Time-dependent changes in insulin requirement for maternal glycemic control during antenatal corticosteroid therapy in women with gestational diabetes: a retrospective study

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Abstract. Though recommended for pregnant women at risk of preterm birth to improve perinatal outcomes, antenatal corticosteroid (ACS) treatment can cause maternal hyperglycemia, especially in cases of glucose intolerance. A standardized protocol for preventing hyperglycemia during ACS treatment remains to be established. We herein retrospectively investigated the time-dependent changes in insulin dose required for maternal glycemic control during ACS treatment in gestational diabetes (GDM). Twelve singleton pregnant women with GDM who received 12 mg of betamethasone intramuscularly twice 24 hours apart were included in this analysis. Of those, eight also received ritodrine hydrochloride for preterm labor. The blood glucose levels were maintained at 70–120 mg/dL with continuous intravenous infusion of insulin and nothing by mouth for 48 hours after the first betamethasone administration. After the first dose of betamethasone, the insulin dosage needed for glycemic control gradually increased and reached a maximum (6.6 ± 5.8 units/hr) at 10 hours, then, decreased to 4.1 ± 1.5 units/hr at 24 hours. Similar changes in the insulin requirement were found after the second betamethasone dose (the maximum insulin dosage: 5.5 ± 1.6 units/hr at 9 hours following the second administration). Women treated with ritodrine hydrochloride needed more insulin than those without ritodrine hydrochloride treatment (130.8 ± 15.0 vs. 76.8 ± 15.2 units/day, respectively, p < 0.05). Our data indicated that the requirement for insulin is highest 9–10 hours after each dose of betamethasone. When GDM is treated with ACS, levels of blood glucose should be carefully monitored, especially in patients treated with ritodrine hydrochloride.

Key words: Antenatal corticosteroid therapy, Gestational diabetes, Continuous intravenous insulin infusion, Ritodrine hydrochloride

IN OBSTETRIC practice, the administration of antenatal corticosteroid (ACS) is recommended for the acceleration of fetal lung maturation in threatened preterm birth < 34 weeks of pregnancy [1, 2]. Steroid administration might induce maternal hyperglycemia, especially in women with gestational diabetes (GDM) or pre-existing diabetes mellitus (DM). The optimal maternal glycemic control is necessary during ACS treatment in pregnancies with GDM as well as DM because maternal hyperglycemia is associated with fetal acidosis [3, 4]. Several authors have demonstrated maternal glycemic control after the corticosteroid administration [5-9]. However, data on the time-dependent changes in insulin requirement during the treatment is limited especially in Japanese women with GDM. With this background, this study was conducted to analyze the time-dependent changes in insulin dosage for the maternal glycemic control after the corticosteroid administration in Japanese women with GDM.

Materials and Methods

With the approval of Keio University School of Medicine an ethical committee, consecutive 12 Japanese singleton pregnancy with GDM who received ACS treatment (i.e. the standard 2-dose course of betamethasone) between 24 and 33 weeks of gestation were retrospectively analyzed. All were cared in Keio University Hospital between 2011 and 2013. GDM was diagnosed by 75-g oral glucose tolerance...
test (OGTT) according to the diagnostic criteria by the Japan Diabetes Society (JDS) [10]. There were six women with a single abnormal OGTT value and six with two abnormal values. No women showed three abnormal OGTT values. All women received dietary treatment including three meals and three snacks. The last snack was served at 7 p.m. the day before ACS treatment. An indication for betamethasone administration was decided by the attending obstetrician and mainly included pregnancy-induced hypertension, preterm labor, and fetal growth restriction.

Each patient received 12 mg of betamethasone intramuscularly, usually at 7 a.m., twice 24 hours apart (i.e. the standard 2-dose course of betamethasone). During ACS treatment, blood glucose levels were maintained at 70–120 mg/dL with continuous intravenous infusion of insulin for 48 hours after the first betamethasone administration with nothing by mouth. Briefly, levels of plasma glucose were measured by ANTSENSE (HORIBA Ltd, Japan) one to three hours interval and the rate of insulin infusion was adjusted by attending physicians. Glucose 10% w/v solution was infused intravenously at a constant rate of 80 mL/hr during this period to prevent maternal ketosis.

In this study, insulin dosage (unit/hr) needed for the optimal glycemic control as well as levels of plasma glucose for 48 hours after the first betamethasone administration was investigated. Data were expressed as mean ± standard deviation (SD). Maternal background and insulin dosage were compared between women with and without ritodrine hydrochloride using student t-test and Mann-Whitney U test. p < 0.05 was considered as statistically significant.

Results

The maternal age, gestational weeks and pre-pregnancy BMI were 37.3 ± 6.9 years, 28.3 ± 4.2 weeks of pregnancy and 21.8 ± 7.4 kg/m², respectively (Table 1). Three women had a family history of type 2 diabetes. Of 12 women, eight received ritodrine hydrochloride for preterm labor (mean ± SD, 125.0 ± 50.0 mg/day). When compared maternal baseline characteristics between women with and without ritodrine hydrochloride, there were no significant differences between the two groups. The dosage of ritodrine hydrochloride did not change during the treatment. Two women had been under insulin therapy before ACS treatment.

Using insulin administration, levels of plasma glucose were mostly controlled within the target glucose range (i.e. 70 to 120 mg/dL) during the therapy (Fig. 1A). After the first betamethasone administration, the insulin dosage (unit/hour) needed for maternal glycemic control gradually increased and reached a maximum (6.6 ± 5.8 units/hr) at 10 hours. Thereafter, it decreased to 4.1 ± 1.5 units/hr at 24 hours (Fig. 1B). The trend in insulin requirement after the second dose of betamethasone was similar to that after the first administration, but with less amount of insulin. The peak insulin dose was 5.5 ± 1.6 units/hr at 33 h (i.e. 9 hours after the second administration). After adjusting for maternal body weight, the similar time-dependent changes in insulin requirement (unit/hr/kg) were found (Fig. 1C). There were no differences in insulin requirement between women with one and two abnormal OGTT values (121.3 ± 60.4 vs. 104.2 ± 28.3 units/day, respectively, p = 0.54). Although the time-dependent trend in insulin requirement during the treatment was comparable between women with and without ritodrine hydrochloride, the total insulin requirement in those with ritodrine hydrochloride was significantly higher than those without ritodrine hydrochloride (130.8 ± 15.0 vs. 76.8 ± 15.2 units/day, respectively, p <0.05). There were no adverse events such as severe

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Data are expressed as means ± standard deviation.
Insulin requirement during ACS therapy

Discussion

The present study clarified changes in glycemic profile and insulin requirement during ACS treatment in women with GDM and clearly demonstrated that trend in insulin requirement was time-dependent and biphasic during the treatment. Although several studies demonstrated maternal hyperglycemia after ACS administration, detailed data on changes in insulin dose needed to achieve glycemic goal have been limited. To the best of our knowledge, this is the first report on hourly changes in insulin requirement as well as levels of plasma glucose during ACS treatment in Japanese singleton pregnancies with GDM.

Our investigation demonstrated levels of plasma glucose and insulin dose required gradually increased with the peak being 9–10 hours after betamethasone administration. Star et al. [8] reported that hyperglycemia were found approximately 3–8 hours following each dose of betamethasone, although levels of plasma glucose were not determined on an hourly basis. In contrast to our subjects, women in their study cohort received a standard hospital diet during ACS treatment. No previous studies have shown glycemic profiles during ACS treatment where women were cared with nothing by mouth. Therefore, our results revealed detailed changes in glycemic profile and insulin requirement during ACS treatment. It is noted that the mean and SD values of insulin requirement were greater in the first 24 hours compared with the second 24 hours. The reason of this might be because the attending physicians could adjust insulin dose more effectively on day 2 than day 1. The greater insulin requirement on day 1 also might be affected by the last meal on the day before ACS treatment.

In this study, a larger amount of insulin infusion was needed for maternal glycemic control in women treated with ritodrine hydrochloride, compared with those without. Ogawa et al. [9] also have shown that women receiving ritodrine hydrochloride needed larger amount of insulin by approximately 30 units per day than those without ritodrine hydrochloride during ACS treatment. Ritodrine hydrochloride, β2-sympathomimetics, is a common tocolytic drug in obstetric practice in Japan, although its efficacy is limited. Taken its pharmacologic effect into consideration, ritodrine hydrochloride could
induce hyperglycemia by promoting hepatic gluconeogenesis and glycogenolysis through activating liver adenylate cyclase [11, 12]. The risk of abnormal glucose metabolism could be further increased by simultaneous ACS treatment, a common combination for threatened preterm birth. Special attention should be paid to maternal plasma glucose concentration when women with ritodrine hydrochloride undergo ACS treatment.

In summary, the peak level of insulin requirement was found 9–10 hours after each dose of betamethasone during ACS treatment. Our data is retrospective, but would be useful for physicians to adjust insulin dose and achieve glycemic goal more effectively and safely during ACS treatment, especially when GDM women receive ritodrine hydrochloride.

**Disclosure**

The authors declare that they have no conflict of interest.

**References**