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Research Letter

Oxytocin antagonist successfully prevents from threatened abortion in 15 weeks' gestation

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A 27-year-old woman, gravida 3, para 0, with a gestational age of 7 weeks, visited our hospital for occasional vaginal bleeding. In the past 12 months, she had suffered from two miscarriages of 6 and 8 gestational weeks, respectively. All of the gynecological and autoimmune surveys were within normal range. Under the suspicion of habitual abortion, prednisolone tablets (10 mg/d) and progesterone natural-M capsule (200 mg/d) were prescribed, as well as bed rest was suggested. Unfortunately, she suffered from persistent vaginal bleeding without abdominal pain 4 weeks after first interview (11 gestational weeks). The repetitive transabdominal ultrasound identified normal fetal heart activities and significant subchorionic hematoma sized as 38 mm × 12 mm. After admission, initial tocolytic treatment consisted mainly of intramuscular progesterone 100 mg/d and oral prednisolone 20 mg/d. Then, she had not experienced significant bleeding for the subsequent few weeks until the gestational age of 15 weeks and 5 days. She suffered from sudden severe lower abdominal cramping pain and profound vaginal bleeding. Regular uterine contractions were noted by tocography. A β-agonist (Ritodrine; Chinese Chemistry pharmaceutical factory, Taiwan) was added. However, the patient experienced severe side effects of Ritodrine, in particular, palpitation and tachycardia. Hence, Ritodrine was tapered and then ceased. Unfortunately, the symptoms got worse, which included fresh vaginal bleeding, severe lower abdominal pain, frequent soreness of back, and strong bearing-down sensations. Regular uterine contractions with moderate pressure were noted. Under ultrasonic examination, the subchorionic hematoma became extended, which was measured as 52 mm × 33 mm (Fig. 1). One new intraplacental hematoma measuring 31 mm × 13 mm was identified as well. The cervical length was poorly identified under transabdominal ultrasound, and transvaginal ultrasound failed because of profound vaginal bleeding and great discomfort. Abortion seemed inevitable. After extended counseling, the patient and her family wanted to try any effort to preserve the pregnancy. Under this circumstance, we decided to administer oxytocin antagonist, atosiban, immediately.

The standard protocol for atosiban was administered as follows: an initial bolus of 6.75 mg, followed by 300 μg/min for 3 hours and 100 μg/min for the next 37 hours (a total of 40 hours). The concomitant medication was magnesium sulfate 33.3 mg/min (2 g/h). After bolus injection, she only experienced light contractions, and the magnitude of uterine contractions subsided gradually (Fig. 2). The patient felt much relief from the pain and bearing-down sensation. The amount of fresh blood from vagina decreased significantly.

We discontinued atosiban 40 hours after the first dose. She did not experience significant vaginal bleeding, and there was low abdominal cramping. The following tocolytic therapy was

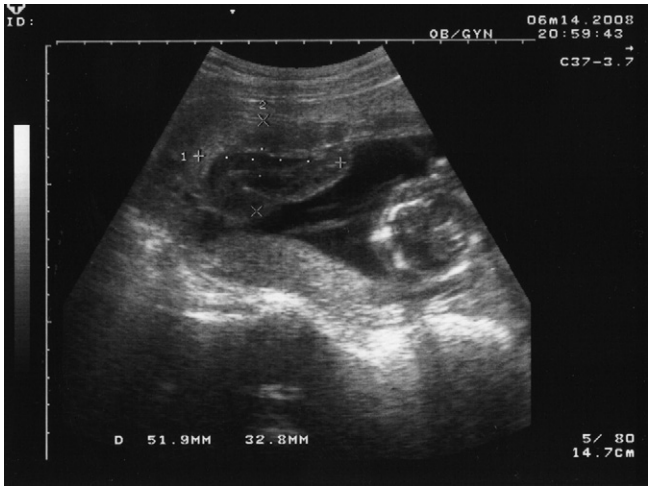

Fig. 1. Hematoma after severe and regular uterine contractions.

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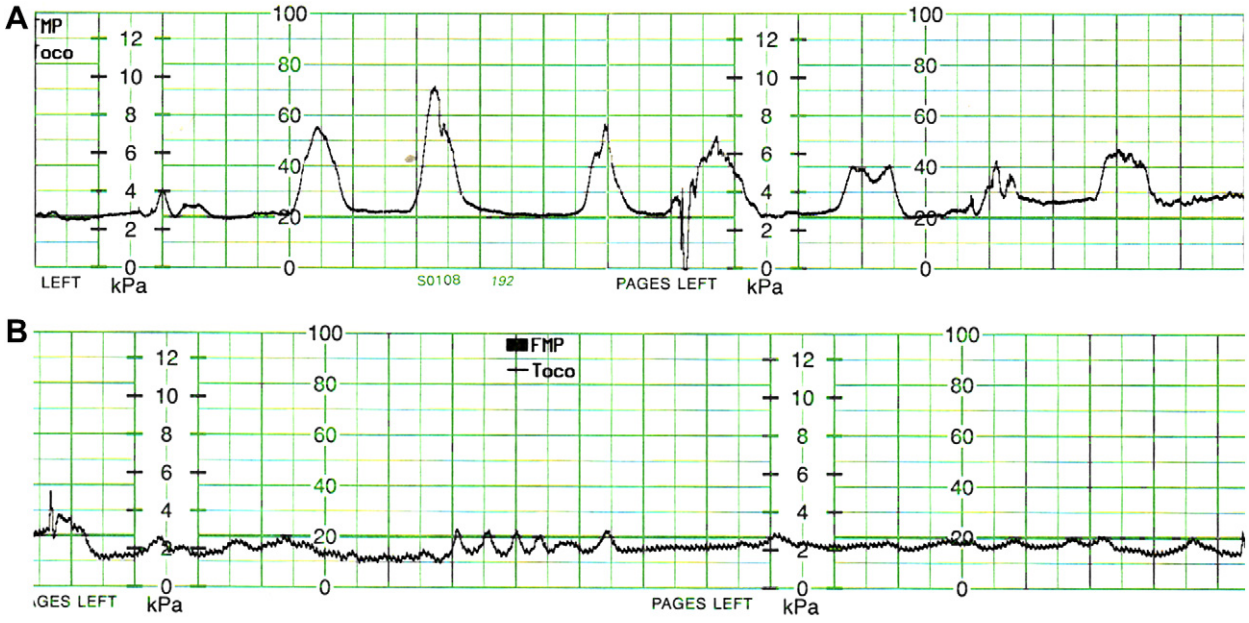

Fig. 2. (A) Regular and significant uterine contractions were noted before the administration of atosiban. (B) The uterine contractions subsided after the administration of atosiban. FMP = fetal monitoring programme; Toco = Tocolysis.

uneventful. The cervical length was relatively unchanged. The patient was discharged at 29 weeks and 6 days of gestation under relatively stable condition. Six weeks later, she began to experience regular uterine contractions and rupture of membrane at 36 weeks' gestation. Within 6 hours, a girl baby weighting 2,130 g was vaginally delivered. The Apgar scores were 6 and 7 after 1 minute and 5 minutes, respectively. Mild subcostal retraction, nasal flaring, and grunting were noticed. Under the diagnosis of Grade I respiratory distress syndrome, the baby received intensive neonatal care without ventilator for 2 days. The postnatal care was smooth, and she was discharged 3 weeks later. The girl was quite healthy at the age of 8 months.

Discussion

To our knowledge, this is the case of the earliest-gestational-age woman receiving successful anti-oxytocin therapy. This case illustrates the possibility of treatment with atosiban to avert severe threatened abortion in the early second trimester.

β_2-Agonists have been the mainstay of tocolytic treatment over the past few decades, during which time they have been the only drugs licensed for this use worldwide. However, their use has been hampered by substantial adverse maternal side effects, which range from the frequent but self-limiting side effects, such as tremor, anxiety, palpitations, nausea, and headaches [1], to the rare but serious side effects, such as pulmonary edema, myocardial ischemia, cardiac failure, and even maternal death [2]. They also cause metabolic side effects, such as hyperglycemia, because of nonspecific activation of adrenergic receptors in the liver, resulting in hyperinsulinemia [3] and, consequently, hypokalemia from insulin-induced intracellular shift of potassium. In the case presented here, the patient experienced severe cardiopulmonary side effects after receiving Ritodrine, including tachycardia, tachypnea, tremor, anxiety, and palpitations. We reluctantly discontinued the β_2-agonist regimen and shifted to atosiban, which proved to be effective.

One study was designed to present successful tocolytic treatment with the specific oxytocin receptor antagonist atosiban in the management of extreme preterm labor in the 18th week through 24th week of gestation [4]. Another study involving a larger number of patients ($n = 501$) has shown that atosiban provided a significantly better tocolytic effect at or beyond 28 weeks' gestation when compared with placebo [5]. No study has demonstrated that atosiban could effectively prevent inevitable or threatened abortion before 18 weeks' gestation. Studies concerning the myometrial oxytocin receptor density during the course of pregnancy have shown an approximately sixfold increase between 13 weeks and 17 weeks of pregnancy compared with the receptor density in the nonpregnant uterus. There is a further increase in myometrial oxytocin receptor density to nearly 80-fold by term, with an additional increase during parturition [6]. More recent findings in both the nonpregnant uterus and the uterus during the early stages of pregnancy have shown that significantly more oxytocin receptors are expressed than was previously assumed [7]. Theoretically, an oxytocin antagonist could exert its effect on the uterus and abate contractions in the very early second trimester. It might be an alternative when traditional tocolytic therapies, such as β-agonists, steroids, and progesterone, are ineffective.

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