Analyzing Pregnancy Outcomes in Women of Extremely Advanced Maternal Age (≥45 years)

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Objective: *To assesses pregnancy outcomes in women of extremely advanced maternal age (≥45 years).*

Material and Method: *Computerized delivery records, collected between January 2002 and December 2012 at Rajavithi Hospital, were retrospectively reviewed. We compared the condition of women of maternal age ≥45 years with singleton delivery and beyond 24 weeks of gestation (n = 82) in a 1:4 ratio with those women age 20 to 29 years (n = 328).*

Results: *Extremely advanced maternal age was significantly associated with a higher incidence of gestational diabetes mellitus (OR = 5.33; CI = 1.90-14.95), preeclampsia (OR = 4; CI = 1.99-8.06), preterm birth (OR = 1.74; 95% CI = 1.15-2.62), cesarean delivery (OR = 4.18; 95% CI = 2.52-6.93), postpartum hemorrhage (OR = 6.5; CI = 2.79-15.16), blood transfusion (3.7% vs. 0%; p = 0.008), placenta previa (OR = 16; 95% CI = 1.18-141.25), low birth weight (OR = 2.77; 95% CI = 1.23-6.25), very low birth weight (OR = 3.00; 95% CI = 1.07-8.4), low Apgar scores at 5 minutes (OR = 2.77; 95% CI 1.23-6.25), and perinatal death (OR = 6.00; 95% CI = 1.73-20.77).*

Conclusion: *Women aged 45 or more experienced increased maternal and neonatal adverse outcomes when compared with younger women. Women in an extreme age group are advised that although they might face a significantly increased risk of complications, most of them could have successful outcomes. An extremely advanced age is not contradicted for pregnancy. Obstetricians must be especially careful when taking care of extremely advanced age pregnancy.*

Keywords: *Advanced maternal age, Pregnancy, Complication, Neonatal, Outcome*

There is a worldwide trend for women to increasingly delay pregnancy until their mid-30s or older. In the USA, the proportion of women giving birth for the first time aged ≥35 years increased more than eight times (from 1% to 8.3%) between 1970 and 2006[1]. In 2010, the birth rate of women aged 40 to 44 was 10.2 births per 1,000 women. This was the highest rate ever reported, representing a two percent increase from that of 2009[2].

The effects of advanced maternal age (≥35 years) on pregnancy outcomes have been studied extensively. Most studies have found that pregnancy outcomes in older women entailed higher obstetrical and perinatal complications than those of younger women[3-7]. However, with proper care, the perinatal outcomes might be comparable in some studies[8-10]. Researches focusing on the outcomes among mothers with extremely advanced maternal age (≥45 years) are rarely described, especially in our country. Moreover, adverse pregnancy outcomes are often associated with other factors including race or socioeconomic status. In order to develop national vital statistics, it is essential to study the extent of the problems in our own geographical areas. Therefore, the authors carried out the present study with the aim of assessing the outcomes among singleton pregnancies of women of extremely advanced maternal age.

Material and Method

The present study was conducted at Rajavithi Hospital, a tertiary care teaching public hospital affiliated to Rangsit University in Bangkok, Thailand, with the ethical approval of the local institutional review board. The study sample consisted of pregnant women who were at least 45 years old at the time of delivery and who gave birth in our hospital between January 2002 and December 2012. Computerized delivery data were assessed and reviewed.

The inclusion criteria consisted of (1) singleton pregnancy, (2) delivery beyond 24 weeks' gestation or birth weight more than 500 gm. Women aged 45 years or more at delivery were classified as the study group

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whereas those at the age of 20 to 29 years formed the control group. The control group was randomly recruited from women giving birth during the same study period with a ratio of 1:4 case to control subjects. Demographic data, cesarean section rate, indications for cesarean section, and maternal and neonatal outcomes were assessed and analyzed. The maternal and neonatal outcomes for comparison included 1) gestational diabetes mellitus (GDM) screened with a 50-gm glucose challenge test and confirmed with a 100-gm, 3-hour oral glucose tolerance test (OGTT) as recommended by the American Diabetes Association guidelines[11] (diagnosis of GDM was confirmed if ≥2 values exceeded the criteria of the National Diabetes Data Group[12]); 2) maternal mortality; 3) cesarean hysterectomy; 4) postpartum hemorrhage (PPH) with estimated blood loss >500 ml for vaginal delivery and >1,000 ml for cesarean delivery[13]; 5) Apgar score of <7 at 5 min; 6) rate of neonatal intensive care unit (NICU) admission; and 7) perinatal death. Some definitions in this study included: 1) malpresentation: breech or transverse presentation; 2) preeclampsia: evidence of proteinuria (300 mg/24 hr) or 1+ by dipstick and hypertension (blood pressure 140/90 mmHg) with or without edema in patients who had normal blood pressure and no evidence of proteinuria prior to 20 weeks of gestation[14]; 3) fetal distress: non-reassuring fetal status based on clinical adjustment of the assigned obstetricians, usually based on intrapartum fetal monitoring of category III and some cases of category II[15].

In performing statistical analyses, categorical variables were compared using the Chi-square test or Fisher's exact test, and continuous variables were compared using unpaired t-test. Statistical significance was set at p<0.05. Odds ratio (OR) with 95% confidence intervals were calculated.

Results

Between 2002 and 2012, 74,404 pregnant women gave birth at Rajavithi Hospital, Bangkok. Among those pregnancies, 83 (0.11%) were at the age of 45 years or more. Of them, 82 were included in the present analysis, one was excluded due to twins pregnancy.

The baseline data of the patients are summarized in Table 1. The mean (± SD) maternal age of the present study group was 45.65±0.94 years and 24.78±2.71 years in the control group. The mean gestational age (± SD) was significantly different between the two groups (37.3±2.96 weeks in the present study group vs. 38.0±2.66 in the control group; p = 0.039). The rate of multiparity was significantly higher in the study group than in the control group (81.7% vs. 45.7%). The rates of previous cesarean delivery, chronic hypertension and pregestational diabetes mellitus (DM) in the present study group were significantly higher than those in the control group (9.8% vs. 4%, p = 0.047; 3.7% vs. 0%, p = 0.008; and 6.1% vs. 0.3%, p = 0.001 respectively). The proportion of Thai women in the study group was significantly higher than in the control group (95.1% vs. 83.8%, p = 0.008).

Table 2 summarizes the pregnancy and delivery outcomes in both groups. The present study group had significantly higher rates of GDM (OR = 5.33; 95% CI = 1.90-14.95), preeclampsia (OR = 4; 95% CI = 1.99-8.06), preterm birth (OR = 1.74; 95% CI = 1.15-2.62), Cesarean delivery (OR = 4.18; 95% CI = 2.52-6.93), postpartum hemorrhage (OR = 6.5; 95% CI = 2.79-15.16), blood transfusion (3.7% vs. 0%; p = 0.008) and placenta previa (OR = 16; 95% CI = 1.18-141.25) than the control group. Indication for cesarean section due to elderly gravida was also significantly higher in the

Table 1. Demographic data of both groups

Demographic	≥45 years (n = 82)	20-29 years (n = 328)	p-value
Maternal age (years) (mean ± SD)	45.65±0.94	24.78±2.71	<0.0001
Gestational age (week)	37.3±2.96	38.0±2.66	0.039
Multiparity, n (%)	67 (81.7)	150 (45.7)	<0.0001
Previous cesarean delivery, n (%)	8 (9.8)	13 (4.0)	0.047
Chronic hypertension, n (%)	3 (3.7)	0 (0)	0.008
Pregestational diabetes mellitus, n (%)	5 (6.1)	1 (0.3)	0.001

Race, n (%)
  Thai
  Others
	
	78 (95.1)
	4 (4.9)
		
		275 (83.8)
		53 (16.2)
			
			0.008

present study group. There were no maternal deaths in either group.

Neonatal outcomes are shown in Table 3. The mean (± SD) birth weight of the study group was 2,760±647 gm and 2,943±537 gm in the control group (p = 0.009). The present study group had significantly higher rates of low birth weight (OR = 2.77; 95% CI = 1.23-6.25), very low birth weight (OR = 3.00; 95% CI = 1.07-8.4), low Apgar scores at 5 minutes (OR = 2.77; 95% CI = 1.23-6.25) and perinatal death (OR = 6.00; 95% CI = 1.73-20.77).

Discussion

The number of women who gave birth at age 45 years or older varied from 0.06 to 0.2%[9,16-18] similar to the present study (0.11%). The majority of the women in our study was 45 or 46 years old and had higher parity (81%). Similar to the studies reported by Jacobson et al[9] and Yogev et al[16], the authors found that women of extremely advanced maternal age had a higher prevalence of pre-gestational medical illnesses such as chronic hypertension and pre-gestational diabetes mellitus. To compare the effects of maternal

Table 2. Pregnancy and delivery outcomes of both groups

	≥45 years (n = 82)	20-29 years (n = 328)	Odds ratio (95% CI)	p-value
Gestational diabetes mellitus, n (%)	8 (9.8)	6 (1.8)	5.33 (1.90-14.95)	0.002
Preeclampsia, n (%)	14 (17.1)	14 (4.3)	4.00 (1.99-8.06)	<0.0001
Duration of gestation, n (%)				
Preterm birth (<37 weeks)	24 (29.6)	56 (17.1)	1.74 (1.15-2.62)	0.011
Late preterm birth (<34 weeks)	7 (8.6)	20 (6.1)	1.42 (0.62-3.24)	0.400
Very preterm birth (<32 weeks)	4 (4.9)	10 (3.0)	1.62 (0.52-5.03)	0.491
Operative vaginal delivery	2 (2.4)	13 (4.0)	0.62 (0.14-2.67)	0.745
Cesarean delivery, n (%)	45 (54.9)	74 (22.6)	4.18 (2.52-6.93)	<0.0001
Indication for cesarean delivery, n (%)				
Cephalopelvic disporportion	9 (20.0)	27 (36.5)	0.44 (0.18-1.04)	0.058
Malpresentation	8 (17.8)	13 (17.6)	1.01 (0.46-2.25)	0.977
Preeclampsia	6 (13.3)	3 (4.1)	3.20 (0.87-12.50)	0.080
Non-reassuring fetal heart rate	3 (6.7)	10 (13.5)	0.49 (0.14-1.70)	0.366
Failed induction	2 (4.4)	4 (5.4)	0.82 (0.16-4.31)	1
Placenta previa	3 (6.7)	1 (1.1)	4.93 (0.53-46.00)	0.151
Elderly gravida	5 (11.1)	0 (0)	-	0.007
Previous cesarean delivery	8 (17.8)	13 (17.6)	1.01 (0.46-2.25)	0.977
Other indication	1 (2.2)	3 (4.1)	0.55 (0.06-5.11)	1
Postpartum hemorrhage, n (%)	13 (15.9)	8 (2.4)	6.50 (2.79-15.16)	<0.0001
Blood transfusion, n (%)	3 (3.7)	0 (0)	-	0.008
Placenta previa, n (%)	4 (4.9)	1 (0.3)	16 (1.81-141.25)	0.006

Table 3. Neonatal outcomes of both groups

	≥45 years (n = 82)	20-29 years (n = 328)	OR (95% CI)	p-value
Birth weight (gm) (mean ± SD)	2,760±647	2,943±537	-	0.009
Macrosomia (≥4,000 gm), n (%)	2 (2.4)	4 (1.2)	2.00 (0.38-10.73)	0.345
Low birth weight (<2,500 gm), n (%)	24 (29.3)	44 (13.4)	2.18 (1.41-3.37)	0.001
Very low birth weight (<1,500 gm), n (%)	6 (7.3)	8 (2.4)	3.00 (1.07-8.4)	0.041
Low Apgar scores at 5 min (<7), n (%)	9 (11.0)	13 (4.0)	2.77 (1.23-6.25)	0.020
Neonatal intensive care unit admission, n (%)	3 (3.7)	6 (1.8)	2.00 (0.51-7.83)	0.392
Perinatal death, n (%)	6 (7.3)	4 (1.2)	6.00 (1.73-20.77)	0.006
Major fetal anomalies, n (%)	2 (2.4)	6 (1.8)	1.33 (0.27-6.49)	0.663
Male sex, n (%)	44 (53.7)	175 (53.4)	1.00 (0.80-1.26)	0.961

age itself on pregnancy outcomes, some studies[16,19] have adjusted the statistics of such medical diseases before comparing the outcomes. Nevertheless, advanced maternal age is directly associated with higher rates of several medical diseases, and such diseases affect the pregnancy outcomes, especially chronic hypertension and pre-gestational diabetes mellitus, resulting in compounded baseline demographic characteristics in extremely advanced maternal age[20-22]. To evaluate the whole effects of advanced maternal age on the pregnancy outcomes, the present study, therefore, did not adjust those risks.

As seen in many other studies[9,16,17,19,23], extremely advanced maternal age was related to more common adverse maternal and fetal outcomes. The present study found that extremely advanced maternal age significantly increased rates of gestational diabetes mellitus, preeclampsia, preterm birth, postpartum hemorrhage, placenta previa, blood transfusion, low birth weight, very low birth weight, low Apgar scores at 5 min and perinatal death. Interestingly, the perinatal death rate was much higher (OR = 6; 95% CI = 1.73-20.77) in the study group than in the control group. In contrast, a population study of American women[24] aged more than 45 years demonstrated a lower risk of perinatal death (OR = 2.40; 95% CI = 1.77-3.27 at gestation age 24 weeks or more and OR: 2.38; 95% CI: 1.64-3.46 at gestation age 32 weeks or more), when compared to that in the present study. The difference perhaps can partly be explained by the fact that several patients in the present study did not undergo comprehensive ultrasound and invasive prenatal chromosome studies to predict fetal anomalies at an early gestation age, resulting in a greater prevalence of poor outcomes. Additionally, the fewer adverse outcomes in developed countries compared to those in developing countries is probably due to their advance antenatal surveillance.

In common with the findings of several previous reports[9,16,18,19,23], the Cesarean section rate was higher in the extremely advanced maternal age group. The significant increase in the cesarean rate is possibly due mainly for non-medical reasons. Maternal request or psychosocial issues have not been accepted as indications for Cesarean delivery in Thailand. Therefore, in taking care of women with extremely advanced maternal age group, the doctors tend to comply or less strict criteria for diagnosis of cephalopelvic disproportion or elderly gravida, which are relatively subjective and more flexible diagnoses.

The strength of the present study was that it had a relatively large sample size to evaluate pregnancy outcomes in women of extremely advanced maternal age. Some limitations included the retrospective nature of the study, which was based on computer searches that might be associated with incomplete data in some areas such as socioeconomic status, education, invasive prenatal chromosome studies, and assisted reproductive technology. Moreover, though the sample size was large enough to assess most outcomes, it was too small to compare some rare occurrences like maternal death, of which there was no incidence in the present study.

Summary, the results of the present study indicate that women aged 45 or more have both increased maternal and neonatal adverse outcomes when compared with younger women. Women in extreme age groups could be advised that while they have significantly increased risk of complications, most could earn successful outcomes, and that extremely advanced age is not a contraindication for pregnancy. Finally, the obstetricians must take extra care in treating women in extremely advanced age groups.

What is already known on this topic?

There has been a worldwide trend towards increasing maternal age. Researches focusing on the outcomes among mothers with extremely advanced age (≥45 years) are rarely described, especially in our country. The impact of extremely advanced maternal age and delayed childbearing on perinatal outcome is associated with increased maternal and fetal risks.

What this study adds?

The present study confirmed the previous studies that extremely advanced maternal age increased maternal and neonatal adverse outcomes.

Potential conflicts of interest

None.

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การวิเคราะห์ผลลัพธ์การตั้งครรภ์ในมารดาที่อายุมากกว่าหรือเท่ากับ 45 ปี

พจนีย์ ผดุงเกียรติวัฒนา, จิตติมา รุจิเวชพงศธร, ธิตินันท์ ตัณสถิตย์, ยุรี ยานาเซะ

วัตถุประสงค์: เพื่อประเมินผลลัพธ์การตั้งครรภ์ในมารดาตั้งครรภ์ที่อายุมากกว่าหรือเท่ากับ 45 ปี

วัสดุและวิธีการ: ทำการศึกษาเก็บข้อมูลจากคอมพิวเตอร์ แบบย้อนหลังในหญิงตั้งครรภ์เดี่ยวที่อายุมากกว่า หรือเท่ากับ 45 ปี ในวันที่คลอดบุตร และได้คลอดบุตรอายุครรภ์มากกว่า 24 สัปดาห์ ในโรงพยาบาลราชวิถีระหว่าง เดือนมกราคม พ.ศ. 2545 ถึง เดือนธันวาคม พ.ศ. 2555 เปรียบเทียบกับหญิงตั้งครรภ์ที่อายุ 20-29 ปี ในวันที่คลอดบุตรในอัตราส่วน 1:4 คิดเป็น 82 ราย และ 328 ราย ตามลำดับ

ผลการศึกษา: ในหญิงตั้งครรภ์ที่อายุมากกว่าหรือเท่ากับ 45 ปี พบการเกิดเบาหวานในขณะตั้งครรภ์ (OR = 5.33; 95% CI: 1.90-14.95), ครรภ์เป็นพิษ (OR = 4; 95% CI: 1.99-8.06), การคลอดก่อนกำหนด (OR = 1.74; 95% CI: 1.15-2.62), อัตรา การผ่าตัดคลอดบุตร (OR = 4.18; 95% CI: 2.52-6.93), การตกเลือดหลังคลอด (OR = 6.5; 95% CI: 2.79-15.16), การให้ เลือดหลังคลอด (3.7% vs. 0%; p = 0.008), ภาวะรกเกาะต่ำ (OR = 16; 95% CI: 1.18-141.25), ทารกมีน้ำหนักตัวแรกคลอด น้อยกว่า 2,500 กรัม (OR = 2.77; 95% CI: 1.23-6.25), ทารกมีน้ำหนักตัวแรกคลอดน้อยกว่า 1,500 กรัม (OR = 3.00; 95% CI: 1.07-8.4), คะแนน Apgar scores ที่ 5 นาที น้อยกว่า 7 คะแนน (OR = 2.77; 95% CI: 1.23-6.25), และอัตรา การตายปริกำเนิด (OR = 6.00; 95% CI: 1.73-20.77) มากกว่าอย่างมีนัยสำคัญ

สรุป: หญิงตั้งครรภ์ที่อายุมากกว่าหรือเท่ากับ 45 ปี มีความเสี่ยงเพิ่มขึ้นต่อทั้งมารดาและทารกในครรภ์มากกว่าหญิงตั้งครรภ์ที่อายุ 20-29 ปี สูติแพทย์จึงควรอธิบายถึงภาวะแทรกซ้อนที่อาจเกิดขึ้นได้ขณะตั้งครรภ์ แต่อย่างไรก็ตามหญิงตั้งครรภ์ที่อายุมากจำนวนมาก ก็พบว่ามีผลลัพธ์การตั้งครรภ์ที่ดี ดังนั้นการตั้งครรภ์ในมารดาที่อายุมากไม่ได้เป็นข้อห้าม แต่ต้องการการดูแลเป็นพิเศษจากสูติแพทย์