Case Reports

Pulmonary edema after ritodrine therapy during pregnancy and subsequent cesarean section with epidural anesthesia

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Summary

Ritodrine, a beta-sympathicomimetic drug that is frequently used for the prevention of preterm birth. Preterm delivery is an important cause of low birth weight. One of the most important side-effects of ritodrine is pulmonary edema. In patients developing pulmonary edema after ritodrine therapy, aggressive fluid resuscitation during the operation period should be avoided. Successful epidural anesthesia can be achieved with a slow-onset epidural block after moderate fluid infusion. We report the management of a pregnant patient developing pulmonary edema after ritodrine therapy and undergoing cesarean section with epidural anesthesia.

Key words: Ritodrine; Pulmonary edema; Epidural anesthesia.

Introduction

There is a 45% increase in plasma volume in normal pregnancy, which is usually offset by a greater decrease in systemic vascular resistance. In preterm patients beta-adrenergic agonists, such as ritodrine and terbutaline, are widely used for inhibition of premature uterine contractions [1, 2]. Probably secondary to excessive intravascular fluid administration, cardiac failure [1-4], and/or pulmonary capillary endothelial damage, these drugs may cause pulmonary edema mostly during the initial phase of tocolytic therapy. The frequency of pulmonary edema in pregnant women who receive ritodrine is 0.25% or less [5, 6].

In the present case we discuss the management of a pregnant patient developing pulmonary edema after ritodrine therapy and undergoing cesarean section with epidural anesthesia.

Case

A 30-year-old primigravid woman in the 33rd week of pregnancy was admitted to our hospital because of preterm uterine contractions. Physical examination revealed a blood pressure of 110/60 mm Hg; heart rate: 100/min and normal cardiopulmonary findings. She weighed 60 kg and was 157 cm in height. She had no underlying cardiopulmonary disease. On speculum examination the cervix was found to be effaced 30-40% and 1 cm dilated. Because of preterm contractions, treatment with intravenous ritodrine was started at 100 µg/min (in 500 ml dextrose). Routine EKG showed no abnormalities. She was also given dexamethasone to enhance the pulmonary maturition of the fetus.

Because the uterine contractions did not respond to the current tocolytic dosage, the ritodrine dose was increased to a dose of 350 µg/min and tocolytic therapy with MgSO4 was added to the therapy with a dose of 1 g/hour on the following day. On the third day of therapy there was no response to the tocolytic drugs and the patient developed dyspnea, tachycardia of 120/min. On her preoperative examination she was found to be ortopneic, basal crackles were heard on auscultation of the chest. Without O2 supply SpO_2 was 79% and with 10 l/min O_2 supply by face mask SpO_2 was 82-89%. EKG showed no abnormalities. Results of the arterial blood gas were as follows: pH: 7.45, pO_2/pCO_2: 44.7/30.4, HCO_3/BE: 21.5/-0.9, O_2 saturation: 83.4% (BE: base excess, SpO_2: peripheral oxygen saturation). Renal function tests and total protein levels were normal. The patient had a full stomach. With these findings cesarean section with epidural anesthesia was planned. An epidural catheter was placed in the patient after infusion of 500 ml cristaloid and adminmistration of 40 mg furosemide. After the administration of a test dose, 0.5% bupivacain 80 mg plus 100 µg fentanyl was given. The patient's body was in the left lateral position and the head in the Fowler position. Oxygen supply with 10 l/min was applied. SpO_2 level was 82-89%. The operation was initiated when the epidural block level reached $T_{4\text{-}5}$.

She gave birth to a baby girl, 2,350 g with an Apgar score of 9 after one minute, 10 after five minutes. SpO_2 follow-up during the operation was between 92-95%. Blood gas analysis during the operation revealed pH: 7.46, pO_2/pCO_2: 73/29.4, HCO_3/BE: 21.3/-1.0. At the end of the operation with spontaneous breathing and supply of 8 l/min O_2, the SpO_2 level was 95-96%. Total urinary output peroperatively was 1,750 ml. She was transferred to the postoperative unit and her blood gas analysis in this postoperative period was pH: 7.46, pO_2/pCO_2: 65.5/47.8 HCO_3/BE: 34.8/+10.8. After a few days the patient was discharged in good condition.

Discussion

Ritodrine hydrochloride and other beta-sympathomimetic agents have been used as tocolytics to suppress premature labor. Especially if there is an accompanying maternal infection, their use in pregnancy is associated with an incidence of acute pulmonary edema of 0-4.4% [7, 8]. Beta-2 adrenergic agonists are capable of inducing peripheral vasodilation promoting volume overload, therefore their administration requires a mandatory fluid

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load to be given simultaneously and prophylactically in the presence of an already overloaded circulation.

The effectiveness of ritodrine and its effect on perinatal outcome in preterm labor have been studied for many years. The first randomized trial of ritodrine in 1971 showed a significant effect in the delay of onset of labor. Other studies showed that ritodrine could only delay birth significantly for 24-48 hours [6-8]. Prolongation of pregnancy even for 24-48 hours however is still of substantial benefit since it allows time to improve perinatal outcome [9]. It also provides time for corticosteroid administration to promote fetal lung maturation, but corticosteroid administration may cause an additional increase in resistance within the pulmonary circulation and therefore increase the risk of pulmonary edema [10]. Several side-effects of ritodrine such as, maternal cardiac arrhythmias, vasodilatation resulting in systolic hypotension, stimulation of the central nervous system, altered thyroid function, maternal pulmonary edema and congestive heart failure have been described.

Possible mechanisms in the pathogenesis of ritodrine-induced pulmonary edema are:

1. Since beta-sympathicomimetics induce release of anti-diuretic hormones and increased secretion of renin, angiotensin and aldosterone, resulting in retention of sodium and water, they may cause fluid overload that could be worsened by the administration of large volumes of intravenous solutions together with ritodrine [2, 11].

2. Beta-sympathicomimetics induce increase in heart rate causing myocardial fatigue or ischemia that may lead to heart failure, especially in women with known valvular or coronary artery disease [2, 11].

3. Injury to the pulmonary capillary resulting in increased permeability still remains controversial but has been reported many times [2, 3].

Physiologic changes of pregnancy may also make patients more susceptible to increased-permeability lung injury. Although they received multiple tocolytic agents and aggressive intravenous hydration, the severity and duration of their lung injury is most consistent with increased permeability and pulmonary edema.

During parturition there is a marked increase in the secretion of epinephrine which is a critical factor in initiating and maintaining lung fluid absorption. Presence of an accompanying infection causing release of endotoxin or cytokine might attenuate the responsiveness of the beta-adrenergic epithelial cell receptors resulting in promotion of pulmonary edema.

The decision regarding the type of anesthesia technique is an important issue in patients undergoing tocolytic therapy with beta-sympathicomimetics agents when cesarean section is planned. There are several studies in the literature as to whether general or regional anesthesia should be preferred in patients under ritodrine therapy. Maternal hypotension is a common complication of ritodrine therapy and it is aggravated when induction of anesthesia occurs within 30 minutes of discontinuation of tocolytic therapy. Shin and Kim [13] retrospectively observed that maternal hypotension is less common when induction of anesthesia is started with a delay of 30 minutes.

In contrast; a prospective study by Uayema *et al.* [14] showed that in cases of cesarean sections who had ritodrine therapy, hemodynamic changes like maternal hypotension are less commonly seen when spinal anesthesia, with or without prophylactic ephedrine, is the technique of choice. Their study provides support for the use of regional anesthesia in patients who have recently received ritodrine. Chesnut *et al.* [15] performed a controlled trial to determine whether prior administration of ritodrine worsens maternal hypotension during epidural anesthesia in chronically instrumented gravid ewes. The investigators suggested that 'the inotropic and chronotropic activity of ritodrine helped maintain maternal cardiac output and uterine blood flow during epidural anesthesia.

Since patients receiving beta-adrenergic tocolytic therapy are at risk of developing pulmonary edema, excessive fluid overload must be avoided before and during induction of anesthesia. Uayema *et al.* [14] preferred administration of a modest fluid bolus like 250-500 ml of Ringer's lactate and then induction of epidural anesthesia slowly.

General anesthesia may be an alternative choice for patients developing pulmonary edema receiving ritodrine therapy. Agents like atropin and pancronium however may exacerbate maternal tachycardia. Residual maternal tachycardia also makes it more difficult to assess the volume status and depth of general anesthesia. Inhalation agents like Halothane sensitizes the myocardium to cathecolamines and exacerbates hypokalemia potentiating the hyperpolarization of cell membranes. These effects must all be considered when general anesthesia is chosen as an alternative technique in patients receiving ritodrine.

With all these findings, in our patient with a full stomach, we preferred epidural anesthesia in cesarean section. In conclusion, ritodrine is one of the most commonly used tocolytic drugs and pulmonary edema is a very dangerous complication resulting from tocolytic therapy with beta-mimetics. The anesthesia technique may have effects on the prognosis of this complication if cesarean section is decided on for termination of pregnancy.

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