


Pregnancy and neonatal outcomes of hyperglycemia caused by atosiban administration during pregnancy

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It is known that atosiban has fewer side effects than conventional tocolytics. In clinical practice, however, hyperglycemia can be commonly observed in mothers who have been administered atosiban. Therefore, we investigated whether intravenous atosiban injection actually causes hyperglycemia and how these changes affect newborns. From December 2015 to July 2018, a retrospective study was conducted on 96 mothers who were diagnosed with preterm labor and were administered atosiban at our institution. Maternal blood glucose was measured and compared before and during the administration of atosiban. The paired *t*-test, independent samples *t*-test, Chi-square test and Fisher's exact test were performed using SPSS version 21.0. A statistically significant increase in fasting blood glucose levels was observed during the administration of atosiban, compared with random blood glucose levels before administration (110.7 mg/dL vs. 86.3 mg/dL). The mean postprandial blood glucose level during administration was 170.75 mg/dL. Gestational diabetes, twin pregnancy, preeclampsia, and polyhydramnios did not significantly affect the degree of blood glucose increase. Statistically significant hypoglycemia was observed after performing a neonatal blood test immediately after birth from mothers who used atosiban. The neonates from the group with elevated maternal blood glucose levels exceeding 20 mg/dL showed lower blood glucose levels. No serious side effects other than hypoglycemia were observed. Atosiban administration in pregnant women results in significantly elevated maternal blood glucose, which results in hypoglycemia in neonates after birth. Therefore, neonates from mothers who received atosiban require a blood glucose test and close monitoring after birth.

Keywords

Atosiban; Preterm labor; Maternal hyperglycemia; Neonatal hypoglycemia

1. Introduction

Spontaneous preterm labor, mainly leading to preterm delivery, is a major cause of neonatal morbidity and death [1]. Currently, magnesium sulfate, non-steroidal anti-inflammatory drugs (NSAIDs), calcium channel blockers (CCBs), β -agonists, and atosiban are universally prescribed to mothers with preterm labor [2]. Among them, β -agonists have been recognized for pregnancy extension of 24–48 hours, but there are risks of serious side effects, such as pulmonary edema, arrhythmia, hyperglycemia, and myocardial

infarction [1]. Magnesium sulfate can affect maternal myometrial contractility and pulmonary edema, and two randomized studies showed its ineffectiveness [3]. NSAIDs pose a risk for oligohydramnios and fetal ductal closure [4], and CCBs can reduce uterine blood flow [5].

Although atosiban, an oxytocin receptor antagonist, did not receive FDA approval, it has been reported that their effects on the prolongation of pregnancy are similar and have relatively fewer side effects when compared with β -agonists in several reports [6, 7]. Therefore, atosiban can be used as a 1st line therapy for high-risk pregnancies such as twin pregnancies, and for mothers with hypertension or gestational diabetes mellitus (GDM). However, although it occurs less frequently and its severity is weaker than other drugs, side effects are observed during atosiban administration, such as nausea, vomiting, tachycardia, and hyperglycemia [6]. In clinical practice, hyperglycemia has often been observed in mothers who received intravenous atosiban.

Therefore, regarding various clinical encounters (twin, GDM, DM mothers, etc.), we investigated whether intravenous atosiban injection causes side effects such as hyperglycemia in mothers, and how these changes actually affect their neonates.

2. Materials and methods

A retrospective study was conducted on patients who received atosiban injection in the obstetrics department of our institution between December 2015 and July 2018 after being diagnosed with preterm labor. In 2016, the American College of Obstetricians and Gynecologists defined threatened preterm labor as regular contractions before 37 gestational weeks with or without other symptoms, such as pelvic pressure, backache, increased vaginal discharge, menstrual like cramps, and bleeding that are associated with cervical change [8–10]. Regular contractions are defined as at least three uterine contractions per 30 minutes [11]. Appropriate change in cervical length should be less than 2.5 cm [8–10].

In total, 265 mothers who had been admitted to our institution were surveyed. The inclusion criteria were gestational age between 24 + 0 weeks and 33 + 6 weeks, patients whose

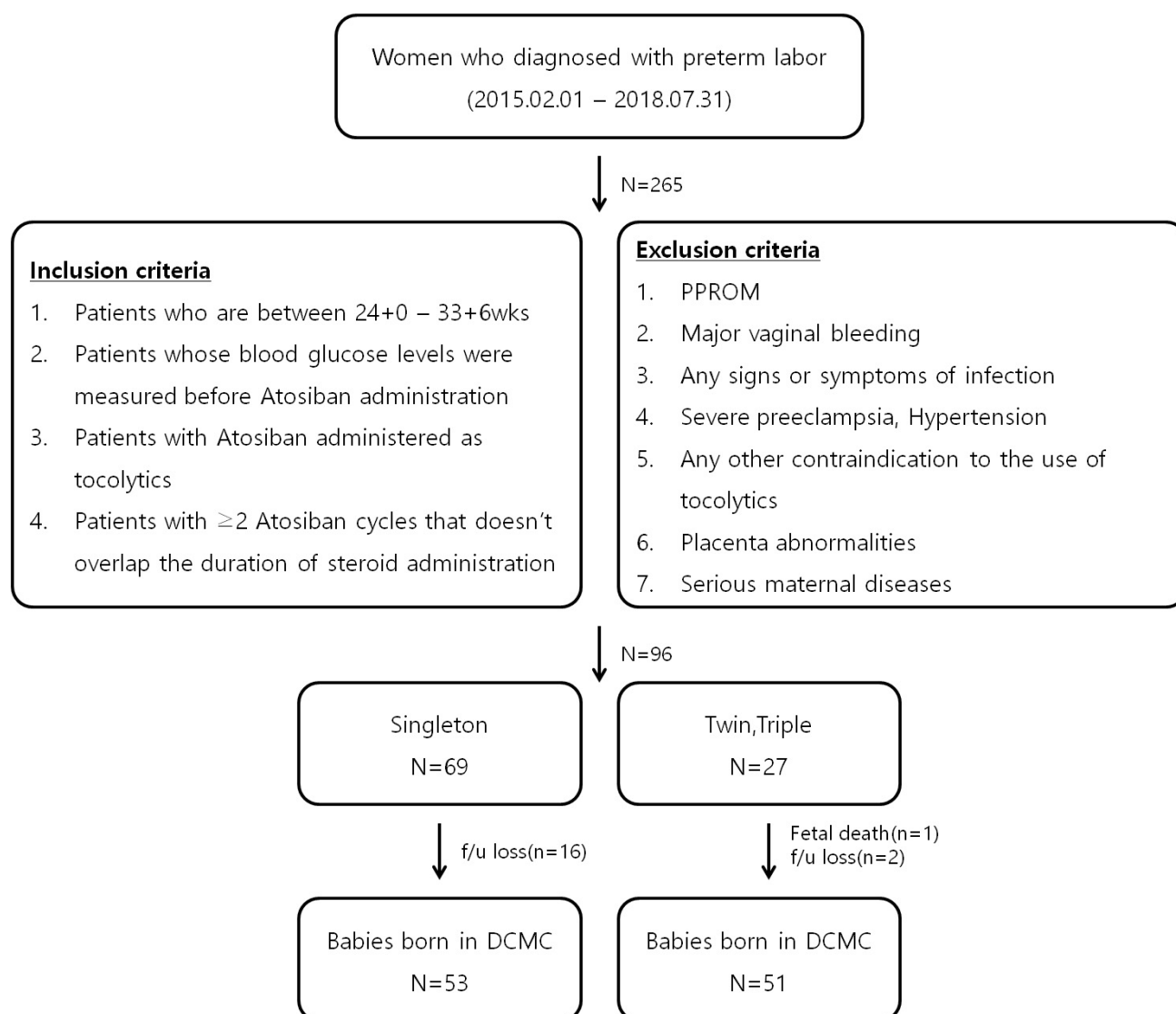


Fig. 1. Inclusion and Exclusion criteria for study subjects.

blood glucose levels were measured before atosiban administration, and patients with atosiban administered as tocolytics for more than 2 cycles, which did not overlap the duration of steroid (dexamethasone, betamethasone) administration.

Exclusion criteria were preterm premature rupture of the membrane, major vaginal bleeding, any signs or symptoms of infection (fever, leukocytosis, uterine tenderness), severe preeclampsia, hypertension, placenta abnormalities, major maternal diseases, and any other contraindications due to the use of tocolytics. There were 96 mothers who met all the above conditions, as described in Fig. 1.

Among the 96 mothers, 69 had singleton pregnancies and 27 had multiple pregnancies. We tracked the births to determine the neonatal outcomes according to the changes in the mothers' blood glucose. Sixteen out of 69 singleton mothers delivered in local medical centers and 53 delivered in our institution. Additionally, 2 out of 27 multiple pregnant mothers delivered in local medical centers, and one of the twins

delivered at our institution died shortly after birth. In total, 104 neonates were surveyed.

In our hospital, we used atosiban as a first-line tocolytic therapy for mothers with GDM, preeclampsia, thyroid problems, or multiple gestations. In the absence of other medical problems, we administered a β -agonist as the primary treatment. When side effects such as maternal tachycardia, hand tremor, and pulmonary edema occurred or the treatment failed to work, we administered atosiban as a secondary treatment. In our hospital, we do not use hexoprenalin as tocolytic therapy.

Atosiban 6.75 mg was administered by bolus intravenously; 75 mg was administered by mixing with 90 mL of normal saline for 3 hours, and then for 45 hours at 8 cc/hour, to make 48 hours in total. After 48 hours of treatment, we evaluated uterine contractions using cardiotocography, and we administered atosiban in the same way if preterm labor continued or recurred. The blood glucose levels measured

Table 1. Baseline characteristics of patients (n = 96).

| | Mean \pm SD | Range |
|--------------------------------------|------------------|-------------|
| Age (years) | 32.4 \pm 4.3 | [20–43] |
| BMI (Kg/m ²) | 24.7 \pm 4.1 | [14.5–41.1] |
| GA at birth (days) | 236.9 \pm 21.9 | [159–277] |
| Nulliparity (n) | 66 | |
| Multiparity (n) | 30 | |
| Reasons for prescribing atosiban (n) | | |
| Multiple gestation | 27 | |
| Preeclampsia | 3 | |
| Polyhydramnios | 1 | |
| β -agonist complication | 51 | |
| Thyroid disease | 5 | |
| GDM | 15 | |
| overt | 1 | |
| A1 | 8 | |
| A2 | 6 | |

SD, standard deviation; BMI, body mass index; GA, gestational age; GDM, gestational diabetes mellitus.

before atosiban administration were compared with those measured during the administration of atosiban. To reduce the effect of external factors, blood glucose measured during steroid administration, which may affect blood glucose levels, was excluded. Since blood glucose measurement before the administration of atosiban was performed immediately after hospitalization, the measurement time was random. During the administration of atosiban, regular blood glucose tests were performed before and 2 hours after meals. Therefore, when comparing blood glucose levels, we used random blood glucose before the administration of atosiban and fasting blood glucose (blood glucose when fasted for 8 hours or more) during the administration of atosiban.

To determine whether other factors acted on the increase in blood glucose level, the underlying diseases or factors were compared by categorizing into a group with maternal blood glucose increase of 20 mg/dL or less and a group with an increase of 20 mg/dL or more. When studying neonatal outcomes, birth weight, hypoglycemia, respiratory distress syndrome (RDS), arterial blood gas analysis results, and other perinatal complications were included to evaluate neonatal morbidity. Whether or not to use artificial ventilator was applied as an indicator of neonatal RDS. Paired *t*-test, independent samples *t*-test, Chi-square test and Fisher's exact test were performed using SPSS version 21.0; *P* < 0.05 was considered statistically significant.

This retrospective study was approved by the institutional ethics committee of our institution. All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and in line with the 1964 Helsinki declaration including its later amendments or comparable ethical standards.

3. Results

The baseline characteristics of patients are shown in Table 1. Fifty-one of 97 women were treated with atosiban because of the complication of β -agonists, while others were treated with atosiban primarily for medical reasons.

Table 2 shows the comparison of blood glucose levels before and after the administration of atosiban. The average value of fasting blood glucose during administration showed a statistically significant increase compared to value of random blood glucose before administration of atosiban (110.7 mg/dL vs. 86.3 mg/dL, *P*-value < 0.001). The mean postprandial blood glucose level (2 hours after meals) during administration was 170.75 mg/dL.

In order to determine if the increase in blood glucose was affected by other medical factors, we divided the patients into two groups and analyzed: the group with an increase in blood glucose \leq 20 mg/dL (group A; n = 46) and the group with an increase > 20 mg/dL (group B; n = 50) (Table 3). There were no significant differences in age, body mass index (BMI), and the status of obstetrical complications (twin pregnancy, preeclampsia, GDM, and polyhydramnios) between the two groups. Hence, it can be observed that there is no influence from other factors on the increase in blood glucose before and after the administration of atosiban.

Table 4 shows the comparison of neonatal outcomes between the two groups. There was no difference in neonatal Apgar score, duration of admission and ventilator use, blood pH, and neonatal morbidity status (sepsis, intraventricular hemorrhage, and neonatal enterocolitis) between the two groups. However, the blood glucose value measured immediately after birth showed a significant difference. The mean neonatal blood glucose level of the mothers in group B was 49.0 mg/dL, which was statistically significantly lower than that of the mothers (57.3 mg/dL) in group A. Of the 49 newborns in group B, 16 (32.7%) showed very low blood glucose levels below 40 mg/dL immediately after birth.

4. Discussion

In this study, atosiban administration during pregnancy for preterm labor can cause statistically significant maternal hyperglycemia and neonatal transient hypoglycemia.

There are sufficient studies comparing the efficacy and safety of atosiban, β -agonists, magnesium, and calcium channel blockers. These comparative studies were of the opinion that the efficacies of these drugs are similar or that atosiban is better [1, 2, 6, 7]. The major difference between the β -agonist and atosiban is the maternal side effects of the drugs [1, 6]. β -agonists have shown higher incidences of side effects such as maternal tachycardia, pulmonary edema, and hyperglycemia, compared with atosiban [6, 7]. In these studies, atosiban appeared as a drug with relatively few side effects, but in practice, maternal hyperglycemia can often be observed during atosiban administration. Therefore, when administering atosiban to a diabetic mother or twin mother, it is difficult to control their blood glucose levels. Wex *et al.*

Table 2. Comparison of blood glucose before and after atosiban (n = 96).

| | Random BG before atosiban (mg/dL) | Mean FBS during atosiban (mg/dL) | P-value |
|---------------------|-----------------------------------|------------------------------------|----------|
| Mean BG (mean ± SD) | 86.3 ± 21.1 | 110.7 ± 15.9 | < 0.001* |
| | Random BG before atosiban (mg/dL) | Mean 2 PBS during atosiban (mg/dL) | |
| Mean BG (mean ± SD) | 86.3 ± 21.1 | 170.8 ± 36.0 | < 0.001* |

* : paired *t*-test.

BG, blood glucose; FBS, fasting blood glucose; SD, standard deviation; 2 PBS, 2 hours postprandial blood glucose.

Table 3. Comparison of characteristics of patient groups with elevated BG levels.

| | A (n = 46) (glucose increase ≤ 20) | B (n = 50) (glucose increase > 20) | P-value |
|--------------------------|------------------------------------|------------------------------------|---------|
| Age (years) | 32.5 ± 4.5 | 32.3 ± 4.1 | 0.786 † |
| BMI (Kg/m ²) | 25.3 ± 4.0 | 24.2 ± 4.1 | 0.191 † |
| Multiple gestation (n) | 13 | 14 | 0.977 ‡ |
| Preeclampsia (n) | 0 | 3 | 0.243* |
| Polyhydramnios (n) | 1 | 0 | 0.479* |
| Hypothyroidism (n) | 4 | 1 | 0.191* |
| GDM (n) | 7 | 8 | 0.916 ‡ |
| Nulliparity (n) | 29 | 37 | 0.247 ‡ |
| Multiparity (n) | 17 | 13 | 0.247 ‡ |

† : independent *t*-test, * : Fisher's exact test, ‡ : Chi-square test.

BG, blood glucose; BMI, body mass index; GDM, gestational diabetes mellitus.

showed that β -agonists had stronger side effects of increasing blood glucose than atosiban [12]. However, from our investigation, atosiban was also observed to induce maternal hyperglycemia at clinically meaningful levels.

According to Table 3, the increase in blood glucose before and after administration of atosiban was not affected by maternal medical conditions. When comparing neonatal outcomes, the difference in neonatal blood glucose was statistically significant. Neonates delivered in the group with an increase in blood glucose > 20 showed lower blood glucose levels than the neonates in the other group.

The Pediatric Endocrine Society criteria recommend maintaining 50 mg/dL or more for the first 48 hours after birth [13]. Additionally, the American Academy of Pediatrics recommend maintaining 45 mg/dL or more for the first 24 hours after birth [14]. Even without symptoms, early feeding should be started when neonatal blood glucose is measured between 40 and 60 mg/dL, and close follow-up is required. More aggressive managements such as early frequent feeding or intravenous glucose administration are required for neonatal blood glucose levels of 40 mg/dL or less. If severe neonatal hypoglycemia persists, subsequent seizures and coma can lead to fatal outcomes [14].

The average blood glucose level of the 104 neonates in our study was 53.6 mg/dL. The neonatal blood glucose level of those in group B (increased maternal blood glucose > 20 mg/dL) was significantly lower than that of those in group A (increased maternal blood glucose ≤ 20 mg/dL). In addition, it should be noted that 16 neonates in group B showed low blood glucose levels under 40 mg/dL. Blood glucose under 40 mg/dL is a level that requires active intervention such as intravenous glucose administration or early frequent feeding.

β -agonists are known to stimulate sympathetic nerves, causing hyperglycemia. However, in the case of atosiban, the obvious cause of hyperglycemia is not well known. Therefore, we hypothesized that, atosiban, an oxytocin antagonist, contrasts with oxytocin, which suppresses cortisol, thereby increasing the level of serum cortisol, and subsequently increasing blood glucose levels [15–19]. To verify this, we conducted a sub-analysis. Ten singleton pregnant mothers were included, and we measured their levels of serum cortisol before and during the administration of atosiban. The cortisol level was not measured during the period of prenatal steroid use. None of the patients had diabetes. The results showed that, in all 10 mothers, the level of serum cortisol increased during atosiban administration, compared to before administration (mean value: 19.53 vs. 32.28 μ g/dL). Although the number of patients included in this sub-analysis was small, consistent results in all patients suggest that it is necessary to verify them in future long-term studies.

The limitation of this study is that the number of study subjects was relatively small. Of the 265 women who were admitted due to preterm labor during the three-year period at the DCMC and received atosiban, the number of women who met the inclusion and exclusion criteria was 96. The second limitation is that the timing of blood glucose measurements before and after administration of atosiban was inconsistent. Before atosiban was administered, maternal blood glucose level measurement was conducted at the time of hospitalization. Therefore, blood collection time was random and there was no uniformity of fasting before blood collection. For accurate comparisons, it is necessary to compare the blood glucose values measured at the same time while consuming a regular meal, with values measured while con-

Table 4. Comparison of neonatal outcomes according to maternal BG increase levels.

| | Neonates of group A (n = 55) | Neonates of group B (n = 49) | P-value |
|-----------------------------------|------------------------------|------------------------------|---------|
| Mean ± SD | | | |
| BW (gram) | 2065.3 ± 745.6 | 2079.3 ± 582.0 | 0.916 † |
| GA at delivery (days) | 232.8 ± 24.3 | 237.0 ± 19.1 | 0.338 † |
| 1 min AS | 7.2 ± 2.0 | 6.8 ± 2.6 | 0.356 † |
| 5 min AS | 9.0 ± 1.3 | 9.0 ± 1.8 | 0.959 † |
| Duration of ventilator use (days) | 3.6 ± 8.6 | 1.9 ± 4.3 | 0.214 † |
| NICU admission (days) | 29.7 ± 24.7 (n = 52) | 25.5 ± 15.9 (n = 46) | 0.298 † |
| Neonatal BG (mg/dL) | 57.3 ± 15.2 (n = 49) | 49.6 ± 13.2 (n = 45) | 0.011 † |
| Neonatal blood pH | 7.26 ± 0.1 (n = 45) | 7.26 ± 0.1 (n = 45) | 0.595 † |
| Neonatal Ca (mg/dL) | 9.3 ± 0.8 (n = 44) | 9.2 ± 1.6 (n = 42) | 0.725 † |
| Neonatal P (mg/dL) | 5.7 ± 0.7 (n = 44) | 5.6 ± 1.1 (n = 42) | 0.585 † |
| Number of patients | | | |
| Sepsis | 7 | 7 | 0.816 * |
| IVH, grade 1 | 0 | 0 | - |
| IVH, grade 2 | 7 | 7 | 0.816 * |
| IVH, grade 3 | 0 | 0 | - |
| IVH, grade 4 | 5 | 2 | 0.309 * |
| NEC | 0 | 0 | - |

† : Independent samples *t*-test; * : Chi-square test.

BG, blood glucose; SD, standard deviation; BW, body weight; GA, gestational age; AS, Apgar score; NICU, neonatal intensive care unit; Ca, calcium; P, phosphate; IVH, intraventricular hemorrhage; NEC, neonatal enterocolitis.

suming the same diet. However, because of the nature of the retrospective study, the conditions could not be met. To compensate for this, we compared the average fasting blood glucose during atosiban administration, which is the lowest blood glucose level in the day, with the average random blood glucose levels before administration. Researching neonatal outcomes, retrospective research was also a limitation. After the successful treatment of preterm labor, few of the subjects who gave birth in a local obstetric hospital at full term were not followed up.

However, we found that atosiban administration in pregnant women can result in significantly elevated maternal blood glucose levels, which may result in neonatal hypoglycemia after birth. Neonates from mothers with higher blood glucose levels had lower blood glucose levels, and these neonatal hypoglycemia levels can drop to levels requiring intervention. However, there were no complications other than hypoglycemia immediately after birth. Therefore, it should be noted that neonatal blood glucose monitoring is necessary, and aggressive treatment is sometimes required for neonates of mothers who received atosiban during pregnancy.

Author contributions

SYH and JYB designed the research study. HJK performed the research. JYB and Hyun JK analyzed the data. HJK, JYB, and Seong Yeon Hong wrote the manuscript. All authors contributed to editorial changes in the manuscript. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Ethics Committee of Daegu Catholic University Hospital Ethical Committee (CR-19-101). All procedures performed, involving human participants, were in accordance with the ethical standards of the institutional and/or national research committee, and they were in line with the 1964 Helsinki declaration including its later amendments or comparable ethical standards.

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Conflict of interest

The authors declare no competing interests.

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