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RESEARCH

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Pregnancy outcomes among women near the end of reproductive age

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Abstract

Objective To investigate the outcomes of pregnancies at extreme fertility age, (≥ 45 years).

Methods A retrospective cohort study was undertaken on women who gave birth at a tertiary center, Thailand, (1992–2022) to compare pregnancy outcomes between women of (≥ 45 years and those of the reproductive age (20–34 years).

Results Of 67,301 pregnancies, 121women at age of ≥ 45, as the study group, and 51,315 controls were included in analysis. The study group had a much higher prevalence of fetal trisomy (9.1% vs. 0.1%) and medical disorders. After excluding cases with abortion and severe anomalies, the rates of preterm birth (39.6% vs. 14.5%; relative risk of 2.73, 95% CI: 2.14–3.47), low birth weight (41.2% vs. 14.5%, relative risk of 2.85, 95% CI: 2.26–3.59), fetal growth restriction, preeclampsia, gestational diabetes, cesarean section, low Apgar score, stillbirth and miscarriage were significantly higher in the study group. After excluding cases with underlying diseases, such adverse outcomes were still significantly higher in the study group, for example; preterm birth rate was still as high as 36.8%. In multivariate analysis, extremely advanced maternal age remains an independent risk factor for preeclampsia, preterm birth, fetal growth restriction, and low birth weight, even after adjusting for other potential risk factors.

Conclusion The age of ≥ 45 was at the 99.8th percentile among Thai population, implying a very close proximity to the end of reproductive life. The rates of fetal trisomy, preterm birth, low birth weight, fetal growth restriction, and other adverse outcomes were markedly higher than ever reported, even after excluding cases with underlying diseases. When compared to previous studies, the much higher adverse outcomes were likely caused by more advanced fertility age despite the same chronological age.

Clinical trial number Not applicable.

Synopsis

Pregnancies at an age near the end of fertility much increase risk of fetal trisomy and adverse outcomes, even in cases without pre-existing underlying diseases.

Keywords Advanced maternal age, Fertility age, Low birth weight, Pregnancy outcome, Preterm birth, Trisomy

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Introduction

Since the past three decades, there has been an increasing trend among women worldwide to delay childbearing [1]. This trend has been associated with a number of reasons [2], including an increasing proportion of women with high education and socioeconomic status, women pursuing their careers before childbirth, and the availability of assisted reproductive technologies helping women become pregnant at an advanced age. Accordingly, the proportion of women giving birth at a maternal age of greater than 35 years has increased, in spite of a decrease in fecundity with advancing age [3]. We have noted that the proportion of women giving birth at 35 years or greater in our center (Chiang Mai University Hospital) continuously increased from 9.5% in 1992 to 26.2% in 2022 [4]. It is well-established that advanced maternal age is strongly associated with an increased risk of adverse pregnancy outcomes, including perinatal / maternal morbidity and mortality. Apparently, bio-physiological changes secondary to aging, especially cardiovascular and reproductive aging, contribute to reduced capability to cope with a dramatic increase in physiological alterations and requirements during pregnancy [5, 6]. Moreover, several underlying medical disorders, especially chronic hypertension, cardiac diseases, diabetes mellitus, obesity and metabolic syndrome, which markedly increase with advancing age, definitely play a role in bad obstetric outcomes among women of advanced age.

On literature review, the studies on outcomes of pregnancy among women at age of 45 or more have been published several times [7–13]. In a large cohort of western population including 45,435 pregnancies, 449 or about 1% were of age 45 or more [13, 14], while we preliminarily reviewed our own database, we found that only 124 (0.18%) out of 67,246 women were of age 45 or more [4]. This observation suggests that the definition of extreme age as a chronological age of 45 or older, commonly used in most studies, may differ significantly when considered in terms of fertility age. Cultural differences, such as the tendency of Western women to have children at relatively older ages compared to Asian women, may also contribute to this variation. Moreover, many studies showed that the prevalence of mothers at age of 45 or more has continuously increased in the recent years, consistent with the prevalence of overall elderly gravida (35 years or more) among our population, but the prevalence of mothers of 45 or more is unchanged, approximately 0.2% throughout the past 30 years. This observation also supports that women in our population at 45 years or more are truly extreme fertility age or a very close proximity to the end of reproductive life. Although the prevalence of elderly mothers has continuously increased in recent years, the incidence of pregnancies at age 45 or older has remained constant due to biological fertility limitations. Accordingly, we used age of 45 or more to define extreme fertility age. Though this study used 45 years as a cut-off age for extreme age as used in many studies, we decided to use this cut-off based on extreme fertility age instead of extreme chronological age. Furthermore, obstetric outcomes vary among different populations as they are associated with ethnic factors, geographical areas, cultures, lifestyles and socioeconomic status. Importantly, the ending age of reproductive life varies among ethnicities. Thus, each population should develop its own data concerning reproductive life and obstetric outcomes. Accordingly, we carried out this study to compare the obstetric outcomes between women of extreme fertility age (45 years or more) and those in the adult group (20–34 years old).

Patients and methods

The retrospective cohort study was conducted based on the obstetric database of the Department of Obstetrics and Gynecology, Chiang Mai University, Thailand. The digital database of pregnant women who gave birth at our center, a university hospital, has been systematically recorded prospectively on the day of discharge since 1992 until the present. This study was ethically approved by the Institutional Review Board, Faculty of Medicine, Chiang Mai University (Research Ethics Committee 4; Faculty of Medicine, Chiang Mai University; Research ID: OBG-2565-9360, Date of Approval 30 January 2023). Written informed consent was not required for the study because of retrospective review of the medical records. The database was firstly accessed to retrieve all consecutive records of pregnant women who gave birth from 1992 to 2022. They were categorized into four age groups: adolescent (less than 20 years), adult (20–34 years), advanced maternal age (35–44 years) and extremely advanced maternal age (45 years or greater). The adult group was considered as the control group in this study, whereas the group of extremely advanced age was considered as the study group. The full medical records of the cases in the study group were comprehensively reviewed by the authors. The exclusion criteria are as follows: 1) multifetal pregnancy, 2) severe fetal abnormalities, indicated for termination of pregnancy, and 3) unknown final outcomes. Demographic and clinical characteristics (e.g. maternal age, parity, underlying medical disorders, etc.) and obstetric outcomes (e.g. maternal complications, gestational age at birth, fetal growth, route of delivery, neonatal outcomes, etc.) were validated, extracted and digitally recorded. The main outcomes of the study were the rates of miscarriage, preterm birth, fetal growth restriction, low birth weight, low Apgar scores, aneuploidy and stillbirth. The secondary outcomes were preeclampsia, gestational diabetes, cesarean section rate, placental abruption, placenta previa, and medical complications. The definitions used in this study are as follows: 1) Preterm birth is defined as a birth after 20 complete weeks and before 37 complete weeks of gestation. 2) Low birth weight is defined as a birth weight of a neonate of less than 2,500 g, not including abortion (20 complete

weeks or earlier). 3) Fetal growth restriction is defined as a birth weight of less than the 10th percentile for each gestational week according to the Thai fetal growth curve. 4) Preeclampsia is defined as a new onset of maternal hypertension (blood pressure of 140/90 mmHg or greater) after 20 weeks together with a new onset of proteinuria (defined as 24-hour urine protein of 300 mg or more). 5) Perinatal death is defined as the death of a fetus in utero after 20 weeks or neonatal death within 7 days after birth. 6) Low Apgar score is defined as a score of less than 7 at 5 min. 7) Miscarriage is defined as spontaneous fetal loss at 20 gestational week or less. Note that Some patients might have experienced more than one pregnancy over the long study period. However, each pregnancy was treated as a single sample, regardless of the total number of women. The number of pregnancies, rather than the number of women, was included in the analysis as an independent variable.

Statistical analysis

The validated data were analyzed, using the statistical package for the social sciences (SPSS) software. The quantitative data are expressed as mean ± SD or median (IQR), according to normality of distribution, whereas the qualitative data are expressed as proportions and percentages. To compare the baseline characteristics and pregnancy outcomes between the study and control groups, the categorical data were compared using Chi-square test and relative risk with 95% confident interval based on univariate analysis, whereas the continuous data were compared using unpaired Student T test or Mann–Whitney U test as appropriate. Statistical significance was defined as a p-value of less than 0.05.

Results

During the thirty-year period of the study, a total of 67,301 pregnant women gave birth at Chiang Mai University hospital. Of them, 67,246 were available for analysis, including 5,876 (8.73%) adolescents, 51,536 (76.64%) adults, 9,710 (14.44%) advanced-age women, and 124 (0.18%) extremely-advanced-age women, as presented in Fig. 1. While the total number of births for each year showed a trend of continuous significant decrease, the rate of pregnancies of advanced age (35 years or greater) exhibited a trend of significant increase,

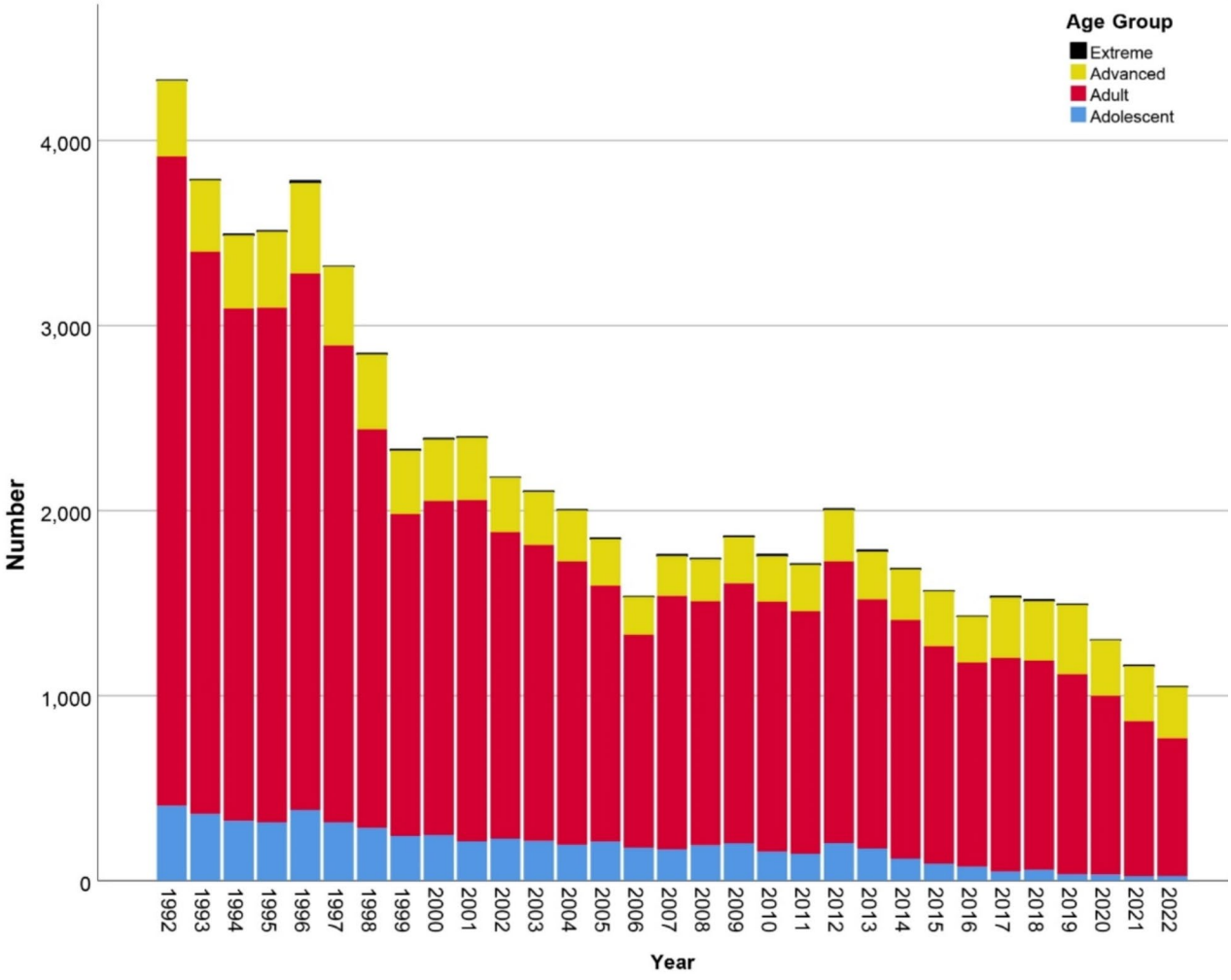

Fig. 1 Distribution of birth frequencies by maternal age group and years of birth

from 9.5% in 1992 to 26.2% in 2022 (p-value < 0.001); but, surprisingly, the percentage of pregnancies with extremely advanced age was relatively constant, at 0.1–0.3%, throughout the 30 year-period of the study, not showing a significant trend (p-value > 0.05). After excluding cases with multifetal pregnancies, a total of 51,315 adults (control group) and 121 women with extremely advanced age (study group) were included in analysis, as presented in Fig. 2.

Among singleton pregnancies, a total of 51,315 in the control group and 121 in the study group were compared for baseline characteristics and the rate of miscarriage as well as trisomy, as presented in Table 1. The mean (± SD) maternal ages of the study and control groups were 45.97 ± 1.38 years and 26.93 ± 4.06 years, respectively. Approximately, 80% of the study group were parous women, compared with 44% in the control group ($p < 0.001$). Women in the study group had significantly higher rates of underlying medical disorders (30.6% vs. 16.4%; $p < 0.001$), especially chronic hypertension (6.6% vs. 1.7%) and pre-gestational diabetes mellitus (2.9% vs. 0.5%). However, the prevalence of most diseases in both groups, such as cardiac disease, chronic hepatitis B viral infection, asthma, urinary tract infection, HIV infection and thalassemia disease, were comparable. The rate of spontaneous abortion in the study group was 8.4%

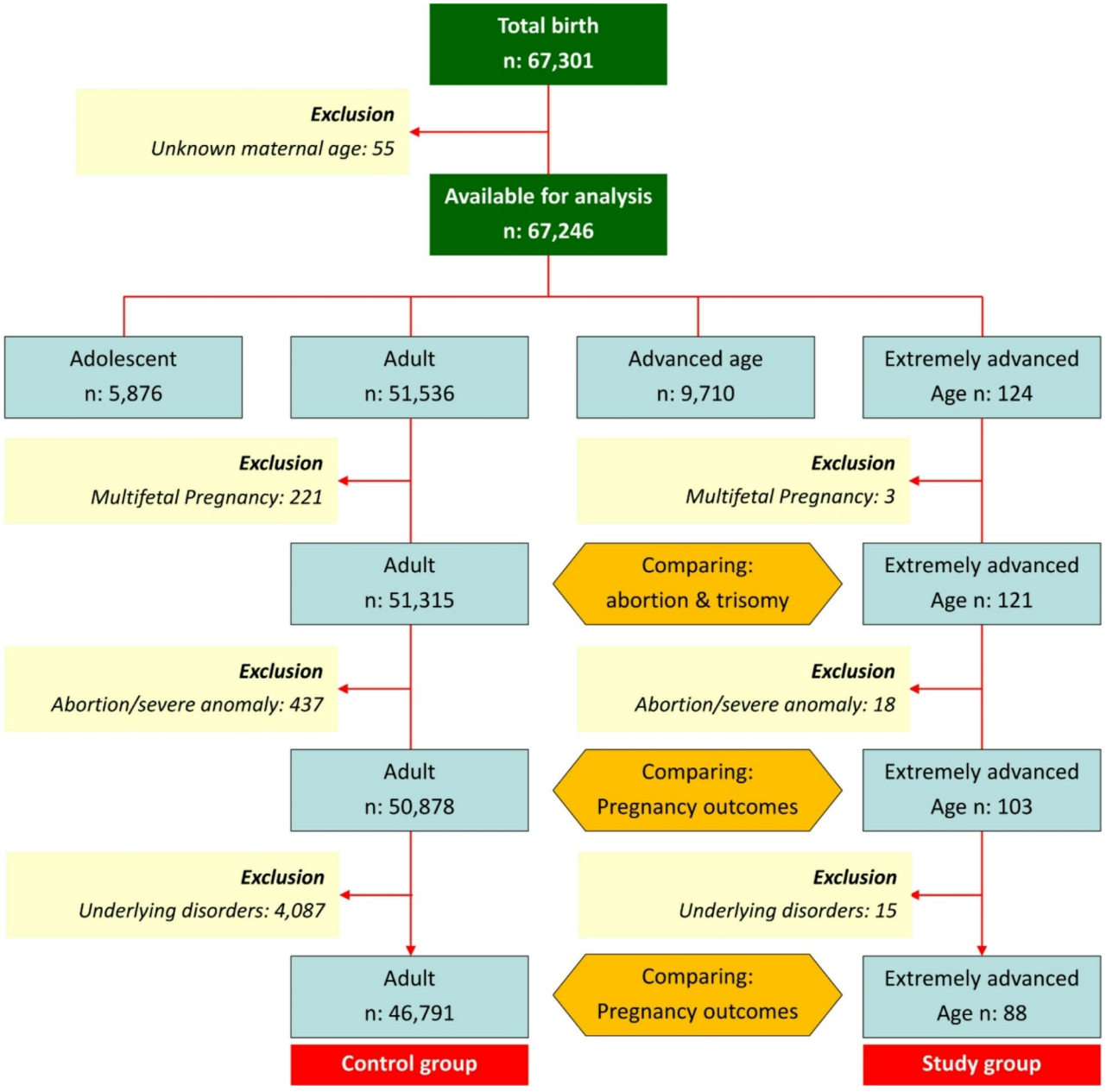

Fig. 2 Flowchart of mother categorization for analysis

Table 1 Comparisons of the baseline variables between the study and control group (singleton)

	Study Group (age ≥ 45 years) *N*: 121	**Control Group (age 20–34 years) *N*: 51,315**	***P***	**RR (95% CI)**
Age	45.97 ± 1.38	26.93 ± 4.06	< 0.001	
Nulliparous	24 (19.8%)	28,516 (55.6%)	< 0.001	
Multiparous	97 (80.2%)	22,779 (44.4%)	< 0.001	
Number of antenatal visits	5.8 ± 4.2	8.1 ± 4.3	< 0.001	
Previous cesarean birth	11 (9.1%)	3,371 (6.6%)	0.264	1.38 (0.79–2.43)
Medical diseases (combined)	37 (30.6%)	8,438 (16.4%)	< 0.001	1.86 (1.42–2.43)
Iron deficiency	1 (0.8%)	850 (1.7%)	0.475	0.50 (0.07–3.51)
Myoma uteri	3 (2.5%)	338 (0.7%)	0.014	3.76 (1.23–11.57)
Epilepsy	0 (0.0%)	123 (0.2%)	0.590	-
Condyloma accuminata	0 (0.0%)	162 (0.3%)	0.536	-
Syphilis	0 (0.0%)	52 (0.1%)	0.726	-
Asthma	2 (1.7%)	553 (1.1%)	0.541	1.53 (0.39–6.08)
Chronic hypertension	8 (6.6%)	849 (1.7%)	< 0.001	4.00 (2.04–7.83)
Pregestational DM	3 (2.9%)	232 (0.5%)	< 0.001	5.96 (1.94–18.29)
HBV carrier	7 (5.8%)	2,929 (5.7%)	0.971	1.01 (0.49–2.08)
HIV infection	1 (0.8%)	833 (1.6%)	0.488	0.51 (0.07–3.59)
Heart disease	2 (1.7%)	454 (0.9%)	0.368	1.87 (0.47–7.40)
SLE	0 (0.0%)	256 (0.5%)	0.436	-
Thalassemia disease	0 (0.0%)	320 (0.6%)	0.384	-
Thyrotoxicosis	2 (1.7%)	478 (0.9%)	0.410	1.77 (0.45–7.03)
Fetal trisomy	11 (9.1%)	61 (0.1%)	< 0.001	76.47 (41.27–141.70)
Miscarriage	10/119 (8.4%)	389 (0.8%)	< 0.001	11.07 (6.07–20.21)

(11/119), significantly higher than that in the control group (0.8%), with a relative risk of 11.07. It is noteworthy that, of the 121 cases of the study group, the prevalence of trisomy was as high as 9.1% (trisomy 18: 5 and trisomy 21: 6 cases), significantly higher than the 0.1% recorded in the control group (p-value < 0.001; relative risk of 76.48 with 95%CI: 41.27–141.70).

After excluding cases with abortion and severe anomalies, a total of 50,878 cases in the control group and 103 cases in the study group were available for comparison of pregnancy outcomes, as presented in Table 2. In the study group, the mean gestational age at birth was significantly lower (35.8 vs. 37.9 weeks, $p < 0.001$). Similarly, the rate of preterm birth was significantly higher in the study group (39.6% vs. 14.5%, $p < 0.001$; with a relative risk of 2.73, 95%CI 2.14–3.47). Notably, the rate of fetal growth restriction was also significantly higher in the study group (17.5% vs. 7.5%, $p < 0.001$). Resulting from the higher rates of preterm birth and fetal growth restriction, the mean birth weight was significantly lower in the study group (2,498 vs. 2924 g, $p < 0.001$), and the rate of low birth weight was much higher in the study group, 41.2% vs. 14.5%, $p < 0.001$; relative risk of 2.85 (95%CI: 2.26–3.59). Note that the rate of large-for-date fetuses was comparable between both groups. The rate of newborns with low Apgar scores, defined as lower than 7 at 5 min, was also significantly higher in mothers of extremely advanced age (14.6% vs. 4.0%; $p < 0.001$). Importantly, the perinatal death rate was significantly higher in the study group, with a relative risk of 2.62 (95%CI: 1.28–5.37). The rate of pre-eclampsia was also markedly increased in the study group (17.5% vs. 6.6%, $p < 0.001$). Additionally, the risk of gestational diabetes mellitus was significantly increased, with a relative risk of 2.23 (95%CI: 1.49–3.34). However, the rates of other common obstetric complications, such as placental abruption, placenta previa, polyhydramnios, etc., were not significantly different between the two groups, as presented in Table 2. Finally, the cesarean section rate was significantly higher in the study group (38.8% vs. 16.9%; $p < 0.001$), mainly indicated by previous cesarean section, dystocia, fetal distress and breech presentation.

After excluding cases with preexisting underlying disorders, a total of 46,791 cases in the control group and 88 cases in the study group were available for comparison of pregnancy outcomes, as presented in Table 3. In the study group, the mean gestational age at birth was significantly lower (35.9 vs. 37.9 weeks, $p < 0.001$). Likewise, the rate of preterm birth was significantly higher in the study group (36.8% vs. 14.3%, $p < 0.001$; with a relative risk of 2.58, 95%CI: 1.96–3.40). Notably, the rate of fetal growth restriction was also significantly higher in the study group (17.0% vs. 7.2%, $p < 0.001$). Resulting from the higher rates of preterm birth and fetal growth restriction, the mean birth weight was significantly lower in the study group (2,528 vs. 2932 g, $p < 0.001$), and the rate of low birth weight was much higher in the study group, 36.8% vs. 14.0%, $p < 0.001$; relative risk of 2.76 (95%CI: 2.12–3.59). Note that the rate of large-for-date

Table 2 Comparisons of the obstetric outcomes between the study and control group

	Study Group (age ≥ 45 years); *N*: 103	**Control Group (age 20–34 years) *N*: 50,878**	***P***	**RR (95% CI)**
Gestational age at birth	35.8 ± 4.6	37.9 ± 3.1	< 0.001	
Birth weight	2498 ± 937	2924 ± 638	< 0.001	
Prolonged premature rupture of membranes	6 (5.8%)	1,520 (3.0%)	0.091	1.95 (0.90–4.25)
Breech presentation	5 (4.9%)	2,288 (4.5%)	0.861	1.08 (0.46–2.54)
Polyhydramnios	0 (0.0%)	276 (0.5%)	0.454	-
Oligohydramnios	0 (0.0%)	485 (1.0%)	0.319	-
Chorioamnionitis	1 (1.0%)	194 (0.4%)	0.333	2.35 (0.33–16.65)
Transverse lie	1 (1.0%)	129 (0.3%)	0.149	3.83 (0.54–27.13)
Incompetent cervix	0 (0.0%)	49 (0.1%)	0.753	-
Placental abruption	0 (0.0%)	39 (0.1%)	0.779	-
Placenta previa	3 (2.9%)	501 (1.0%)	0.083	2.96 (0.97–9.05)
Acute pyelonephritis	2 (1.9%)	380 (0.7%)	0.160	2.60 (0.66–10.29)
Gestational DM	19 (19.0%)	4,317 (8.5%)	< 0.001	2.23 (1.49–3.34)
Preeclampsia	18 (17.5%)	3,337 (6.6%)	< 0.001	2.66 (1.75–4.06)
Cesarean delivery	40 (38.8%)	8,575 (16.9%)	< 0.001	2.30 (1.81–2.94)
Preterm birth	40 (39.6%)	7,386 (14.5%)	< 0.001	2.73 (2.14–3.47)
Low birth weight	42 (41.2%)	7,338 (14.5%)	< 0.001	2.85 (2.26–3.59)
Fetal growth restriction	18 (17.5%)	3,804 (7.5%)	< 0.001	2.34 (1.53–3.66)
Large-for-date fetuses	16 (15.5%)	5,027 (9.9%)	0.055	1.57 (1.00-2.47)
Low Apgar scores	15 (14.6%)	2,036 (4.0%)	< 0.001	3.64 (2.27–5.82)
Perinatal death	7 (6.8%)	1,317 (2.6%)	0.007	2.62 (1.28–5.37)

fetuses was comparable between both groups. The rate of newborns with low Apgar scores, defined as lower than 7 at 5 min, was also significantly higher in mothers of extremely advanced age. Importantly, the perinatal death rate was significantly higher in the study group, with a relative risk of 2.69 (95%CI: 1.24–5.84). The rate of preeclampsia was also markedly increased in the study group (18.2% vs. 6.2%, $p < 0.001$). Additionally, the risk of gestational diabetes mellitus was significantly increased, with a relative risk of 2.12 (95%CI: 1.34–3.36). Also, the rates of cesarean section and placenta previa were significantly higher in the study group (39.8% vs. 16.5%; $p < 0.001$, and 3.4% vs. 1.0%; $p = 0.022$, respectively). However, the rates of other common obstetric complications, such as placental abruption, polyhydramnios, etc., were not significantly different between the two groups, as presented in Table 3. In multivariate analysis, extremely advanced maternal age remains an independent risk factor for preeclampsia, preterm birth, fetal growth restriction, and low birth weight, even after adjusting for other potential risk factors, as presented in Table 4.

Discussion

The insights gained from this study are as follows: 1) Our findings indicate significant adverse effects of extremely advanced maternal age on pregnancy outcomes, including increased rates of miscarriage, perinatal death, preterm birth (~40%), low birth weight, and fetal growth restriction. 2) Women aged 45 years or older accounted for only 0.2% (99.8th percentile) of the cohort, a marked difference from the 1% reported in some studies, suggesting potential variations in the age of fertility cessation. 3) The prevalence of trisomy or non-disjunction was as high as 9.1%. 4) Even after excluding cases with underlying diseases, the rates of adverse outcomes remained significantly higher compared to the control group, highlighting the independent impact of aging on pregnancy outcomes.

The reasons for increased poor pregnancy outcomes are certainly associated, at least in part, with pre-existing medical disorders, which are more common in advanced age, particularly chronic hypertension, pre-gestational diabetes mellitus and subtle vascular damages secondary to aging. Nevertheless, aging itself can also be responsible for such poor outcomes, as seen in cases without any underlying diseases. These adverse outcomes may be caused by incapability of adaptation to bio-physiologic changes induced by pregnancy, directly related to advanced aging, as supported by several previous reports. For example, De Weger et al. [6] reported that uterine vasculature in women of advanced age had less capability to adapt to increased hemodynamic requirement. Likewise, Hsieh et al. [5] demonstrated that women of advanced age had a high prevalence of sclerotic lesions in myometrial arteries, which can certainly cause abnormal placentation, which can lead to several adverse pregnancy outcomes, such as preterm birth, miscarriage, or perinatal death, in spite of exclusion of cases complicated with underlying medical diseases.

Interestingly, the magnitude of risk of most adverse outcomes in our study seemed to be higher than those in

Table 3 Comparisons of the obstetric outcomes between the study and control group after excluding pregnancies with underlying medical disorders

	Study Group (age ≥ 45 years) *N*: 88	**Control Group (age 20–34 years) *N*: 46,791**	***P***	**RR (95% CI)**
Gestational age at birth	35.9 ± 4.5	37.9 ± 3.1	< 0.001	
Birth weight	2,528 ± 931	2,932 ± 635	< 0.001	
Prolonged premature rupture of membranes	4 (4.5%)	1,422 (3.0%)	0.411	1.50 (0.57–3.90)
Breech presentation	5 (5.7%)	2,140 (4.6%)	0.619	1.24 (0.53–2.91)
Polyhydramnios	0 (0.0%)	238 (0.5%)	0.502	-
Oligohydramnios	0 (0.0%)	434 (0.9%)	0.364	-
Chorioamnionitis	1 (1.1%)	182 (0.4%)	0.261	2.92 (0.41–20.62)
Transverse lie	1 (1.1%)	116 (0.2%)	0.095	4.58 (0.65–32.45)
Incompetent cervix	0 (0.0%)	46 (0.1%)	0.769	-
Placental abruption	0 (0.0%)	36 (0.1%)	0.795	-
Placenta previa	3 (3.4%)	463 (1.0%)	0.022	3.45 (1.13–10.51)
Acute pyelonephritis	2 (2.3%)	331 (0.7%)	0.081	3.21 (0.81–12.70)
Gestational DM	15 (17.4%)	3,837 (8.2%)	0.002	2.12 (1.34–3.36)
Preeclampsia	16 (18.2%)	2,906 (6.2%)	< 0.001	2.93 (1.88–4.57)
Cesarean delivery	35 (39.8%)	7,708 (16.5%)	< 0.001	2.41 (1.87–3.13)
Preterm birth	32 (36.8%)	6,663 (14.3%)	< 0.001	2.58 (1.96–3.40)
Low birth weight	34 (38.6%)	6,541 (14.0%)	< 0.001	2.76 (2.12–3.59)
Fetal growth restriction	15 (17.0%)	3,370 (7.2%)	< 0.001	2.37 (1.49–3.76)
Large-for-date fetuses	14 (15.9%)	4,652 (9.9%)	0.062	1.60 (0.99–2.59)
Low Apgar scores	14 (15.9%)	1,828 (3.9%)	< 0.001	4.07 (2.51–6.59)
Perinatal death	6 (6.8%)	1,185 (2.5%)	0.011	2.69 (1.24–5.84)

several previous studies. For example, in previous studies, the rates of preterm birth in women of extremely advanced age were shown to have a relative risk ranging from 1.2 to 2.1 [7, 9–11, 14], while we recorded values of more than 3.0 in our cohort for both total preterm birth rate and spontaneous preterm birth rate. Importantly, preterm birth, fetal growth restriction and low birth weight are the main problems in our cohort, found in as high as approximately 40% of cases, which is far too high or greater than the values reported in most previous studies, for example 18.7% in the study of Laskov et al. [9]. Note that while some studies did not demonstrate an increase in the risk of low birth weight in the group of very advanced maternal age [7, 9], our study showed a marked increase, reflecting a higher rate of preterm birth and fetal growth restriction.

Our study showed that the prevalence of preeclampsia and gestational diabetes were significantly higher in women of extremely advanced age, consistent with the findings in most previous studies [8–11, 13, 14]. Convincingly, subtle pre-existing vascular damage, which was more prevalent in women of extremely advanced age, is the main predisposing factor to preeclampsia development. The risk of gestational diabetes, which is also consistently found among various reports, is likely due to an independent effect of age on such a risk, as documented in the FASTER trial [15].

The cesarean rate among women of extremely advanced age was 36.7%, approximately two times higher than that of the controls, in agreement with the results of other previous studies [7, 10, 11, 16]. Additionally, the rate of primary cesarean in our study was significantly higher.

Although fertility rate dramatically drops after 45 years of age, only 100 pregnancies per 1000 exposed women [17], the age at the end of reproduction may vary across populations. As previously mentioned, in spite of a large cohort of pregnant women over a study period of 30 years, only 0.2% of them were in the age range of 45 years or more. However, though slightly less than that of Israel, which was 0.3%, as reported by Laskov et al. [9], and that of Japan, which was 0.25% [11], our incidence was much less than those reported in western studies, in which the incidence was approximately 1% of the obstetric population [13, 14], approximately five times our incidence. In other words, our study cases were closer to the age of fertility ending than the cases of western studies, despite using the same definition of 45 years or more. Probably, the age at which fertility ends in our population is earlier than that of western women. Additionally, some other observations in this study supported that our study cases were truly near the end of reproduction, as follows. While some studies suggest that the number of pregnancies of 45 years or more has risen dramatically in recent years [8, 17], our study showed a constant rate of about 0.2% over the past 30 years, in contrast to the number of elderly mothers of 35–44 years in the same study, which dramatically increased from 8% in 1992 to 25% in 2022 [4]. This

Table 4 Crude and adjusted odd ratios for the risk of preeclampsia, preterm birth, fetal growth restriction, and low birth weight derived from logistic regression analysis

Potential risk factors	Univariate analysis		Multivariate analysis	
	P-value	Crude odds ratio (95% CI)	*P*-value	Adjusted odds ratio (95% CI)
Preeclampsia				
Extremely-advanced age	< 0.001	3.36 (1.95–5.78)	< 0.001	4.24 (2.35–7.66)
Socio-economic status (ref: low)	0.409	1.04 (0.95–1.14)	0.837	0.99 (0.90–1.09)
Pre-pregnancy BMI (Kg/m^2)	0.741	1.00 (0.99–1.01)	0.615	1.00 (0.99–1.01)
Parity (ref: 0)	0.172	0.96 (0.91–1.02)	0.009	0.91 (0.85–0.98)
Number of antenatal care visits	0.117	0.99 (0.98-1.00)	0.088	0.99 (0.98-1.00)
Smoking (ref: no)	0.930	0.98 (0.62–1.53)	0.822	0.94 (0.56–1.59)
Preterm birth				
Extremely-advanced age	< 0.001	3.50 (2.26–5.42)	< 0.001	3.35 (2.00-5.61)
Socio-economic status (ref: low)	< 0.001	0.86 (0.80–0.91)	0.486	0.98 (0.91–1.05)
Pre-pregnancy BMI (Kg/m^2)	0.029	0.99 (0.99-1.00)	0.036	0.99 (0.98-1.00)
Parity (ref: 0)	< 0.001	1.14 (1.10–1.18)	0.373	0.98 (0.94–1.03)
Number of antenatal care visits	< 0.001	0.83 (0.83–0.84)	0.000	0.83 (0.83–0.84)
Smoking (ref: no)	0.032	1.35 (1.03–1.78)	0.496	1.12 (0.80–1.58)
Fetal growth restriction				
Extremely-advanced age	0.001	2.65 (1.52–4.62)	< 0.001	3.64 (1.93–6.86)
Socio-economic status (ref: low)	< 0.001	0.83 (0.76–0.90)	< 0.001	0.82 (0.75–0.90)
Pre-pregnancy BMI (Kg/m^2)	0.014	0.99 (0.98-1.00)	0.007	0.99 (0.98-1.00)
Parity (ref: 0)	< 0.001	0.76 (0.72–0.80)	< 0.001	0.69 (0.65–0.74)
Number of antenatal care visits	< 0.001	0.95 (0.94–0.96)	< 0.001	0.95 (0.94–0.96)
Smoking (ref: no)	0.276	1.23 (0.85–1.79)	0.167	1.34 (0.88–2.03)
Low birth weight				
Extremely-advanced age	< 0.001	3.86 (2.51–5.94)	< 0.001	4.67 (2.85–7.65)
Socio-economic status (ref: low)	0.010	0.92 (0.87–0.98)	0.468	0.98 (0.91–1.04)
Pre-pregnancy BMI (Kg/m^2)	0.018	0.99 (0.98-1.00)	0.012	0.99 (0.98-1.00)
Parity (ref: 0)	< 0.001	0.93 (0.89–0.96)	< 0.001	0.81 (0.77–0.85)
Number of antenatal care visits	< 0.001	0.89 (0.88–0.89)	< 0.001	0.88 (0.88–0.89)
Smoking (ref: no)	0.069	1.30 (0.98–1.71)	0.137	1.28 (0.93–1.77)

(BMI: body mass index)

suggests that despite a great increase in the number of pregnancies at advanced age in recent years, the number did not increase for women of extremely advanced age in spite of attempts to conceive due to biological reasons of fertility failure. Moreover, we have noted that of the 124 cases of extremely advanced age, only three (2.4%) were 50 years or greater (50, 51 and 53), much less than 15.3% (27 out of 177), the figure recorded in the study of Yogev et al. [7]. We emphasized above that our cases are truly at the extreme point of fertility to illustrate that the more pronounced adverse outcomes in our study might partly be associated with the higher proportion of our study cases confined to the group of truly poor reproductive health, near fertility ending.

The strengths of this study are as follows: 1) The data of mothers of extremely advanced age were directly derived from a comprehensive review of medical records, not extracted from crude registry databases of the hospital, as performed in many studies. 2) Adequate sample size to address the main outcomes. 3) Our results are more representative of pregnancy outcomes near the end of reproductive age than the results of many previous studies, since our study cases were confined to only 0.2% of women at the extreme end of reproductive age. The weaknesses of this study are as follows: 1) Though the sample size of women of 45 years or greater was relatively large, it might be too small for comparison of rare outcomes, such as placenta accreta spectrum, placental abruption, etc. 2) Because of the retrospective nature, some interesting data might not be available or might be less reliable. 3) Numerous changes in obstetric care during the long-time frame of this study could influence the pregnancy outcomes. 4) Although we excluded major confounding factors, such as medical conditions and multifetal pregnancies, other potential confounders; including parity, socioeconomic background, cultural factors, and education, were not adjusted for in a multivariate analysis. Also, the effect of multiple pregnancies over time in the same women, which may influence the outcomes, was not considered for adjustment. As a result, the reliability of the outcome comparisons may be limited.

In conclusion, this study focuses on extreme fertility age rather than extreme chronological age, and we recommend

that future studies report the percentile of age as a basis for comparison. This study provides evidence that pregnancy at an age near the end of reproductive life is associated with a significantly higher risk of adverse pregnancy outcomes, even in cases without pre-existing underlying diseases. Additionally, the rate of fetal trisomy was observed to be as high as 9%. This information should be communicated to women of advanced maternal age who plan to conceive. Such individuals should seek preconception counseling, initiate early prenatal care, and receive care through a multidisciplinary approach to minimize the risk of adverse obstetric outcomes.

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Author contributions
UC: conceptualization, proposal development, acquisition of data, data validation, manuscript writing; SP: conceptualization, proposal development, acquisition of data, data validation, manuscript editing, final approval; SL: data validation, acquisition of data, manuscript editing, final approval; SS: data validation, acquisition of data, manuscript editing, final approval; TT: data validation, formal analysis and manuscript editing, final approval; All authors have read and agreed to the published version of the manuscript.

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Data availability
The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institute Review Board (Research Ethics Committee 4; Faculty of Medicine, Chiang Mai University; Research ID: OBG-2565-9360, Date of Approval 30 January 2023).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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