Rapid progression of nulliparous labor increases the risk of preterm delivery in a subsequent pregnancy

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Running title

Does rapid progression of labor matter?

Abstract

Objective: We examined the relationship between the duration of nulliparous labor at term and threatened preterm delivery (PTD) in a subsequent pregnancy.

Materials and methods: We retrospectively reviewed the records of 154 uncomplicated singleton multiparas with no history of second-trimester spontaneous abortion or PTD. We conducted multivariate logistic regression analyses to determine risk factors for threatened PTD. Parameters included the duration of nulliparous labor i.e., the times from onset of labor to full dilation and from 4cm to full dilation, maternal age, body mass index, gravidity, parity, smoking, gestational age at delivery, and birth weight in a subsequent pregnancy.

Results: The duration of nulliparous labor was associated with the need for rescue with cerclage and/or tocolysis in a subsequent pregnancy, when < 6.5h were required for full dilation from onset of labor and when < 2.0h were required to progress from 4cm to full dilation. These durations were considered optimal cut-off values. The duration of nulliparous labor at term < 6.5h from onset to full cervical dilation predicted subsequent threatened PTD with sensitivity, specificity, and positive and negative predictive values of 84.6%, 67.0%, 23.9%, and 97.3%, respectively. Those values for duration < 2.0h from 4cm to full dilation were 76.9%, 64.2%, 20.8%, and 95.8%, respectively. The combined sensitivity, specificity, and positive and negative predictive values of both parameters were 69.2%, 77.4%, 27.3%, and 95.3%, respectively.

Conclusion: Women with rapid progression of nulliparous labor are at risk of requiring treatment for PTD in a subsequent pregnancy.

Key words: Cervical cerclage, Cervical length, Precipitous labor, Threatened preterm labor and Tocolysis.

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Introduction

Preterm delivery (PTD) is the leading cause of neonatal morbidity and mortality in developed countries [1–3] and its prevention is one of the main objectives of current obstetric care. Preventive care should be based on the patient's known risk factors, most notably spontaneous second-trimester abortion or PTD in previous pregnancies. Other risk factors include being of African origin, smoking, obesity, history of cone biopsy, uterine anomalies, and multiple pregnancies [4].

Vyas et al. reported that pregnant women who experienced a precipitous term delivery were more likely to have cervical insufficiency in a subsequent pregnancy [5]. This suggests that rapid progression of nulliparous labor at term is a risk factor for threatened PTD in a subsequent pregnancy. However, there have been no studies to evaluate the association between a nulliparous precipitous delivery at term and PTD and threatened PTD in a subsequent pregnancy. Therefore, we conducted this study to examine the relationship between rapid progression of nulliparous labor at term and threatened PTD in a subsequent pregnancy.

Materials and Methods

A total of 2067 pregnant women received care between January 2010 and December 2011, at Fukuoka University Hospital and Iizuka Hospital, the tertiary perinatal care centers for high-risk pregnancies in our region. Of the 1099 multiparous women in this population, 303 with uncomplicated singleton pregnancy met the following inclusion criteria: transvaginal nulliparous delivery with no history of spontaneous second-trim ester abortion, PTD, or preterm premature rupture of membranes before 37 weeks' gestation, and availability of delivery records. All delivery

records were checked for completeness, accuracy, and consistency. After applying exclusion criteria for nulliparous delivery that included induction or augmentation of labor and cervical dilation > 4cm at admission, a final total of 154 women were included in this study. The institutional review boards of Fukuoka University Hospital and Iizuka Hospital approved the study protocol, and all patients provided informed consent.

In the subsequent pregnancy during the study period, cervical length (CL) measurements were obtained using an ultrasound unit (Aloka alpha 6, Tokyo, Japan) with 5-MHz curvilinear transvaginal transducers, at 4-week intervals until 30 weeks' gestation and at 2-week intervals when CL was <25mm. Treatments to prevent PTD, such as rescue cervical cerclage and/or tocolysis, were performed according to our institutional protocol. Rescue cervical cerclage was performed when CL was <15mm before 26 weeks' gestation [6-8]. Ritodrine hydrochloride (intravenous, 50 -200μg / min) and/or magnesium sulfate (intravenous 4g over 20min then 1-2g/h drip infusion) were administered up to 36 weeks' gestation to patients with cervical maturation on digital examination and who were having regular uterine contractions on cardiotocogram, which were sustained after admission and use of the bathroom. Combinations of ritodrine hydrochloride and/or magnesium sulfate are the standard tocolysis in Japan, and were used in the present study.

We selected the following parameters as potential risk factors for needing preventive PTD treatment: the duration of nulliparous labor [4, 9-14], maternal age, body mass index, gravidity, parity, smoking, gestational age at delivery, birth weight in the subsequent pregnancy during the study period. The duration of nulliparous labor was evaluated using two parameters: time from onset of labor to full cervical dilation

and time taken from 4cm to full dilation. Onset of labor was defined as the time when regular painful contractions occurred at 10-min intervals or six times per hour. Both times were expressed as 30-minunits, with fractions rounded up.

Statistical analyses were performed using SAS software (SAS Institute Inc, Cary, NC, USA). Crude odds ratios (ORs) and 95% confidence intervals (CIs) of the need for PTD treatment were estimated using logistic regression analyses. Multiple logistic regression analyses were used to simultaneously adjust for all selected possible parameters. We further determined the most suitable cut-off values for the significant parameters using a receiver operating characteristic (ROC) curve and calculated the sensitivity, specificity, and positive and negative predictive values.

Results

Of the 154 women included in this study, patients requiring treatment for PTD in the subsequent pregnancy during the study period (rescue cervical cerclage, n=8; tocolysis, n=13) were included in group A (n=21, 13.6%), and patients who did not require treatment for PTD were included in group B in the subsequent pregnancy during the study period (n=133, 86.4%). Patients in group A had lower gestational age at delivery, lower birth weight, and shorter duration of labor than patients in group B (Table 1). Tocolysis with a single drug was more common than with combinations of drugs (n=10, 76.9% of maintenance tocolysis). Median pregnancy prolongation was 56 days, (range, 13 – 166 days) and mean gestational age at delivery was 270±10.3 days. In two cases (1.3%), PTD occurred before 37 weeks' gestation, while eight patients (5.2%) with threatened PTD before 37 weeks' gestation delivered within 7 days after cessation of tocolysis [15].

According to the crude analyses, gestational age at delivery and the duration of nulliparous labor had a significant inverse relationship with the risk of requiring PTD treatment in a subsequent pregnancy. After simultaneously adjusting for the duration of nulliparous labor and maternal age, body mass index, gravidity, parity, smoking, gestational age at delivery, birth weight in a subsequent pregnancy, the inverse association between gestational age at delivery and the risk of requiring treatment for PTD in a subsequent pregnancy disappeared. However, shorter duration of nulliparous labor remained an independently associated risk factor for PTD treatment in a subsequent pregnancy (**Table 2**).

ROC curve analyses indicated that 6.5h and 2.0h were the optimum cut-off values for time from onset of labor to full cervical dilation and from 4cm to full dilation in nulliparous labor, respectively (**Figure 1**). The ROCs was 0.838 and 0.841 for time from onset of labor to full dilation and from 4 cm to full dilation, respectively. Nulliparous labor duration of < 6.5h from onset to full cervical dilation predicted the need for subsequent PTD treatment in a subsequent pregnancy with a sensitivity, specificity, and positive and negative predictive values of 84.6%, 67.0%, 23.9%, and 97.3%, respectively. These values for nulliparous labor lasting < 2.0h from 4 cm to full dilation were 76.9%, 64.2%, 20.8%, and 95.8%, respectively. The combined sensitivity, specificity, and positive and negative predictive values of both parameters were 69.2%, 77.4%, 27.3%, and 95.3%, respectively (**Table 3**).

Discussion

We demonstrated that women with rapid progression of nulliparous labor, i.e., < 6.5h from onset of labor to full cervical dilation or < 2.0h from 4cm to full dilation,

had a higher risk of requiring rescue cervical cerclage and/or tocolysis in a subsequent pregnancy. Zhang et al. evaluated the normal progression of first stage labor and reported an average interval of 5.5h between 4cm and full cervical dilation [16]. The average interval from 4cm to full dilation nulliparous women in our study who later needed treatment to prevent PTD was < 2.0h, which is less than half the previously reported average.

In cases of incompetent cervix, the mechanical or biochemical properties of the cervix varied from those of the normal cervix, as a result of reduced elasticity of the cervical tissues [17,18]. Different extra cellular matrix components, such as collagen, sulfated glycosaminoglycans, and hyaluronic acid, are present in the favorable cervix compared with the unfavorable cervix. In addition, changes in the characteristics of the cervical collagenous tissues during labor can affect duration of labor [19–22]. We speculate that cervical tissues in cases with CL shortening, had more elasticity compared to cases with non-CL shortening, before the onset of labor. Patients with rapid progression of nulliparous labor have inherent tendencies toward cervical weakness, possibly leading to premature cervical maturation in a subsequent pregnancy.

We evaluated the first stage of nulliparous labor using two parameters: intervals from onset of labor to full dilation and from 4cm to full dilation. Time from onset of labor to full cervical dilation is a clinically convenient but inaccurate parameter, because onset of labor, defined as the time when painful uterine contractions occur every 10min or six times per hour, relies on accurate patient reporting. Time from 4cm to full dilation is more accurate, because it is based on the objective parameter of cervical dilation. Time from onset of labor to full cervical dilation and time from 4cm to full dilation were related to each other; the correlation coefficient between them was

0.58 (p = < 0.001). We used these two parameters as independent variables in the multivariate model.

Our protocol indicated that rescue cervical cerclage should be performed when the CL progressively shortened to < 15mm before < 26 weeks' gestation. This protocol was based on previous reports indicating that CL < 15mm is a clinically appropriate criterion for rescue cervical cerclage to prevent PTD [6-8]. The indications for tocolysis were regular and painful uterine contractions with maturation of the cervix. In these cases ritodrine hydrochloride and/or magnesium sulfate were administered up to 36 weeks' gestation. Although we encountered only eight cases with threatened PTD treated up to 36 weeks' gestation with tocolytic drugs, the gestational age at delivery in group A was significantly lower than in group B (p = 0.004), suggesting that our tocolysis protocol was instrumental in preventing delivery before 36 weeks' gestation.

This study has some limitations. First, the primary outcome in our study was absence of treatment to prevent PTD (rescue cervical cerclage and/or tocolysis) before 36 weeks' gestation, but not PTD or threatened PTD. Second, this is a retrospective study, and conducting a study in which PTD treatments are withheld would be unethical. Based on the above-mentioned limitations of our study, future large-scale prospective studies are required to confirm that rapid progression of nulliparous labor is a risk factor for subsequent PTD.

In conclusion, our study showed that rapid progression of nulliparous labor is a significant risk factor for needing PTD treatment in subsequent pregnancies. Future large-scale prospective studies are required to determine whether rapid progression of nulliparous labor is a risk factor for PTD.

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Figure legend

Figure 1: Receiver operating characteristic (ROC) curve for time from onset of labor to full cervical dilation (T_1) and from 4cm to full dilation (T_2).

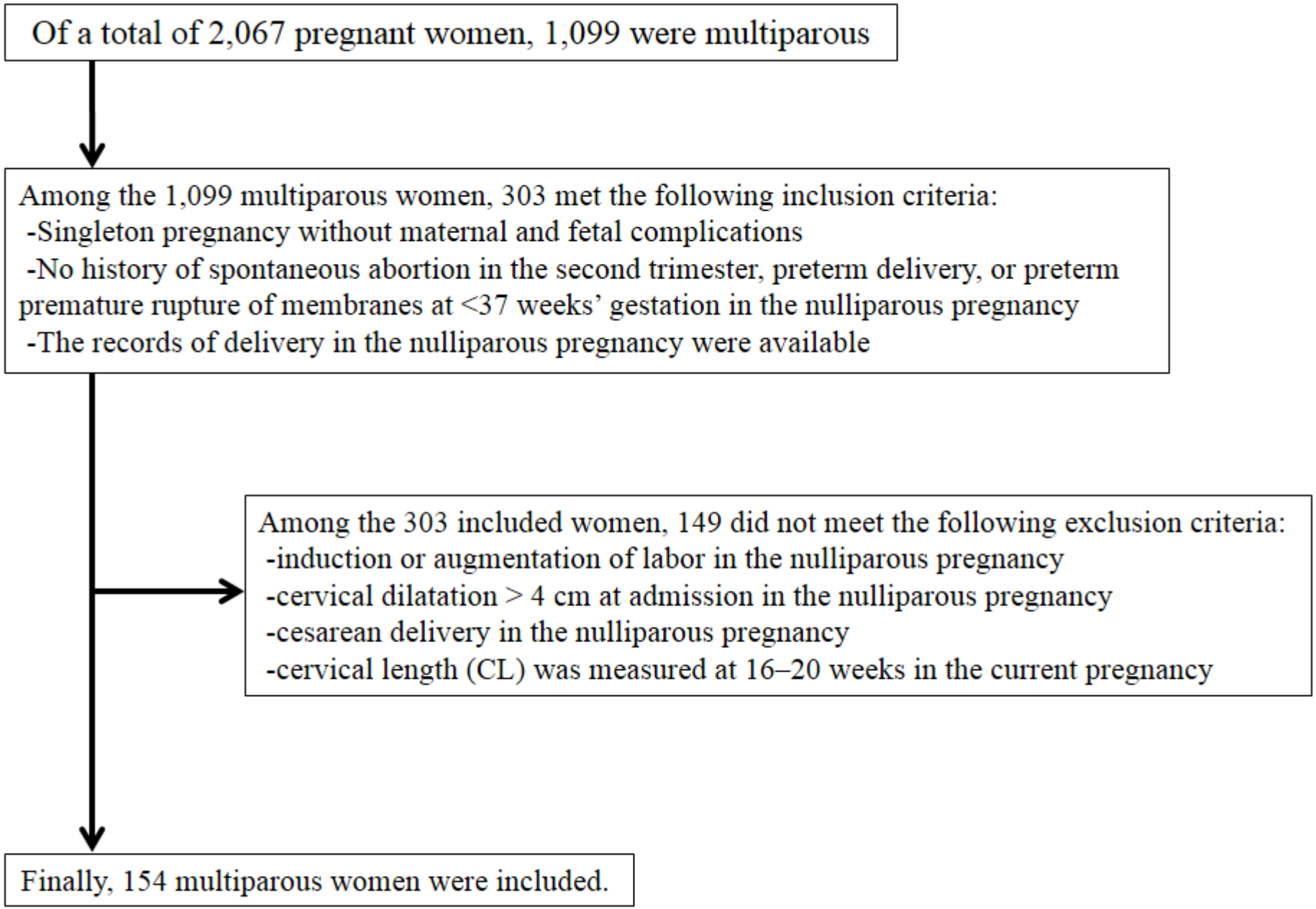
Of a total of 2,067 pregnant women, 1,099 were multiparous
Among the 1,099 multiparous women, 303 met the following inclusion criteria:
-Singleton pregnancy without maternal and fetal complications
-No history of spontaneous abortion in the second trimester, preterm delivery, or preterm premature rupture of membranes at <37 weeks' gestation in the nulliparous pregnancy
-The records of delivery in the nulliparous pregnancy were available
Among the 303 included women, 149 did not meet the following exclusion criteria:
-induction or augmentation of labor in the nulliparous pregnancy
-cervical dilatation > 4 cm at admission in the nulliparous pregnancy
-cesarean delivery in the nulliparous pregnancy
-cervical length (CL) was measured at 16–20 weeks in the current pregnancy
Finally, 154 multiparous women were included.

Figure 1

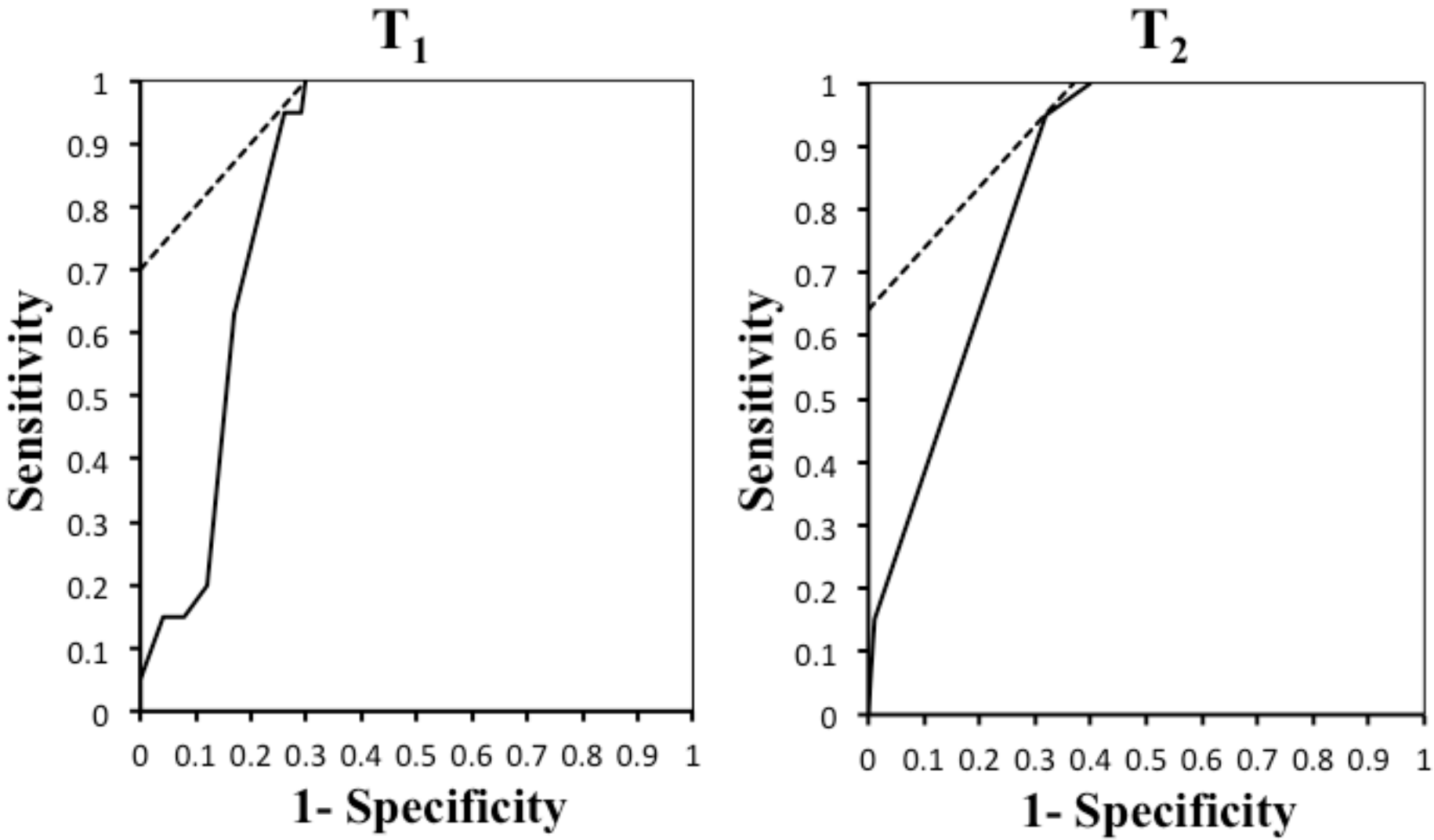

Figure 1

Table 1. Characteristics of the study population

	Group A (n = 21)	Group B (n = 133)	*p* value
Maternal age (years)	29.9 ± 4.9	30.7 ± 5.5	0.55
Body mass index (kg/m^2)	21.2 ± 4.7	20.8 ± 2.9	0.69
Gravidity	2.0 ± 1.1	2.0 ± 1.2	0.96
Parity	1.2 ± 0.5	1.3 ± 0.5	0.65
Number of smokers	3 (14.3 %)	12 (9.0 %)	0.43
Gestational age at delivery (days)	270.0 ± 10.3	274.8 ± 8.0	0.01
Birth weight (g)	2739 ± 327	2937 ± 356	0.02
Duration of nulliparous labor			
Time from the onset of labor to full dilatation (h)	4.4 ± 1.1	10.9 ± 7.1	< 0.0001
Time required for 4 cm to full dilatation (h)	1.4 ± 0.6	3.9 ± 2.7	< 0.0001

Numbers indicate mean ± SD, except for the number of smokers, which is expressed as n (%).

Group A comprises patients who required treatment for preterm delivery; Group B comprises patients who did not require treatment for preterm delivery.

Table 2. Odds ratios for requiring treatment for preterm delivery by selected parameters

	Crude OR	Adjusted OR
Maternal age (years)	0.97 (0.89 - 1.06)	0.98 (0.88 - 1.09)
Body mass index (kg/m^2)	1.04 (0.90 - 1.18)	0.99 (0.83 - 1.19)
Gravidity	1.01 (0.66 - 1.48)	1.08 (0.59 - 1.95)
Parity	0.80 (0.27 - 1.92)	1.27 (0.32 - 5.39)
Smoking	1.68 (0.36 - 5.93)	2.38 (0.34 - 14.91)
Gestational age at delivery (days)	0.94 (0.89 - 0.99)	1.02 (0.94 - 1.11)
Birth weight (g)	0.998 (0.997 - 1.000)	0.999 (0.997 - 1.001)
Duration of nulliparous labor		
Time from the onset of labor full dilatation (h)	0.63 (0.47 - 0.78)	0.76 (0.56 - 0.93)
Time required for 4 cm to full dilatation (h)	0.27 (0.12 - 0.49)	0.36 (0.13 - 0.77)

Parentheses indicate the 95% confidence interval. OR, odds ratio

Table 3. Sensitivity, specificity, and predictive values for presence of absence of treatments for preterm delivery

	Sensitivity	Specificity	PPV	NPV
Duration of nulliparous labor				
Time from the onset of labor to full dilatation	84.6	67.0	23.9	97.3
< 6.5 h vs. ≥ 6.5 h	(59.5 - 95.6)	(63.9 - 68.3)	(24.6 - 27.0)	(92.8 - 99.2)
Time required for 4 cm to full dilatation	76.9	64.2	20.8	95.8
< 2.0 h vs. ≥ 2.0 h	(59.5 - 95.6)	(63.9 - 68.3)	(13.9 - 24.8)	(91.1 - 98.5)
Time from the onset of labor full dilatation < 6.5 h and time required for 4 cm to full dilatation < 2.0 h vs. Time from the onset of labor full dilation ≥ 6.5 h and time required for 4 cm to full dilatation ≥ 2.0 h	69.2 (44.1 - 86.9)	77.4 (74.3 - 79.5)	27.3 (17.4 - 34.2)	95.3 (91.6 - 98.0)

PPV, positive predictive value, NPV, negative predictive value, ( ), 95% confident interval.