Preterm birth (PTB) is defined as birth before 37 completed weeks of gestation, which occurs in approximately 10% of all pregnancies [1]. PTB causes about 70% of all neonatal deaths of non-anomalous infants, as well as neonatal morbidities including respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia and long-term complications such as cerebral palsy [2,3]. The PTB rate has risen worldwide, and in South Korea, the PTB rate has also risen from 4.3% in 1995 to 10% in 2003 [1,4]. There are many known risk factors for PTB, but one of the most

Objective
To evaluate whether the administration of vaginal natural micronized progesterone is associated with reduction of recurrent preterm birth (PTB) in women with prior history of spontaneous PTB.

Methods
We retrospectively evaluated the obstetric and neonatal outcomes of all women with history of spontaneous PTB that delivered from January 2008 through April 2012. Spontaneous PTB was defined as PTB before 37 weeks of gestation due to spontaneous preterm labor or preterm premature rupture of membranes. Pregnancies with multiple gestation and those who received cerclage operation during previous or current pregnancy were excluded. Patients in the progesterone group were instructed to self-administer 100 or 200 mg vaginal micronized natural progesterone capsule. We evaluated the difference in recurrent PTB rate between the progesterone group (n = 73) and the non-user group (n = 158).

Results
The incidence of recurrent spontaneous PTB before 37 weeks’ gestation was significantly lower in the progesterone group than the non-user group (21.9% vs. 43.0%, \(P = 0.002\)). Multivariate analysis showed that progesterone therapy was associated with a decrease in the incidence of recurrent PTB before 37 weeks’ gestation (odds ratio, 0.382; 95% confidence interval, 0.169-0.863; \(P = 0.021\)) independent of confounding variables.

Conclusion
Micronized vaginal progesterone supplement therapy was associated with a reduction of recurrent PTB risk in women with previous spontaneous PTB history.

Keywords: Progesterone; Preterm birth; Recurrence; Prevention
important factors is previous history of PTB [1]. As mentioned before, global incidence of PTB rate is approximately 10%, but the rate of PTB increases up to 20%–50% in women with history of PTB, and the risk of PTB increases considerably with the number of previous PTBs [5-8].

For more than 30 years, progesterone administration has been advocated for the prevention of PTB in women considered to be at high risk for PTB [9]. However, the results of the earlier studies on the efficacy and safety of this treatment were controversial [10]. In 2004, two randomized controlled trials suggested that the prophylactic administration of progesterone in pregnant women at high risk for PTB, including those with prior history of PTB, is associated with a reduction of 60% to 78% in PTB rate [11,12]. After on, several randomized controlled trials reported that the use of progesterone reduced the risk of recurrent PTB [13-19]. In 2008, the American College of Obstetricians and Gynecologist published a committee opinion recommending the use of progesterone supplementation to prevent recurrent PTB in women with a singleton pregnancy and a prior spontaneous PTB due to spontaneous preterm labor or premature rupture of membranes [20].

However, the efficacy of the progesterone supplement therapy during pregnancy to prevent a recurrent PTB has never been studied in Korea. Therefore, primary objective of this retrospective study was to evaluate whether the prophylactic administration of vaginal micronized progesterone is associated with the reduction of recurrent PTB risk in women with a prior history of spontaneous PTB in Korean women.

Materials and Methods

We retrospectively evaluated the obstetric and neonatal outcomes of all women with history of one or more previous spontaneous PTB that delivered from January 2008 to April 2012. Spontaneous PTB was defined as PTB before 37 weeks of gestation due to spontaneous preterm labor or preterm premature rupture of membranes (PPROM). The exclusion criteria were multiple gestations either previous or current pregnancy, cerclage during both previous or current pregnancy, and previous intentional PTB due to maternal or fetal indications, such as preeclampsia and fetal growth restriction.

Patients who used progesterone were instructed to self-administer vaginal micronized natural progesterone (Utrogestan, Besins Healthcare, Brussels, Belgium or Yenatron, Acraf S.p.A., Roma, Italy) 100 or 200 mg capsule. The treatment was initiated at 16 weeks of gestation or at first visit to our hospital beyond 16 weeks of gestation. The treatment was continued until either 34 to 37 completed weeks of gestation or occurrence of PTB.

Control group consisted of singleton pregnant women with history of one or more previous spontaneous PTB and delivered in our hospital during the same study period, but who never used progesterone during current pregnancy. Patient selection, the dose of progesterone and the time of initiation and duration of the treatment were decided by the physicians’ discretion.

Information of the previous pregnancy outcome such as number of previous term birth, number of previous PTB, gestational age and indication of the previous PTB was collected. Obstetric outcome of the current pregnancy including the rate of recurrent PTB before 34 weeks and 37 weeks of gestation of the two groups was compared.

The Fisher's exact test or Pearson’s chi-square test was used for categorical variables. The Student’s T-test or Mann-Whitney U test was used for continuous variables. The relationship between the incidence of PTB and independent variables including the number of previous PTB history, gestational age at previous PTB, indications of previous PTB and midtrimester cervical length were analyzed by multiple logistic regression analysis. A P-value of less than 0.05 was considered statistically significant.

Results

A total of 231 women were included in the study: 73 in the progesterone group and 158 in the non-user group. There were no significant differences in maternal characteristics including number of previous term and preterm births, and gestational age at previous PTB between the non-user group and progesterone group (Table 1). But there were more PPROM of indication for previous PTB in the progesterone group compared to the non-user group. Although mean cervical length during midtrimester ultrasound was not significantly different between two groups, more women in the progesterone group had cervical length less than 25 mm.

The incidence of recurrent PTB before 37 weeks of gestation was significantly lower in the progesterone group than the non-user group (21.9% vs. 43.0%, P=0.002) (Table 2). However, the rate of recurrent PTB before 34 weeks of gestation was similar in the two groups. There were no significant differences in other outcomes such as delivery mode, birth weight, 1-minute and 5-minute Apgar scores, and admission to neonatal intensive care unit.

Relationship between the incidence of PTB and independent vari-