Adverse outcomes in advanced maternal age: A case-control study

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Abstract

Objective: To compare pregnancy outcomes between women aged 35 years and older with those under 35 years old.

Methods: A retrospective cohort study was conducted at Vajira hospital, Navamindradhiraj University from 1 October 2012 to 31 December 2013. Total 896 gravidas whose aged at least 20 years old at delivery were obtained. The study group (n = 448) consisted of women with aged 35 years and older while the control group (n = 448) were those 20-34 years old. Pregnancy outcomes between the two groups were compared including GDM, preeclampsia, placenta previa, preterm birth, operative vaginal delivery, rate of cesarean section (CS), PPH, birth weight, Apgar score at 5 minutes, fetal anomalies and perinatal death.

Results: Data of all 896 women were obtained. The study group had significantly higher risks of GDM, preeclampsia, preterm birth, cesarean delivery and PPH than the control group. The rate of low birth weight and low Apgar score at 5 minutes were different in both groups.

Conclusion: Women with advanced maternal age (AMA) had significantly higher risks of adverse pregnancy outcomes than women aged 20-34. This information may aid the clinicians to aware of adverse outcome in AMA.

Keywords: advanced maternal age, pregnancy outcomes, aged 35 years or older

ผลลัพธ์ที่ไม่พึงประสงค์ของการตั้งครรภ์ในมารดาอายุมาก: การศึกษาแบบมีกลุ่มควบคุม

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บทคัดย่อ

วัตถุประสงค์: เพื่อเปรียบเทียบผลลัพธ์ของการตั้งครรภ์ในมารดาที่อายุมากกว่าหรือเท่ากับ 35 ปีกับมารดาที่อายุน้อยกว่า 35 ปี

วิธีดำเนินการวิจัย: ศึกษาข้อมูลแบบย้อนหลังในหญิงตั้งครรภ์เดี่ยวที่อายุ 20 ปีขึ้นไป ณ วันคลอดจำนวน 896 ราย ที่มาคลอดที่โรงพยาบาลวชิระ มหาวิทยาลัยนวมินทราธิราช ตั้งแต่ 1 ตุลาคม 2555 ถึง 31 ธันวาคม 2556 แบ่งเป็นกลุ่มศึกษาซึ่งมีอายุมากกว่าหรือเท่ากับ 35 ปีจำนวน 448 รายและกลุ่มควบคุมซึ่งมีอายุ 20-34 ปี จำนวน 448 ราย โดยเปรียบเทียบผลลัพธ์ของการตั้งครรภ์ ได้แก่ เบาหวานขณะตั้งครรภ์ ครรภ์เป็นพิษ รกเกาะต่ำ คลอดก่อนกำหนด การใช้หัตถการช่วยคลอดทางช่องคลอด อัตราการผ่าคลอด ภาวะตกเลือดหลังคลอด น้ำหนักทารกแรกคลอด Apgar score ที่ 5 นาที ความพิการของทารก และทารกเสียชีวิต

ผลการวิจัย: หญิงตั้งครรภ์ที่มีอายุมากกว่าหรือเท่ากับ 35 ปีมีความเสี่ยงต่อการเกิดเบาหวานขณะตั้งครรภ์ ภาวะครรภ์เป็นพิษ การคลอดก่อนกำหนด ภาวะตกเลือดหลังคลอด ทารกน้ำหนักตัวน้อยและค่า Apgar score ต่ำที่ 5 นาที มากกว่ามารดาที่อายุ 20-34 ปีอย่างมีนัยสำคัญทางสถิติ

สรุป: หญิงตั้งครรภ์ที่อายุมากกว่าหรือเท่ากับ 35 ปี มีความเสี่ยงต่อภาวะแทรกซ้อนเพิ่มขึ้นทั้งในมารดาและทารกมากกว่าหญิงตั้งครรภ์ที่อายุ 20-34 ปี สูติแพทย์ผู้ดูแลจึงควรเฝ้าระวังภาวะแทรกซ้อนที่อาจเกิดขึ้นได้เมื่อต้องให้การดูแลหญิงตั้งครรภ์ที่อายุมากกว่าหรือเท่ากับ 35 ปี

คำสำคัญ: สตรีอายุมาก, ผลลัพธ์ของการตั้งครรภ์, อายุมากกว่าหรือเท่ากับ 35 ปี

Introduction

Advanced maternal age (AMA), refers as women who are pregnant at aged 35 years or older at expected date of delivery[1], is currently a worldwide growing tendency. Data from the United Stated showed that in the last decade, the first birth rate of women aged 35 years and older has risen. In 2012 the first birth rate for women aged 35-39 years was 48.3 per 1,000 women, up 2% from 2011 rate (47.2 per 1,000 women) and much higher from 2002 rate (41.6 per 1,000 women). The first birth rate of women aged 40-44 and 45-49 years increased from 8.3 and 0.5 per 1,000 women in 2002 to 10.4 and 0.7 per 1,000 women in 2012, respectively[2]. The WHO Multicountry Survey on Maternal and Newborn Health in 29 countries including Africa, Asia, Latin America, and the Middle East demonstrated that the overall prevalence of AMA was 12.3% and varied greatly from 2.8% in Nepal to 31.1% in Japan. The highest prevalence of 9.5% was seen in women aged 35-39 years, and only 0.5% was seen in women aged 45 years and older[3]. Several factors have been related to AMA including delayed marriage, increasing rates of divorce, higher levels of women's education and social activity, effective birth control and advance in assisted reproductive technology[4].

Pregnancy outcomes associated with AMA pregnancy have been widely researched. Most studies demonstrated the adverse maternal outcomes compared poorly with those younger women including preeclampsia, gestational diabetes, placenta previa, placental abruption, higher risk of caesarean delivery, postpartum hemorrhage or even death[3-8]. Furthermore, perinatal morbidities and mortality such as preterm delivery, low Apgar score, macrosomia and still birth were also relevant to AMA[3-8]. Nevertheless, some conflicting pregnancy outcomes still occurred and there are a few researches about AMA in Thailand including our institute, Vajira hospital, which responsibility for pregnant women live in the central area of Bangkok. The authors have observed that the prevalence of AMA in our institute became increasing from 13.73% in 2012 to 14.14% in 2013. Hence, the aim of this study was to evaluate the pregnancy outcomes among pregnant women with AMA compared to those who aged 20-34 years.

Methods

The present study was conducted at Vajira hospital, Navamindradhiraj University with the ethical approval of Vajira Institutional Review Board (Registered Number 024/57). The retrospective cohort study was designed. The population was all pregnant women at least 20 years old at the time of delivery and gave either live births or still births. The sample size was calculated and used the study of T'sang-T'ang Hsieh et al[5] for reference. The 448 subjects for each group were thereafter recruited using computer generated numbers started retrospectively from 31 December 2013 until the sample size was attained. The inclusion criteria consisted of (1) singleton pregnancy (2) delivery at or beyond 24 weeks of gestation which calculated from last menstrual period and confirmation with first or second trimester ultrasonography. The exclusion criterion was the subjects with incomplete pregnancy outcome information.

Data of the women were collected from the hospital's computer file and obstetric charts. The complete data were classified into two maternal age groups who 35 years old or more were the study group whereas those aged 20-34 years formed the control group. The maternal characteristics of both groups were assessed regarding maternal ethnicity, prepregnancy body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), previous medical history including diabetes mellitus, chronic hypertension and others, parities, previous cesarean deliveries. The following maternal and neonatal outcomes were evaluated: gestational diabetes mellitus (GDM), preeclampsia, placenta previa, vaginal delivery and operative vaginal delivery (forceps or vacuum-assisted vaginal delivery), cesarean delivery, postpartum hemorrhage (PPH), birth weight, preterm birth, Apgar scores at 5 min, major fetal

anomalies and perinatal death. GDM was defined as diabetes mellitus diagnosed the first time during pregnancy by screening with 50 g glucose challenge test and was confirmed by 100 g, three-hour oral glucose tolerance test (OGTT), diagnosis was made when 2 values or more were met the Carpenter and Coustan's criteria (fasting ≥ 95, 1 hr ≥ 180, 2 hr ≥ 155 and 3 hr ≥ 140 mg/dL)[9]. Preeclampsia was defined as blood pressure 140/90 mmHg or more after 20 weeks of gestation with 300 mg or more of 24-hour proteinuria or 1+ by dipstick[10]. Placenta previa was diagnosis on screening ultrasonography findings by either transabdominal or transvaginal examination that placenta tissue/edge covered, touched or lay close to the internal os[11], which was confirmed by repeated ultrasonography within a week prior to delivery. PPH was diagnosed when estimated blood loss 500 ml or more for vaginal delivery and 1,000 ml or more for cesarean delivery[12]. Low birth weight referred to neonatal birth weight 1,500 to 2,500 g and very low birth weight referred to those between 500 and 1,500 g[13]. Macrosomia was defined as newborns who weight 4,000 g or more at birth[14]. Preterm birth was a delivery before the completion of 37 weeks of gestation. Late preterm and moderate preterm birth were defined, respectively, as delivery between $34^{0/7}$ and $36^{6/7}$ weeks and between $32^{0/7}$ and $33^{6/7}$ weeks. Infants born before 32 weeks were considered very preterm birth[15].

Analysis of maternal characteristic and pregnancy outcomes of both groups was performed using Chi-square test or Fisher's exact test for categorical variables and unpaired t-test was applied for continuous variables. A p-value of < 0.05 was considered statistically significant and Odds ratio (OR) with 95% confidence intervals were also calculated. Statistical analysis was performed with the SPSS software package version 17 (SPSS Inc., Chicago, IL, USA).

Results

Data of all 896 women (448 study and 448 control subjects) were totally obtained. Demographic and clinical characteristics of the both groups were shown in table 1. Most of women had prepregnancy BMI within normal range. Almost all of cases were Thai people. About three-quarter (77.5%) pregnant women in the study group and more than one half of the control group (57.8%) were multiparity. There was nearly two-fold higher rate of previous cesarean section in the study group compared with the control group. The study group had statistically significant higher rate of preexisting medical condition including pregestational diabetes mellitus and chronic hypertension.

Table 2 demonstrated the maternal outcomes between study and control groups. The rate of GDM was five-times higher in the study group as compared to the control group. Likewise, pregnant women in the study group had significant higher rate of preeclampsia, late preterm birth and PPH than those of the control group. However, there was no statistically different regarding of placenta previa, moderate preterm and very preterm between the groups. The cesarean section rate was statistically significant higher in the study group compared to the control group whereas the operative vaginal delivery rate did not. Indication for cesarean delivery between both groups had no statistically different except the indication for cephalopelvic disproportion which was lower in the study group and elderly gravida which was the indication totally found in the study group.

Comparison of neonatal outcomes between the two groups was summarized in table 3. Only low birth weight and low Apgar score at 5 minutes were considered significant higher in the study group. The remainder including very low birth weight, macrosomia, perinatal death and fetal anomaly had similar result between the both groups. There was only 1 case of perinatal death founded in the control group.

Discussion

During 1 January 2013 to 31 December 2013 there were 2,637 deliveries in Vajira hospital. Of these, 373 women or 14% gave birth at age 35 years or older. This rate of AMA is comparable to the study of The WHO Multicountry Survey on Maternal and

Newborn Health which reported 15% prevalence of women with AMA in Thailand[3]. As the other studies[3-5,12-13], most of woman with AMA in the present study were aged 35-39 years.

The present study confirmed that the risk of adverse pregnancy outcomes increased in AMA group. These adverse outcomes composed of GDM, preeclampsia, preterm birth, cesarean delivery, PPH, low birth weight and low Apgar score at 5 minutes. The pre-existing medical condition especially pregestational diabetes mellitus and chronic hypertension might play the role in part of adverse maternal outcome as their incidence were significantly increased in AMA group compared with the control group. These pre-existing diseases play the risk for adverse outcomes such as GDM, preeclampsia in older pregnant women as shown in the present study. The findings were consistent with other studies. Gilbert et al[16] reported fivefold increased risk of chronic hypertension in older nulliparas and ninefold in older multiparas. Preeclampsia was also increase in both older nulliparas and older multiparas compare with the control group. Similarly, Kahveci B et al[17] recently demonstrated that the risks of preeclampsia and gestational hypertension were significantly higher in pregnant women aged over 35 years compared with younger pregnancy.

Women with AMA are more likely to have GDM as AMA is one of the known risk factors. The higher risk of GDM can be result from alteration of pancreatic B-cell function and insulin sensitivity that decrease with advanced age[18]. In the present study, pregnancy with age 35 years and older had significant higher risk of GDM than the control group. This result was compatible with the previous studies. Gilbert et al[16] showed that both older nulliparas and multiparas had a fourfold increased risk of GDM. Similar findings were found from study of Tan KT et al[19] and Cleary-Goldman et al[20].

Table 1:

Maternal characteristic by maternal age

Maternal characteristics	≥ 35 years (n = 448)	< 35 years (n = 448)	p-value
Maternal age (years) (mean ± SD)	38.27 ± 2.48	27.46 ± 3.67	
Nulliparous, n (%)	101 (22.5)	189 (42.2)	< 0.001
Multiparous, n (%)	347 (77.5)	259 (57.8)	
BMI (kg/m2) (mean ± SD)			
Underweight	6 (1.3)	52 (11.6)	
Normal	304 (67.9)	311 (69.4)	
Overweight	97 (21.7)	55 (12.3)	
Obese	41 (9.1)	30 (6.7)	
Race, n (%)			
Thai	443 (98.5)	445 (99.3)	0.725*
Others	5 (1.1)	3 (0.7)	
Previous cesarean delivery, n (%)	67 (15.0)	34 (7.6)	< 0.001
Pre-existing medical condition, n (%)	45 (10.0)	4 (0.9)	< 0.001*
Pregestational diabetes mellitus, n (%)	7 (1.6)	0 (0)	0.015*
Chronic hypertension, n (%)	21 (4.7)	2 (0.4)	< 0.001*

* Fisher exact test

Table 2:

Obstetrics outcomes by maternal age

Obstetrics outcomes	≥ 35 years (n = 448)	< 35 years (n = 448)	Odds ratio (95% CI)	p-value
Gestational diabetes mellitus, n (%)	68 (15.2)	14 (3.1)	5.55 (3.07-10.02)	< 0.001
Preeclampsia, n (%)	76 (17.0)	21 (4.7)	4.15 (2.51-6.87)	< 0.001
Placenta previa, n (%)	14 (3.1)	7 (1.6)	2.03 (0.81-5.08)	0.122
Gestational age at delivery (mean ± SD)	38.25 ± 2.87	38.16 ± 3.24		
Preterm birth				
Late preterm	66 (14.7)	45 (10.0)	1.55 (1.03-2.32)	0.033
Moderate preterm	12 (2.7)	9 (2.0)	1.34 (0.56-3.22)	0.508
Very preterm	2 (0.4)	3 (0.7)	0.67 (0.11-4.0)	1.000*
Operative vaginal delivery, n (%)	13 (6.0)	15 (4.7)	1.31 (0.61-2.81)	0.489
Cesarean delivery, n (%)	233 (52.0)	128 (28.6)	2.71 (2.10-2.57)	< 0.001
Indication for cesarean delivery, n (%)				
Cephalopelvic disproportion	54 (23.2)	44 (34.4)	0.58 (0.36-0.93)	0.022
Malpresentation	20 (8.6)	18 (14.1)	0.57 (0.29-1.13)	0.105
Preeclampsia	5 (2.1)	1 (0.8)	2.79 (0.32-24.1)	0.429*
Non-reassuring fetal heart rate	26 (11.2)	20 (15.6)	0.68 (0.36-1.27)	0.223
Antepartum hemorrhage	10 (4.3)	5 (3.9)	1.10 (0.37-3.3)	0.861
Elderly gravida	31 (13.3)	0 (0)	0.61 (0.56-0.67)	< 0.001
Previous cesarean delivery	67 (28.8)	34 (26.6)	1.12 (0.69-1.81)	0.657
Other indication	20 (8.6)	6 (4.7)		
Postpartum hemorrhage, n (%)	34 (7.6)	10 (2.2)	3.59 (1.76-7.37)	< 0.001

* Fisher exact test

Table 3:

Neonatal outcomes by maternal age

Neonatal outcomes	≥ 35 years (n = 448)	< 35 years (n = 448)	Odds ratio (95% CI)	p-value
Birth weight (mean ± SD)	2,946 ± 624	3,084 ± 573		
Low birth weight (< 2,500 gm), n (%)	63 (14.1)	43 (9.6)	1.54 (1.02-2.33)	0.039
Very low birth weight (< 1,500 gm), n (%)	4 (0.9)	6 (1.3)	0.66 (0.19-2.37)	0.525
Macrosomia (≥ 4,000 gm), n (%)	13 (2.9)	5 (1.1)	2.65 (0.94-7.49)	0.057
Low Apgar scores at 5 min (< 7), n (%)	19 (4.2)	7 (1.6)	2.79 (1.16-6.71)	0.017
Perinatal death, n (%)	0	1 (0.2)	0.5 (0.47-0.53)	1.000*
Major fetal anomalies, n (%)	5 (1.1)	2 (0.4)	2.52 (0.49-13.04)	0.287*

* Fisher exact test

Placenta previa was found to be significantly increase with AMA in several studies[5,16,18]. High parity and previous CS were significant factors related to the high incidence of PP. In the present study, most of AMA in the study group were multiparas and the rate of previous CS was significant higher than the control group. However, there was no significantly different in the rate of PP. This result may be because of the low incidence of PP in the present study.

Several studies have suggested AMA is a risk factor for obstetric intervention like CS and operative vaginal delivery[6,8,18]. The present study demonstrated only the association of AMA with CS. A systematic review of AMA and risk of CS including 21 studies illustrated an increased risk among older women both nulliparous and multiparous. The most potential factor for increasing CS rate was dystocia. The possible physiologic changes were the myometrium incompetency in conjunction with lack of labor-induced gap junction formation and decreased number of oxytocin receptors[21]. Similarly, the most significant factor for CS in the present study was CPD. Another significant indication was elderly gravida. Maternal age was considered as a high-risk factor along with maternal anxiety may influence the physician's decision in select CS as mode of delivery in AMA.

Postpartum hemorrhage was one of a significant risk found in AMA in the present study. This increasing rate of PPH might be due to the high CS rate in AMA group. However, whether maternal age is the risk factor of PPH is uncertain. Some studies reported the association between AMA and PPH[18,22]. In contrast, a retrospective study of 12,686 parturients aged 35 years or older indicated that increasing of PPH associated AMA was relates to risk factors, complications and interventions, while the advanced age had a protective effect against PPH. The mechanism of this phenomenon may be related to reduce uterine vascular with aging[23].

Regarding the neonatal morbidity, the present study found statistic higher rate of late preterm birth, low birth weight and low Apgar score at 5 minutes in AMA group. These risks might be the consequence of obstetric complications including GDM and preeclampsia. Perinatal death and still birth associated AMA is the one of the interesting issue in several studies[3,5,6,8,17]. There was only one perinatal death found in younger group in the present study. A systematic review included nine studied published between 2000 and 2010 suggested that rates of stillbirth and adverse perinatal outcome were clearly linked to AMA. However, the increasing rate were modest until the age of 40 or more[24].

The present study has the limitation of relatively small sample size and we did not consider the confounding factors. In addition, the naturally pattern of retrospective study is likely to have incomplete data collection. Nevertheless, as we known, this is the first report of our institute and it provides the baseline information of our own data and activates our physicians to interest and beware of AMA that is rising in the present days.

Conclusion

The present study demonstrated that pregnancy with AMA more likely to have adverse pregnancy outcomes compare with the younger pregnant women. Because women with delayed child bearing age trend to increase, health care providers who manage with these women should emphasize the importance of this issue. Women who decide to pregnant at advanced age should be counseled to early antenatal care to keep her pregnancy under surveillance for the best outcomes. In addition, further research should be conducted to determine which AMA period is most likely to cause the most adverse pregnancy outcomes.

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Potential conflicts of interest

The authors declare no conflict of interest.

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