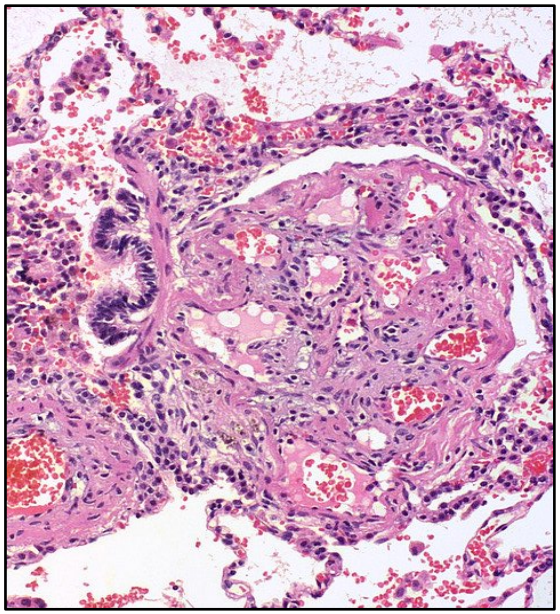
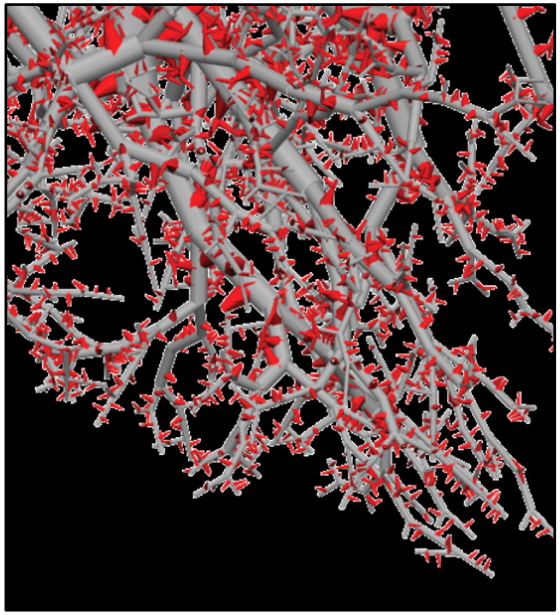
Pregnancy and Pulmonary Hypertension: Prevention and Management





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Statement on pregnancy in pulmonary hypertension from the Pulmonary Vascular Research Institute

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Special Considerations for the Pulmonary Hypertension Patient

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Kristina T. Kudelko, Roham T. Zamanian, and Vinicio A. De Jesus Perez

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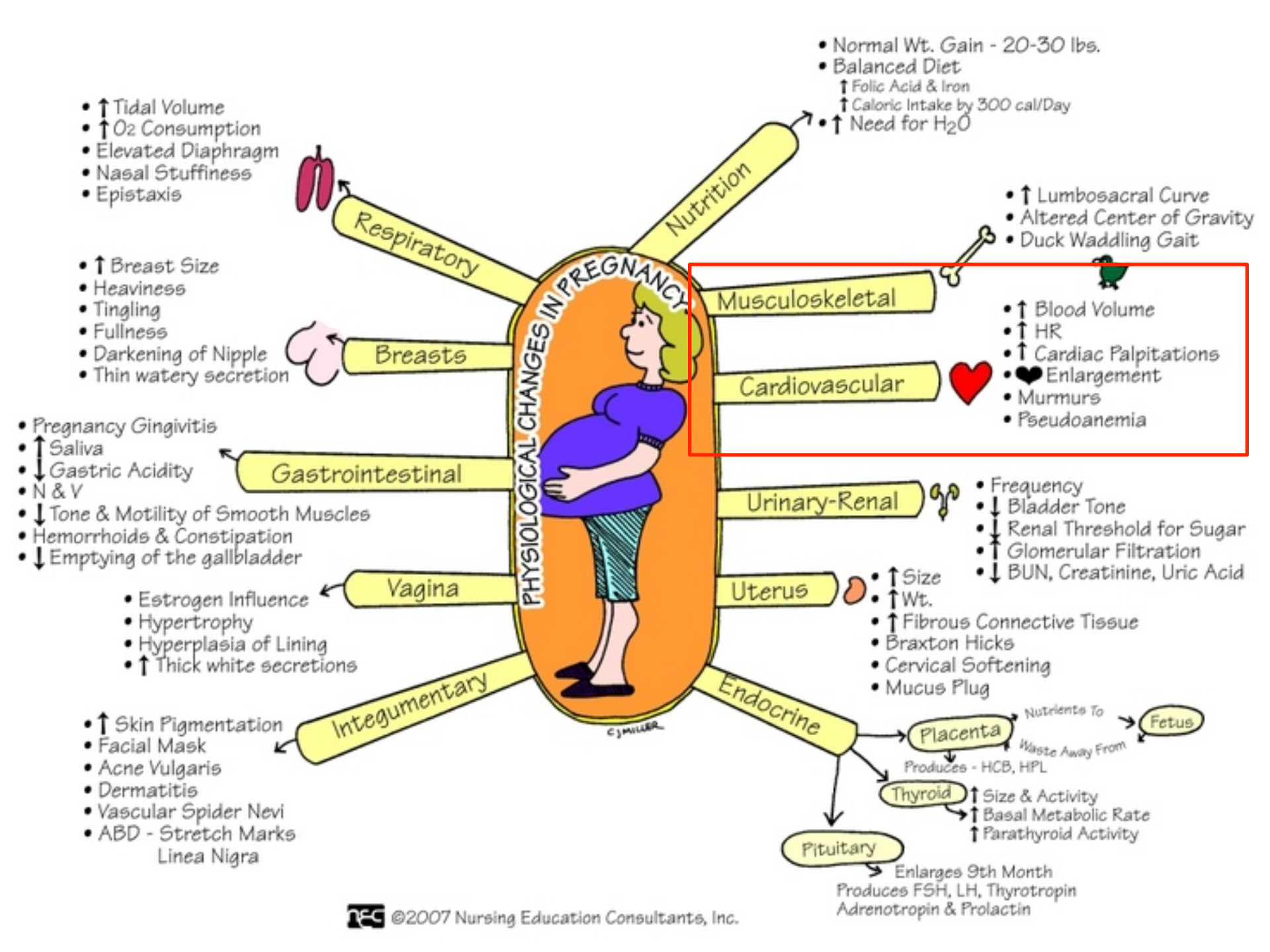
PHYSIOLOGICAL CHANGES IN PREGNANCY
Nutrition
• Normal Wt. Gain - 20-30 lbs.
• Balanced Diet
↑ Folic Acid & Iron
↑ Caloric Intake by 300 cal/Day
• ↑ Need for H_2O
Respiratory
• ↑ Tidal Volume
• ↑ O_2 Consumption
• Elevated Diaphragm
• Nasal Stuffiness
• Epistaxis
Musculoskeletal
• ↑ Lumbosacral Curve
• Altered Center of Gravity
• Duck Waddling Gait
Breasts
• ↑ Breast Size
• Heaviness
• Tingling
• Fullness
• Darkening of Nipple
• Thin watery secretion
Cardiovascular
• ↑ Blood Volume
• ↑ HR
• ↑ Cardiac Palpitations
• ❤ Enlargement
• Murmurs
• Pseudoanemia
Gastrointestinal
• Pregnancy Gingivitis
• ↑ Saliva
• ↓ Gastric Acidity
• N & V
• ↓ Tone & Motility of Smooth Muscles
• Hemorrhoids & Constipation
• ↓ Emptying of the gallbladder
Urinary-Renal
• Frequency
• ↓ Bladder Tone
• ↓ Renal Threshold for Sugar
• ↑ Glomerular Filtration
• ↓ BUN, Creatinine, Uric Acid
Vagina
• Estrogen Influence
• Hypertrophy
• Hyperplasia of Lining
• ↑ Thick white secretions
Uterus
• ↑ Size
• ↑ Wt.
• ↑ Fibrous Connective Tissue
• Braxton Hicks
• Cervical Softening
• Mucus Plug
Integumentary
• ↑ Skin Pigmentation
• Facial Mask
• Acne Vulgaris
• Dermatitis
• Vascular Spider Nevi
• ABD - Stretch Marks
Linea Nigra
Endocrine
Placenta
Nutrients To
Fetus
Waste Away From
Produces - HCB, HPL
Thyroid
↑ Size & Activity
↑ Basal Metabolic Rate
↑ Parathyroid Activity
Pituitary
Enlarges 9th Month
Produces FSH, LH, Thyrotropin
Adrenotropin & Prolactin
C J MILLER
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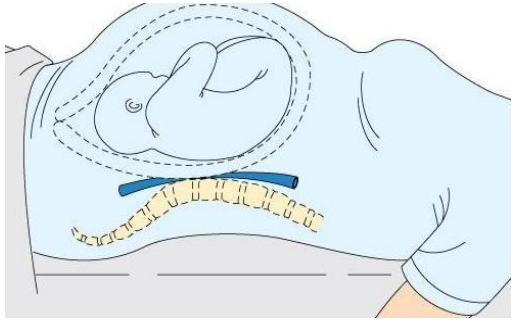
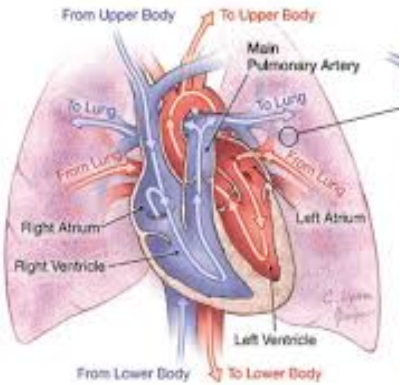
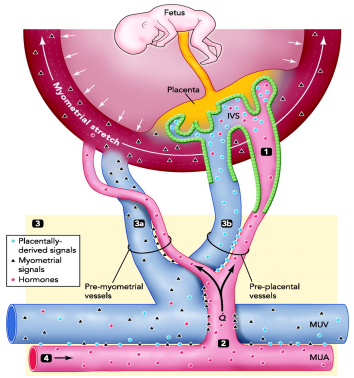
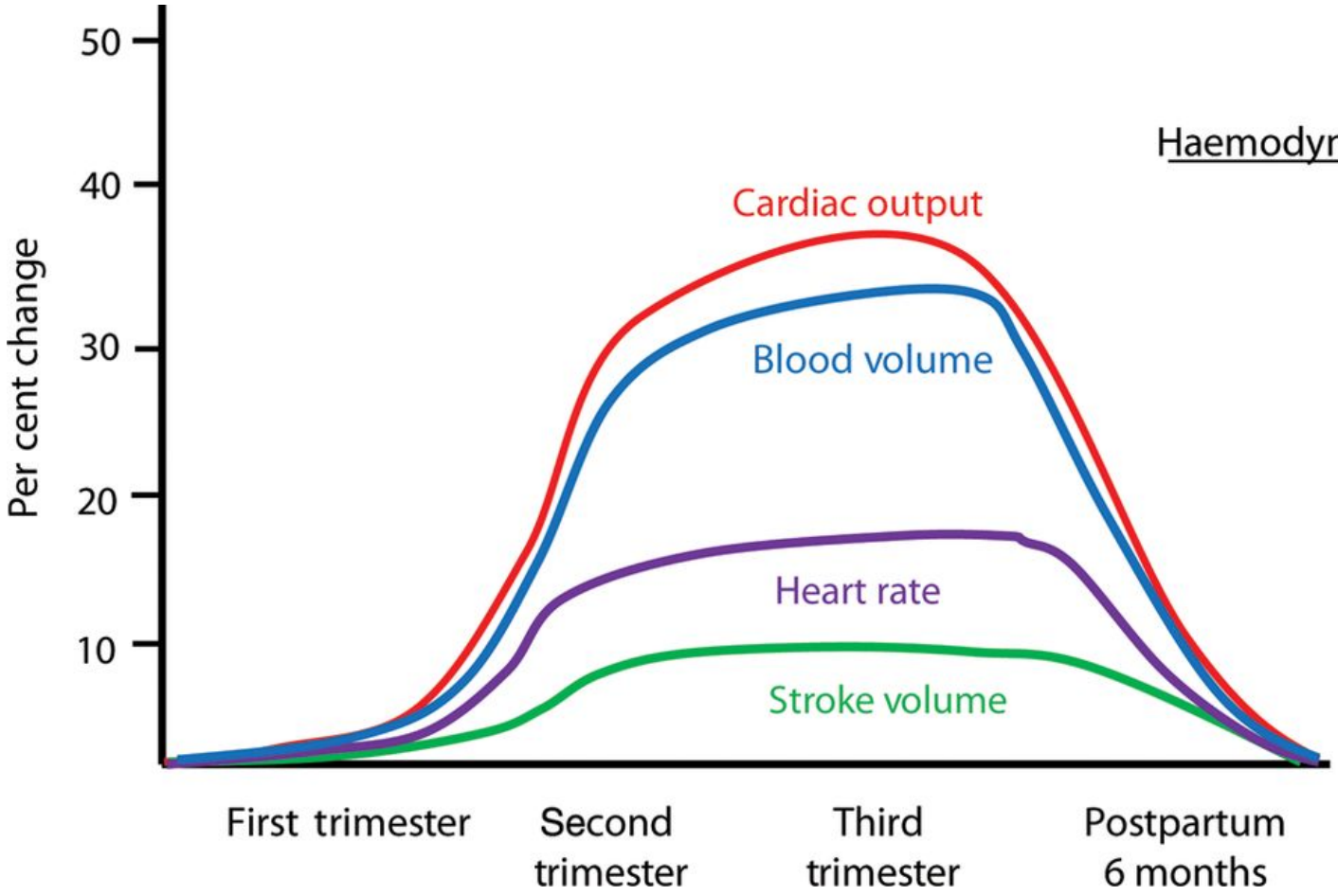








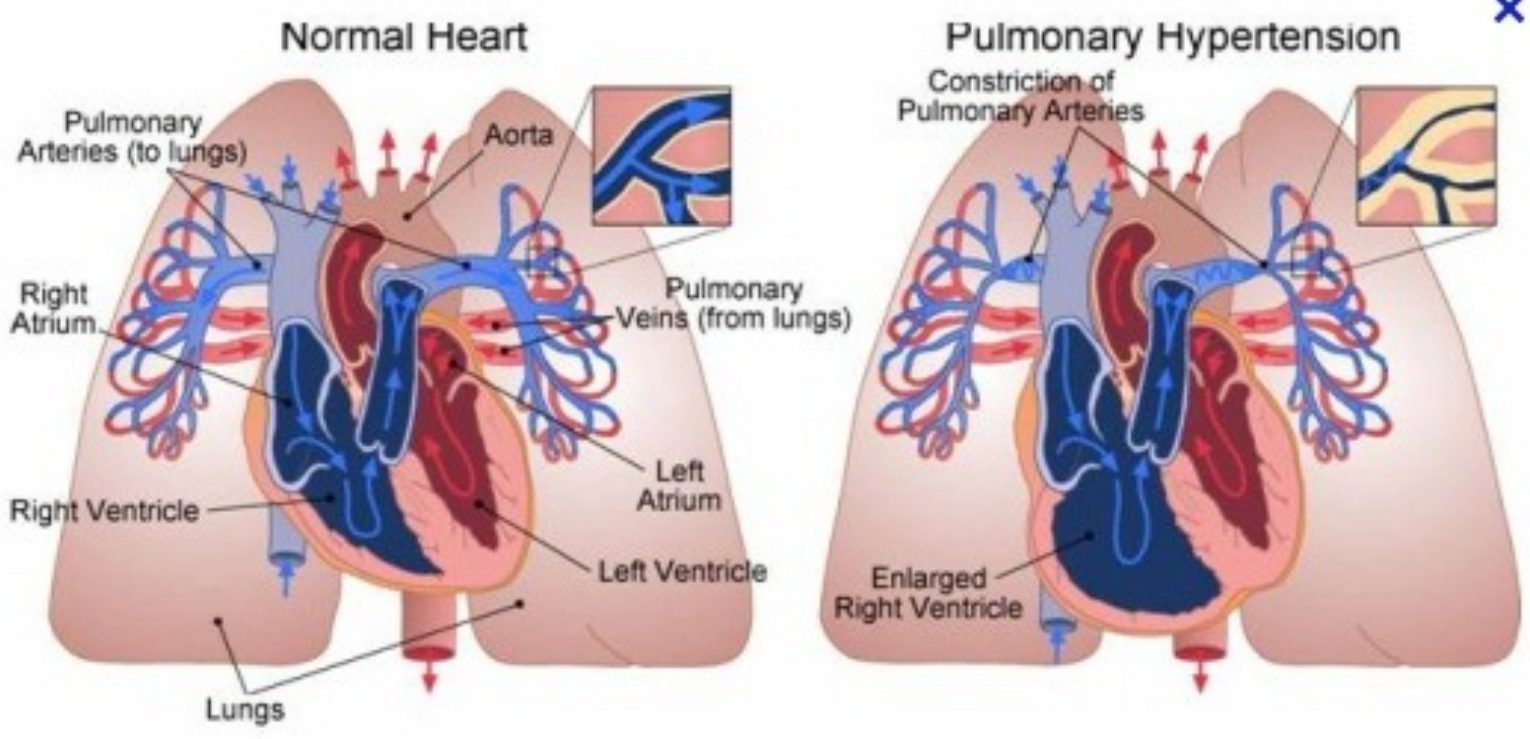
Haemodynamic parameter at term

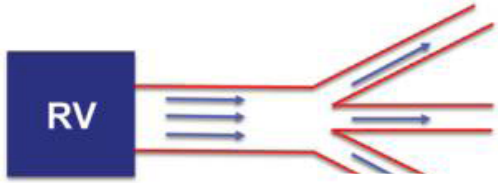
Cardiac output 6.2 ± 1.0 L/min[1]

Blood volume 3689 mL[2]

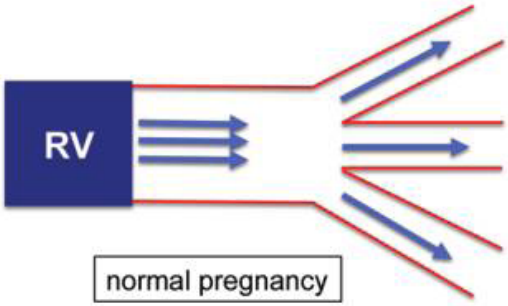
Heart rate 83 ± 1.0 beats/min[1]

Stroke volume 80 ± 2 mL[1]

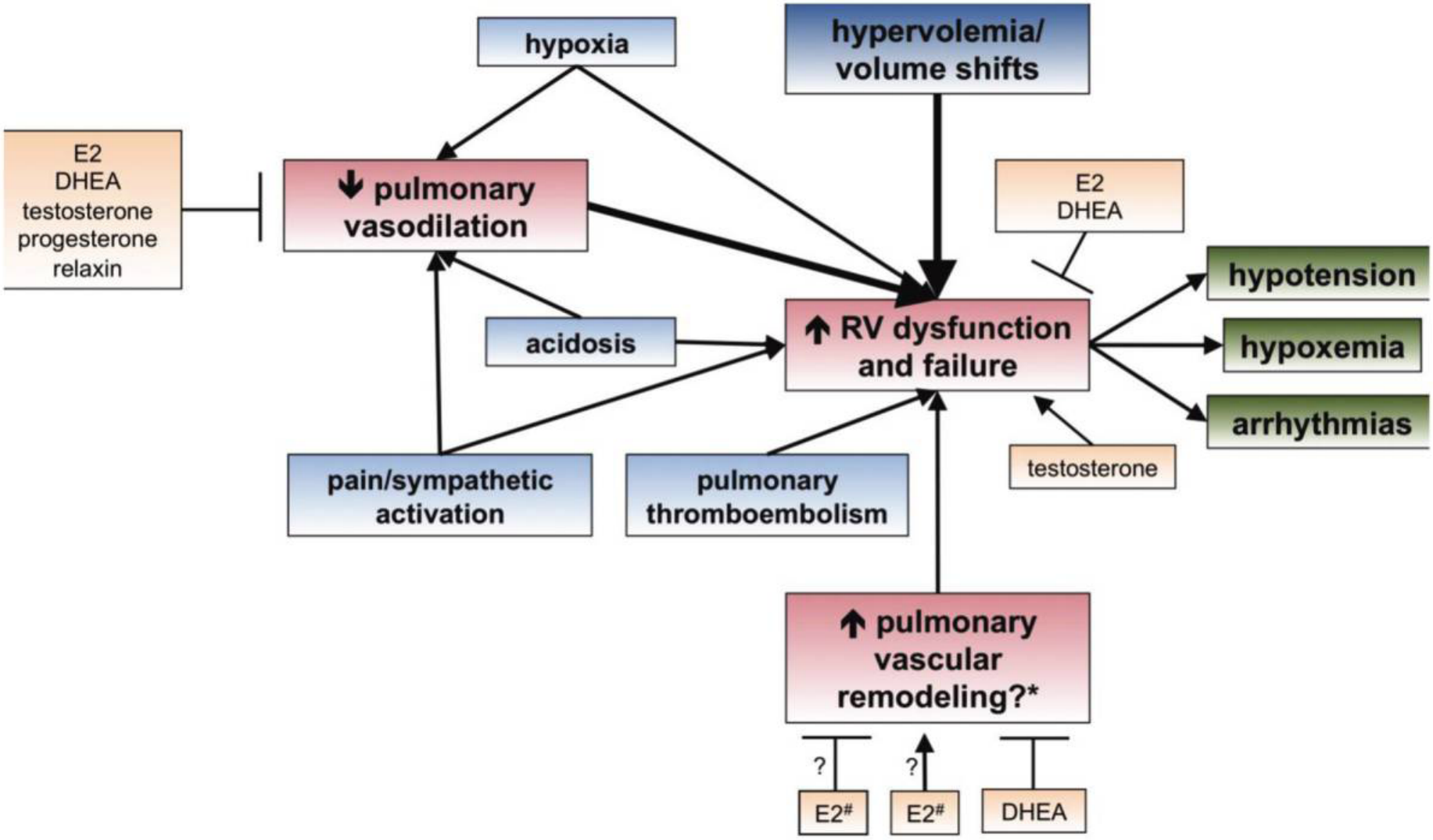




normal



normal pregnancy


hypoxia
hypervolemia/
volume shifts
E2
DHEA
testosterone
progesterone
relaxin
↓ pulmonary
vasodilation
E2
DHEA
hypotension
acidosis
↑ RV dysfunction
and failure
hypoxemia
arrhythmias
pain/sympathetic
activation
pulmonary
thromboembolism
testosterone
↑ pulmonary
vascular
remodeling?*
?
?
E2#
E2#
DHEA

Why do Pregnant Patients with PH Die?

- There is concern that pro-survival and pro-proliferative effects of estrogens may worsen the pulmonary vascular remodeling in pregnant PAH patients.

- It is unknown whether the frequently observed worsening of PAH in pregnancy is indeed due to direct effects of sex hormones on the pulmonary vasculature.

- Deterioration during labor and delivery or in the postpartum phase frequently is triggered by volume shifts and intravascular pressure swings.

- The majority of maternal deaths occurred in the peri-partum period, mainly within the first month of delivery, with RV failure and circulatory collapse being the main causes of death.

Hormones, Pregnancy and PH: Is there a Link?

- The overarching problem in the pregnant PH patient is that the physiologic compensatory vasodilator response of the pulmonary vasculature is decreased or absent.

- Deterioration is most frequent between weeks 20 and 24, during labor and delivery, or in the postpartum period.

- Since worsening of PAH frequently occurs in the postpartum period and therefore at a time point at which sex hormone levels decrease dramatically, it is possible that a "sex hormone withdrawal phenomenon" results in PA vasoconstriction in the postpartum state.

- Studies investigating whether pulmonary vascular remodeling indeed progresses in pregnant PAH animals are needed.

Pregnancy in PAH Survival: Before the Modern Medication Era

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Outcome of Pulmonary Vascular Disease in Pregnancy: A Systematic Overview From 1978 Through 1996

BRANKO M. WEISS, MD, LEA ZEMP, BURKHARDT SEIFERT, PHD, OTTO M. HESS, MD*

Zurich and Bern, Switzerland

Table 3. Management and Outcome of Pregnant Women With Eisenmenger's Syndrome (n = 73)

	Maternal Survival	Maternal Mortality
No. (%)	47 (64%)	26 (36%)‖
95% CI	52–75	25–48
Age (years)*	26.4 ± 4.8 (18–37)	24.9 ± 4.5 (18–33)
Hospital admission (weeks of pregnancy)*	26.7 ± 6.5 (10–39)	31.4 ± 5.9 (21–40)
Toxemia of pregnancy†	2 (4%)	3 (12%)
Delivery (weeks of pregnancy)*|	35.1 ± 3.5 (26–40)	34.4 ± 4.4 (26–40)
Vaginal delivery†	27 (57%)	11 (48%)
Operative delivery†	20 (43%)	12 (52%)‖
Monitoring		
Noninvasive, not reported†	24 (51%)	15 (63%)
Invasive SAP and/or CVP†	23 (49%)	9 (37%)
Invasive PAP†	8 (17%)	6 (25%)
Anesthesia/analgesia		
Not reported†	13 (28%)	5 (22%)
Regional techniques†	22 (47%)	8 (35%)
General anesthesia†	12 (25%)	7 (30%)
Local anesthesia/analgesia†	0	3 (13%)
Oxytocic drugs†	14 (30%)	4 (17%)
Antithrombotic therapy†	28 (60%)	12 (46%)
Neonatal survival†	43 (96%)§	20 (77%)
95% CI	85–99	56–91
Maternal death, days postpartum (n = 23)‖	—	5 (0–30)‡

Table 4. Management and Outcome of Pregnant Women With Primary Pulmonary Hypertension (n = 27)

	Maternal Survival	Maternal Mortality
No. (%)	19 (70%)	8 (30%)§
95% CI	50–86	14–50
Age (years)*	25.7 ± 5.3 (14–36)	23.3 ± 4.4 (18–31)
Hospital admission (weeks of pregnancy)*	26.9 ± 5.5 (15–36)	28.7 ± 5.9 (18–36)
Toxemia of pregnancy†	1 (5%)	0
Delivery (weeks of pregnancy)*	35.2 ± 3.9 (29–39)	33.3 ± 5.4 (26–40)
Vaginal delivery†	12 (63%)	3 (37%)
Operative delivery†	7 (37%)	5 (63%)
Monitoring		
Not reported†	8 (42%)	4 (50%)
Invasive SAP and/or CVP†	11 (58%)	4 (50%)
Invasive PAP†	9 (47%)	5 (63%)
Anesthesia/analgesia		
Not reported†	8 (42%)	2 (25%)
Regional techniques†	9 (47%)	5 (63%)
General anesthesia†	2 (11%)	1 (13%)
Oxytocic drugs†	7 (37%)	3 (37%)
Antithrombotic therapy†	6 (32%)	3 (37%)
Neonatal survival†	18 (95%)	6 (75%)
95% CI	74–100	35–97
Maternal death, days postpartum§	—	6 (2–35)‡

Outcome of Pulmonary Vascular Disease in Pregnancy: A Systematic Overview From 1978 Through 1996

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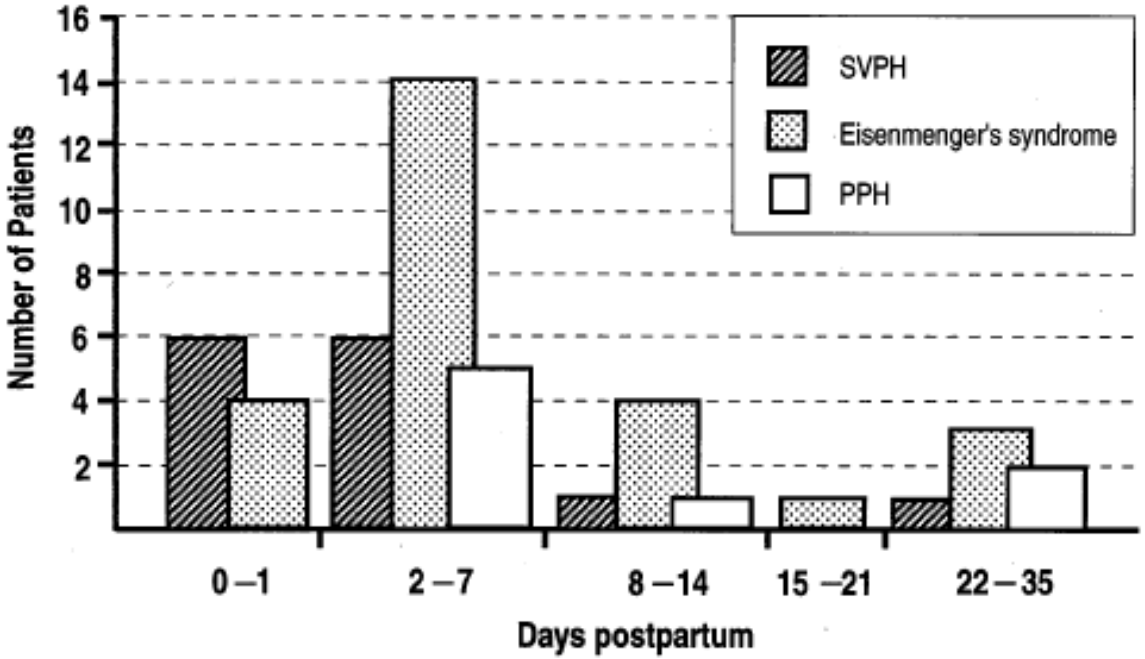

Figure 1. Time of maternal death in parturients with Eisenmenger's syndrome (n = 26), PPH (n = 8) and SVPH (n = 14). The 0–1 day postpartal period includes three patients with Eisenmenger's syndrome who died during pregnancy.

Pregnancy in PAH Survival: Before the Modern Medication Era

- Causes of death: pulmonary hypertensive crisis with therapy-resistant heart failure, sudden death, autopsy-confirmed pulmonary thromboembolism, cerebral thromboembolism, and rupture and dissection of the PA.

- Late diagnosis (P = 0.002, odds ratio: 5.4) and late hospital admission (P = 0.01, odds ratio: 1.1 per week of pregnancy) are independent predictive risk factors of maternal mortality.

- Parturients who received general anesthesia are 4 times more likely to die than parturients receiving regional anesthesia.

Pregnancy in PAH Survival: The Modern Medication Era

- Retrospective Chinese Study: The overall maternal mortality rate was 17%, but patients with Eisenmenger's syndrome had 50% mortality. There were 4 fetal/neonatal deaths (13%), and 16 infants were born preterm. All 26 live born infants survived.

- Prospective PH Multicenter Study: Out of 26 pregnancies, 62% were successful. Deaths occurred due to spontaneous abortions and in the immediate postpartum.

- Outcomes were better in patients with lower (500+/- 352 dynes) vs. very high (1,667 +/- 209 dynes) PVR.

- 50% of women with successful pregnancies had a positive vasodilator response and nearly normal pulmonary hemodynamics on CCBs.

Pre-pregnancy Counseling and Contraception

- Studies indicate that women are often not well informed about the necessity of contraception and the available options.

Method	Failure rate,[a] %		Women continuing use at 1 year, %
	Typical use	Perfect use	
Diaphragm[b]	12	6	57
Progestin-only pill	9	0.3	67
Depo-provera	6	0.2	56
Intrauterine			
ParaGard (copper T)	0.8	0.6	78
Mirena (levonorgestrel)	0.2	0.2	80
Progesterone implant	0.05	0.05	84
Female sterilization	0.5	0.5	100

Note: Adapted from Trussell.[205]

[a] Women experiencing unintended pregnancy within the first year of use.

[b] With spermicidal cream or jelly.

- Progestin only implants are safe and their efficacy is similar to sterilization.
- Progesterore releasing IUDs are also safe for PAH patients.
- Hysteroscopic sterilization should be considered over surgical sterilization.
- Estrogen containing compounds are relatively contraindicated due to risk of DVT/PE.
- Dual contraception is strongly advised.

Management of Pregnancy in PH Patients: Therapeutic Abortion

- Termination should be offered regardless of WHO FC or other markers of prognosis.
- The first trimester is the safest time for elective pregnancy termination; however, in the PH patient, pregnancy termination carries greater risk than in the general population and should be performed in an experienced center.
- Uterine dilatation and evacuation is the safest procedure.
- If surgical evacuation is not feasible, medical abortion using prostaglandins E1 or E2 or misoprostol can be administered to evacuate the uterus.
- Termination should also be considered in the second trimester up to the point of fetal viability. After that, early delivery may be considered if clinically indicated.

Management of Pregnancy in PH Patients: Assessment and Monitoring

- Individualized management plans for each patient must be discussed and updated before delivery.
- During labor and delivery, continuous monitoring of electrocardiogram, pulse oximetry, central venous pressure, and intra-arterial blood pressure should be routine.
- Close attention must be paid to avoiding conditions that may lead to PA vasoconstriction and worsening RV function.
- The patient should be as euvolemic as possible, and major fluid shifts must be avoided as much as possible.
- Vasopressors and inotropes should be readily available for hemodynamic support. Intravenous prostacyclins should be readily available.

Management of Pregnancy in PH Patients: Method of Delivery

- Although vaginal delivery is usually associated with fewer bleeding complications and infections in the healthy population, the hemodynamic and physiological changes associated may be detrimental to the mother with PH.
- Cesarean section is the preferred mode of delivery and should be used unless not available or in cases of emergencies.
- Elective cesarean section avoids labor and allows for careful, multidisciplinary planning and preparation of anesthesia, optimization of hemodynamics, and development of contingency plans.
- Regional anesthesia is always preferred over general.
- In stable women, planned delivery around weeks 34– 36 is recommended, with delivery before this if there is evidence of symptomatic decline.

Management of Pregnancy in PH Patients: Post-Partum Management

- Parturition and the first postpartum week have been recognized as particularly vulnerable periods for patients with PAH.
- Most of these women died in the first month after delivery, and the main causes of death were heart failure, sudden death and PE.
- Patients should be closely monitored for several days postpartum; monitoring in an intensive care unit in the first few days after delivery is recommended.
- If a PAH patient has been receiving anticoagulation therapy before pregnancy, Warfarin should be stopped and either unfractionated or low molecular- weight heparins used.
- Prophylactic heparin is recommended in the peripartum period.

Management of Pregnancy in PH Patients: Use of PH Specific Therapies

Table 5. FDA-assigned risk category for PAH medications

Drug	Pregnancy risk category[a]
Epoprostenol	B
Treprostinil	B
Sildenafil	B
Tadalafil	B
Nitric oxide	C
Iloprost	C
Bosentan	X
Ambrisentan	X
Macitentan	X
Riociguat	X

Management of Pregnancy in PH Patients: Use of PH Specific Therapies

- Parenteral prostaglandins are recommended for pregnant patients with PAH in WHO FC IV or where there is evidence of severe RV impairment.
- Inhaled iloprost or treprostinil may be used in patients with less severe symptoms, and their safe and successful use in pregnancy has been reported.
- sildenafil has generally been used in combination with a prostaglandin. There is no experience with tadalafil.
- If there is no rapid clinical improvement, immediate delivery should be considered because of the high risk of maternal death.
- For those patients meeting strict criteria for an acute response to inhaled nitric oxide, CCBs should be continued.

Management of Pregnancy in PH Patients: PH Specific Management

- The treatment goals during delivery are to maintain systemic and right atrial pressures, to monitor fluid balance, and to avoid volume overload, particularly in the first 48 hours.
- A rising right atrial pressure after delivery may simply reflect fluid overload and can be managed by judicious use of diuretic therapy.
- For stable patients receiving iv prostanoids, doses would usually remain unchanged before and during delivery. Low dose should be started in treatment naïve patients before delivery.
- If patients are receiving oral sildenafil, consideration should be given to using the iv preparation of the drug.
- For surgery under regional anesthesia, patients receiving nebulized iloprost or treprostinil therapy may continue to nebulized during the procedure.

Management of Pregnancy in PH Patients: Proposed Algorithm

Pregnant PAH Patient

Counsel on Pregnancy Risks

Discuss Therapeutic Abortion

(Recommended especially in high risk patients)

In patients electing to continue pregnancy

1st trimester →

Stop ETRA & warfarin/coumadin
Refer to high risk obstetrician
Monthly clinic visits
Monthly echocardiogram, BNP & 6MWT
Optimize PAH therapy
Start LMWH – if bed rest or inpatient
Recommend therapeutic abortion if right heart failure develops

2nd trimester →

Multidisciplinary approach with high risk obstetrician, PAH physician & anesthesiologist
Monthly clinic visits
Monthly echocardiogram, BNP & 6MWT
Start LMWH – if bed rest or inpatients
Optimize PAH therapy

Indicators of PH patients at high risk of poor outcomes in pregnancy:

1) early clinical deterioration
2) severe RV dysfunction
3) BNP elevation
4) FC III or IV symptoms

3rd trimester →

Multidisciplinary approach with high risk obstetrician, PAH physician & anesthesiologist
Weekly clinic visits
Weekly echocardiogram, BNP & 6MWT
Optimize PAH therapy
Start LMWH – if bed rest or inpatient
Elective cesarean section at week 34
Close post-operative ICU monitoring

Management of Pregnancy in PH Patients: Conclusions

- PH in pregnancy is a high-risk medical condition.
- Efforts should be made to educate patients and promote safe contraceptive methods.
- Planning for delivery is a process that requires a team approach.
- Pay attention to the impact of PH drugs on pregnancy.
- Patients in the post-partum period are most vulnerable to death and should be closely monitored in an ICU setting.
- Be an advocate for your patient and encourage alternatives to pregnancy for conception.