Management of Eisenmenger Syndrome in Pregnancy With Sildenafil and L-arginine

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BACKGROUND: Eisenmenger syndrome in pregnancy may be a life-threatening disease despite recent additions to the treatment options.

CASE: We present a woman with severe pulmonary hypertension due to Eisenmenger syndrome treated during pregnancy and delivery and postpartum with L-arginine and sildenafil to enhance the nitric oxide pathway. This combination was associated with significant improvement in the mother's clinical and hemodynamic condition and fetal well-being.

CONCLUSION: The concomitant use of sildenafil and L-arginine for the management of pulmonary hypertension in pregnancy, combined with multidisciplinary care, permitted a good outcome for the mother and her infant. (Obstet Gynecol 2004;103:1118–20. © 2004 by The American College of Obstetricians and Gynecologists.)

Atrial septal defects of the secundum type are common cardiac lesions, occurring in 10% of pregnant patients with congenital heart disease. Despite the fact that pulmonary hypertension complicating atrial septal defect–Eisenmenger syndrome–is relatively uncommon and does not usually occur until the fourth decade of life, several cases among pregnant women have been reported.[1–3] Management of these patients includes inhaled nitric oxide and prostacyclin, with variable responses. Although sildenafil and L-arginine reduce pulmonary hypertension in nonpregnant patients,[4,5] there are no reports on their chronic combined use in pulmonary hypertension in nonpregnant or pregnant women. We present the case of a patient with pulmonary hypertension, treated during the last weeks of pregnancy and postpartum with sildenafil (Viagra; Pfizer, New York, NY) and L-arginine in whom a good maternal and neonatal outcome was achieved despite superimposed preeclampsia.

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CASE

A 22-year-old nullipara developed progressive exertional dyspnea accompanied by syncope over 6 months. An atrial septal defect of the secundum type, with an estimated systolic pulmonary arterial pressure 121 mm Hg and a transpulmonary gradient 112 mm Hg, was diagnosed. Pulmonary hypertension was unresponsive to inhaled oxygen 100% and to sublingual nifedipine 20 mg, while sildenafil 50 mg orally managed a 40-mm Hg decrement. The atrioventricular defect was closed with a pericardial graft. Eight days postoperatively minor changes were observed in estimated pulmonary arterial pressure (Figure 1A). At that time she reported 7 weeks of amenorrhea and had a positive pregnancy test. Diltiazem 60 mg/d and sildenafil 150 mg/d were initiated. At 9 weeks of gestation sildenafil was discontinued because of its high cost, and diltiazem was increased to 180 mg/d. Three weeks later pulmonary artery pressure decreased. Thereafter her cardiac status progressed from New York Heart Association class II to class IV, in association with an increase in pulmonary artery pressure (Figure 1A).

At 31 weeks of gestation, the patient was dyspneic on minimal exertion, was cyanotic, and had moderate pretibial edema. Her blood pressure was 130/65 mm Hg, and heart rate 75 beats per minute. Ultrasonographic fetal evaluation estimated a fetal weight in the 15th percentile. Sildenafil 150 mg/d was initiated and diltiazem was discontinued. After 1 week of no clinical improvement L-arginine 3 g/d was added. Four days later her cardiac status improved to New York Heart Association class III. During the next 2 weeks fetal weight increased to the 35th percentile. At 36 weeks of gestation, obstetric evaluation revealed an arrest in fetal growth, and the ultrasonogram showed an increase in pulmonary artery pressure (Figure 1A). Blood pressure was 140/82 mm Hg, platelets 97,000/mm^3 (versus 141,000 platelets/mm^3 at 33 weeks of gestation), + proteinuria and uricemia 6.7 mEq/dL; serum creatinine and hepatic enzyme levels and electrocardiogram were normal. The patient was hospitalized for labor induction because her condition was aggravated by superimposed preeclampsia.

On admission the patient was receiving sildenafil 150 mg/d and L-arginine 3 g/d and had a respiratory rate of 32 breaths per minute, blood pressure 133/85 mm Hg, mild peripheral cyanosis, an oxyhemoglobin saturation of 99%, and moderate pretibial edema. Invasive monitoring, with a radial artery catheter and a Swan-Ganz with the thermodilution method, revealed a pulmonary artery pressure 84/24 mm Hg (normal values for pregnancy[6] are included in parenthesis, 15–30/4–12 mm Hg), pulmonary

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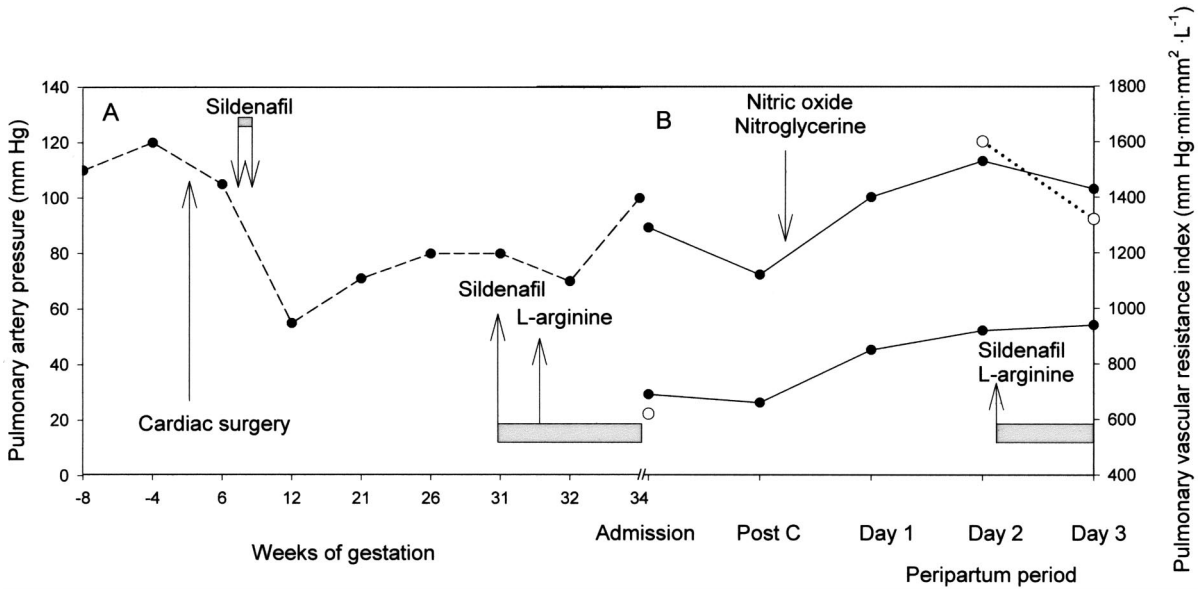

Figure 1. Systolic pulmonary pressures *(interrupted line)* before cardiac surgery, and up to the 34th week of gestation, estimated by Doppler ultrasound (A). Systolic and diastolic pulmonary artery pressure *(full circles)* and resistance *(empty circles)* on prepartum admission, immediately after cesarean delivery (Post C) and postcesarean delivery days, determined by invasive monitoring with a radial artery line and a Swan-Ganz catheter (B).

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vascular resistance 636 dn/s/cm (78 ± 22 dn/s/cm)[5] (Figure 1B), cardiac output 6.45 L/min (6.2 ± 1 L/min), left ventricle stroke work index 50.4 g/m/m^2 (48 ± 6 g/m/m^2), systemic vascular resistance 908 dn/s/cm (1,210 ± 266 dn/s/cm),[5] central venous pressure 5 mm Hg (3.6 ± 2.5 mm Hg) and pulmonary capillary wedge pressure 6 mm Hg (7.5 ± 1.8 mm Hg). All vasoactive agents were discontinued overnight in preparation for delivery.

Labor failed to progress after 8 hours of oxytocin infusion, and a cesarean delivery was scheduled. Epidural anesthesia was begun with fractionated doses of bupivacaine (65 mg), lidocaine (280 mg), and fentanyl (100 μg), achieving a T-6 anesthesia level after 35 minutes. During surgery the patient was asymptomatic; her blood pressure was 115–130/62–75 mm Hg, heart rate 80–100 beats per minute, pulmonary artery pressure 81–98/24–42 mm Hg (Figure 1B), and oxyhemoglobin saturation 99%. Crystalloids were restricted to 1 L to avoid pulmonary congestion. The surgical procedure was uneventful and a male infant of 2,290 g, Apgar score of 9 at 1 and 5 minutes, was delivered. Postoperative pain was managed with epidural morphine. After delivery, an increase in pulmonary artery pressure and ensuing dyspnea prompted the use of nitroglycerin, 0.05–0.5 μg/kg/min and subsequently of nitric oxide up to 64 ppm through a facemask, obtaining no hemodynamic improvement. Oxygen supplementation increased Spo_2 (93 to 98%). Sildenafil and L-arginine were reinitiated at 150 mg/d and 6 g/d, respectively respectively, achieving within a few hours a significant clinical improvement and a decrease in pulmonary artery pressure and pulmonary vascular resistance (Figure 1B). The patient was discharged 7 days postpartum on sildenafil 150 mg/d, L-arginine 6 g/d, and diltiazem 180 mg/d.

At 85 days postpartum, the patient had a stable cardiac status (New York Heart Association class II) while taking sildenafil, L-arginine, diltiazem, and coumadin. Fourteen months later she remains in New York Heart Association class II.

COMMENT

L-arginine, a semi-essential amino acid, is converted to nitric oxide by nitric oxide synthase. Nitric oxide activates guanilate cyclase to produce cyclic guanosine monophosphate (cGMP), which promotes smooth muscle relaxation. However, sildenafil is a selective phosphodiesterase-5 inhibitor of cGMP degradation, abundant in the corpum cavernossum and lung, promoting a greater availability of cGMP and hence smooth muscle relaxation.

In nonpregnant patients sildenafil and L-arginine decrease pulmonary hypertension.[4,5] When a single dose of sildenafil was combined with inhaled nitric oxide, the effects on cGMP and on pulmonary resistance were greater than when nitric oxide was administered alone,

supporting a synergy of actions directed at different sites of the nitric oxide–cGMP pathway.[4] The use of sildenafil in pregnancy is restricted to a few reports, which evaluate the effect of short-term intravaginal administration in the success of in vitro fertilization, and describe no deleterious effects on mother and fetus.[7] L-arginine has been administered to preeclamptic patients and to mothers with intrauterine growth restriction, with good tolerance and beneficial effects on maternal blood pressures and uteroplacental blood flow.[8] It is plausible to associate the prepartum improvement in pulmonary artery resistance and fetal growth to a beneficial effect of this combination in the maternal and placental hemodynamics. The mild decrease in systolic pulmonary pressure, previously refractory to nitric oxide and nitroglycerin, as well as the significant reduction in the pulmonary artery resistance index, after the reinitiation of sildenafil and L-arginine, support this contention. However, it is not feasible to speculate whether the marked decrease in estimated pulmonary artery pressure observed at 12 weeks of gestation was due to a residual vasodilatation of the previous use of sildenafil, to the increment of diltiazem, or to the endogenous vasodilator surge of pregnancy.

Epidural anesthesia, chosen to avoid airway instrumentation with its potential detrimental effects on pulmonary hemodynamics, caused no hypotension despite sildenafil and L-arginine given up to 16 hours previously.

In summary, we present a case of severe cardiac compromise from Eisenmenger syndrome accompanied by preeclampsia, treated with sildefanil and L-arginine, by a coordinated team of obstetricians, cardiologists, and anesthetists in a tertiary clinical setting. This management was associated with a significant maternal benefit and a transient fetal improvement.

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Stage IIIC Small Cell Carcinoma of the Ovary: Survival With Conservative Surgery and Chemotherapy

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BACKGROUND: Small cell carcinoma of the ovary is an aggressive tumor primarily affecting young women. Despite adjuvant therapy, the majority of patients described in the literature have fared poorly, even when the disease is diagnosed at an early stage.

CASE: A 19-year-old nulligravida with small cell carcinoma of the left ovary underwent conservative surgery with staging and was found to have stage IIIC disease. She received multiagent chemotherapy with vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin, and etoposide and is alive and doing well more than 2 years after completion of her therapy, with no evidence of disease.

CONCLUSION: In young patients who desire future fertility, conservative surgery followed by aggressive multiagent chemotherapy may be an effective treatment regimen and warrants further consideration. (Obstet Gynecol 2004; 103:1120–3. © 2004 by The American College of Obstetricians and Gynecologists.)

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