Fetal Optimization During Maternal Sepsis

SFOAI Varmote 2023

Skåvsjöholm

Lawrence C. Tsen, MD
Department of Anesthesiology, Perioperative & Pain Medicine, Brigham & Women's Hospital
Associate Professor of Anaesthesia
Harvard Medical School

No Disclosures
Movie “Rango”

Maternal Sepsis
Fetal Optimization

- Definitions
- Identify Risks
- Therapies

Definition

Dellinger RP, et al. Surviving Sepsis Campaign, CCM 2023

No universally accepted definition in obstetric practice

Puerperal sepsis, fever, infection, pyrexia; genital tract sepsis; intrapartum septic pyrexia, infection; maternal sepsis, pyrexia, fever

Surviving Sepsis Campaign, 2021
Systemic inflammatory response syndrome **(SIRS)** recognized by:

- General Variables
- Inflammatory Variables
- Hemodynamic Variables
- Organ Dysfunction Variables
- Tissue Perfusion Variables

Sepsis
SIRS + Infection

Severe Sepsis
+ Organ Dysfunction
+ Hypoperfusion*
+ Hypotension
*lactic acidosis, oliguria, mental status changes

Septic Shock
+ Hypotension despite adequate fluid resuscitation
***inotropic/vasopressor**

Definition

Dellinger RP, et al. Surviving Sepsis Campaign, CCM 2023
Shah AD, et al. UK NIH Critical Care Collaborative 2021

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Surviving Sepsis Campaign, 2021
Systemic inflammatory response syndrome **(SIRS)** recognized by:

- General Variables
- Inflammatory Variables
- Hemodynamic Variables
- Organ Dysfunction Variables
- Tissue Perfusion Variables

SOFA
29K

Sepsis 14.8K
SIRS + Infection 50.7%

Severe Sepsis
+ Organ Dysfunction
+ Hypoperfusion*
+ Hypotension
*lactic acidosis, oliguria, mental status changes

Septic Shock 4.1K 27.6%
+ Hypotension despite adequate fluid resuscitation
*inotropic/vasopressor

Definition

Dellinger RP, et al. Surviving Sepsis Campaign, CCM 2023
Stephens AJ, et al. Maternal Sepsis Guidelines, AJ Perinat 2023

No universally accepted definition in obstetric practice

Puerperal sepsis, fever, infection, pyrexia; genital tract sepsis; intrapartum septic pyrexia, infection; maternal sepsis, pyrexia, fever

Early Goal Directed Therapy

- CVP + SVC Oxygen Saturation (not supported)
- Early Resuscitation

Fluids

- Crystalloid to Albumin to Balanced Crystalloid
- Downgraded 30 mL/kg (not supported)

Steroids

- Hydrocortisone 200 mg/d IV to subtle against to favor

Maternal Sepsis and Septic Shock

Definitions, Criteria and Tools Differ

Management Recommendations Similar

Sepsis Criteria

systemic inflammatory response syndrome (SIRS)
quick sequential (sepsis-related) organ failure assessment (qSOFA)
maternal early warning (MEW) criteria

Table 3. Sensitivity and Specificity of Criteria for Sepsis

Criteria	N (%) Sepsis Cases	N (%) Controls	Sensitivity (95% CI)	Specificity (95% CI)
SIRS[a]				
WBC <4 or >12	38 (74.5)	62 (41.1)	0.75 (0.60–0.86)	0.59 (0.51–0.67)
HR þ90	49 (96.1)	104 (55.3)	0.96 (0.87–1.00)	0.45 (0.37–0.52)
RR >20	28 (62.2)	18 (9.9)	0.62 (0.47–0.76)	0.90 (0.85–0.94)
T <36°C or >38°C	33 (68.7)	52 (28.7)	0.69 (0.54–0.81)	0.71 (0.64–0.78)
T >38 or <36 and HR >90	33 (68.8)	33 (18.2)	0.69 (0.54–0.81)	0.82 (0.75–0.87)
T >38 or <36 and RR >20	23 (53.5)	7 (4.0)	0.53 (0.38–0.69)	0.96 (0.92–0.98)
T >38 or <36 and WBC >12 or<4	27 (56.3)	14 (9.8)	0.56 (0.41–0.71)	0.90 (0.84–0.95)
HR >90 and RR >20	28 (62.2)	15 (8.3)	0.62 (0.47–0.76)	0.92 (0.87–0.95)
HR >90 and WBC >12 or <4	36 (70.6)	32 (21.3)	0.71 (0.56–0.83)	0.79 (0.71–0.85)
RR >20 and WBC >12 or <4	20 (44.4)	6 (4.2)	0.44 (0.30–0.60)	0.96 (0.92–0.98)
Any 2 SIRS	40 (93.0)	51 (36.7)	0.93 (0.81–0.99)	0.63 (0.55–0.71)
qSOFA[a]				
RR ≥22	28 (62.2)	17 (9.4)	0.62 (0.47–0.76)	0.91 (0.85–0.94)
SBP ≤100 mm Hg	26 (55.3)	76 (40.4)	0.55 (0.40–0.70)	0.60 (0.52–0.67)
Neurological changes	17 (37.8)	0	0.38 (0.24–0.53)	1.00 (0.98–1.00)
RR ≥22 and SBP ≤100 mm Hg	14 (33.3)	9 (5.0)	0.33 (0.20–0.50)	0.95 (0.91–0.98)
Any 2 qSOFA	19 (50.0)	9 (5.0)	0.50 (0.33–0.67)	0.95 (0.91–0.98)
Modified MEW[a]				
SBP <90 mm Hg	17 (36.2)	13 (6.9)	0.36 (0.23–0.51)	0.93 (0.88–0.96)
HR >120	30 (58.8)	12 (6.4)	0.59 (0.44–0.72)	0.94 (0.89–0.97)
RR >30	14 (31.1)	0	0.31 (0.18–0.47)	1.00 (0.98–1.00)
Neurological changes	17 (37.8)	0	0.38 (0.24–0.53)	1.00 (0.98–1.00)
Any MEW trigger	31 (81.6)	24 (13.3)	0.82 (0.66–0.92)	0.87 (0.81–0.91)

SIRS: Systemic Inflammatory Response Syndrome; **MEW:** Maternal Early Warning
qSOFA: quick Sequential (Sepsis Related) Organ Failure Assessment

Bauer ME, Chau MD, Einav S, Leffert L, Toledo P, Tsen LC, Bateman B. A&A 2018

Sepsis Criteria

	N (%) Sepsis	N (%) Controls	Sensitivity	Specificity
SIRS (Any 2)	40 (93%)	51 (36.7%)	0.93 (0.81-0.99)	0.63 (0.55-0.71)
qSOFA (Any 2)	19 (50%)	9 (5%)	0.50 (0.33-0.67)	0.95 (0.91-0.98)
Modified MEW (Any 1)	31 (81.6%)	24 (13.3%)	0.82 (0.66-0.92)	0.87 (0.81-0.91)

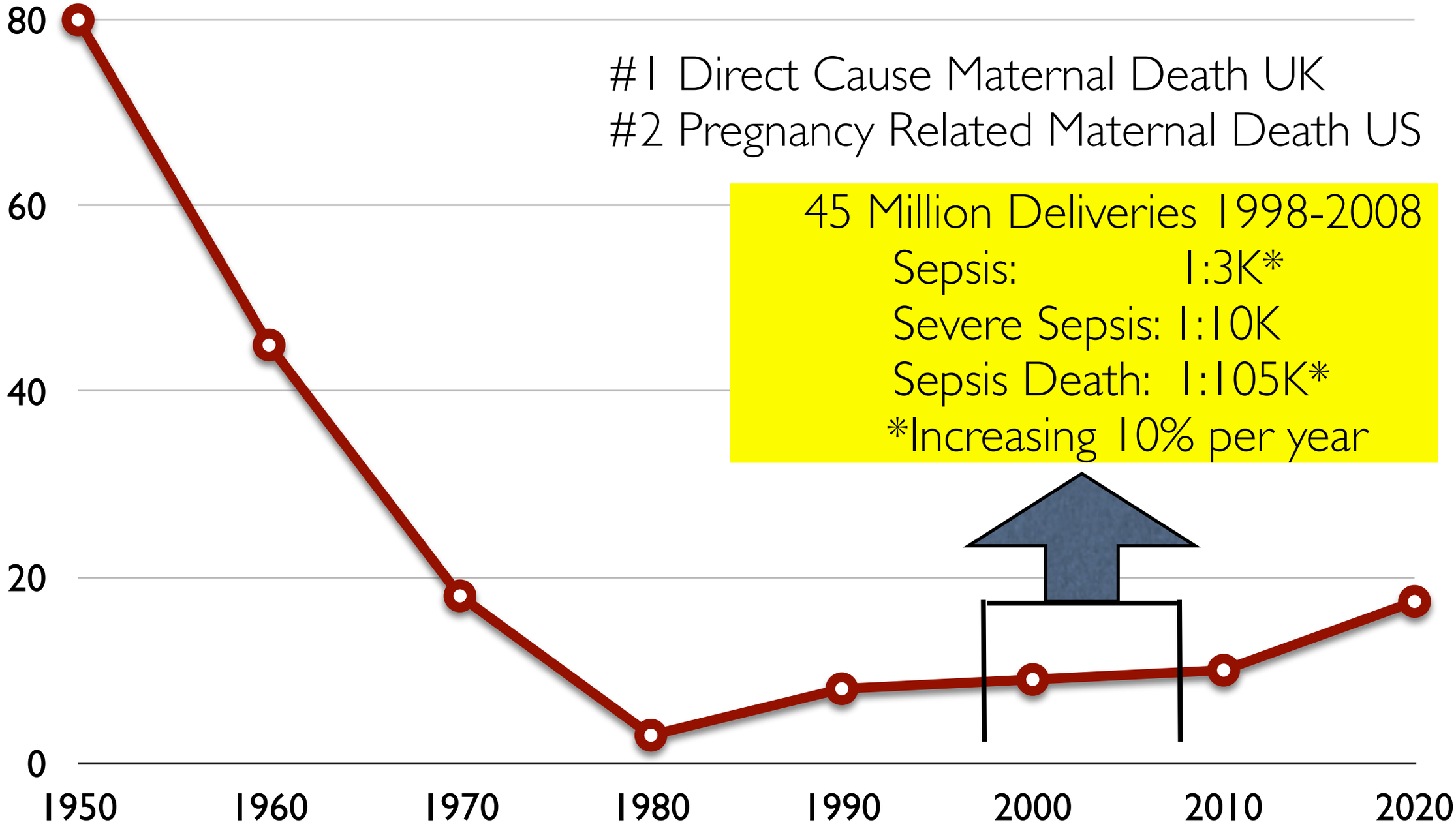
Validated Maternal Sepsis Cases: 1995 to 2012, 78 Cases

Causes: Chorioamnionitis and Endometrosis = 50%

Mortality: Antibiotics <1 hr, 8.3%; > 1 hr, 20%

Bauer ME, Chau MD, Einav S, Leffert L, Toledo P, Tsen LC, Bateman B. A&A 2018

Mortality Rate for Sepsis/Million Maternities



CDC Pregnancy Mortality 2020; Loudon I. Maternal Mortality 1800-1950. 1992.
Lucas DN, et al. IJOA 2012;21:56-67; Bauer ME, et al. Anesth Analg 2013;117;944-50

Infection Risks: Risk Factors for Sepsis

Obstetric Management

- Amniocentesis/Invasive intrauterine procedures
- Prolonged ROM
- Prolonged labor with >5 vaginal examinations
- Vaginal trauma
- Cervical suture
- Cesarean delivery
- Retained products

Maternal Factors

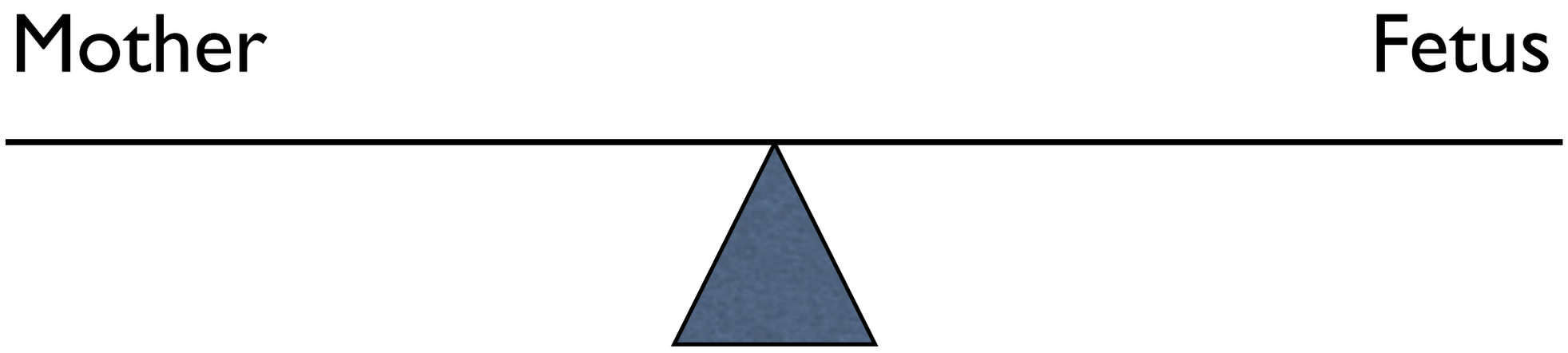
- Impaired immunity
- Impaired GTT
- Obesity
- Sickle cell anemia (Asplenia)
- Vaginal discharge
- Hx pelvic infection
- Hx GBS infection
- Socioeconomic
- Age

Fetal Factors

- Limited immunity
- Low gestational age
- Febrile (38C)
- ROM duration
- Maternal infection
- GB Strep infection

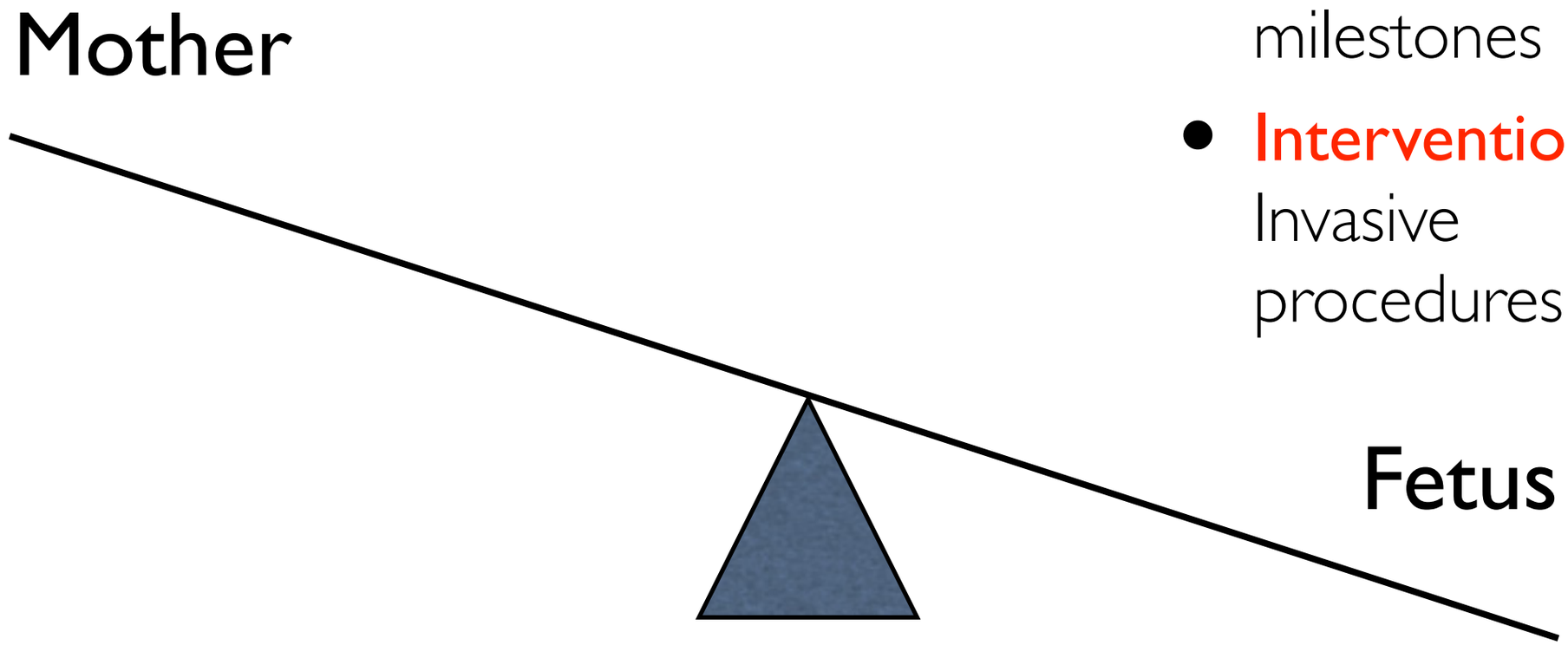
Shields A, et al. Clinical Expert Series, Obstet Gynecol 2021, Puopolo 2013, Bamfo 2013
Bauer ME, Chau MD, Einav S, Leffert L, Toledo P, Tsen LC, Bateman B. A&A 2018

Sepsis Concerns: Maternal vs. Fetal Needs



Sepsis Concerns: Maternal vs. Fetal Needs

- **Dependence:** O2 & perfusion thresholds
- **Competition:** Gestational milestones
- **Intervention:** Invasive procedures



Identify Risks To The Fetus

- Infection
- Perfusion
- Oxygenation

Infection Risks

Puerperal Infection (World Health Organization)

Infections of GU system related to labour, delivery, periperium

- Uterus and Associated Structures (Chorioamnionitis, Endometritis)
- Wound Infection: CD 5-20 x VD, especially if emergent
- Urinary Tract

Infections related to the birth

- Breast Abscess
- Pyelonephritis
- Pelvic thrombophlebitis

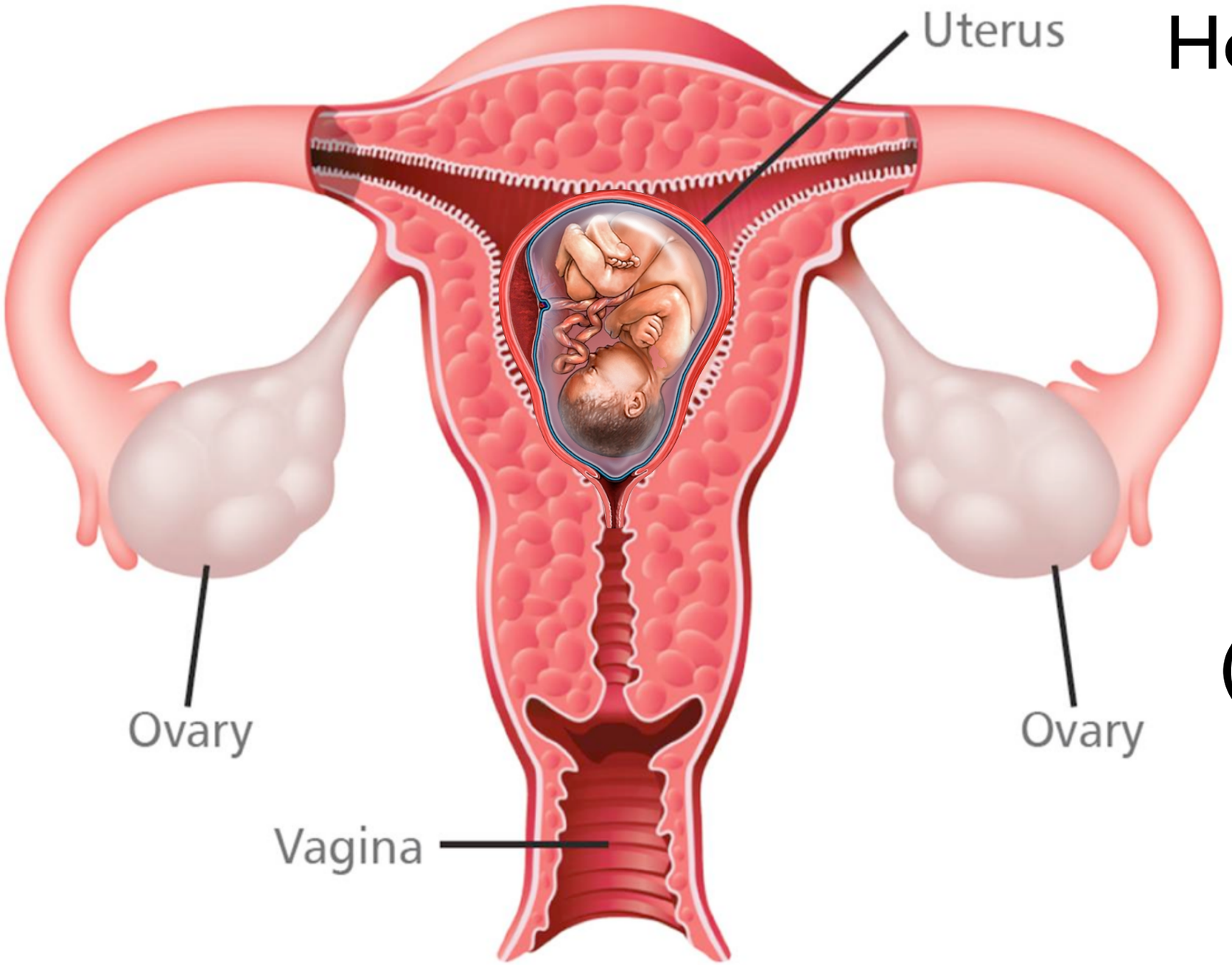
Incidental Infections

- HIV, Pneumonia, TB, Malaria

Concurrent Dx (n=3177)	%
Pneumonia	29.7
GU Infection	29.7
Chorioamnionitis	18.4
Endometritis	8.6
Pyelonephritis	5.8
Wound Infection	4.7

World Health Organization Collaborative Study Team, 2000; Bauer et al. A&A 2013
Bauer ME, Chau MD, Einav S, Leffert L, Toledo P, Tsen LC, Bateman B. A&A 2018

Infection Risks: Pathway to the Fetus



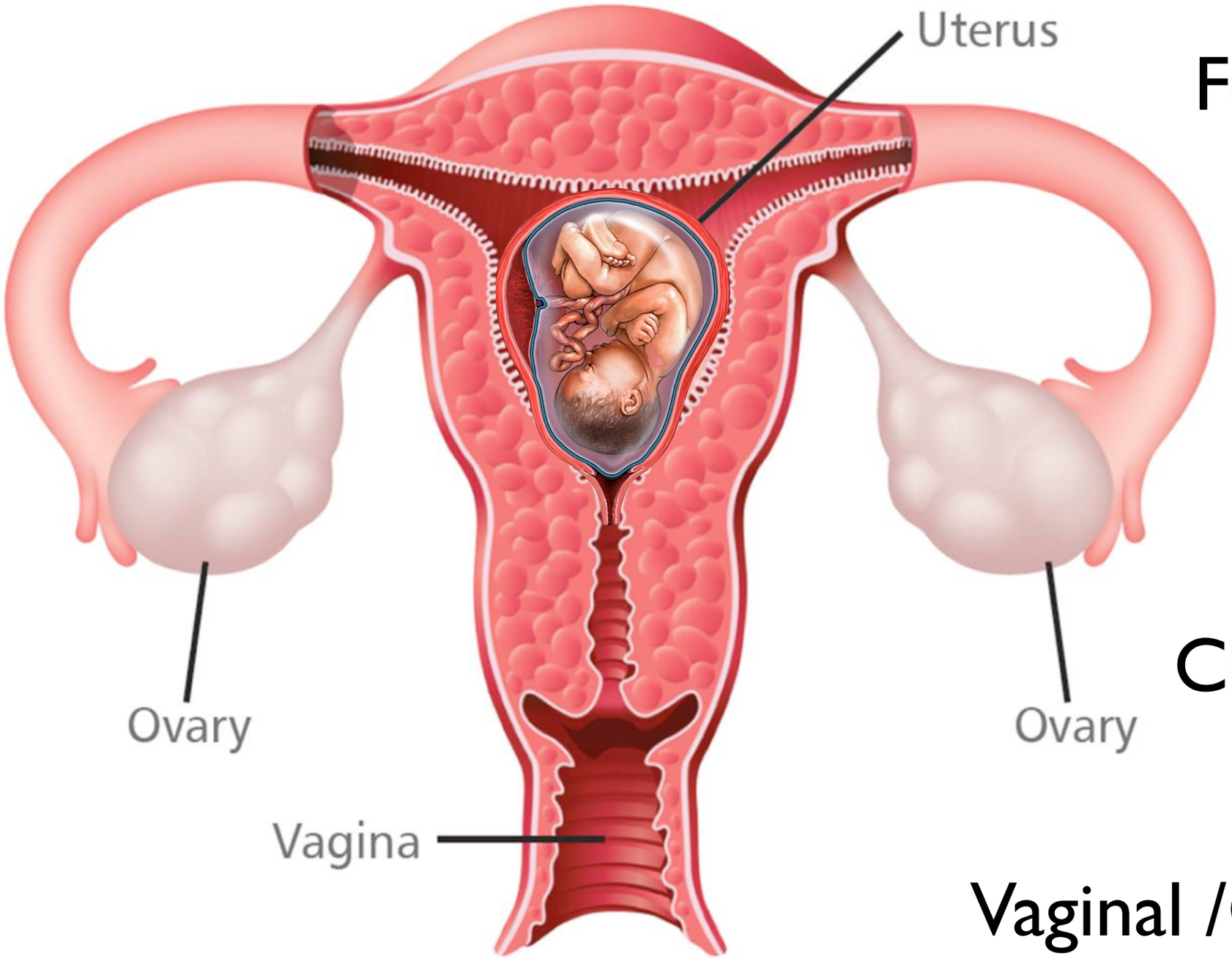
Hematogenous

Retrograde

Incidental
(Amnio, CVS)

Ascending

Infection Risks: Pathway to the Fetus



Stage 4
Fetal Infection

Stage 3
Amnionitis

Stage 2
Deciduitis
Chorioamniitis

Stage 1
Vaginal /CervicalFlora

Infection Risks: Fetal Response

Fetal Tachycardia (40-70%)

35 wks autonomic nervous system maturity

Fetal Movement

Fetal Inflammatory Response Syndrome

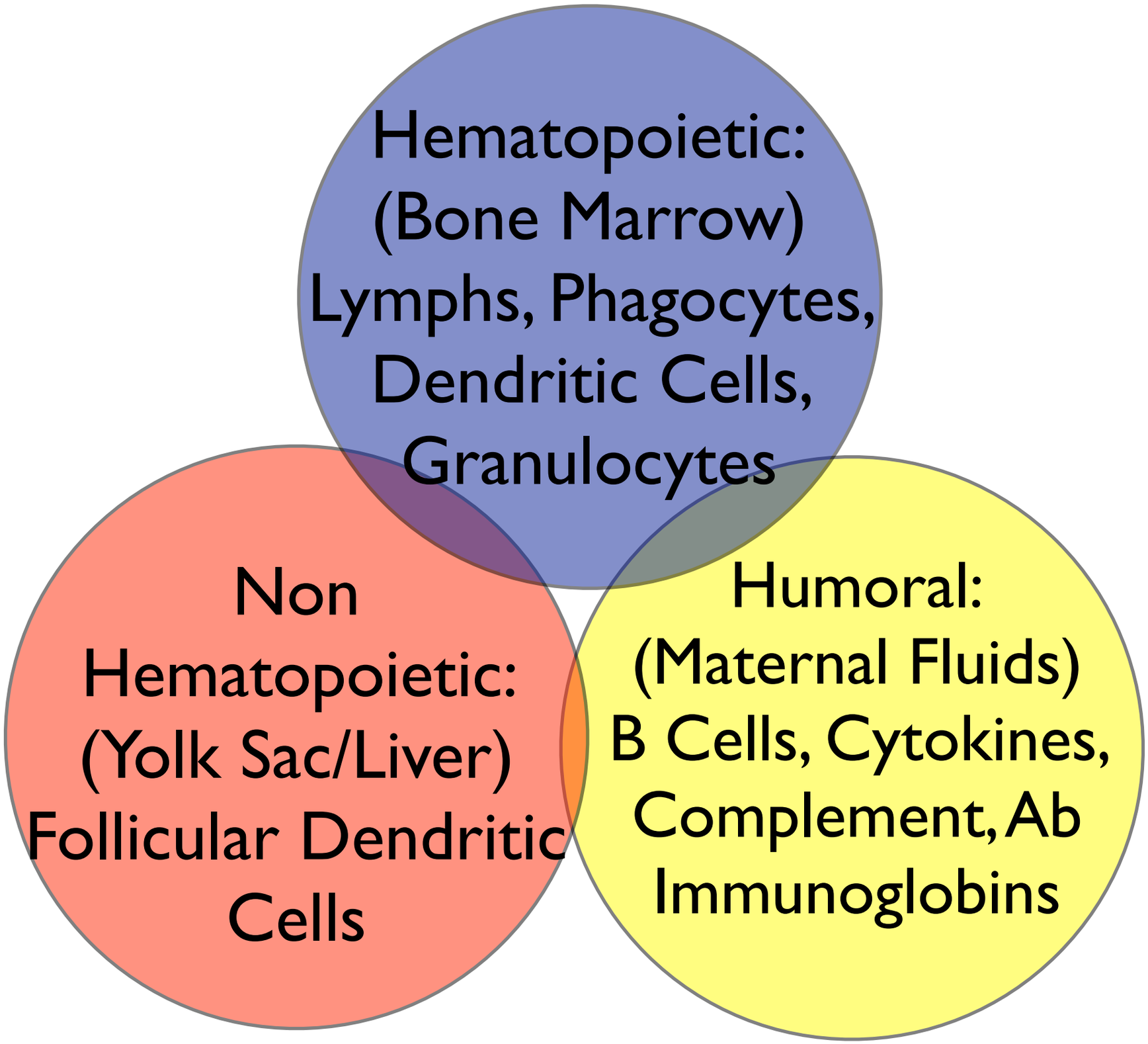
Histologic, rather than clinical, diagnosis

1. Increased systemic cytokines (IL6)
2. Funisitis (umbilical cord inflammation)
3. Vasculitis in the chorion

Associated with Cerebral and Respiratory Pathology

Anderson BL. OB Gyn 2014; Su et al. J Perinatol 2014; Schneider U, et al. PLoS One 2018

Infection Risks: Fetal Response

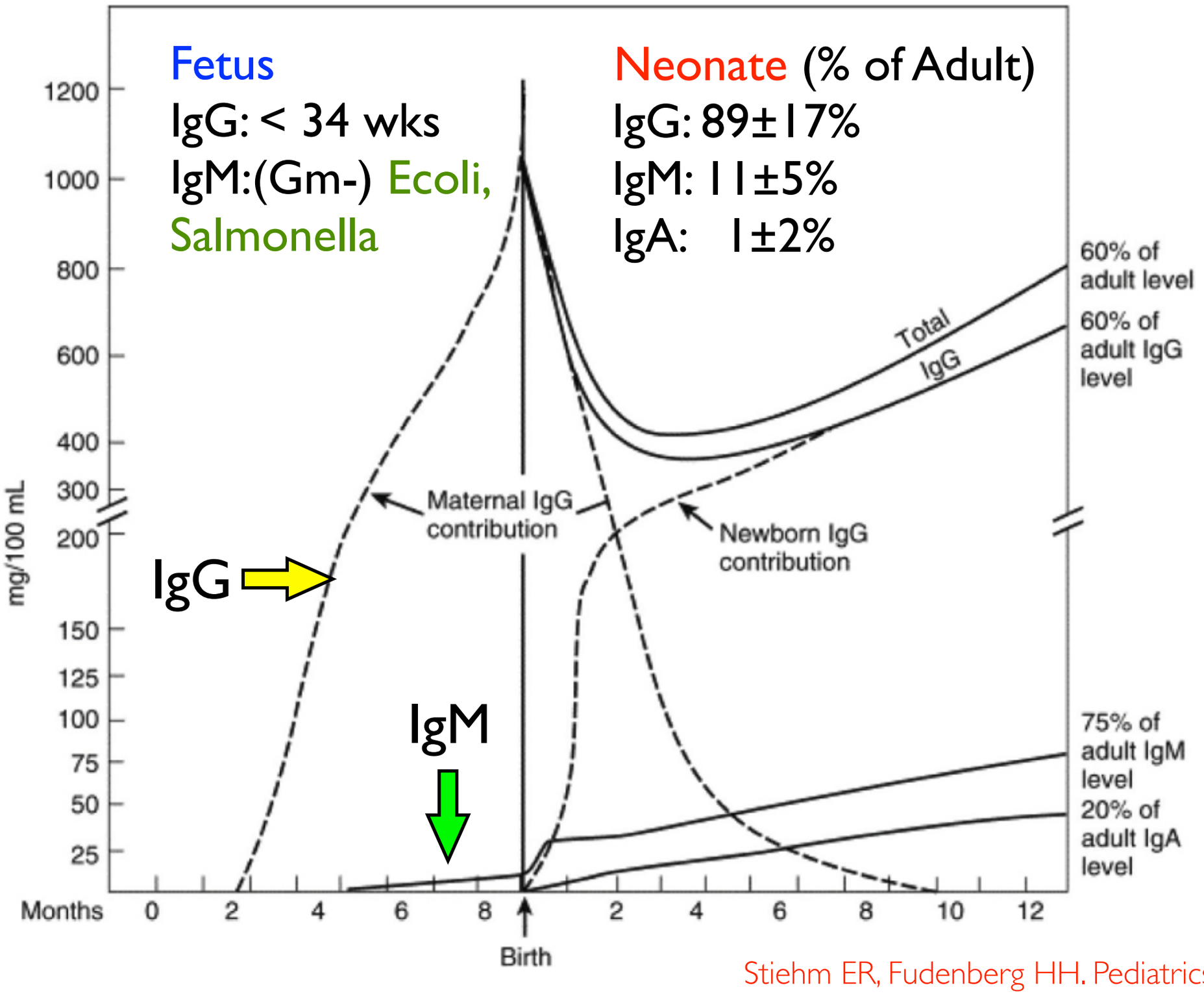


Stirrat 1991

Infection Risks: Fetal Response

Fetus
IgG: < 34 wks
IgM:(Gm-) Ecoli, Salmonella

Neonate (% of Adult)
IgG: 89±17%
IgM: 11±5%
IgA: 1±2%



Stiehm ER, Fudenberg HH. Pediatrics 1966:37:715

Risks to the Fetus
Perfusion

Uteroplacental Blood Flow

Uterine Blood Flow

Not autoregulated

Maximally dilated

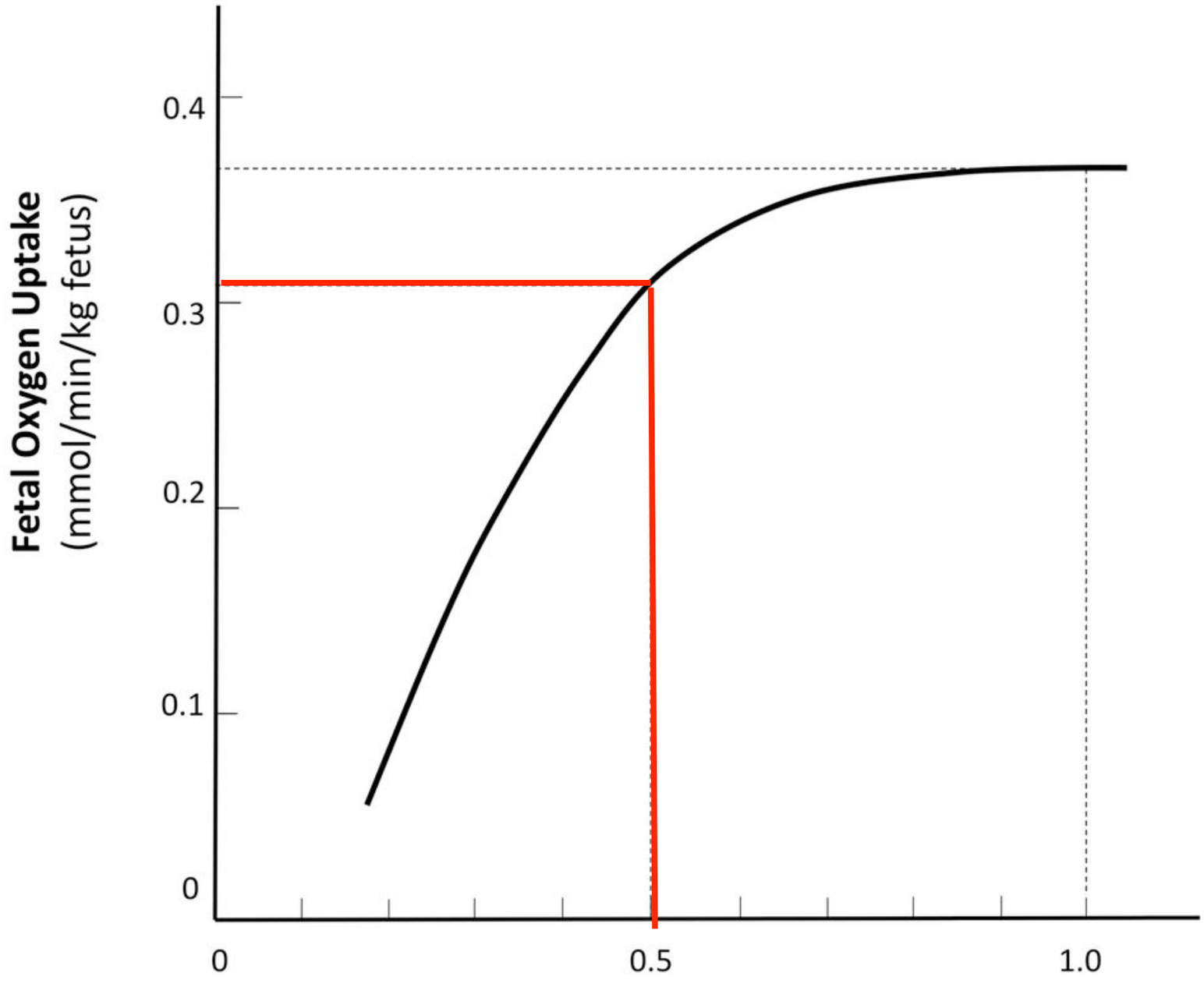
Uterine Vessels

More responsive

to alpha-agonists

Divert to systemic

vasculature/organs



Chau A, Tsen L. Curr Opin Anesth 2014

Tsen L, Gelman S. IJOA 2022

Uteroplacental Blood Flow: Sheep

	Ephedrine a1, b1, b2	Metaraminol a1, b1	Phenylephrine a1, a2
MBP	↑	↑	↑
UA Flow	↑	↓	↓
Fetal pH	↑	↓	↓

Ralston et al., Anesthesiology 1974;40:354-70

Uteroplacental Blood Flow: Human

	Ephedrine	Phenyl + Ephedrine	Phenyl	P Value
V-A pH	0.07	0.07	0.05	0.003
A-V pCO_2	14	13	11	0.006
UA Base Deficit	-2.2	-1.4	-1.8	0.16
Acidotic Fetuses	10	1	1	

Cooper D, et al. Anesthesiology 2002;97:1582-1590
Ngan Kee et al. Anesthesiology 2009;111:506-512

Uteroplacental Blood Flow: Human

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Cooper D, et al. Anesthesiology 2002;97:1582-1590
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Perfusion: Hypotension

Sepsis

Capillary Permeabiliy
Vascular Damage
Vasodilation

Catecholamine Release

Leukocytes
Histamine
Serotonin
Bradykinin

Neutrophils
Superoxide
Hydroxyl
Peroxide

Leukotrienes

Cytokines

Sugerman, 1981

Myocardial Failure

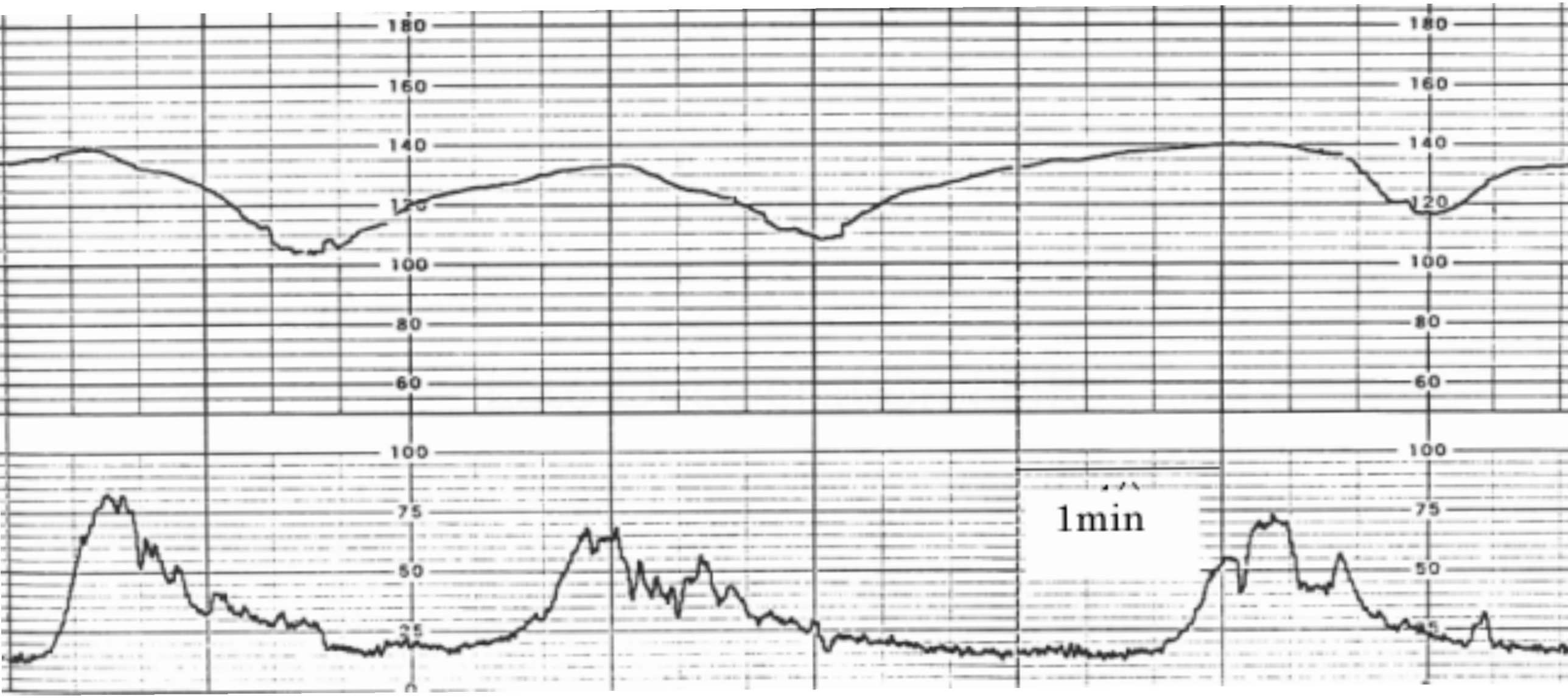
Vessel Constriction

Acidosis
Decreased PVR

Decreased Venous Return

Decreased CO
Decreased MAP

Perfusion: Hypotension on Fetus



Septic Hypotension + Uterine Hypertonus: FHR bradycardia
Shunting of blood from splanchnic (uterine) bed

Morishima HO, et al. Am J Obstet Gynecol 1978;131:899-902

Perfusion: Hypotension on Fetus

Fetal Biophysical Profile (fetal BPP), 30 min

Normal 8-10; Equivocal <6, repeat in 12-24 hrs

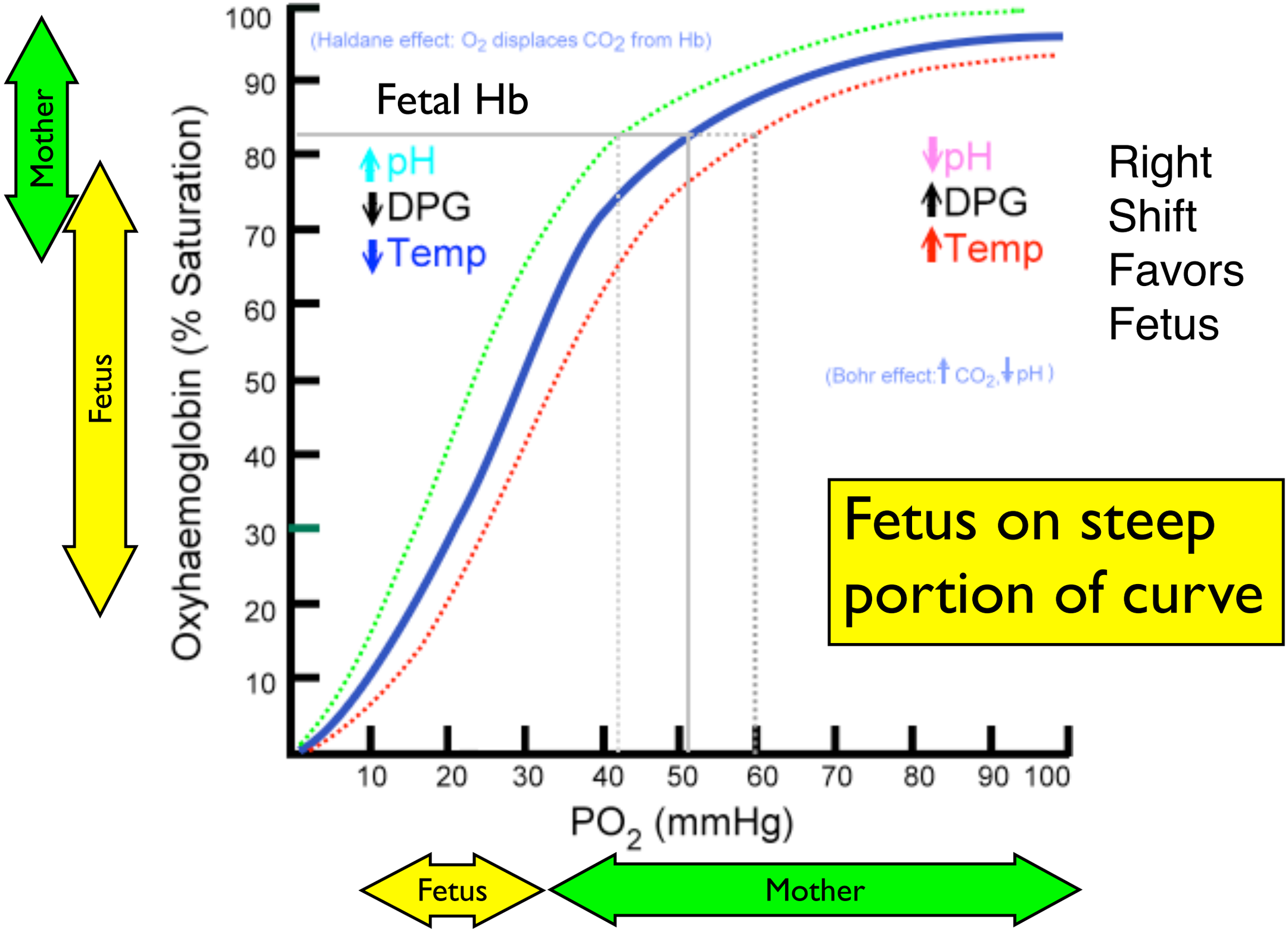
Component	Normal	Score
Nonstress Test	Reactive	**2**
Fetal Breathing	Duration ≥ 1	**2**
Fetal Movement	≥ 3 Movements	**2**
Fetal Tone	Flex/Extend Limb	**2**
Amniotic Fluid Volume	Am Fluid Index > 5 cm	**2**
Max Score		**10**

Phelan and Lewis, 1981; Phelan, 1988

Risks to the Fetus
Oxygenation

Oxygenation

Towell ME: Perinatal Med 1976



Right Shift Favors Fetus

Fetus on steep portion of curve

Oxygenation

$DO_2 = [1.39 \times Hb \times SaO_2 + (0.003 \times PaO_2)] \times Q$

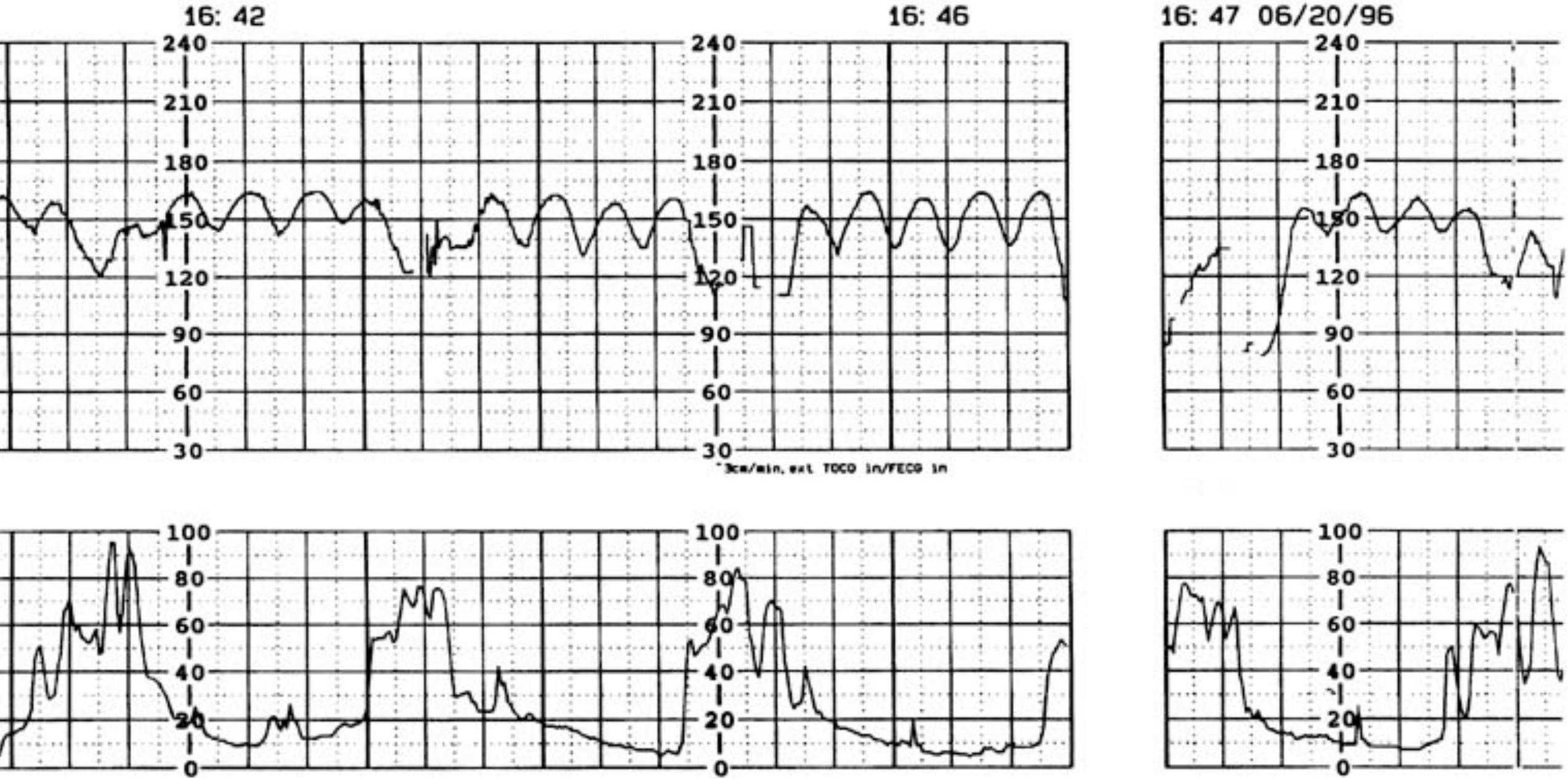
Hb Alterations
Reduced Production
Reduced Deformity
Impaired Microcirculation
DIC Hemolysis
Anemia

SaO_2
Acidosis-Right Shift
Temp-Right Shift
Anemia-Right Shift

Cardiac Output
Less Preload
Less Contractility

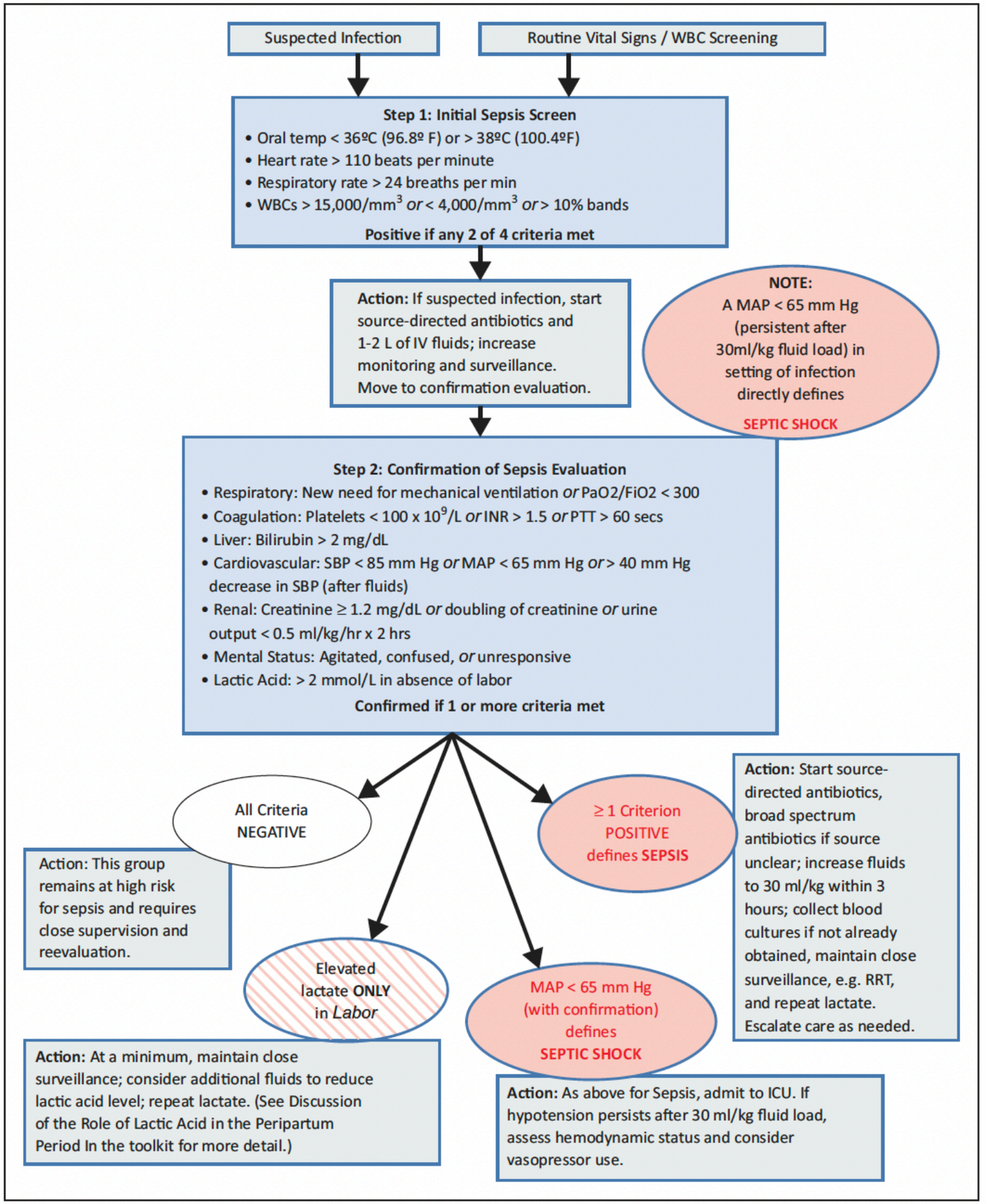
Goyette RE, et al. Hematologic changes in sepsis. Sem Resp Crit Care Med 2004;25:645-658

Oxygenation



Therapies

California Maternal Quality Care Collaborative Maternal Evaluation Sepsis Flow Chart 2019

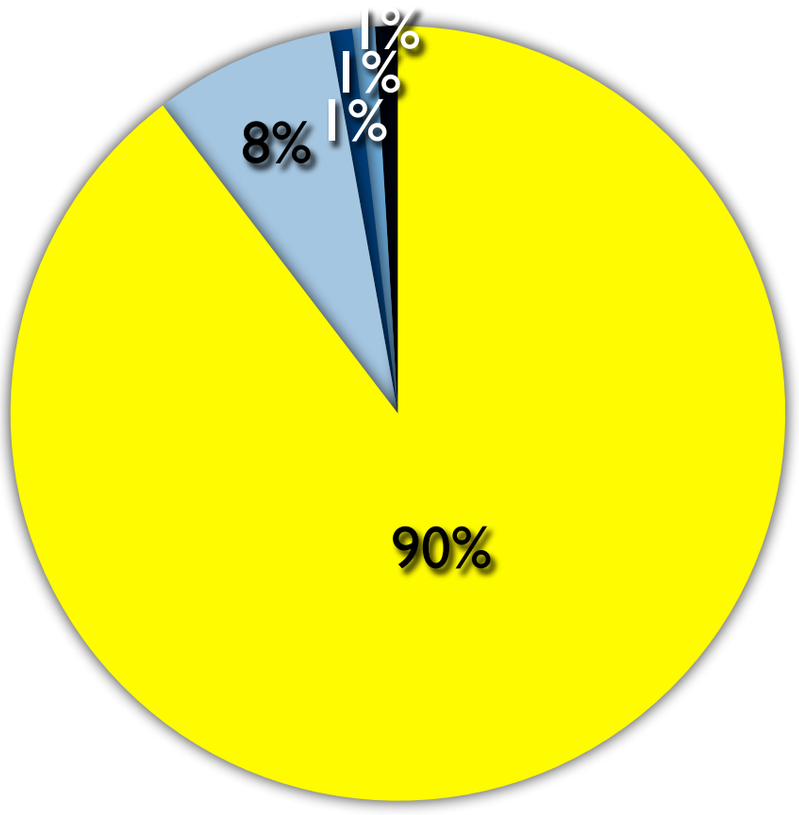


Abir G, Bauer M. Maternal Sepsis Update, Current Opinion. 2021

Step 1: Identify and Treat Pathogen

Surviving Sepsis Campaign
Clinical Care Bundle/
Grouped Interventions

1. Obtain culture (blood or swab) prior to antibiotics
2. Administer broad spectrum antibiotic within 1 hour



http://www.survivingsepsis.org/Bundles/Pages/default.aspx

Step 1: Identify and Treat Pathogen

	Gram +			Gram -		Other	
	Cocci	Rods	Acid-Fast	Cocci	Rods	Spiral Rods	Misc
Aerobic	Staph 22.2% Strep 20.1%	Coryne-bacterium			E.Coli 26%		Ureaplasma
Anaerobic		Clostridium Lactobacillis			Bacteroides 2%		

CDC Revised Guidelines 2010

Bauer ME, Chau MD, Einav S, Leffert L, Toledo P, Tsen LC, Bateman B. A&A 2018

Step 1: Identify and Treat Pathogen

Obtain Blood Cultures Prior to Antibiotics

Unknown Organism, Not Critical

Co-amoxiclav 1.2 g q 8 hrs	Cefotaxime (3rd) 1-2 gm q 8 hrs	Cefuroxime (2nd) 1.5 g q 8 hrs

Metronidazole 500 mg q 8 hrs

If allergic to penicillin or cephalosporins

Clindamycin 600-1200 mg q 6 to 8 hrs	Gentamicin 500 mg q 8 hrs	Clarithromycin 500mg q12 hrs

Step 1: Identify and Treat Pathogen

Severe Sepsis or Septic Shock

Piperacillin-Tazobactam 4.5 g q 8 hrs

Ciprofloxacin 600 mg q 12 hrs

Gentamicin 3-5 mg/kg daily divided q 8 hrs

Meropenem 500-1000 mg q 8 hrs

Metronidazole 500 mg q 8 hrs

Group A Strep

Clindamycin 600-1200 mg q 6 to 8 hrs

MRSA Septicemia Risk

Linezolid 600 mg q12 hrs

Teicoplanin 10 mg/kg q12 hrs x 3 doses, then q day

Step 1: Identify and Treat Pathogen

Postpartum Sepsis Workup

	Symptomatic	Asymptomatic
CBC, Blood Culture	X	X
CSF Studies, Chest X-Ray	X	
Empiric Antibiotics	X	

Empiric Antibiotic Risk in Uninfected

Fungal infections, bacterial late onset sepsis, necrotizing enterocolitis, recurrent wheezing disorder at 12 months, death.

Verani JR, et al. Prevention of Perinatal GBS. CDC Revised Guidelines. MMWR 2010
Mukhopadhyay S, Puopolo KM. Risk Assessment in Neonatal Early Onset Sepsis, Sem Perinatl 2012

Step 1: Identify and Treat Pathogen

Postpartum Sepsis Workup

	Term Infants	VLBW (<1500 gm)
Sepsis Cause	Group B Strep	E. Coli
Respiratory, Pressure Support	50%	100%
Death	2-3%	20-30%

Intrapartum Group B Strep Antibiotic Prophylaxis

Neonatal Sepsis: 3-4 to 0.8-1.0 cases/1000 live births

Neonatal GBS Sepsis 0.3-0.4 cases/1000 live births

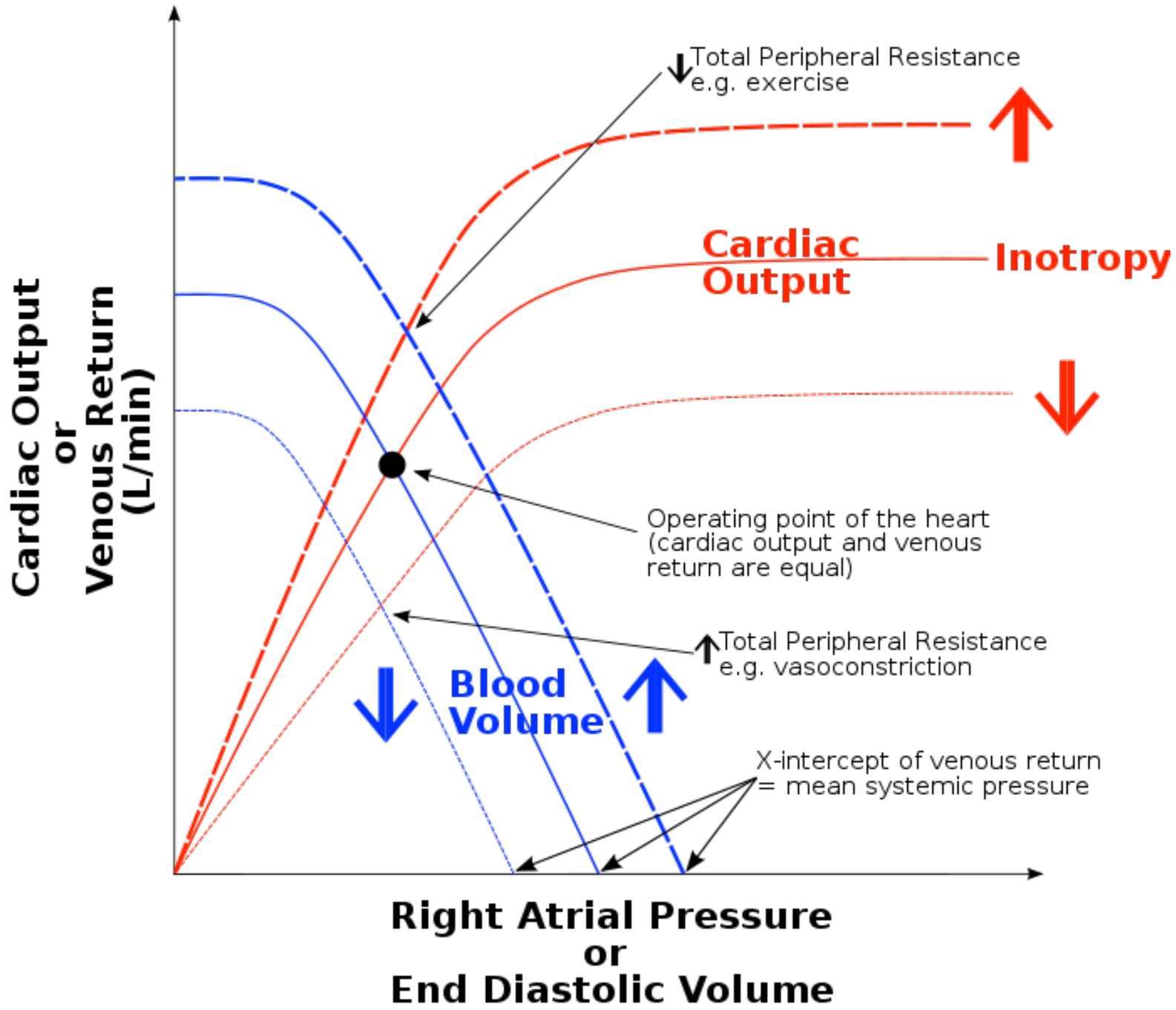
Verani JR, et al. Prevention of Perinatal GBS. CDC Revised Guidelines. MMWR 2010

Mukhopadhyay S, Puopolo KM. Risk Assessment in Neonatal Early Onset Sepsis, Sem Perinatl 2012

Step 2: Restore Perfusion

MAP, HR, UO
Hematocrit
FHR

CVP, PA, Echo



Shippy et al., 1984,Shoemaker et al. 1990, Lindeborg 1993

Step 2: Restore Perfusion

Parameter	Nonpregnant	Pregnant	Change (%)
CO (L/min)	4.3	6.2	43
HR (bpm)	71	83	17
COP (mmHg)	20.8	18	-14
COP-PCWP	14.5	10.5	-18
SVR (dyne/s/cm^5)	1530	1210	-21
PVR (dyne/s/cm^5)	119	78	-34
MAP (mmHg)	86.4	90.3	NC
CVP (mmHg)	3.7	3.6	NC
PCWP (mmHg)	6.3	7.5	NC
LVSWI (g/m/m^2)	41	48	NC

Clark SL, et al. Central hemodynamic assessment of normal term pregnancy. AJOG 1989:161:1439-42

Step 2: Restore Perfusion

Hypotension or Lactate > 4 mmol/L

Goals	**Remeasure**
MAP > 65 mmHg CVP > 8 mmHg (12 if ventilated)	If Initial Lactate > 2

Volume Challenge

CO/PCWP/LVSWI

COP-PCWP Gradient

Fluids
Crystal/Colloid

Dwell Time

Crystalloid: 28% at 30 min

Colloid: 100% at 30 min

Roberts, 1971; Hawkins 1980; Kaufman 1984; Ueyama et al. Anesthesiology 1999

www.survivingsepsis.org/Bundles/Pages/default.aspx

Step 2: Restore Perfusion

Hypotension or Lactate > 4 mmol/L

Goals
MAP > 65 mmHg
CVP > 8 mmHg (12 if ventilated)

Maternal Macro/
Microvascular
Shunt v Perfusion
Lactic Acid

Vasopressor
Phenylephrine
NorEpi/Epi

Maternal v Fetal
FHR Tracing

Fluids
Crystal/Colloid

Inotrope
Dopamine
Dobutamine

Hyperdynamic Ability
CI > 4.5L/min/m^2
DO_2 >0.6L/min/m^2

Porembka 1993; Rolbin 1979; Martin 1993; Shoemaker 1988; Gattinoni 1995; Rivers 2001

Step 3: Improve Oxygenation

Hypotension or Lactate > 4 mmol/L

Goals
MAP > 65 mmHg
CVP > 8 mmHg (12 if ventilated)

Steroids

Vasopressor
Phenylephrine
Norepi/Epi

Oxygen

Fluids
Crystal/Colloid

Inotrope
Dopamine

Hemoglobin
> 7 gm/dL

Step 3: Improve Oxygenation

Hypotension or Lactate > 4 mmol/L

High Dose Steroids
Short term, Superinfections, ARDS
Fetal Pulmonary Maturation

Steroids

Decreased Ability to Extract O2
Cellular and Mitochondrial Dysfunction
Microvascular Shunting
Autoregulation Loss

Oxygen

Left Shift O_2Hb Dissociation Curve
Hypophosphatemia, Alkalosis, Transfusions

Hemoglobin
> 7 gm/dL

Tuchschmidt 1991; Gutierrez 1989; Duff 1969; Shoemaker 1983, 1991; Demling 1984; Pinsky 1989

Step 4: Consider Interventions

Magnesium
Fetal neurologic protection
Reduced sepsis mortality (2-3 x)

Histologic Analysis
To determine fetal infection

Induction or Cesarean Delivery
Fetus as source of infection
Fetal viability

Magnesium

Cord Sampling

Delivery

Jenkins TM, AJOG 2003; Tomlinson MW, OB Gyn 1998; Chau A, Tsen LC, Curr Opin Anesth 2014

Step 4: Consider Interventions

COVID-19 with mild ARDS	COVID-19 with Mod to Severe ARDS	Rescue/Adjunctive therapy
✓ **Do:** Vt 4-8 ml/kg and P_{plat} < 30 cm H_2O	⚠ **CONSIDER:** Higher PEEP	? **Uncertain:** Antivirals, chloroquine, anti-IL6
✓ **Do:** Investigate for bacterial infection	⚠ **CONSIDER:** NMBA boluses to facilitate ventilation targets	⚠ **CONSIDER:** if proning, high P_{plt}, asynchrony NMBA infusion for 24 h
✓ **Do:** Target SpO2 92% - 96%	⚠ **CONSIDER:** if PEEP responsive Traditional Recruitment maneuvers	⚠ **CONSIDER:** Prone ventilation 12-16 h
⚠ **CONSIDER:** Conservative fluid strategy	⚠ **CONSIDER:** Prone ventilation 12-16 h	⚠ **CONSIDER:** STOP if no quick response A trial of inhaled Nitric Oxide
⚠ **CONSIDER:** Empiric antibiotics	⚠ **CONSIDER:** if proning, high P_{plt}, asynchrony NMBA infusion for 24 h	⚠ **CONSIDER:** follow local criteria for ECMO V-V ECMO or referral to ECMO center
? **Uncertain:** Systematic corticosteroids	⛔ **Don't do:** Staircase Recruitment maneuvers	
	⚠ **CONSIDER:** Short course of systemic corticosteroids	
	? **Uncertain:** Antivirals, chloroquine, anti-IL6	

Fig. 3 Summary of recommendations on the management of patients with COVID-19 and ARDS

Alhazzani W, et al. Surviving Sepsis: COVID 2019: Int Care Med 2020;46:854-887

Take Home Messages

Take Home Messages

Fetal Optimization During Maternal Sepsis

MEW: Maternal Early Warning
SIRS: Systemic Inflammatory Response Syndrome
qSOFA: quick Sequential Organ Failure Assessment

- Definitions
- Identify Risks
- Therapies

1. Early & Appropriate Antibiotics
2. Maximize Uteroplacental Flow
3. Minimize Fetal Oxygen Demand
4. Avoid Preterm Delivery
5. Monitor/Intervention

https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/Adult-Patients

Stephens AJ, et al. Maternal Sepsis Guidelines, AJ Perinat 2023