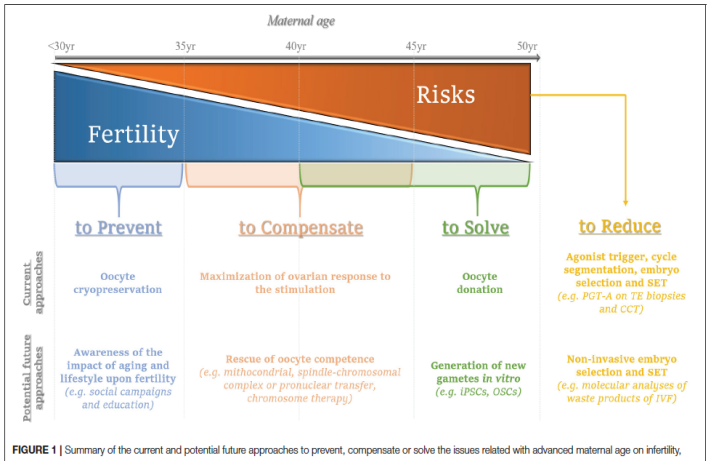
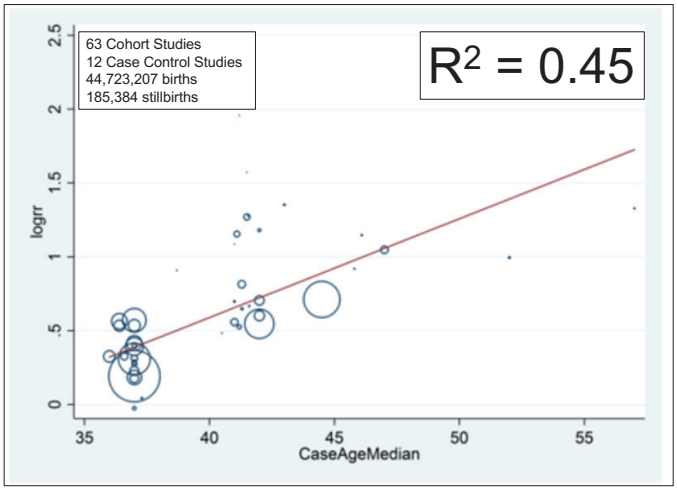


FIGURE 1 | Summary of the current and potential future approaches to prevent, compensate or solve the issues related with advanced maternal age on infertility.

Ubaldi FM et al. Frontiers in Endocrinology. Feb 2019

Stillbirth is positively correlated to Increasing Maternal Age



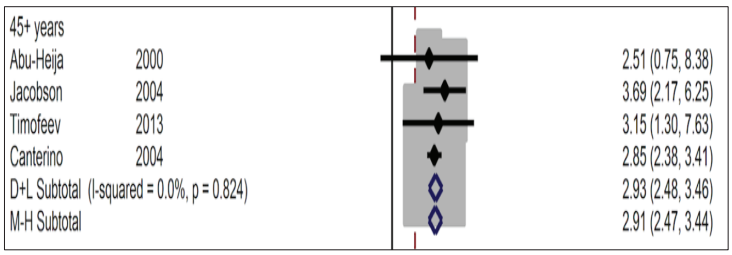
Lean SC et al. PLoS One 12(10):e0186287

AMA & Adverse Pregnancy Outcomes: Systematic Review and Meta-analysis

AMA & Adverse Pregnancy Outcomes: Systematic Review and Meta-analysis

Meta-analysis
63 cohort studies
12 case control

45+ yrs



Lean SC et al. PLoS One 12(10):e0186287

The effect of fertility treatment on adverse perinatal outcomes in women aged at least 40 years

8244 singleton preg

IVF	2.8%
Ovul Ind	1.0%
Spont	96.2 %

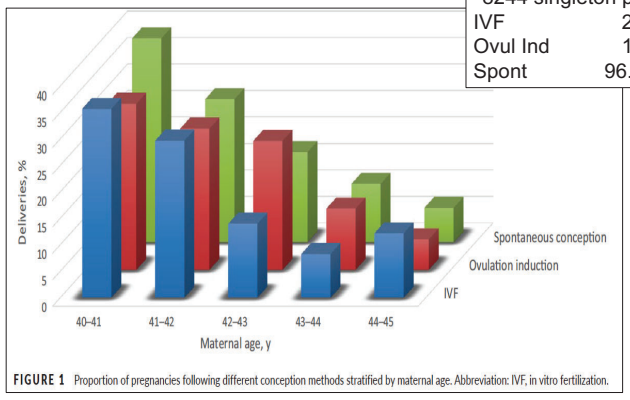


FIGURE 1 Proportion of pregnancies following different conception methods stratified by maternal age. Abbreviation: IVF, in vitro fertilization.

Beer Sheva, Israel Jan 1, 1991- Dec 31, 2013

Harlev A et al. Int J Gynecol Obstet 2018;140: 98-104

The effect of fertility treatment on adverse perinatal outcomes in women aged at least 40 years

Variable	IVF n (%)	Ovul Induction n (%)	Spont Preg n (%)	p value
IUFD	2 (.9)	2 (2)	110 (1.4)	.607
SGA	14 (6.1)	9 (10)	329 (4.1)	.006
PPH	3 (1.3)	0	55 (.7)	.401
PTB	53 (23.1)	9 (10)	809 (10.2)	<.001
GDM	58 (25.3)	32 (37)	1516 (19.1)	<.001
HTN Disorders	36 15.7	16 (19)	908 (11.5)	.017
Cesarean del	162 (70.7)	49 (57)	2116 (26.7)	<.001

Harlev A et al. Int J Gynecol Obstet 2018;140: 98-104 Beer Sheva, Israel Jan 1/91- 12/ 31, 13

63 Cohort Studies
12 Case Control Studies

Meta-analysis of secondary outcomes

44,723,207 births
185,384 stillbirths

Cond	Overall OR (95% CI)	≥35	35-39	≥40	40-49	≥45	≥50	R^2
SGA	1.16 (1.06-1.27)	1.22 (.86-1.73)	1.06 (.86-1.31	1.20 (1.07-1.33)	.97 (.96-.98)	1.57 (1.17-2.10)	NS	.00 07
LBW (<2.5g)	1.37 (1.26-1.50)	1.44 (1.09- 1.50)	1.10 (.83-1.46)	1.46 (1.18-1.80)	1.40 (1.38-1.42)	2.05 (1.67-2.52)	1.33 (1.02-1.74)	.10
PTB	1.45 (1.38-1.53)	1.52 (1.26-1.83)	1.28 (1.17-1.40)	1.52 (1.44-1.61)	1.28 (1.26-1.30)	2.01 (1.50-2.68)	1.17 (.9-1.54)	.17
NND*	1.48 (1.30-1.67)	2.29 (.93-5.66)	1.21 (1.04-1.410	1.41 (1.14-1.75)	1.62 (1.38-1.90)	1.95 (1.24-3.06)	10.26 (5.85-17.97)	.81
PEC	1.99 (1.65-2.36)	1.18 (.86-1.60)	1.63 (1.09-2.44)	2.42 (1.85-3.55)	1.65 (1.09-2.48)	3.67 (1.12-11.97)	2.47 (1.83-3.34)	.11
Abr	1.52 (1.35-1.70)	1.17 (.73-1.96)	1.38 (1.13-1.69)	2.02 (1.54-2.65)	1.44 (1.09-1.91)	2.29 (.93-5.65)	1.55 (.64-3.74)	.12
GDM	2.85 (2.46-3.32)	2.85 (2.46-2.12)	1.95 (1.27-3.02)	3.76 (2.99-4.73)	3.82 (2.89-5.04)	4.81 (2.65-8.72	NS	.44

Lean SC. . PLoS One 2017; 12(10):e0186287

* Only NICU Admission and NND are significantly correlated to increasing maternal age.

Pregnancy at very advanced maternal age: a UK population-based cohort study

Comparison N= 812
Median age 31 (16-46)

Older women N= 406
Median age 49 (48-61)

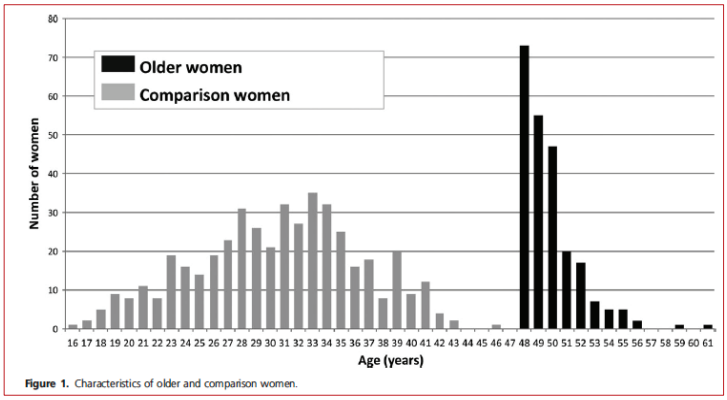


Figure 1. Characteristics of older and comparison women.

Fitzpatrick KE et al. BJOG 2016; 124:1097- 1106

Pregnancy at very advanced maternal age: a UK population-based cohort study

Characteristic	Older (%)	Comparison (%)	p val
Obese	23	19	.0318
Nulliparous	53	44	.0299
Preexisting medical conditions	44	28	.0001
Multiple gestation	18	2	<.0001
Achieved with ART	78	4	<.0001

Fitzpatrick KE et al. BJOG 2016; 124:1097- 1106

Pregnancy at very advanced maternal age: a UK population-based cohort study

Outcome	Older (%)	Comparison (%)	Unadj OR (95% CI)	Unadj p val	Model 4 (singleton)
PEC	6	2	2.66 (1.15-6.16)	.0225	.8483
GDM	18	4	5.41 (3.04-9.65)	< .0001	.0151
PPH PPH w transfusion	26 6	15 2	1.95(1.32- 2.88) 3.67 (1.52-8.90)	.0009 .0039	.0279 .0308
Labor Induction	31	29	1.1 (.78-1.55)	.5945	.056
Cesarean del	78	33	7.29 (5.03-10.55)	< .0001	.0024

Fitzpatrick KE et al. BJOG 2016; 124:1097- 1106

Pregnancy at very advanced maternal age: a UK population-based cohort study

Table 3. (Continued)

	Number (%)* of older women (n = 233)	Number (%)* of comparison women (n = 454)	Unadjusted OR (95% CI)	P-value	Model 1 Adjusted OR (95% CI)	P-value	Model 2 Adjusted OR (95% CI)	P-value	Model 3 Adjusted OR (95% CI)	P-value	Model 4 Adjusted OR (95% CI)	P-value
Gestational age at delivery (weeks)												
Term (37+ weeks)	176 (78)	420 (93)	1		1		1		1		1	
Iatrogenic preterm (<37 weeks)	32 (14)	17 (4)	**4.49 (2.43–8.30)**	**<0.0001**	**4.49 (2.39–8.43)**	**<0.0001**	**4.23 (2.19–8.18)¥**	**<0.0001**	1.01 (0.30–3.45)#	0.9845	1.72 (0.40–7.34) ¥,#	0.4671
Spontaneous preterm (<37 weeks)	18 (8)	17 (4)	**2.53 (1.27–5.02)**	**0.0081**	**2.44 (1.17–5.09)**	**0.0169**	**2.34 (1.09–5.00)¥**	**0.0287**	1.11 (0.28–4.45)#	0.8832	0.75 (0.14–4.15) ¥,#	0.7431
Admitted to ITU												
No	224 (97)	453 (100)	1		1		1		1		1	
Yes	6 (3)	1 (0)	**12.13 (1.45–101.40)**	**0.0212**	**10.98 (1.28–94.01)**	**0.0288**	**10.96 (1.28–94.17)**	**0.0291**	**33.53 (2.73–412.24)**	**0.0061**	**37.53 (2.98–472.18)**	**0.005**
In nulliparous women												
Caesarean delivery												
No									1			
Yes									9.90 (3.64–26.92)	<0.001		
In women parity 1+												
Caesarean delivery												
No									1			
Yes									0.71 (0.31–1.66)	0.431		

Model 1: Adjusted for socio-demographic factors (Ethnic group, marital status, socio-economic group, body mass index and smoking status).
Model 2: Adjusted for variables included in model 1 plus previous medical history (previous uterine surgery not including previous caesarean section and previous or preexisting medical conditions where ¥ is shown, or just previous or preexisting medical conditions where ¥ is not shown).
Model 3: Adjusted for variables included in model 2 plus pregnancy related factors (parity, multiple pregnancy, how conceived and previous caesarean delivery where # is shown, or just parity, multiple pregnancy and how conceived if # is not shown.
Model 4: Women with singleton pregnacies only, adjusted for socio-demographic factors (Ethnic group, marital status, socio-economic group, body mass index and smoking status) plus previous medical history (previous uterine surgery not including previous caesarean section and previous or preexisting medical conditions where ¥ is shown, or just previous or preexisting medical conditions where ¥ is not shown) plus pregnancy related factors (parity, how conceived and previous caesarean delivery where # is shown, or just parity and how conceived if # not shown).
Statistically significant values are bolded.
*Percentage of individuals with complete data.

Fitzpatrick KE et al. BJOG 2016; 124:1097- 1106

ICSI Cycles with surgically recovered sperm
Retrospective Cohort 24, 763 IVF Cycles,
SART CORS Database 2004- 2015

Pregnancy Outcome	<30y	30-34y	35-37y	38-42y	>42y	p val
Live Birth (% per ET)	58.1	54.1	47.9	37.3	19.0	<0.001
# Liveborn, mean (SD)	1.37 (.53)	1.35 (.52)	1.29 (.48)	1.24 (.47)	1.0 (0)	0.002
Stillbirth (% per IUP)	.5	.8	.2	.3	0	.45
Abortion (% per IUP)	9.1	11.0	15.8	26.2	50.0	<0.001

Number of Blastocysts transferred, n= 5094

Mahesan AM et al. Journal Assist Reprod Genet 2018; 35:1239-1246

ICSI Cycles with surgically recovered sperm
Retrospective Cohort 24, 763 IVF Cycles,
SART CORS Database 2004- 2015

Neonatal Outcome	<30y	30-34y	35-37y	38-42y	>42y	p val
Number Live Birth (% total birth)	1574 (66.8)	2708 (69.1)	1368 (73.7)	790 (92)	16 (80)	.026
GA Del (days), mean (SD)	271.5 (7.7)	272.2 (16.0)	271.4 (17.5)	270.5 (18.7)	270.9 (12.5)	.21
Term Delivery (%)	1182 (87.7)	.2033 (89.1)	1019 (88.2)	597 (87.9)	14 (100)	.69
Preterm Delivery (%)	165 12.3)	248 (10.9)	138 (11.8)	82 (12.1)	0	.69

Mahesan AM et al. Journal Assist Reprod Genet 2018; 35:1239-1246

Received: 10 September 2018 | Revised: 10 April 2019 | Accepted: 2 May 2019 | First published online: 21 May 2019

DOI: 10.1002/ijgo.12839

CLINICAL ARTICLE

Obstetrics

WILEY GYNECOLOGY OBSTETRICS FIGO

Cluster analysis identifying clinical phenotypes of preterm birth and related maternal and neonatal outcomes from the Brazilian Multicentre Study on Preterm Birth

Renato T. Souza[1] | Jose G. Cecatti[1,*] | Renato Passini Jr[1] | Rodolfo C. Pacagnella[1] | Paulo F. Oliveira[2] | Cleide M. Silva[2] | the Brazilian Multicentre Study on Preterm Birth study group[a]

Souza RT, Cecatti JG, Passini R Jr, Pacagnella RC, Oliveira PF, Silva CM; Brazilian Multicentre Study on Preterm Birth study group. Cluster analysis identifying clinical phenotypes of preterm birth and related maternal and neonatal outcomes from the Brazilian Multicentre Study on Preterm Birth. Int J Gynaecol Obstet. 2019 Jul;146(1):110-117. PMID: 31055833

TABLE 1 Definition of maternal, fetal, and placental conditions potentially associated with preterm birth.

Condition	Definition
Maternal	
Extrauterine infection during pregnancy	Prenatal care chart or medical record of syphilis, tuberculosis, HIV, HPV, hepatitis, febrile diarrhea, pneumonia, sinusitis, toxoplasmosis, genital herpes, asymptomatic bacteriuria, cystitis, pyelonephritis or sepsis during pregnancy
Clinical chorioamnionitis	Medical record of clinical chorioamnionitis
Maternal chronic disease	Medical record of history of diabetes, HIV, chronic hypertension, hypo-/hyperthyroidism, nephropathy, sickle cell disease or other chronic anemia, cardiopathy, pneumopathy, epilepsy, lupus, other collagenosis, chronic gastrointestinal, psychiatric, neurologic or orthopedic disease, neoplasms, thrombosis, thrombophilia, or bariatric surgery
Pre-eclampsia/eclampsia/HELLP syndrome	Medical record of pre-eclampsia, eclampsia and/or HELLP syndrome
Fetal	
Antepartum stillbirth	Antepartum stillbirth (>22 gestational weeks) before or after hospital admission
FGR (suspicious or confirmed)	Suspicious or confirmed FGR, including cases with ultrasound scan estimated fetal weight <10th percentile during prenatal care and neonates with birthweight small for gestational age
Perinatal sepsis	Medical record of clinical or laboratory diagnosis of neonatal sepsis
Multiple pregnancy	Pregnancy with more than one live fetus after 12 gestational weeks
Fetal anomaly	Suspicious (ultrasound findings of fetal anomaly) or confirmed (after delivery) minor or major fetal anomaly
Placental	
Early bleeding	Reported bleeding before 13 gestational weeks
Mid/late pregnancy bleeding	Reported bleeding after 14 gestational weeks
None	PTB cases with none of the above conditions

Abbreviations: FGR, fetal growth restriction; HPV, human papilloma virus; PTB, preterm birth.

Souza RT, Cecatti JG, Passini R Jr, Pacagnella RC, Oliveira PF, Silva CM; Brazilian Multicentre Study on Preterm Birth study group. Cluster analysis identifying clinical phenotypes of preterm birth and related maternal and neonatal outcomes from the Brazilian Multicentre Study on Preterm Birth. Int J Gynaecol Obstet. 2019 Jul;146(1):110-117. PMID: 31055833

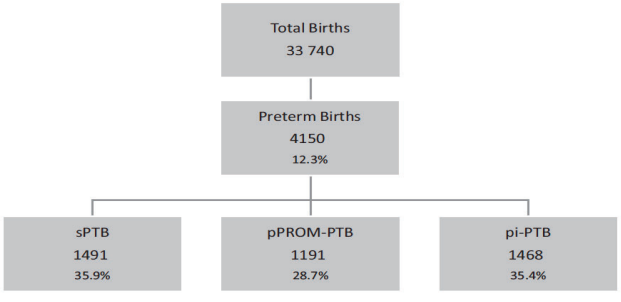


FIGURE 1 Flowchart showing the study population of the Brazilian Multicentre Study on Preterm Birth. The preterm birth subtypes were spontaneous preterm birth (sPTB); preterm birth due to preterm premature rupture of membranes (pPROM-PTB); and provider-initiated preterm birth (pi-PTB).

Souza RT, Cecatti JG, Passini R Jr, Pacagnella RC, Oliveira PF, Silva CM; Brazilian Multicentre Study on Preterm Birth study group. Cluster analysis identifying clinical phenotypes of preterm birth and related maternal and neonatal outcomes from the Brazilian Multicentre Study on Preterm Birth. Int J Gynaecol Obstet. 2019 Jul;146(1):110-117. PMID: 31055833

TABLE 3 Distribution of maternal, fetal and placental conditions according to clusters of preterm birth phenotype.

Condition	Cluster 1 (n=650)	Cluster 2 (n=2319)	Cluster 3 (n=1181)
Extrauterine infection, no.	0	986	343
Row, %	0	74.19	25.81
Column, %	0	42.52	29.04
Clinical chorioamnionitis, no.	0	173	0
Row %	0	100.0	0
Column %	0	7.46	0
Maternal chronic disease, no.	0	809	222
Row, %	0	78.47	21.53
Column, %	0	34.89	18.80
Pre-eclampsia/eclampsia/ HELLP syndrome, no.	0	51	1013
Row, %	0	4.79	95.21
Column, %	0	2.20	85.77
Antepartum stillbirth, no.	0	147	17
Row, %	0	89.63	10.37
Column, %	0	6.34	1.44
Fetal growth restriction, no.	0	49	380
Row, %	0	11.42	88.58
Column, %	0	2.11	32.18
Perinatal sepsis, no.	0	564	212
Row, %	0	72.68	27.32
Column, %	0	24.32	17.95
Multiple pregnancy, no.	0	362	75
Row, %	0	82.84	17.16
Column, %	0	15.61	6.35
Fetal anomaly, no.	0	383	112
Row, %	0	77.37	22.63
Column, %	0	16.52	9.48
Early bleeding, no.	0	431	134
Row, %	0	76.28	23.72
Column, %	0	18.59	11.35
Mid/late pregnancy bleeding, no.	0	468	86
Row, %	0	84.48	15.52
Column, %	0	20.18	7.28
None, no.	650	0	0
Row, %	100	0	0
Column, %	100	0	0

Row, %: Distribution of women with a given condition in a particular cluster.
Column, %: Distribution of different conditions in a particular cluster.

Souza RT, Cecatti JG, Passini R Jr, Pacagnella RC, Oliveira PF, Silva CM; Brazilian Multicentre Study on Preterm Birth study group. Cluster analysis identifying clinical phenotypes of preterm birth and related maternal and neonatal outcomes from the Brazilian Multicentre Study on Preterm Birth. Int J Gynaecol Obstet. 2019 Jul;146(1):110-117. PMID: 31055833

TABLE 4 Preterm birth subtypes according to preterm birth phenotype cluster.

PTB subtype	Cluster 1, n (%)	Cluster 2, n (%)	Cluster 3, n (%)	*P* value
sPTB	343 (52.77)	1018 (43.90)	130 (11.01)	<0.001
pPROM-PTB	264 (40.62)	832 (35.88)	95 (8.04)	
pi-PTB	43 (6.62)	469 (20.22)	956 (80.95)	
All cases	650 (100)	2319 (100)	100	

Abbreviations: sPTB, spontaneous preterm birth; pPROM-PTB, preterm birth due to preterm premature rupture of membranes; pi-PTB, provider-initiated preterm birth.

Souza RT, Cecatti JG, Passini R Jr, Pacagnella RC, Oliveira PF, Silva CM; Brazilian Multicentre Study on Preterm Birth study group. Cluster analysis identifying clinical phenotypes of preterm birth and related maternal and neonatal outcomes from the Brazilian Multicentre Study on Preterm Birth. Int J Gynaecol Obstet. 2019 Jul;146(1):110-117. PMID: 31055833

Key Points

- The use of progesterone as a treatment/preventive strategy is uncertain.
- Advancing maternal age, reproductive technologies and common health issues (obesity/metabolic syndrome) will continue to have a significant impact on reproductive health, including preterm birth and preterm preeclampsia.
- Innovative research is required to better understand disparities, underlying pathogenic mechanisms, preventive and treatment strategies for preterm birth.

The decidua-the maternal bed embracing the embryo-maintains the pregnancy.

Mori M et al. Semin Immunopathol. 2016 Nov;38(6):635-649.

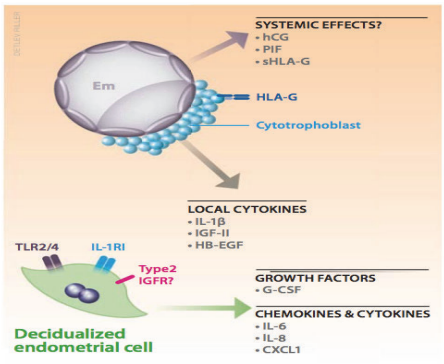
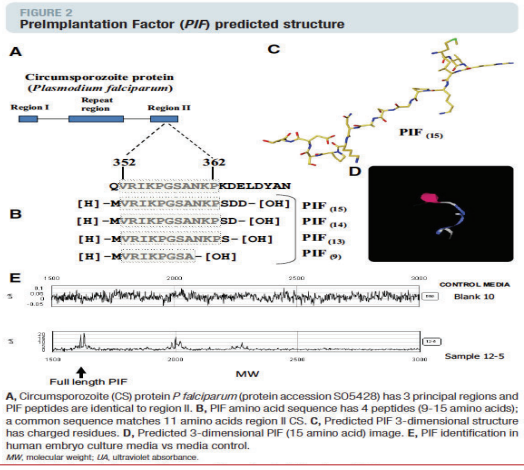


Fig. 3 Possible human decidua-embryo interaction indicated by in vitro

Calix R, Ornaghi S, Wilson J, Fernandez N, Vialard F, Barnea ER, **Paidas MJ**. PreImplantation Factor* (PIF), Endocrinology of Implantation and Establishment of

PreImplantation Factor



Pos	Abbr	AA
1	M	Met
2	V	Val
3	R	Arg
4	I	Ile
5	K	Lys
6	P	Pro
7	G	Gly
8	S	Ser
9	A	Ala
10	N	Asn
11	K	Lys
12	P	Pro
13	S	Ser
14	D	Asp
15	D	Asp

Barnea ER, Kirk D, Ramu S, Rivnay B, Roussev R, Paidas MJ. PreImplantation Factor (PIF) orchestrates systemic antiinflammatory response by immune cells: effect on peripheral blood mononuclear cells. Am J Obstet Gynecol. 2012 Oct;207(4):313.e1-313.e11

PIF:ESSENTIAL FOR PREGNANCY

PIF influences three key areas: maternal immunity, embryo-decidual adhesion, & regulation of adaptive processes.

BASIC SCIENCE: OBSTETRICS

A genomic and proteomic investigation of the impact of preimplantation factor on human decidual cells

Michael J. Paidas, MD; Graciela Krikun, PhD; S. Joseph Huang, MD, PhD; Richard Jones, PhD; Michael Romano; Jack Annunziato; Eytan R. Barnea, MD

OBJECTIVE: Preimplantation factor (PIF) is a novel, 15 amino acid peptide, secreted by viable embryos. This study aims to elucidate PIF's effects in human endometrial stromal cells (HESC) decidualized by estrogen and progestin, which mimics the preimplantation milieu, and in first-trimester decidua cultures (FTDC).

STUDY DESIGN: HESC or FTDC were incubated with 100 nmol/L synthetic PIF or vehicle control. Global gene expression was analyzed using microarray and pathway analysis. Proteins were analyzed using quantitative mass spectrometry, and PIF binding by protein array.

RESULTS: Gene and proteomic analysis demonstrate that PIF affects immune, adhesion, and apoptotic pathways. Significant up-regulation in HESC (fold change) include: nuclear factor-k-β activation via interleukin-1 receptor-associated kinase binding protein 1 (53); Toll-like receptor 5 (9); FK506 binding protein 15, 133kDa protein (2.3); and Down syndrome cell adhesion molecule like 1 (16). B-cell lymphoma protein 2 was down-regulated in HESC (21.1) and FTDC (27.1). Protein array demonstrates PIF interaction with intracellular targets insulin-degrading enzyme and beta-K$^+$ channels.

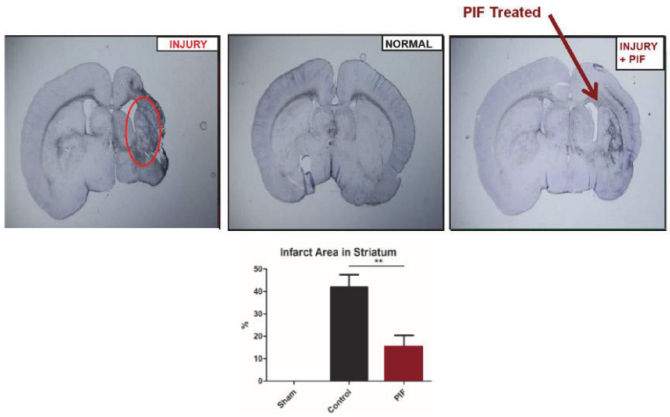
CONCLUSION: PIF displays essential multitargeted effects, of regulating immunity, promoting embryo-decidual adhesion, and regulating adaptive apoptotic processes.

Key words: decidual cells, genomics, implantation, preimplantation factor, proteomics

Cite this article as: Paidas MJ, Krikun G, Huang SJ, et al. A genomic and proteomic investigation of the impact of preimplantation factor on human decidual cells. Am J Obstet Gynecol 2010;202:459.e1-8.

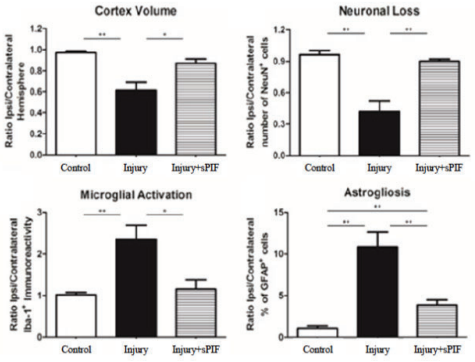
PIF PROMOTES BRAIN REGENERATION

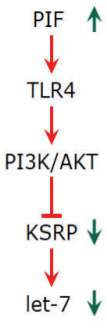
Restores the Striatum Region



Mueller M, Zhou J, Yang L, Gao Y, Wu F, Schoeberlein A, Surbek D, Barnea ER, Paidas M, Huang Y. PreImplantation factor promotes neuroprotection by targeting

sPIF RESCUES CORTICAL VOLUME NEURAL LOSS
Decreasing Microglial Activity *in vivo*

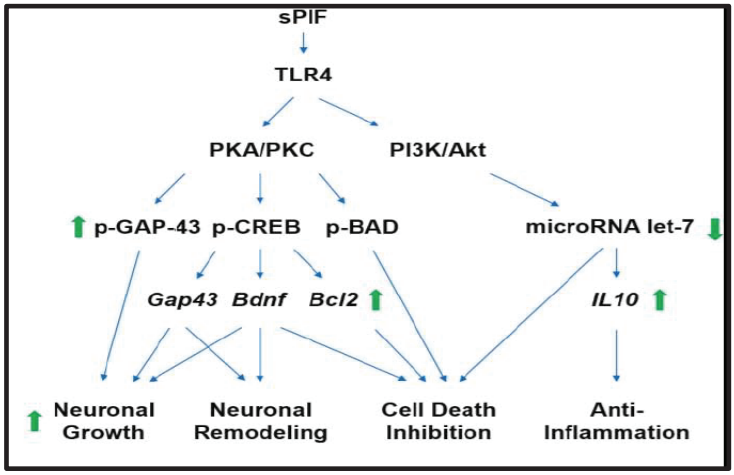




Mueller M, Zhou J, Yang L, Gao Y, Wu F, Schoeberlein A, Surbek D, Barnea ER, Paidas M, Huang Y. PreImplantation factor promotes neuroprotection by targeting

Proposed Model for sPIF induced neuronal protection

Mueller M et al. CDD 2015 Dec;22(12):2078-86.



Acknowledgements

Yale Women and Children's Center for Blood Disorders and Preeclampsia Advancement:
Jean Wilson, Sara Omaghi, Martin Muller, Elizabeth Triche, Roberto Caliix, Ryan Ball, Michael Romano, Jack Annunziato,
Clinical Research Team: Bonnie Sandlaufer

Yale Reproductive Biology Unit, Dept Obstet, Gyn, & Reprod Sci:
Seth Guller, Graciela Krikun, Yingqun Huang, S. Min Li, Xiao Xu

Yale Fertility Center:
Pasquale Patrizio

Yale Department of Comparative Anatomy:
Carmen Booth, Susan Compton

Yale Department of Pathology
Alexander Vortmeyer, Raffaella Morotti

Yale Department of Pediatrics
Richard Ehrenkranz, deceased

Pediatric Neurology
Laura Ment

Yale Department of Neurosurgery, Cellular and Molecular Physiology
Angelique Bordey, Anthony van den Pol

Yale Department of Therapeutic Radiology
Sara Rockwell (deceased), Nicholas Daniak, Peter Glazer

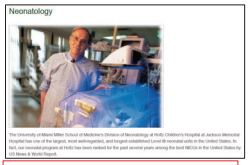
Yale Comprehensive Cancer Center
Daniel Zelterman, Biostatistics

University of Copenhagen
Ellen Christine Leth Loekkegaard
Hellen Edwards
Jens Langhoff-Roos
Jacob Lykke
Jesper Friis Petersen

Funding:
BioIncept (MJP)
Paul Titus Fellowship (MJP)
Merck-Serono GFI grant (MJP)
Preeclampsia Center of Advancement, rEVO (MJP)
CBIT, Yale (MJP)
Progenity (MJP)
CSL Behring (MJP)
STTR (NIH/NIAID) (MJP)

Eytan Barnea, BioIncept, LLC & Society for Investigation of Early Pregnancy

UMMSCOM Collaborators



Eduardo Bancalari, MD
Neonatology

Jonah Bardos, MD
UM OB/GYN, Genetics

Sara Ornaghi MD,

Ryan Longman, M.D.
Reproductive and Cancer Genetics, OB Ultrasound

UHealth UNIVERSITY OF MIAMI HEALTH SYSTEM
UNIVERSITY OF MIAMI MILLER SCHOOL of MEDICINE

THANK YOU

UHealth UNIVERSITY OF MIAMI HEALTH SYSTEM

Jackson HEALTH SYSTEM
Miracles made daily.