Pulmonary Hypertension, Prostacyclin Analogues, and Platelet Function: A Case Series

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Background

Pulmonary hypertension in pregnancy is accompanied by a markedly increased risk of morbidity and mortality. Prior to the discovery of prostacyclin in the 1970's, treatment options were limited.

VASCULAR REMODELING

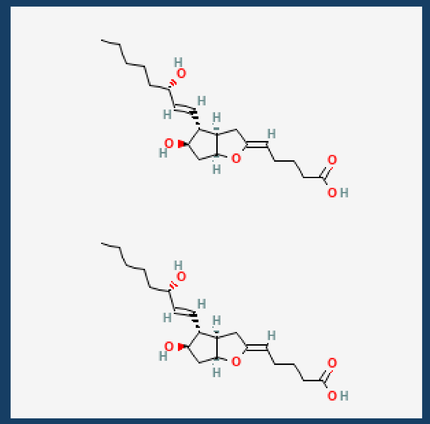
- Increased cell proliferation rates
- Reduced apoptosis

MEDIATOR IMBALANCE

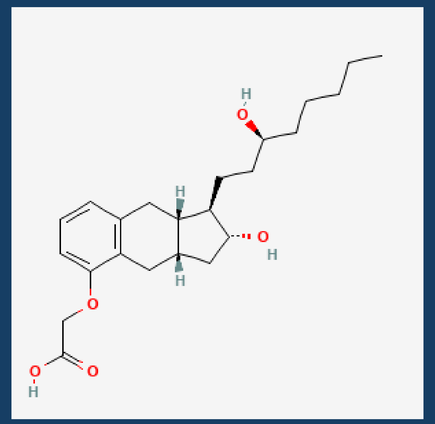
- Imbalance of vasoconstrictive & vasodilatory mediators
  - ↑ Thromboxane
  - ↑ Endothelin
  - ↓ Prostacyclin
  - ↓ Nitric oxide

ION CHANNEL DYSFUNCTION

- Loss of potassium channel activity & expression
- Upregulation of TRPC channels → smooth muscle membrane depolarisation & Ca^2 influx

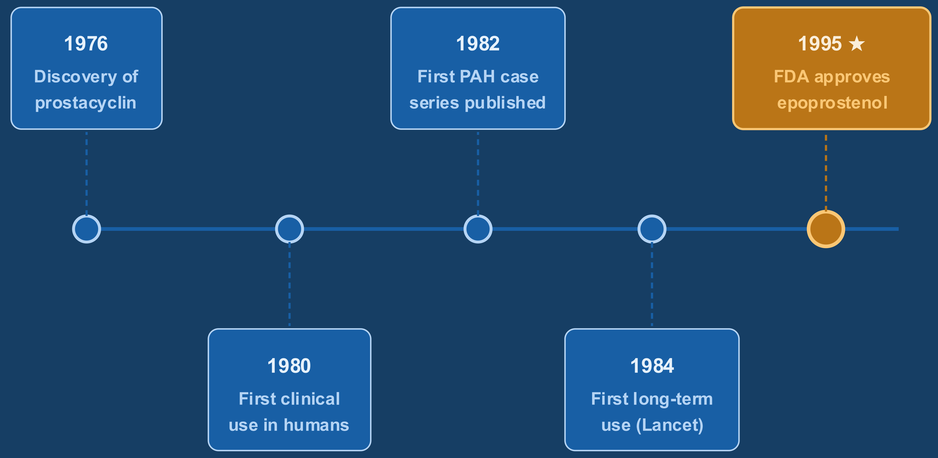


$C_{40}H_{64}O_{10}$ (PGI_2)

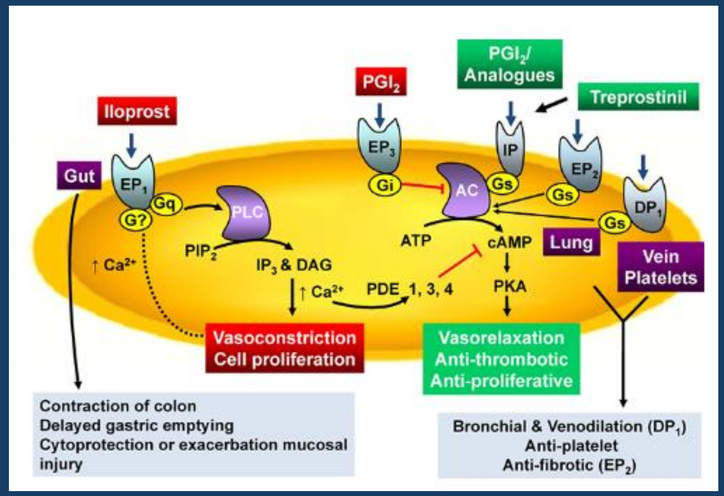


$C_{23}H_{34}O_5$ (Treprostinil)

Drug	Predominant Target
Prostacyclin (PGI_2) Epoprostenol	IP, DP, EP_3
Iloprost	IP, DP, TP, EP_1
Treprostinil	IP, DP, EP_2
Selexipag	Highly selective IP agonist



Landmark RCT published 1996 confirmed survival benefit, validating the 1995 approval



(Clapp et al., 2015)

The Cases

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Case 1

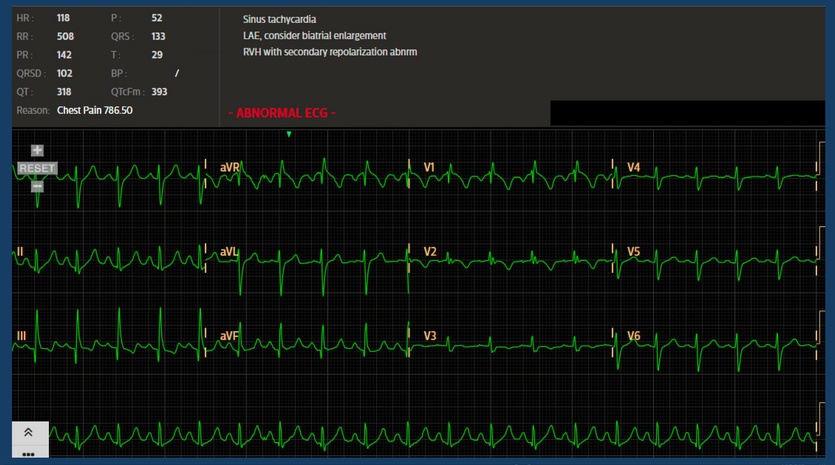
40 y/o G6P4014 presenting at 30w5d for a cardiac workup in the setting of shortness of breath.

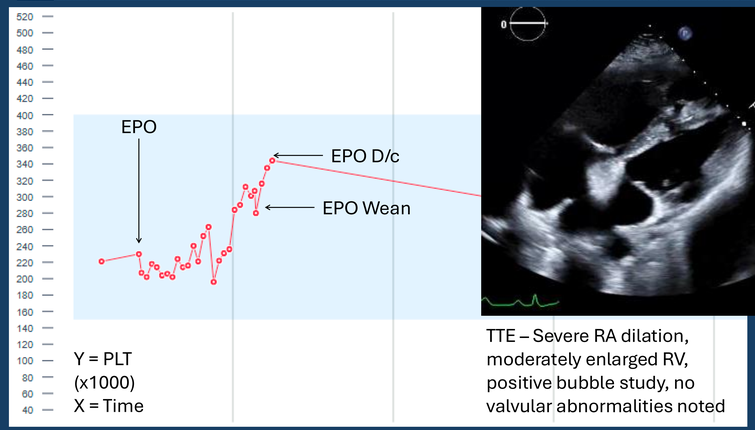
- NYHA II heart failure, pre-capillary pulmonary hypertension on RHC.
- RHC mPAP 31, PCWP 6
- 3x episodes of SVT, self resolved
- PO sildenafil -> MICU -> IV EPO
- Arterial line and epidural placed prior to IOL, level maintained at T6 with 0.375% bupivacaine
- Delivered at 32w5d by cesarean section (CS).
- PLT remained between 200-260
- PFA (epinephrine/col of 202 and ADP/collagen 120) was borderline abnormal
- ROTEM evaluation WNL.

<u>Outcomes</u>

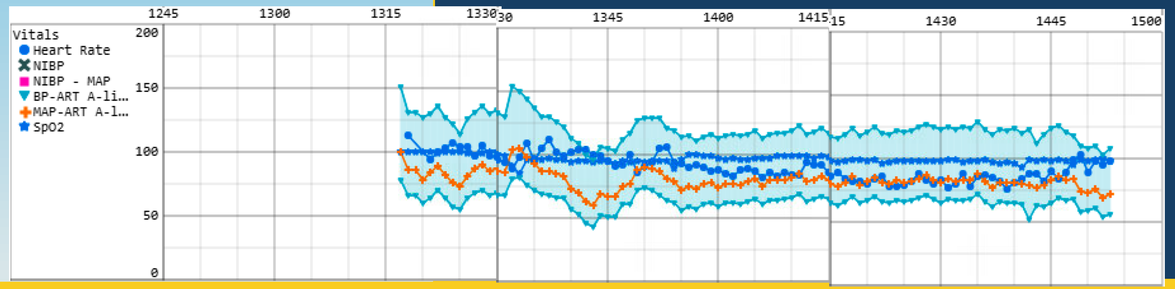
Mom: 33 day admission. D/c on Macitentan 10mg daily, sildenafil 20mg TID. On f/u, NYHA II -> III, added Lasix 20mg daily and planned to add sotatercept and inh prostaglandin following repeat TTE

Baby: NICU graduate. Discharged home with mom, doing well.





TTE – Severe RA dilation, moderately enlarged RV, positive bubble study, no valvular abnormalities noted



Case 2

28 y/o G2P0010 at 27w5d with rheumatic heart disease c/b HFpEF and pulmonary hypertension, presented for progressive peripheral edema.

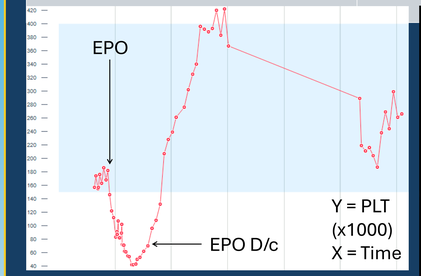
- pHTN: Suspect component of groups 1 & 2
- RHC: mPAP 59, PCWP 17, TPG >12
- Admitted to the MICU, EPO initiated, Swan-Ganz catheter, A-line placed
- Delivered at 28w4d by CS for worsening maternal and fetal condition. Epidural placed (PLT 82, 1u PLT transfused) and titrated with 2% Lido w/ Epi & Bicarb in 2-3 mL boluses
- ROTEM on EPO day 3 (PLT 102)
  - INTEM: Reduced alpha angle (64 deg), prolonged clotting time (212 s) and clot formation time (135 s)
  - EXTEM: Prolonged clot formation time (144 s)
- PF4 negative, HELLP, Pre-E w/ SF, ITP all less likely

<u>Outcomes</u>

Mom: 35 day admission. D/c on sildenafil and IV Treprostinil; Readmission 1 month later for line infection, decompensated HF. Now doing well on IV Treprostinil 20 ng/kg/min (line replaced), Sotatercept 45mg subQ q3wks, Macitentan 10mg daily, Sildenafil 20mg TID, Bumex 2mg daily

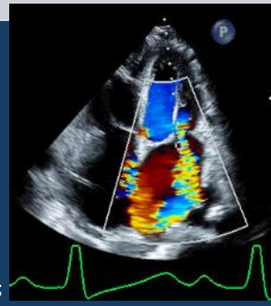
Baby: NICU graduate (5 month admission)

Maternal Concerns	Fetal Concerns
- pHTN - HFpEF - Valvular disease - Gestational HTN - Volume overload - Congestive hepatopathy - Thrombocytopenia	- Severe FGR - pAEDF in both umbilical arteries (intermittent -> persistent) - Concern for impending fetal deterioration

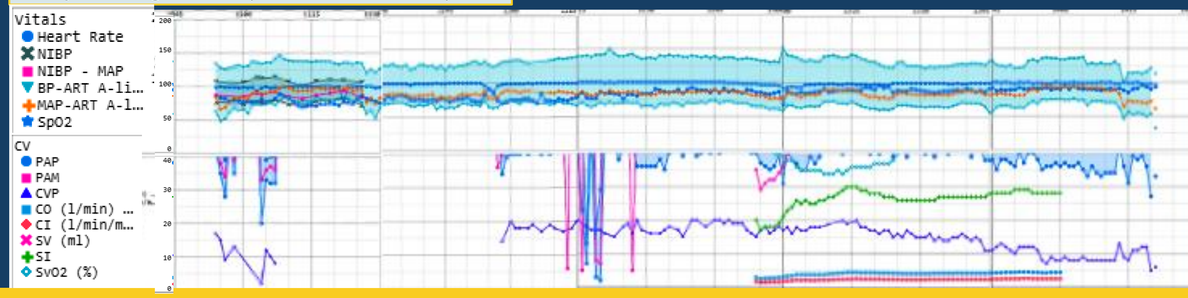


1st ABG @ 1220 Ph 7.48; pCO2 34.5; pO2 178; BE 2; HCO3 27; NA 137; K 3.3; iCa 1.00; Glu 95; Hgb 14.9

Last ABG @ 1342 Ph 7.391; pCO2 37.9; pO2 375; HCO3 23; Na 136; K 3.5; iCa 1.08; Glu 130; Hgb 15.3



TTE – Severe MS, MR, TR, RA dilation, and severely elevated PASP



Discussion

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Teaching Points

1. EPO is commonly utilized to treat severe or symptomatic pulmonary hypertension during pregnancy.
2. Studies estimate 35-65% of patients treated with EPO will experience thrombocytopenia
3. Many case reports describe bleeding complications in these patients, particularly when paired with concomitant anticoagulation
4. This has implications for neuraxial intervention, PPH, other surgical and unrelated bleeding complications
5. Laboratory testing, including platelet function assays and viscoelastic testing may provide value in the evaluation of coagulopathy in these patients.

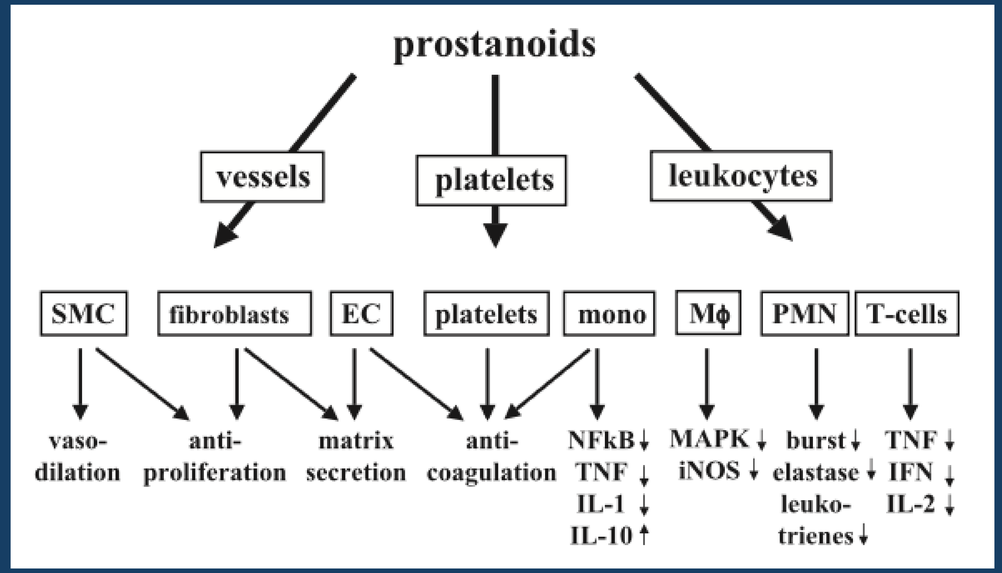
TABLE 2. Treatment Scheme for Prostacyclin-Induced Thrombocytopenia

Platelet Count	Procedure
$>50 \times 10^9$/l and/or asymptomatic patients	Continuation of the treatment with an unchanged dosage
$<50 \times 10^9$/l and/or mild symptoms of bleeding diathesis - slight bruising, insignificant purpura	Dosage reduction/follow-ups with strict blood count once a month and close observation of the patient
$<30 \times 10^9$/l and/or significant symptoms of bleeding diathesis	Reduction of the drug dosage/discontinuation of the drug and administering a different drug
$<10 \times 10^9$/l and/or clinically significant bleeding	Absolute discontinuation of the drug/platelet concentrate/ immunoglobulin/steroid therapy/plasmapheresis. A medical contraindication to administer a specific prostacyclin analogue again.

(Grzesk et al., 2020)

Impact on platelets – adverse effect or feature?

- Platelets express functional IP, DP_1, and EP_2 receptors
- Polymorphisms in the IP receptor have been associated with platelet disorders and accelerated cardiovascular disease
- Downstream effects include:
  - Reduced platelet activation
  - Reduced platelet aggregation
  - Reduced release of platelet derived growth factor (PDGF)



(Olschewski et al., 2004)

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