Thai Journal of Obstetrics and Gynaecology
July 2010, Vol. 18, pp. 98-105

OBSTETRICS

Risk Factors for Two Consecutive Preterm Births in Southern Thailand

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ABSTRACT

Objective: To identify the risk factors for two consecutive preterm births in southern Thailand.

Materials and Methods: A case-control study was conducted at Songklanagarind Hospital, the tertiary care hospital in the south of Thailand. Medical records of all women who had had a second live birth from 1997 to 2006 were reviewed. Term and preterm birth in both pregnancy were identified. The women having two preterm births were classified as the case group, and the women having preterm/term, term/preterm or term/term births were the control group. Socio-demographic characteristics, obstetric information and pregnancy complications were analyzed using univariate and multivariate analysis with a p-value of 0.05.

Results: During the study period, 94 women with two preterm births were included in the cases, and 385 controls were randomly selected from all eligible records. Women aged <20 years had an increased risk of two preterm births compared to those aged 20-34 years. An interpregnancy interval of <12 months was also more frequent in double preterm birth cases in univariate analysis, but not in multivariate analysis. Premature rupture of membranes (adjusted OR 2.1, 95%CI 1.2-3.6), urinary tract infection (adjusted OR 8.7, 95%CI 2.3-33.5) and pregnancy-induced hypertension (adjusted OR 4.0, 95%CI 1.7-9.2) were independent factors in both univariate and multivariate analyses.

Conclusions: Maternal age, premature rupture of membranes, urinary tract infection and pregnancy-induced hypertension were the significant factors in women having two consecutive preterm births. It is important for obstetricians to be aware of these risk factors in women who become pregnant after a previous preterm birth.

Keywords: predictor, preterm birth, recurrent preterm

Introduction

Prematurity is one of the important public health issues in maternal and child health globally. Preterm infants are at 60-80% increased risk of death in both the perinatal and infant periods. The incidence of preterm births was reported worldwide at 5-10%, with a rate of 9-10% in developing countries and 6-12% in developed countries[1,2]. Likewise, in Asian countries, the rate was in 7.4-14.3%[3]. Apart from the increased risk of death, preterm infants are more prone to develop

cognitive and physical abnormalities leading to financial and social burdens for their management and child care[4], and have an increased risk of underweight and stunting in the first two years of life[5].

The etiologies for preterm birth are multifactorial, including maternal, biological and genetic factors; however, precise mechanisms have not yet been determined[2]. Maternal factors have most commonly been studied, especially in developing countries due to the high cost of investigation of biological and genetic markers. Previous studies on maternal factors have found that previous preterm birth, short interval between pregnancies, lower gestational age, a high number of prior preterm births, premature rupture of membranes and the race of the mother are the risk factors for preterm birth[6-13].

Most studies have emphasized on various risk factors for preterm births, but very few of them have examined specifically on two consecutive preterm births by one woman. Two previous studies, one from Israel and one from the US, have examined the risk factors or predictors for two consecutive preterm births from the same mother[10,11]. Since we know that the incidence of preterm births varies according to the number of births[12] and the race of the mother[13]. More information on the risk of two preterm births among women in southeast Asian countries with the same number of births is needed in order to provide information for pregnant women at risk. This current study was aimed to identify the risk factors for two consecutive preterm births in southern Thailand.

Materials and methods

Study setting and participants

This case-control study was conducted at Songklanagarind Hospital, an university hospital and the main tertiary care unit and referral center in southern Thailand. The study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University. All women who delivered their singleton, second live births at this hospital between 1997 and 2006 were included. Women who had a previous abortion or miscarriage were excluded. Women who gave two consecutive preterm births (preterm/preterm) were classified as the case group, and the control group was drawn from the remaining women including term/term, term/preterm or preterm/term births.

The sample size was calculated based on the proportion of short interpregnancy interval (less than 12 months) between the case and control groups from a previous study which were 23% of short interpregnancy interval in the case and 10% of that in the control[10]. According to a 95% confidence interval, power of 80%, a ratio between case and control of 1 to 4, a minimum of 470 medical records, 94 cases and 376 controls (at least 125 for each category of term/term, term/preterm or preterm/term), were needed.

Data collection process

Medical records was obtained from the computerized database of the Statistical Unit of the Department of Obstetrics and Gynecology at Songklanagarind Hospital. Of 9,902 eligible medical records in the study period, ninety-four records met the case inclusion criteria and were reviewed. The lists of women in each category of control were made and randomly selected from women who delivered at the same period with preterm cases by computer-generated random numbers with simple random sampling. Data from 385 medical records were reviewed as a control.

Variables

The main variables from second birth were reviewed including maternal age, occupation, religion, educational attainment, monthly income, interpregnancy interval, gestational age at first prenatal visit, body mass index (BMI) at first prenatal visit, pregnancy complications (urinary tract infection, pregnancy-induced hypertension and premature rupture of membranes) and route of delivery. A preterm birth was defined as a birth before completed 37 weeks of gestation. Gestational age of the pregnancy was based on a reliable, self-reported last menstrual period (LMP) or ultrasonography done early in the pregnancy if the LMP was unknown. If both estimations were available and were within 14 days of one another, the LMP was used. If the difference exceeded 14 days, gestational

age by ultrasonography was used.

A distinction was made between spontaneous and indicated preterm birth. Spontaneous preterm birth was defined as a preterm birth occurring as a result of the spontaneous onset of labor or spontaneous rupture of membranes, while indicated preterm birth was defined as a medically induced preterm birth either as induced labor or prelabor cesarean section. The interpregnancy interval was defined as the time between the women's previous delivery and the first day of the last menstrual period for the index pregnancy. A 'short interval' was defined as a second pregnancy beginning within 12 months of a delivery as a study of Krymko et al[10]. Asian classifications for BMI were used- <18.5, 18.5-22.9 and ≥23 kg/m^2 represented underweight, normal weight, overweight to obese, respectively[14]. The pregnancy complications were recorded using the available diagnosis noted in the medical records and details of clinical symptoms revealed.

Data analysis

Data were recorded in Epidata 3.1 on a double entry basis and analyzed by R software version 2.8.0 (the R Foundation for Statistical Computing 2008, Austria). The agreement of case ascertainment between the computerized database of the Statistical Unit and medical record review was analyzed using kappa statistics. Continuous data were presented descriptively by mean if data were normally distributed or median if data were not normally distributed. Factors associated with the occurrence of two preterm births were determined by univariate and multivariate analysis. Statistical significance was considered achieved when the p-value was less than 0.05.

Results

Of the 479 records, the agreement of case diagnosis between the computerized database of the Statistical Unit and the medical record review was perfect with a Kappa coefficient of 0.9. Mean and standard deviation of maternal age was 30.1±5.6 years (range 17-44 years). Majority of the women was Buddhist (89.4%) and had a high-school educational attainment (37.4%). Most women were employees (54.5%) and their monthly income ranged from 5,000 to 10,000 baht in 31.1%. Of 385 controls, women with term/term, preterm/term and term/preterm were 129, 126 and 130 cases, respectively.

Table 1 depicts the demographic, socioeconomic and obstetric characteristics of the cases and controls. Religion, route of previous delivery, gestational age and BMI at first prenatal visit were not significantly different between the two groups. Of women in the control group, 66% had had a preterm birth in either their first or second delivery. The proportion of induced preterm birth was 13.8% and 16.5% between case and control, respectively. The cases group had a higher proportion of mothers aged <20 years, being a student, having less education, lower income, interpregnancy interval of <12 months, presenting with urinary tract infection, pregnancy-induced hypertension and premature rupture of membranes during pregnancy.

Table 2 shows the final multiple logistic regression model identifying the factors related to the risk of consecutive preterm births, in which age, interpregnancy interval, premature rupture of membranes, urinary tract infection and pregnancy-induced hypertension were identified as significant risk factors. Teenage mothers had an increased risk of two preterm births (adjusted OR 3.4, 95% CI 1.1-11.2) compared to adult mothers aged 20-34 years. An interpregnancy interval of <12 months was more frequent in cases in univariate (crude OR 2.2, 95% CI 1.3-4.0) but not in multivariate analysis. Premature rupture of membranes (adjusted OR 2.1, 95% CI 1.2-3.6), urinary tract infection (adjusted OR 8.7, 95% CI 2.3-33.5) and pregnancy-induced hypertension (adjusted OR 4.7, 95% CI 1.7-9.2) were independently associated with two consecutive preterm births in both univariate and multivariate analyses. When subgroup analysis was considered, only PROM was a significant associated factors between term/term subgroup compared to preterm/preterm case.

Table 1. Comparisons of demographic and obstetric characteristics between case and control by univariate analysis.

	Control N= 385	Case N=94	p-value
Age (years)			0.008
<20	7 (1.8)	6 (6.4)	
20-34	276 (71.7)	73 (77.7)	
≥35	102 (26.5)	15 (16)	
Occupation			0.043
Housewife	98 (25.5)	23 (24.5)	
Government/State enterprise	87 (22.6)	12 (12.8)	
Agriculture	37 (9.6)	17 (18.1)	
Worker	112 (29.1)	25 (26.6)	
Merchant	49 (12.7)	15 (16.0)	
Student	2 (0.5)	2 (2.1)	
Religion			0.9
Buddhist	345 (89.6)	84 (89.4)	
Islam	40 (10.4)	10 (10.6)	
Education			0.031
None	6 (1.6)	2 (2.1)	
Primary	98 (25.4)	24 (25.5)	
Secondary	132 (34.3)	47 (50.0)	
Bachelor or more	132 (34.3)	20 (21.3)	
Missing data	17 (4.4)	1 (1.1)	
Monthly income (baht)			0.004
Less than 5000	47 (12.2)	20 (21.3)	
5000-10000	129 (33.5)	20 (21.3)	
>10000	84 (21.8)	13 (13.8)	
No income	44 (11.4)	10 (10.6)	
Missing data	81 (21)	31 (33)	
Interpregnancy interval (months)			0.005
<12	47 (12.2)	22 (23.4)	
≥12	336 (87.3)	70 (74.5)	
Missing data	2 (0.5)	2 (2.1)	
Route of previous delivery			0.487
Normal delivery	223 (59.9)	60 (63.8)	
Forceps or vacuum extraction	25 (6.5)	7 (7.5)	
Cesarean section	126 (32.7)	25 (26.6)	
Missing data	11 (2.9)	2 (2.1)	

Table 1. Comparisons of demographic and obstetric characteristics between case and control by univariate analysis. (cont.)

	Control N= 385	Case N=94	p-value
Gestational age at first prenatal visit (weeks)			0.08
Median (IQR)	11 (8,16)	13 (9,20)	
BMI at first prenatal visit (kg/m^2)			0.538
<18.5	26 (6.8)	7 (7.4)	
<18.5-22.9	123 (31.9)	31 (33)	
≥23	93 (24.2)	28 (29.8)	
Missing data	143 (37.1)	28 (29.8)	
Urinary tract infection during pregnancy			0.005
No	381 (99)	88 (93.6)	
Yes	4 (1)	6 (6.4)	
Pregnancy-induced hypertension			0.002
No	370 (96.1)	82 (87.2)	
Yes	15 (3.9)	12 (12.8)	
Premature rupture of membranes			0.029
No	308 (80.0)	65 (69.2)	
Yes	77 (20.0)	29 (30.8)	
Gestational age at delivery (weeks) Median (IQR)	38 (36,38)	35 (32,36)	< 0.001

BMI: Body Mass Index; IQR: Interquartile range

Table 2. Final logistic regression model showing significant factors influencing the risk of two consecutive preterm births

Factors	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value
Age (years)			0.012
20-34	1	1	
<20	3.2 (1.1-9.9)	3.4 (1.1-11.2)	
≥35	0.6 (0.3-1.0)	0.5 (0.3-1.0)	
Interpregnancy interval (months)			0.09
≥12	1	1	
<12	2.2 (1.3-4.0)	1.7 (0.9-3.2)	
Premature rupture of membranes			<0.01
No	1	1	
Yes	1.8 (1.1-3.0)	2.1 (1.2-3.6)	
Urinary tract infection during pregnancy			<0.01
No	1	1	
Yes	6.5 (1.8-23.4)	8.7 (2.3-33.5)	
Pregnancy-induced hypertension			<0.01
No	1	1	
Yes	3.6 (1.6-8.0)	4.0 (1.7-9.2)	

LR: likelihood ratio test

Discussion

Maternal age, premature rupture of membranes, urinary tract infection and pregnancy-induced hypertension were the significantly independent factors in women having two consecutive preterm births. It is well-known that women who deliver preterm in their first pregnancy have an increased risk of preterm delivery in a subsequent pregnancy compared with women who give birth at term in the first delivery[6]. Prematurity was known to have a serious effect not only on the immediate and long-term health of the infant, but also on the well-being of the mothers and families[1,4,5]. Since having two preterm births in one family is known to be a serious risk, the identification of factors contributing to this situation is essential background knowledge for educational and planning strategies of maternal and child health issues both nationally and internationally.

Although a complete elucidation of the etiologies of preterm birth have not been perfectly determined, many associated maternal factors have been identified with a good degree of confidence, factors which can be recognized in situations where expensive or sophisticated tests such as biological or genetic markers are not available[2]. In the present study, we found that teenage pregnancy was more common in women who had two consecutive preterm births similar to previous studies, although the study designs and subject were difference[11,13]. The risk of preterm birth in teenage mothers is also associated with low socioeconomic status and other poor pregnancy outcomes[15,16]. In contrast, teenage pregnancy was not found to be a risk factor in the study of Krymko et al[10], which compared the factors between women having two preterm births and those having preterm at first but term at second birth. A similar result between these two subgroups was also found in our study (data not shown).

Women who had premature rupture of membranes and preterm delivery had a significant greater risk of recurrent preterm delivery in the following pregnancy than the control group[8]. Another study found that premature rupture of membranes from was an important associated factor of preterm birth[17]. Urinary tract infection was also a common complication in pregnancy which can lead to preterm birth and low birthweight[18]. A presence of genitourinary tract infection stimulates the production of inflammatory cytokines leading to the pathophysiological mechanisms of induction of labor and dilatation of the cervix[19]. Pregnancy-induced hypertension has been associated with induced delivery due to the mother's condition. A large prospective cohort study found that the risk of pregnancy-induced hypertension was increased in subsequent pregnancies[20]. However, the presence of pregnancy-induced hypertension in the first live birth was not determined in our study, because our records included many women who had had their first births outside the participating hospital thus no accurate information on this complication was noted in the medical records available for our study.

Another previous study found that a short interpregnancy interval of less than 12 months was related to preterm births[10]. This factor was not deemed as significant in our study by multiple logistic regression analysis. Cut-off values defining a short interpregnancy interval were varied from 6 to 12 and to 18 months. In most studies which have examined this variable, short interval pregnancies have been associated with preterm birth less than 34 weeks gestation[7,9,11]. Previous studies on maternal factors identified with preterm births have found that previous preterm birth, short interval between pregnancies, lower gestational age, high number of prior preterm births, premature rupture of membranes and race of the mother were factors which were associated with a higher risk of preterm births[6-13]. Taken together, these studies indicated that there are a number of factors contributing to the risk of two preterm births, and vary depending on different study populations, or demographic and socioeconomic characteristics, obstetric history or genetic markers, and also different study designs. Only PROM was identified as a significant associated factor between preterm/preterm case and term/term subgroup. This might be because PROM is a strong factor and the difference of proportion of potential associated factors in women who had any one preterm birth compared to the case was low.

Although our limitation was a retrospective data collection depending on the reporting system, most of the important data could be extracted from both the

computerized database of our statistical unit and also from the medical records. The finding showed that a good agreement of case ascertainment was obtained. This study was conducted at the major referral center in southern Thailand, where most high-risk pregnancies are routinely sent, and thus we had a large enough sample of two consecutive preterm births to make our results statistically significant over the study period of 10 years. The number of women having indicated preterm birth was small so subgroup analysis between spontaneous and indicated preterm births was not performed. However, the number of women who had no two consecutive preterm births in each subgroup category of the control was considered equally to reduce the overestimated or underestimated effect of the control group. Finally, the complications during pregnancy or delivery routinely collected from medical records may result in underestimation of diagnosis.

In conclusion, our study in southern Thailand found that teenage or premature rupture of membranes, urinary tract infection during pregnancy and pregnancy-induced hypertension were more likely to be detected in women with two consecutive preterm births than in other pregnancies. This information can be used for counseling at prenatal and postpartum care clinics for Thai pregnant women, and probably for other Asian women. Women who had a preterm birth at their first pregnancy in their teens should be counseled to avoid having another child before the age of 20 years. Risk factors for premature rupture of membranes, pregnancy-induced hypertension and urinary tract infection should be carefully monitor from early stage of a pregnancy in order to provide proper care to prevent premature births.

Acknowledgments

This study was supported by a grant from the Faculty of Medicine, Prince of Songkla University. We would like to thank the personnel in the Statistical Unit of the Department of Obstetrics and Gynecology for providing the list of eligible women.

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ปัจจัยที่มีผลต่อการคลอดก่อนกำหนดซ้ำสองท้องในภาคใต้ของประเทศไทย

ธิติ อัจจิมากุล, ทิพวรรณ เลียบสื่อตระกูล

วัตถุประสงค์ *: เพื่อหาปัจจัยที่มีผลต่อการคลอดก่อนกำหนดซ้ำสองท้องในภาคใต้ของประเทศไทย*

วิธีการ *: การศึกษาเปรียบเทียบระหว่างกลุ่มศึกษาและกลุ่มควบคุม ได้ดำเนินการในโรงพยาบาลสงขลานครินทร์ที่เป็นโรงพยาบาลมหาวิทยาลัยในภาคใต้ของประเทศไทย โดยการรวบแฟ้มเวชระเบียนของหญิงตั้งครรภ์ท้องที่สอง ที่คลอดทารกเกิดมีชีพในช่วงปีพ.ศ.2540 ถึง พ.ศ.2549 โดยจำกัดเฉพาะหญิงที่คลอดครบกำหนดหรือคลอดก่อนกำหนดในการคลอดครรภ์แรกและครรภ์ที่สองเท่านั้นโดยหญิงที่คลอดก่อนกำหนดสองท้องเป็นกลุ่มศึกษาส่วนหญิงที่ไม่ได้คลอดก่อนกำหนดทั้งสองท้องจัดเป็นกลุ่มควบคุม โดยอาจเป็นคลอดก่อนกำหนดครรภ์แรก คลอดครบกำหนดครรภ์ที่สองหรือคลอดครบกำหนดครรภ์แรก คลอดก่อนกำหนดครรภ์ที่สองหรือคลอดครบกำหนดทั้งสองท้องโดยศึกษาลักษณะทางประชากรข้อมูลทางสูติกรรมและภาวะแทรกซ้อนที่พบในสตรีตั้งครรภ์*

ผลการศึกษา *: ในช่วงเวลาที่ศึกษาพบกลุ่มศึกษาจำนวน 94 รายและกลุ่มควบคุม 385 ราย ซึ่งได้มาจากการสุ่มจากจำนวนที่เข้าเกณฑ์ทั้งหมด อายุเฉลี่ยของหญิงตั้งครรภ์ 30.1±5.6 ปี หญิงที่อายุน้อยกว่า 20 ปี มีความเสี่ยงที่คลอดก่อนกำหนดซ้ำสองท้องสูงขึ้น 3.4 เท่า เมื่อวิเคราะห์ความถดถอยเชิงพหุ [adjusted OR 3.4 (1.1-11.2)] เปรียบเทียบกับช่วงอายุ 20-34 ปี ส่วนระยะห่างระหว่างการตั้งครรภ์น้อยว่า 12 เดือน เพิ่มการเกิดการคลอดก่อนกำหนด 2 ท้อง ด้วยการวิเคราะห์แบบตัวแปรเดียวแต่ไม่พบนัยสำคัญ ด้วยการวิเคราะห์ความถดถอยเชิงพหุ การเกิดน้ำคร่ำแตกก่อนการเจ็บครรภ์ [adjusted OR 2.1(1.2-3.6)] การติดเชื้อทางเดินปัสสาวะ[adjusted OR 8.7(2.3-33.5)] และพิษแห่งครรภ์ [adjusted OR 4.0(1.7-9.2)] พบมากขึ้นในหญิงที่คลอดก่อนกำหนดซ้ำสองท้องอย่างมีนัยสำคัญด้วยการวิเคราะห์แบบตัวแปรเดียวและวิเคราะห์ความถดถอยเชิงพหุ*

สรุป *: อายุครรภ์ของมารดา น้ำคร่ำแตกก่อนการเจ็บครรภ์ การติดเชื้อทางเดินปัสสาวะและพิษแห่งครรภ์ เป็นปัจจัยที่มีความสำคัญที่มีผลต่อการคลอดก่อนกำหนดซ้ำสองท้อง การให้คำแนะนำที่ดีเกี่ยวกับปัจจัยที่มีผลหลังจากการคลอดท้องแรก โดยเฉพาะการคลอดก่อนกำหนด มีความสำคัญอย่างยิ่ง*