Hemodynamic Effects of Prostaglandin E₂

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Prostaglandin (PG) E₂ has been used in obstetrics for several years as a mid-trimester abortifacient. The known side effects of PGE₂ include an increase in heart rate, pyrexia in 40% of patients, and tachypnea, which are well known to obstetricians. These cases rarely come to the attention of an anesthesiologist. Although the central and peripheral effects of PGE₂ have been studied in animals, the potentially significant hemodynamic changes detectable by monitoring with a pulmonary-artery catheter are minimally explored in humans. An increased peak cardiac output (64.5%) has been demonstrated in patients undergoing second-trimester abortion using an ultrasonic Doppler computer. We report our observations in a patient with the diagnosis of preeclampsia monitored with a pulmonary-artery catheter during treatment with PGE₂.

CASE REPORT

A 30-yr-old G2P₁ woman presented with the diagnosis of alpha thalassemia minor and an intrauterine pregnancy of an estimated 25 weeks gestation having physical and sonographic findings consistent with hydrops fetalis. At admission, the patient had generalized edema, deep tendon reflexes, 3+ proteinuria, and elevated systemic blood pressure with diastolic pressure of 85 mm Hg. She was admitted for observation with the diagnosis of probable preeclampsia.

Her initial course was unremarkable, but the following morning at 6:30, rates were noted over both lung fields. A chest radiograph revealed diffuse interstitial edema indicating a diagnosis of severe preeclampsia. Her vital signs were not significantly changed from those at admission, excepting increased diastolic pressure of 90 mm Hg. Arterial blood gas (ABG) and measurements while she was breathing room air revealed a pH 7.41, PaCO₂ 25 mm Hg, PaO₂ 90 mm Hg, and base deficit —6.0. An anesthesiologist was asked to evaluate the patient preoperatively in case surgical delivery was required and to insert a pulmonary-artery catheter to monitor hemodynamics. Her initial hemodynamic values were a central venous pressure (CVP) of 8 mmHg, pulmonary-artery pressure (PAP) of 37/21, and pulmonary-artery wedge pressure (PAWP) of 20 mmHg. Other laboratory values were remarkable for a white blood cell count (WBC) of 7.2 × 10⁹, hematocrit of 29%, hypochromic, microcytic red blood cell indices (consistent with alpha thalassemia), and a platelet count of 90 × 10⁹.

Prothrombin and partial thromboplastin time were normal. Urinalysis revealed 3+ proteinuria and further laboratory data included a blood urea nitrogen of 20 mg%, and serum creatinine of 1.4 mg%.

Because of the maternal risks associated with eclampsia and the probable poor prognosis for the fetus, immediate vaginal delivery was recommended and the patient reluctantly agreed. The obstetrical plan at that time, 8:00 A.M., included: 1) inducing a vaginal delivery using PGE₂ vaginal suppositories at 3-h intervals to avoid the morbidity of surgical delivery; 2) phenytoin (500 mg) for seizure prophylaxis; 3) furosemide administration to achieve a PAWP < 15 mmHg; 4) restriction of fluids; and 5) supplemental O₂ administration at 6 l flow by mask. The patient was monitored by pulse oximetry (SpO₂), ECG, and PA pressures.

At approximately 10:00 A.M., anesthesiology personnel were again asked to assist in patient management, including further invasive monitoring. With patient consent, we inserted an arterial catheter and recommended a urinary catheter. Her apparent response to one-quarter of a PGE₂ vaginal suppository (approximately 5 mg) she received 2 h earlier was agitation and restlessness with a heart rate (HR) of 115 beats/min in sinus rhythm. Her systemic arterial pressure (Bp) was 100/50 mm Hg, respiratory rate (RR) 32/min, and urine output (U/O) averaging 0.5 ml·kg⁻¹·h⁻¹.

At 11:00 A.M., the patient was given a half of a PGE₂ vaginal suppository (10 mg). Thirty to sixty minutes later, her agitation increased, with HR at 155 beats/min, BP 110/75 mm Hg, and RR 48/min. Her temperature was 39° C, U/O unchanged, PAP 80/20 mm Hg, PAWP 18 mm Hg, and CVP 10 mm Hg. Cardiac output (CO) was 15 l/min (by thermodilution technique), with systemic vascular resistance (SVR) of 384 dyn·s⁻¹·cm⁻⁵, and ABG values of pH 7.53, PaCO₂ 23 mmHg, and PaO₂ 170 mmHg. Mixed venous blood O₂ saturation (SvO₂) was 73%, and WBC was 18 × 10⁹ with no left shift, 96% neutrophils. We informed the attending obstetricians that we considered some of these values consistent with, but not diagnostic of, early sepsis. Having no experience with pulmonary-artery catheter monitoring in this patient group, their clinical impression was that elevated temperature and heart and respiratory rates were probably attributable to PGE₂, but that the extent of change was excessive. The obstetrical staff decided to continue to effect a vaginal delivery, monitor the respiratory and cardiovascular status of the patient, and treat her fever with a cooling blanket, acetaminophen, and coverage with broad spectrum antibiotics. ABGs were measured every 30–60 min, appropriate blood chemistries drawn to characterize metabolic acidosis, and body fluids collected for bacterial identification and sensitivities.

Over the next 6 h, the patient remained agitated with occasional bouts of emesis and diarrhea. HR persisted at 150–160 beats/min, BP declined to 90–100 mm Hg systolic, and RR increased, averaging 50 breaths/min. Temperature fluctuated, averaging 40° C, and U/O increased to 2 ml·kg⁻¹·h⁻¹, while PAP, PAWP, and CVP decreased to 21/10 mm Hg, 6–9 mm Hg, and 5–7 mm Hg, respectively. CO declined to 12, then 8, l/min and SVR increased from 384 to 500 to 660 dyn·s⁻¹·cm⁻⁵. At 1400 h, she had received the last 10-mg dose of PGE₂ (total 25 mg). At 1700 h, ABG measurements indicated a progressive metabolic acidosis (pH 7.30 and base deficit to −10.4) with a consistent respiratory alkalosis (PaCO₂ 23 mmHg). SpO₂ stable at 99% (PaO₂ 6 l flow by mask) and SVO₂ 72%.
DISCUSSION

Parturients presenting with moderate to severe pre-eclampsia and a mid-trimester pregnancy with hydrops fetalis may have significant hemodynamic changes after PGE2 administration. Figure 1 provides the hemodynamic data and other physiologic observations for this patient. The temporal relationship of changes in cardiovascular and metabolic status to PGE2 administration is evident in figure 1. Two earlier case reports delineate similar pyrexial and hemodynamic changes after intravaginal PGE2 to facilitate evacuation of uterine contents secondary to intrauterine fetal demise and missed abortion. The authors similarly considered the etiology as endotoxemia. As with our case, all symptoms resolved with cessation of PGE2. These authors noted a moderate hypotension and tachycardia, but only speculated on the other possible hemodynamic changes. Recently, Willis et al. noted the increase in cardiac output after PGE2 administration. Cardiac output was determined by noninvasive ultrasonic Doppler in ten women being treated with PGE2 vaginal suppositories for mid-trimester abortions. A mean increase in peak cardiac output of 64.5% was demonstrated, but their data were limited by the lack of central vascular pressures. They also excluded patients with hypertensive disease. Secher et al. administered PGE2 alpha and PGE2 intravenously to women undergoing suction abortions with general anesthesia. Swan-Ganz catheters and femoral artery catheters were inserted to monitor the patients. The subjects were in the first trimester of pregnancy, which excluded the circulatory changes seen in later pregnancy. Further, the patients were observed for only 50 min. However, during infusion of PGE2, a 31% decrease in systemic blood pressure and a 33% decrease in systemic vascular resistance was noted, as well as a 36% increase in cardiac output. No note of temperature change was made and, because the patients received a general anesthetic and were given pancuronium bromide, the marked tachypnea seen in our patient could not be observed.

In the United States, PGE2 may be the agent of choice for mid-trimester evacuation of the products of conception, especially when oligohydramnios is present. PGE2 has a success rate of 90% or higher over approximately 12 h, depending on the parity. Although intravenous, intramuscular, and oral routes of administration have been tried, intravaginal suppositories allow easy, inexpensive administration, more localization to target organ, and reduced systemic exposure when compared with other routes. PGE2 suppositories are contraindicated with...
a viable fetus secondary to the risk of prolonged and uncontrollable uterine hyperstimulation. Nevertheless, low concentrations of PGE₂ in different slow-release vehicles are being investigated for topical application to dilate the cervix and increase the success of oxytocin induction at or near term pregnancy.⁶-⁸ Oxytocin as the primary agent has a poor success rate of induction with an un ripened cervix or early in pregnancy.⁹,¹⁰ Some obstetricians at our institution titrate the dose of PGE₂ to the side effects, while others administer a full 20-mg suppository every 3 h and decrease the dose if the patient cannot tolerate the side effects. The most common side effects are gastrointestinal disturbances manifested by nausea, vomiting, and diarrhea. Most patients have some degree of pyrexia and heart rate elevation accompanied by a slight decrease in systemic blood pressures.⁹ As a result, it is common to pretreat with antipyretics, antiemetics, and antidiarrheal medications.

When amniotic fluid is present, PGE₂ alpha had been the abortifacient of choice as an intra-amniotic injection, and the methyl analogue is now used as an intramuscular injection for the same purpose; these are drugs with which more clinicians have experience. PGE₂ has more effect on cervical dilation, which is distinct from uterine smooth muscle stimulation. PGF₂ alpha¹² acts more by direct uterine smooth muscle stimulation with less cervical dilatation, which explains why PGF₂ alpha may be used more effectively for an intramyometrial injection to control postpartum hemorrhage.¹¹,¹² Different prostaglandin groups, such as the PGF series versus the PGE series, may have opposite effects on one organ while having similar effects on another organ. For example, PGE₂ alpha has little effect on heart rate and causes bronchial and vascular smooth muscle constriction, while PGF₂ has the opposite effect. Secher et al. demonstrated that pulmonary vascular resistance doubled with the administration of PGF₂ alpha, while there was no change with PGE₂.² On the other hand, both PGE₂ and PGF₂ alpha cause increased intestinal motility.¹³

The action of PGE₂ is mediated through activation of adenylate cyclase.¹⁵ The duration of effect is 2–6 h after administration of a vaginal suppository. Cervical dilation or "ripening" is the result of enzymatic breakdown of collagen. In humans, pulmonary and systemic vasodilation has been shown to be a direct effect causing a reflex compensatory increase in cardiac output to maintain mean arterial pressure.¹⁴,¹⁵ Animal studies have failed to show any direct inotropic effect on cardiac muscle.¹⁶,¹⁷ PGE₂ also causes a diuresis, as seen in our patient, by virtue of increased renal blood flow secondary to renal artery dilation.¹⁵ Direct effects upon the hypothalamus may be a separate mechanism for the increase in heart rate and temperature.¹⁸,¹⁹ With the observed effects of PGE₂ described in this (non-septic) case, it is not surprising that prostaglandins are being actively investigated as mediators of septic shock.²⁰ Enzymatic inactivation of PGE₂ into fatty acids by the lungs under normal physiologic conditions helps clear the plasma and decrease systemic effects. In addition, enzymes that catalyze the degradation of PGE₂ are found in kidneys, spleen, adipose tissue, intestine, liver, and testicles, which act to preserve the local function of prostaglandins to these organs.¹⁴ It has been speculated that the extreme degree of side effects, as seen in our patient, may result from overwhelming the rate-limiting enzyme that inactivates prostaglandin, 15-hydroxyprostaglandin dehydrogenase, in a dose-dependent fashion or from ineffective inactivation of prostaglandins secondary to pulmonary pathology or genetic predisposition.¹

In conclusion, we report a case demonstrating the potential of profound and often confusing side effects of PGE₂ in obstetric patients. Recent theories of the etiology of preeclampsia invoke a relative deficit of PGI₂ (prostacyclin) or PGE₂, both of which have similar effects on the cardiovascular system. In our patient, the usual signs associated with preeclampsia, including elevated systemic and pulmonary vascular resistances and decreased urine output, were reversed by PGE₂. Over the last 15 yr, prostaglandins and their inhibitors have become an increasingly important part of pharmacologic intervention in various disease states. We expect that their impact on anesthetic management will increase as the use of these agents expands to more varied medical situations.

REFERENCES


