Thai Journal of Obstetrics and Gynaecology
October 2012, Vol. 20, pp. 166-172

OBSTETRICS

Association between Advanced Paternal Age and Low Birthweight in Thai Population

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ABSTRACT

Objectives: To determine the association between advanced paternal age and low birthweight

Materials and Methods: This was a case-control study including primigravida women, age ≥ 18 years old, who delivered at Siriraj Hospital during January 2008 to December 2010. This study included 398 women who delivered the low birthweight infants. Matching total of 400 women with infant weight ≥ 2,500 g were served as the control group. Paternal age, parental characteristics and certain obstetric complications were compared between these two groups.

Results: There was no statistically significant associations between paternal age older than 34 years old and low birthweight. Maternal age younger than 20 years had an increased risk of having a low birthweight infant comparing with the mothers aged 20-34 years (adjusted OR 2.31, 95%CI: 1.14-4.71). Severe preeclampsia, superimposed preeclampsia and eclampsia are significantly increased the risk of low birthweight (adjusted OR 3.59, 95%CI: 1.65-7.82). The association between preterm birth and low birthweight was remarkably significant (adjusted OR 16.06, 95%CI: 10.07-25.63).

Conclusion: Advanced paternal age is not associated with low birthweight in Thai population. Teenage pregnancy, pregnancy associated hypertension at the level of severe preeclampsia or more, and preterm birth increased risk of low birthweight.

Keywords: low birthweight, paternal age

Introduction

Low birthweight has been defined by the World Health Organization (WHO) as weight at birth of less than 2,500 grams regardless of gestational age[1]. According to the data from Ministry of Public Health of Thailand, the incidences of low birthweight in 2006 to 2008 were as high as 11.4, 11 and 10.8%, respectively[2]. Similarly, the incidences of low birthweight in Siriraj Hospital were 10.57, 10.95 and 11.13% in the year 2006 to 2008, respectively[3]. Low birthweight is one of the most common causes of perinatal mortality that raises the health care cost[4-6]. Several previous studies have reported maternal factors affecting low birthweight[1, 7, 8]. However, the association between paternal factors and low birthweight infant has not been established.

The possible effect of advanced paternal age on low birthweight have been described based on the effect

on gene mutation[9]. Gene mutation has been shown to increase with advanced paternal age. Imprinted genes are mostly expressed in the placenta which, if mutated, may affect the placenta function[10]. Therefore, advanced paternal age may result in abnormal placental function via mutation of paternal imprinting genes expressing in the placenta[11]. This, in turn, can cause low birthweight. The effect of increasing paternal age on birth defects has been reported[12]. Some of birth defects are followed by miscarriage[13], fetal death[14], preeclampsia[15] and low birthweight[16, 17].

In 2006, Reichman and Teitler reported from a cohort study of 75 hospitals in the United States of America that paternal age was an independent risk factor for low birthweight, especially in the group of fathers older than 34 years (odds ratio of 1.7 (95%CI =1.3-2.2))[18]. However, other studies demonstrated different results[19-23].

To our knowledge, no study investigate the association between advanced paternal age and low birthweight in Asian population. This study was conducted to determine the association in Thai population in order to obtain information for counseling such couples in family planning and also for attempting to decrease incidence of low birthweight and perinatal mortality in the future.

Materials and Methods

This was a retrospective case-control study that aimed to explore the association between advanced paternal age and low birthweight in Thai population. After the approval from Siriraj Institutional Review Board (SIRB) Committee, Faculty of Medicine Siriraj Hospital, Mahidol University, the data were collected from database of the Department of Obstetrics and Gynecology, Siriraj Hospital. Inclusion criteria were primigravid women with a singleton live-born, parental aged of at least 18 years old, delivered in Siriraj Hospital during January 2008 and December 2010. Subjects with multifetal pregnancy were excluded. According to Siriraj database in 2009, the prevalence of low birthweight with the paternal age of more than 34 years old was 28.5%. According to previous study[18], the fathers whose age were more than 34 years had an odds ratio of 1.7 to have a low birthweight infant and with 5% type I error and 80% type II error. A total of 383 cases were needed for this study.

Total10,396 pregnant women match our inclusion criteria, 1,247 mother delivered low birthweight infant (< 2,500 gm) and 9,149 delivered normal birthweight infant (≥ 2,500gm). A total of 400 in each group (matching one by one) were selected for reviewed by systematic random sampling technique. Paternal age was not recorded in 2 cases of the study group.

Paternal age was categorized into 3 groups: < 20, 20-34 (reference group) and >34 years. Other paternal data including demographic information, socioeconomic status and underlying diseases were collected. Maternal age was categorized in the same fashion. Gestational age (GA) at delivery and maternal demographic data, socioeconomic status, lifestyle (e.g., alcohol consumption, smoking), underlying conditions such as heart disease, diabetes mellitus (DM), hypertension (HT), thalassemia, and anemia (defined as hemoglobin concentration less than 10 g/dl or hematocrit level less than 30%) were retrieved. Data of medical complications during pregnancy including gestational diabetes mellitus (GDM), pregnancy induced hypertension (PIH) were also collected.

Data were analyzed using SPSS (Statistical Package for the Social Sciences) for Microsoft Windows version 18. Descriptive statistics were used to describe the distribution of paternal, maternal and infant characteristics in each paternal age group. Variables were compared between the study group and control group using Chi-square test or Fisher's exact test. Multiple logistic regression analysis was used to identify the independent factors of low birthweight. Adjusted odds ratios with 95% confidence intervals were calculated. A p-value of < 0.05 was considered as statistically significant.

Results

The distributions of paternal, maternal and infant characteristics by paternal age group and birthweight condition are shown in Table 1. There was no significant difference of paternal age category between low birthweight group and control group in the following

factors: maternal age, marital status, parental low education and low income, maternal lifestyles (alcohol consumption and smoking), maternal underlying condition, pregnancy induced hypertension, gestational diabetes mellitus, preterm birth and infants' gender

Table 1. Distribution of paternal, maternal and infant characteristics, by paternal age group and birthweight condition [No. (%)]

	Paternal age(y)								p
	<20[n=41]		20-34[n=585]		>34[n=172]		All[n=798]		
	LBW [n=25]	Control [n=16]	LBW [n=295]	Control [n=290]	LBW [n=78]	Control [n=94]	LBW [n=398]	Control [n=400]	
Maternal age(y)									
<20	16(64)	8(50)	22(8)	10(3)	2(3)	2(2)	40(10)	20(5)	0.755
20-34	9(36)	8(50)	259(88)	266(92)	49(63)	54(58)	317(80)	328(82)	0.902
>34	0(0)	0(0)	14(4)	14(5)	27(35)	38(40)	41(10)	52(13)	0.451
Marital status									
Single	5(20)	2(13)	36(12)	31(10)	7(9)	11(12)	48(12)	44(11)	0.304
Married	20(80)	13(81)	251(85)	257(89)	71(91)	83(88)	342(86)	353(88)	0.314
Separate	0(0)	1(6)	8(3)	2(1)	0(0)	0(0)	8(2)	3(1)	0.087
Maternal low education	23(92)	16(100)	192(65)	147(51)	38(49)	33(35)	253(64)	196(49)	0.839
Paternal low education	25(100)	15(94)	208(70)	161(55)	42(54)	33(35)	275(69)	209(52)	0.749
Maternal low income	25(100)	16(100)	258(88)	224(77)	57(73)	49(52)	340(85)	289(72)	0.654
Paternal low income	25(100)	16(100)	237(80)	200(69)	44(56)	39(42)	306(77)	255(64)	0.677
Maternal alcohol consumption	2(2)	0(0)	9(3)	3(1)	0(0)	1(1)	11(3)	4(1)	0.174
Maternal smoking	2(8)	1(6)	10(3)	3(1)	1(1)	0(0)	13(3)	4(1)	0.791
Maternal underlying condition	0(0)	2(13)	36(12)	18(6)	13(17)	11(10)	49(12)	31(8)	0.114
PIH	1(4)	2(12)	55(19)	15(5)	16(20)	10(10)	72(18)	27(7)	0.075
GDM	1(4)	1(6)	13(4)	13(4)	5(6)	9(10)	19(5)	23(6)	0.681
Preterm birth	16(64)	3(19)	154(52)	17(6)	43(55)	4(0)	213(54)	24(6)	0.667
Infant gender									
Male	15(60)	10(62)	148(50)	139(48)	37(47)	43(49)	200(50)	192(48)	0.456
Female	10(40)	6(38)	147(50)	151(52)	41(53)	51(51)	198(50)	208(52)	0.388

Preterm: GA <37 weeks, PIH: pregnancy induced hypertension, GDM: gestational diabetes mellitus
Low education: below Diploma Vocational Certificate, Low income: <15,000 Baht/month
Maternal underlying condition: heart disease, diabetes mellitus, hypertension, thalassemia

As shown in Table 2, there were 398 cases in study group (low birthweight) and 400 in control group. The majority of infants in both groups (74% in study group and 73% in control group) were born to paternal age 20-34 years old. Low birthweight infants and infants in the control group were born to paternal age more than 34 years at the percentages of 20 and 23 respectively. No significant difference of paternal age was found between both groups (p=0.174), while low birthweight infants were significantly borned fromthe teenage mothers (p=0.017). Univariate analysis reveals that potential associated factors for low birthweight were parental low education and low income, maternal smoking and underlying conditions, pregnancy induced hypertension and preterm birth. Our study found no difference in infants' gender between low birthweight and control groups.

Table 2. The Association between Low birthweight and Paternal age/other covariates: Univariate Analysis

	LBW n=398(%)	Control n=400(%)	p
Paternal age(y)			0.174
<20	25(6)	16(4)	
20-34	295(74)	290(73)	
>34	78(20)	94(23)	
Maternal age(y)			0.017
<20	40(10)	20(5)	
20-34	317(80)	328(82)	
>34	41(10)	52(13)	
Married	342(86)	353(88)	0.270
Paternal low education	275(69)	209(52)	<0.001
Maternal low education	253(64)	196(49)	<0.001
Paternal low income	306(77)	255(64)	<0.001
Maternal low income	340(85)	289(72)	<0.001
Maternal alcohol consumption	11(3)	4(1)	0.067
Maternal smoking	13(3)	4(1)	0.027
Maternal underlying condition	49(12)	31(8)	0.032
PIH	62(18)	27(7)	<0.001
GDM	19(5)	23(6)	0.537
Preterm birth	213(54)	24(6)	<0.001

PIH: pregnancy induced hypertension, GDM: gestational diabetes mellitus

With adjustment for maternal age and other covariates (multiple logistic regression analysis), there were no statistically significant effects of paternal age of less than 20 years and more than 34 years on low birthweight (paternal aged 20-34 years being the reference group). For maternal age, we found that mothers aged younger than 20 years had a higher risk of having a baby with low birthweight than those of aged 20-34 years (Table 3, adjusted OR 2.31, 95%CI: 1.14-4.71) whereas mothers aged more than 34 years were not significantly associated with low birthweight after adjusting for other covariates. We also observed an increase in risk of low birthweight with maternal low income.

Unsurprisingly, it was apparent that severe preeclampsia and eclampsia increased risks of low birthweight (adjusted OR 3.59, 95% CI: 1.65-7.82).The impact of preterm birth on low birthweight was strongly significant (adjusted OR 16.06, 95%CI: 10.07-25.63).

Table 3. The Association between Low birthweight and Paternal age/other covariates: Multiple Logistic Regression Analysis

	Low birthweight		
	Adjusted Odd ratios	95% CI	p
Paternal age(y)[a]			
<20	0.61	0.25-1.46	0.266
>34	0.97	0.62-1.54	0.910
Other covariates	78(20)	94(23)	
Maternal age(y)[b]			
<20	2.31	1.14-4.71	0.021
>34	0.85	0.47-1.54	0.600
Maternal low income	1.75	1.14-2.69	0.010
Maternal smoking	3.42	0.92-12.71	0.066
Anemia in pregnancy	1.27	0.71-2.27	0.420
PIH[c]			
GHT/Mild preeclampsia	1.62	0.74-3.53	0.225
Severe/Superimposed/Eclampsia	3.59	1.65-7.82	<0.001
Preterm birth	16.06	10.07-25.63	<0.001

Reference group of each item: a; paternal age 20-34 y, b; maternal age 20-34 y, c; mother without PIH
Adjusted for paternal age, maternal age, maternal income, maternal smoking, anemia in pregnancy, PIH, Preterm birth
Preterm: GA<37 weeks, PIH: pregnancy induced hypertension, GHT: Gestational hypertension

In subgroup analysis of term infants, we found that maternal low income (adjusted OR 1.77, 95%CI: 1.11-2.81), severe preeclampsia, superimposed preeclampsia and eclampsia (adjusted OR 2.9, 95%CI: 1.22-7.09) still increased the risk of low birthweight.

Discussion

We found that neither advance-aged fathers nor teenage fathers were associated with low birthweight after adjusting for maternal age and covariate factors. Teenage mothers had an increased risk of low birthweight. The effect of maternal low income, severe preeclampsia and eclampsia are independent risk factors for low birthweight.

There was no significant difference of paternal age category between low birthweight group and control group, this might be limited by small sample size in each subgroup. So the larger sample size may be required to explore any association of the paternal age and low birthweight in the future studies.

Parity, multifetal pregnancy[20], previous low birthweight and preterm birth were independent risk factors for low birthweight, therefore we restricted our study to primigravidas with a singleton pregnancy.

Univariate analysis showed several parental factors (parental low socio-economic conditions and education) to be significantly associated with low birthweight. This is similar to previous studies[1, 7, 8]. However, with multiple logistic regression analysis, only some maternal factors (teenage mothers, low income, pregnancy induced hypertension) and preterm birth remained independent risk factors of low birthweight. In our study, advanced paternal ages were not associated with low birthweight. This result is in

consistent with previous studies[19, 24, 25]. Nahum and Stanislaw reported that paternal age did not influence birth weight in singleton term pregnancy[24]. Subgroup analysis in the group of term infants in our study had the similar result (p=0.832). Abel found the effect of paternal age on low birthweight to be different from maternal age effect, the paternal age effect being in U-shaped (the risk of low birthweight was increased at the age younger than 20 years and decreased through age 35 years, and then increased again)[25]. We also demonstrated that extremely advanced paternal age group (paternal age older than 40 years) was not associatedwith low birthweight. Riechman and Teitler identified that paternal age was an independent risk factor for low birthweight[18]. In their study, the population comprised of various ethnic groups, while almost all (98%) of our population were Thai. However, complications during pregnancy were not adjusted for analysis in the previous studies[18, 19, 24, 25].

Our unexpected results may be explained that a certain number of embryos or fetuses are lost before reaching viability due to the association between paternal age and fetal loss in the first and early second trimesters[11, 14]. Hence, the effect of genetic mutations in spermatozoa and placenta which are influenced by paternal age, on low birthweight may be indiscernible. To prove the possibility of this theory, the authors suggest a study of the correlation between paternal age and abortion rate in Thai population. Regarding birth defects and advanced paternal age, our study population contains only a few cases of birth defect, therefore, the relationship of paternal age and birth defects cannot be ascertained.

Data of several paternal characteristics were not available due to retrospective nature of the design. This can be a major limitation of the study as those characteristics may influence fetal growth. The authors suggest a larger prospective study, probably focusing on extremely advanced paternal age group (older than 40 years).

This is the first study involving the association between paternal age and low birthweight in Thai population. Although no such association was found, the authors established positive and independent associations between low birthweight and teenage pregnancy, maternal low income, pregnancy induced hypertension at the level of severe preeclampsia or more and preterm birth.

Acknowledgements

The authors sincerely thank Miss Pimrapat Tengtrakulcharoen for her assistance on statistical analysis. Funding was supported by the Siriraj Grant for Research Development, Faculty of Medicine Siriraj Hospital, Mahidol University.

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ความสัมพันธ์ระหว่างบิดาอายุมากกับภาวะทารกน้ำหนักแรกเกิดน้อยในประชากรไทย

พาวรรณ ลิ้มวรพิทักษ์, บูรยา พัฒนจินดากุล, พรพิมล เรืองวุฒิเลิศ.

วัตถุประสงค์ : *เพื่อศึกษาความสัมพันธ์ระหว่างอายุบิดามาก กับภาวะทารกน้ำหนักแรกเกิดน้อย*

วัสดุและวิธีการ : *การศึกษาแบบกลุ่มศึกษาและกลุ่มควบคุมของสตรีตั้งครรภ์แรกอายุตั้งแต่ 18 ปีขึ้นไป ที่มีทารกน้ำหนักแรกเกิดน้อยกว่า 2,500 กรัม ทั้งหมด 398 คน (กลุ่มศึกษา) และที่มีทารกน้ำหนักแรกเกิดมากกว่า 2,500 กรัม ทั้งหมด 400 คน (กลุ่มควบคุม) ที่มาคลอดในโรงพยาบาลศิริราชตั้งแต่ เดือนมกราคม พ.ศ.2551 ถึง เดือนธันวาคม พ.ศ.2553 เพื่อเปรียบเทียบอายุบิดา ข้อมูลทั่วไปของบิดามารดา และผลแทรกซ้อนของการตั้งครรภ์ระหว่างสองกลุ่ม*

ผลการศึกษา : *ไม่พบความสัมพันธ์ทางสถิติในบิดาอายุมากกว่า 34 ปี กับภาวะทารกน้ำหนักแรกเกิดน้อย และภาวะคลอดก่อนกำหนด พบว่ามารดาอายุน้อยกว่า 20 ปี มีความเสี่ยงเพิ่มขึ้นต่อภาวะทารกน้ำหนักแรกเกิดน้อยเมื่อเทียบกับมารดากลุ่มอายุ 20-34 ปี (adjusted OR 2.31, 95% CI: 1.14-4.71) ภาวะครรภ์เป็นพิษรุนแรง, ครรภ์เป็นพิษในมารดาที่เป็นโรคความดันโลหิตสูง, และภาวะชักจากครรภ์เป็นพิษ เพิ่มความเสี่ยงต่อภาวะทารกน้ำหนักแรกเกิดน้อย (adjusted OR 3.59,95% CI:1.65-7.82) ความสัมพันธ์ระหว่างภาวะคลอดก่อนกำหนดกับภาวะทารกน้ำหนักแรกเกิดน้อยมีนัยสำคัญอย่างชัดเจน (adjusted OR 16.06, 95%CI: 10.07-25.63)*

สรุป : *บิดาอายุมากไม่มีความสัมพันธ์กับภาวะทารกน้ำหนักแรกเกิดน้อยในประชากรไทย มารดาวัยรุ่น ภาวะครรภ์เป็นพิษระดับรุนแรงหรือมากกว่า และภาวะคลอดก่อนกำหนดเพิ่มความเสี่ยงต่อภาวะทารกน้ำหนักแรกเกิดน้อย*