

Pregnancy Outcomes of Mothers with Very Advanced Maternal Age (40 Years or More)

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Objective: To assess pregnancy outcomes in women at age of 40 years or more compared with those at age of 20 to 30 years
Material and Method: The retrospective cohort study was conducted at Maternal Fetal Medicine unit, Chiang Mai University Thailand, to identify the delivery. All consecutive records between January 2002 and December 2012 were searched. Singleton pregnancies with maternal age of 20 years or older were recruited for study. The primary outcomes for comparison were the rates of various obstetric outcomes, such as preterm birth, cesarean section, etc.

Results: During the study period, 797 women at age of 40 years or more and 18,802 women at age of between 20 and 30 years were recruited. Women in the study group had significantly higher rates of medical diseases, such as chronic hypertension or pregestational diabetes mellitus. Cesarean rate, preterm delivery, and fetal growth restriction were significantly higher in the study group.

Conclusion: Maternal age of 40 years or more is associated with medical complications and more operative deliveries. Furthermore, very advanced maternal age is significantly associated with adverse perinatal outcomes such as abortion, preterm birth, and fetal growth restriction. This information may be useful for obstetric counseling.

Keywords: Very advanced maternal age, Age at or more than 40 years, Pregnancy outcome

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During the last two decades, the worldwide trend in childbearing age is changing towards an older maternal age. For example, the proportion of maternal age over 35 years and over 40 years in the United States increased nearly 40 and 70% respectively from year 1991 and 2001⁽¹⁾. Similarly, such a trend has also been observed in Asia. In Korea, the first birth of maternal age over 35 years increased from 5 to 14% between 1996 and 2008⁽²⁾. We have also observed that the percentage of deliveries among women over 35 years in our institute was increased by approximately 6% between 1993 and 2013. Many factors have influenced this change such as higher education and carrier goal of women. Additionally, advances in reproductive medicine helping women becoming pregnant at an increasing age might also account for such a change.

Advanced maternal age is known to be a high risk factor for adverse obstetric outcomes, due to biological changes of aging process. The uterine vascular system has less ability in adapting to

increased hemodynamic demand during pregnancy^(3,4). Furthermore, many underlying medical conditions such as hypertension, diabetes mellitus, heart disease, overweight, or gynecologic disease are increased with age. These certainly contribute to adverse pregnancy outcomes in elderly mothers. However, some studies on pregnancy outcomes in elderly gravid women have contradictory results. Moreover, many demographic factors and lifestyles of pregnant women have been changed during the last two decades such as marked difference in socioeconomic status, less smoking, and regular attention in antenatal care, which influences the outcomes. Therefore, the data may not reflect the outcomes of the population in the recent years. Though several studies on advanced maternal age have been reported, most recruited women were confined to those at 35 to 39 years. The data on pregnancy outcomes among women at age of 40 or older are relatively limited. Finally, as already known, pregnancy outcomes are varied among different geographical areas, markedly different between developed and developing countries and any population should use its own data. Therefore, we conducted the present study to evaluate the pregnancy outcomes among women at age of 40 years or older, compared to those younger.

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Material and Method

The retrospective cohort study was conducted at Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, with ethical approval by the Institute Review Boards. The database of Maternal Fetal Medicine Unit, Department of Obstetrics and Gynecology was assessed to identify the pregnancies and deliveries between January 2002 and December 2012. All consecutive records were searched and singleton pregnancies with maternal age of 40 years or more were recruited and assigned as the study group or the group of very advanced maternal age. All singleton pregnancies at age of between 20 and 30 years giving births in the same period were included as the control group.

The maternal baseline characteristics, pre-existing medical conditions, pregnancy outcomes, and obstetric complications were evaluated. The primary outcomes of the study were the rates of maternal complications including gestational diabetes, preeclampsia, cesarean section, operative vaginal delivery, placenta previa, postpartum hemorrhage, and perinatal outcomes including low Apgar scores, abortion, stillbirth, low-birth weight, preterm delivery, and fetal growth restriction. The selected cases with incomplete data were excluded from analysis.

Comparison of baseline characteristics and pregnancy outcomes between the two groups were analyzed using t-test and Chi-square test for continuous and categorical data, respectively. A *p*-value <0.05 was

considered significant. The relative risk with 95% confidence interval was also calculated. Statistical analysis was performed using SPSS software (IBM Corp. Released 2012; IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

Results

During the study period, 19,599 women of age of 20 years or more, had delivery at our hospital. Of them, 797 women (4.1%) were aged at 40 years or more (the study group), and 18,802 women were aged between 20 and 30 years (the control group). The means (\pm SD) age of the study and control group were 41.49 \pm 1.7 years and 27.06 \pm 3.96 years, respectively. Nearly 80% of cases in the study group were multiparous, and two-folds higher than those in the control group.

Women in the study group had significantly higher rates of pre-existing medical conditions. The rates of chronic hypertension and pregestational diabetes mellitus were 7.2% and 19.3% respectively in the study group and 0.9% and 5.0% in the control group. This is significantly different (*p*<0.0001). Additionally, thyroid disease was also more prevalent in the present study group (1.8% vs. 0.9%, *p*<0.009). Nevertheless, medical complications, such as asthma, hepatitis B viral carrier, heart disease, SLE, HIV infection, or thalassemia were not significantly different between the groups. The demographic characteristics of the study and control group are presented in Table 1.

Table 1. The demographic characteristics

| | Number (%) or mean \pm SD | | <i>p</i> -value |
|----------------------|-------------------------------|------------------------------|-----------------|
| | Age \geq 40 years (n = 797) | Age 20-30 years (n = 18,802) | |
| Age | 41.5 \pm 1.7 | 27.06 \pm 4.0 | <0.001 |
| Parity | | | |
| Nulliparous | 165 (20.7) | 11,069 (58.8) | 0.001 |
| Multiparous | 632 (79.3) | 7,733 (41.1) | |
| Asthma | 10 (1.3) | 195 (1.0) | 0.554 |
| Chronic hypertension | 57 (7.2) | 177 (0.9) | <0.001 |
| Diabetes Mellitus | 154 (19.3) | 945 (5.0) | <0.001 |
| HBV carrier | 38 (4.8) | 1,177 (6.3) | 0.087 |
| HIV infection | 8 (1.0) | 270 (1.4) | 0.312 |
| Heart disease | 9 (1.1) | 139 (0.7) | 0.213 |
| SLE | 2 (0.3) | 65 (0.3) | 0.653 |
| Thyrotoxicosis | 14 (1.8) | 162 (0.9) | 0.009 |
| Thalassemia disease | 1 (0.1) | 91 (0.5) | 0.147 |

HBV = hepatitis B virus; HIV = human immunodeficiency virus; SLE = systemic lupus erythematosus

Comparison of the obstetric outcomes of the groups is shown in Table 2. There was nearly a four-fold increase in abortion rate, defined as delivery before 24 weeks, in the study group. The mean gestational age at delivery was significantly lower in the study group (35.26 vs. 37.38 weeks, $p < 0.001$). Rates of preterm and early preterm birth were significantly higher in the study group ($p < 0.001$). Likewise, the stillbirth rate was three times higher

in the study group ($p < 0.001$), even after excluding the fetal anomaly, which was a common cause of stillbirth. About one third of women in the study group were delivered by cesarean section. Cephalopelvic disproportion (CPD), fetal distress, and breech presentation were the main indications for primary cesarean delivery. Additionally, rates of operative vaginal delivery were also higher in the study group (14.2% vs. 9.4%, $p < 0.001$). Prevalence of

Table 2. Perinatal outcomes

| | Number (%) or mean \pm SD | | p-value | RR | 95% CI |
|-----------------------------|-------------------------------|------------------------------|---------|------|-----------|
| | Age \geq 40 years (n = 797) | Age 20-30 years (n = 18,802) | | | |
| No. of ANC | 8.54 \pm 3.8 | 9.00 \pm 3.6 | 0.001 | | |
| GA at delivered | 35.26 \pm 6.5 | 37.38 \pm 4.1 | <0.001 | | |
| Abortion (\leq 24 weeks) | 95 (11.9) | 592 (3.1) | <0.001 | 3.79 | 3.09-4.65 |
| Preterm (weeks) | | | | | |
| \leq 36 | 177 (24.1) | 2,850 (15.4) | <0.001 | 1.56 | 1.37-1.78 |
| \leq 34 | 103 (14.0) | 1,473 (8.0) | <0.001 | 1.76 | 1.46-2.12 |
| Stillbirth | 105 (13.2) | 768 (4.1) | <0.001 | 3.23 | 2.66-3.91 |
| After exclude anomaly | 34 (4.7) | 385 (2.1) | <0.001 | 2.24 | 1.59-3.15 |
| Cesarean section | 273 (34.3) | 3,912 (20.8) | <0.001 | 1.65 | 1.49-1.82 |
| Primary cesarean | 178 (22.3) | 2,859 (15.2) | <0.001 | 1.57 | 1.38-1.80 |
| Due to distress | 26 (3.3) | 325 (1.7) | 0.002 | 1.89 | 1.27-1.80 |
| Due to breech | 34 (4.3) | 664 (3.5) | 0.272 | 1.21 | 0.86-1.69 |
| Due to CPD | 82 (10.3) | 1,457 (7.7) | 0.008 | 1.33 | 1.08-1.64 |
| Operative Vg delivery | 113 (14.2) | 1,775 (9.4) | <0.001 | 1.50 | 1.26-1.79 |
| Apgar score | | | | | |
| 1-minute | 7.60 \pm 4.7 | 8.57 \pm 7.7 | <0.001 | | |
| 5-minute | 8.42 \pm 3.4 | 9.52 \pm 24.1 | 0.196 | | |
| Low Apgar score (<7) | | | | | |
| At 1 minute | 176 (22.1) | 2,018 (10.7) | <0.001 | 2.06 | 1.79-2.36 |
| At 5 minutes | 115 (14.4) | 1,071 (5.7) | <0.001 | 2.53 | 2.12-3.03 |
| Weight | 2,583.79 \pm 1,030.4 | 2,874.58 \pm 710.9 | <0.001 | | |
| Low birth weight | 178 (24.3) | 2,756 (14.9) | <0.001 | 1.62 | 1.42-1.85 |
| FGR | 68 (9.3) | 1,045 (5.7) | <0.001 | 1.54 | 1.21-1.94 |
| Macrosomia | 111 (15.1) | 2,479 (13.4) | 0.544 | 1.06 | 0.89-1.26 |
| PIH | 105 (13.2) | 1,232 (6.6) | <0.001 | 2.01 | 1.67-2.42 |
| Placenta previa | 14 (1.8) | 183 (1.0) | 0.030 | 1.81 | 1.05-3.09 |
| PPH | 20 (2.5) | 184 (1.0) | <0.001 | 2.56 | 1.63-4.05 |
| GDM | 154 (19.3) | 857 (6.5)* | <0.001 | 3.84 | 3.29-4.49 |
| UTI | 5 (0.6) | 110 (0.6) | 0.811 | 1.07 | 0.44-2.62 |
| IDA | 3 (0.4) | 199 (1.1) | 0.070 | 0.36 | 0.11-1.11 |

RR = risk ratio; ANC = antenatal care; GA = gestational age; CPD = cephalo-pelvic disproportion; Vg = vaginal; FGR = fetal growth restriction; PIH = pregnancy-induced hypertension; PPH = postpartum hemorrhage; GDM = gestational diabetes mellitus; UTI = urinary tract infection; IDA = iron deficiency anemia

* Calculated from mother at age 25-30 years. According to Maharaj Nakorn ChiangMai Hospital policy, mother at age 25 or more is one of the indications for GDM screening.

pregnancy-induced hypertension was significantly higher in the study group (13.2% vs. 6.6%, $p < 0.001$). Gestational diabetes mellitus (GDM) was compared with mothers at age over 25 to 30 years, because our screening policy started at age 25 years. The results showed that advanced age mothers had significantly higher rate of GDM (19.3% vs. 6.5%, $p < 0.001$). The other obstetric complications such as bleeding from placenta previa, iron deficiency anemia during pregnancy, and urinary tract infection, except postpartum hemorrhage, were not significantly different.

Regarding neonatal outcomes, the mean birth weight was significantly lower in the study group ($p < 0.001$). The rates of low birth weight and fetal growth restriction were 24.3% and 9.3% in the study group, significantly different from those in the control group, 14.9% vs. 5.7% respectively, ($p < 0.001$). However, rates of macrosomia were comparable between the two groups. Rates of neonates with low Apgar scores, defined as below 7, at 1- and 5-minutes was found to be higher in the study group ($p < 0.001$), as also showed in Table 2.

Discussion

Our results show significant effects of maternal age on perinatal outcomes. The rates of abortion, stillbirth, preterm delivery, low birth weight, and fetal growth restriction were significantly increased in very advanced maternal age group. Although some previous studies did not demonstrate the correlation between maternal age and abortion^(2,5,6), this contradictory result may be due to the difference in definition of abortion, which varied in studies. The risk of stillbirth might be related to higher incidence of medical complications, which were associated with increased age. Rate of preterm delivery in the present study was consistent with that of several previous studies, which reported to have a relative risk ranging from 1.2 to 2.1^(2,3,5,7-9). Many studies did not show statistical significance in the rate of low birth weight^(3-5,9), but the present study showed a significant increase in the group of very advanced maternal age, probably reflecting higher rate of preterm birth and fetal growth restriction.

About one third of the study group were delivered by cesarean section, which is significantly higher than those in the control group. The relative risk (RR) for cesarean section in the study group is about 1.65, slightly lower than that in other studies, which showed the RR of 1.9-3.9^(2,3,5,7,8). This might be due to

the difference in the strictness of indication criteria for cesarean section. Rate of primary cesarean delivery in the study group was also significantly higher. This attitude towards higher rates of cesarean deliveries was described earlier⁽⁵⁾. The main contributor was primiparity in advanced maternal age and infertility treatment.

Within the present study group, age-related increase of pregnancy induced hypertension and gestational diabetes mellitus were noted, as reported in previous studies^(2,3,8,9). Because of the vascular impairment, more commonly seen in mothers with advanced age, the study group mothers are susceptible to develop pregnancy-induced hypertension (PIH). Additionally, the prevalence of diabetes as well as obesity, which is associated with PIH, is higher among elderly mothers. Risk of GDM was also observed in the present study group. This may be due to an independent effect of age on the risk of GDM as demonstrated in the FASTER cohort⁽¹⁰⁾. Finally, similar to Yogev et al⁽⁶⁾, postpartum hemorrhage increased in advanced age, possibly associated with poor uterine contractility.

These adverse outcomes may be explained by the mal-adaptation to physiologic change during pregnancy, directly associated with advanced maternal age. Frederike et al⁽⁴⁾ reported that uterine vasculature in older women had a decrease ability to adapt to increased hemodynamic demands. Hsieh et al⁽³⁾ suggested that high incidence of sclerotic lesions in myometrial arteries in elderly women might play an important role. Another reason that could explain why pregnancy at increased age has a higher risk is that these women tend to have pre-existing illnesses such as chronic hypertension, diabetes mellitus, or some subtle underlying vascular diseases.

The present study has some limitations, although the sample size of women age at or over 40 years was larger than that in several previous studies, but it was still relatively small for evaluation of some rare events like fetal death, placental adherence etc. Moreover, the present study did not consider some potential confounding factors such as the socioeconomic status and educational level.

Because delayed child bearing is becoming a common event, the scope of maternal and fetal complications is important for decision management. As shown in the present study, as maternal age increases, the risk of adverse pregnancy outcome is accordingly elevated. This information should be given to women who plan late pregnancy. The elderly

women should seek early antenatal care and be taken care by the appropriate multidisciplinary team to minimize the risk for mother and her infant.

What is already known on this topic?

Although generally accepted, the association between increasing maternal age and adverse pregnancy outcome is still inconsistent.

What this study adds?

The present study, which was conducted locally, can represent our patients better than data from other areas.

New data is needed because the environment, social status, and perinatal care have changed. The patients aged 40 years or more should be counseled with up-to-date information.

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Potential conflicts of interest

None.

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ผลลัพธ์การตั้งครรภ์ของสตรีที่อายุมากกว่าหรือเท่ากับ 40 ปี ที่มาคลอดในโรงพยาบาลมาราชนครเชียงใหม่

กฤษณี ไตรศรีศิลป์, ชีระ ทองสง

วัตถุประสงค์: เพื่อศึกษาผลลัพธ์การตั้งครรภ์ของสตรีที่อายุมากกว่าหรือเท่ากับ 40 ปี เปรียบเทียบกับกลุ่มอายุ 20-30 ปี
วัสดุและวิธีการ: เป็นการศึกษาแบบเก็บข้อมูลย้อนหลังของสตรีตั้งครรภ์เดี่ยว ที่มาคลอด ณ โรงพยาบาลมาราชนครเชียงใหม่ ระหว่างเดือนมกราคม พศ. 2545 ถึง ธันวาคม พศ. 2555 โดยเปรียบเทียบผลลัพธ์ของกลุ่มศึกษาคือสตรีที่อายุมากกว่าหรือเท่ากับ 40 ปี และกลุ่มควบคุมคือสตรีที่อายุ 20-30 ปี

ผลการศึกษา: ในช่วงระยะที่ทำการศึกษา มีสตรีตั้งครรภ์ที่อายุมากกว่าหรือเท่ากับ 40 ปี 797 ราย และอายุระหว่าง 20-30 ปี 18,802 ราย พบว่ากลุ่มศึกษามีโรคทางอายุรกรรมอยู่เดิม เช่น ความดันโลหิตสูง เบาหวาน สูงกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ สำหรับผลลัพธ์ทางสูติกรรมพบว่า อัตราการแท้ง อัตราการผ่าตัดคลอด การคลอดก่อนกำหนด และทารกเติบโตช้าในครรภ์ สูงขึ้นในสตรีตั้งครรภ์ที่อายุมากกว่าหรือเท่ากับ 40 ปี อย่างมีนัยสำคัญ

สรุป: สตรีตั้งครรภ์ที่อายุมากกว่าหรือเท่ากับ 40 ปี จะมีโรคทางอายุรกรรมอยู่เดิม ทำให้เพิ่มผลลัพธ์ที่ไม่ดีต่อการตั้งครรภ์ ทั้งการแท้ง การคลอดก่อนกำหนด ทารกโตช้าในครรภ์ การคลอดโดยใช้หัตถการช่วยคลอด ซึ่งข้อมูลดังกล่าวจะมีประโยชน์ในการให้คำปรึกษาแก่สตรีตั้งครรภ์กลุ่มนี้
