

# The impact of advanced maternal age and parity on obstetric and perinatal outcomes in singleton gestations

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## Abstract

**Objective** To investigate the effect of advanced maternal age (AMA) separately in nulliparous and multiparous women on obstetric and perinatal outcomes in singleton gestations.

**Study design** A historical cohort study on data from 6,619 singleton pregnancies between 2004 and May 2007 was performed. AMA was defined as 35 years and older. Obstetric and perinatal outcomes in AMA versus women younger than 35 years (non-AMA) were compared for both nulli- and multiparae with Student's *t*-test and Chi-square test in univariate analysis. Multiple logistic regression analysis was performed to examine the independent effect of AMA.

**Results** Out of 6,619 singleton pregnancies, the frequency of nulliparity was 42.7 and 33.4% of the parturients were of AMA. Among nulliparous women, AMA was significantly associated with a higher frequency of caesarean section both before labour (OR 2.26 with 95% CI 1.74–2.94), in labour (OR 1.44 with 95% CI 1.07–1.93), and more instrumental vaginal deliveries (ORs 1.49 with 95% CI 1.13–1.96). Among multiparous women, AMA was only significantly associated with a higher caesarean section rate before labour (ORs 1.42, 95% CI 1.19–1.69). There were no significant differences between the two age groups in the prevalence of other adverse obstetric outcomes and adverse perinatal outcomes.

**Conclusions** Operative delivery is increased in AMA, including caesarean sections, as well as instrumental vaginal deliveries in nulliparous women. In multiparous women, however, only the rate of caesarean section before labour was increased. AMA had no significant effect on other adverse obstetric and perinatal outcomes irrespective of parity.

**Keywords** Advanced maternal age (AMA) · Parity · Obstetric outcome · Perinatal outcome

## Introduction

During the last three decades, there has been an increasing trend among women in the industrialised world to delay childbearing [1]. In the United States, birth rates for women aged 35–39 and 40–45 years have steadily increased and reached their highest level in 2006 with 47.3 and 9.4 births per 1,000 women, respectively [2]. In Norway, age-dependent fertility rates for age groups 30–34 years, 35–39 years and 40–44 years have more than doubled during the last 30 years [3]. The proportion of women who were 35 years and older when they gave birth was 19.1% in 2008, compared to 12% in 1995 (See *The Medical Birth Registry of Norway*, available at <http://www.fhi.no>).

Traditionally, pregnant women of 35 years or more (advanced maternal age, AMA) have been considered at increased risk of certain pregnancy complications such as pre-eclampsia, gestational diabetes, placenta abruption, pre-term delivery and caesarean delivery [4–7]. In addition, perinatal complications are reported to be higher in this patient population [8, 9]. Recently, however, the question has arisen as to what extent AMA poses a risk factor for

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adverse obstetric and perinatal complications [9–12] for women who do not suffer from hypertension or diabetes. Callaway et al. [11] studied pregnancy outcomes in 76 women of very advanced maternal age ( $\geq 45$  years) and found no significant differences of maternal and neonatal outcomes when compared to mothers of younger age, except for a significantly increased rate of caesarean sections in the older age group. In a small study on women who were conceived by IVF, Suzuki et al. [10] compared obstetric outcomes in nulliparous women 35 years and older with nulliparous women 34 years and younger at delivery. They found that the incidence of pregnancy-induced hypertension in the younger group was significantly higher than that in the older group, while there were no measurable differences in other obstetric outcomes, such as placental abnormality, premature delivery or neonatal asphyxia between the two groups. Moreover, there are few studies that have studied parity in relation to AMA [7]. The purpose of this study was to investigate the effect of maternal age in strata of parity on obstetric and perinatal outcomes in singleton gestations.

## Materials and methods

This is a hospital-based retrospective analysis of 6,619 birth registry records retrieved from a local database at Oslo University Hospital, Rikshospitalet, in Oslo, Norway between January 2004 and May 2007 (birth registry data were not fully available before then). Because of the intrinsic risk of multiple pregnancies, this study was restricted to singleton pregnancies. AMA was defined as 35 years and older according to the definition of the International Federation of Gynaecology and Obstetrics (FIGO) in 1958 on “Elderly primigravidae”, and younger than 35 years was defined as non-AMA. Gestational age was defined as the number of completed weeks of gestation based on an ultrasound screening examination performed between gestational weeks 18 and 20 as determined by the date of the last normal menstrual period. Nulliparity included women who had not previously delivered a viable foetus ( $>24$  weeks of gestation), while multiparity included women who had at least one prior pregnancy that progressed beyond 24 weeks of gestation, regardless of the actual parity number. We studied the following obstetric outcomes: pre-eclampsia (blood pressure  $\geq 140/90$  mmHg after 20 weeks gestation and a dipstick test for protein in urine  $\geq +1$  and/or total protein/creatinine ratio in urine  $\geq 30$ ), gestational diabetes (WHO 1999 criteria), antepartum haemorrhage (bleeding after 20 weeks gestation and before labour), pre-term delivery (defined as delivery at  $<37$  weeks of gestation), delivery methods (divided into normal vaginal delivery, vacuum/forceps delivery, caesarean delivery

before labour and in labour), placental abruption, postpartum haemorrhage ( $>500$  ml during the first 24 h after birth), breech presentation, low birth weight  $<2,500$  g, Apgar score  $<7$  at 5 min, abnormal cardiotocography (CTG) (FIGO classification) and intrauterine foetal death. The same variables were compared after stratification according to parity.

Statistical analysis was performed using SPSS statistical programme version 16 (SPSS, Chicago, IL, USA). An independent sample Student's *t*-test was used for comparison of means of continuous variables with normal or approximately normal distributions. The Chi-square test was used to analyse discrete variables for the assessment of association between maternal age and pregestational chronic maternal disease (hypertension, heart disease, diabetes mellitus, renal disease and epilepsy), or to examine the effect of maternal age on obstetric outcomes (preterm delivery, pre-eclampsia, antepartum haemorrhage, gestational diabetes, breech presentation, placenta abruption, delivery methods and postpartum haemorrhage) and on perinatal outcomes (low birth weight, intrauterine foetal death, abnormal CTG and Apgar score  $<7$  at 5 min). Multiple logistic regression (backward stepwise model) was performed to determine the independent effect of AMA on outcome differences being significant in the univariate analysis. Delivery methods were used as main factor (normal vaginal delivery as reference category) in the model. Pregestational maternal heart disease and postpartum haemorrhage were used as covariate factors among multiparae, while abnormal CTG was used as covariate factors among primiparae in the model, respectively. The statistical significance threshold was set to  $p \leq 0.05$  (two-tailed). Odds ratios (ORs) with 95% confidence intervals (95% CI) were calculated.

## Results

A total of 6,619 singleton pregnancies were reviewed in the study period. There were 2,829 (42.7%) nulliparous and 3,790 (57.3%) multiparous women. The percentage of AMA was 21.8 and 42.1% among nulliparous and multiparous women, respectively. Overall, the mean maternal age  $\pm$  SD was  $32.7 \pm 4.5$  years, mean birth weight  $\pm$  SD was  $3457 \pm 675$  g and mean gestational age  $273 \pm 18$  days (39 weeks). In the total parturient population of Norway for 2004, the mean maternal age at birth, mean birth weight and mean gestational age was 30.1 years, 3,514 g and 39 weeks, respectively (<http://www.fhi.no>).

Table 1 summarises pregestational chronic maternal morbidity after stratification according to parity. There were no differences between the two age groups for maternal chronic disease irrespective of parity, including chronic hypertension, diabetes mellitus, chronic renal

**Table 1** Pregestational chronic morbidity

	Nulliparous			Multiparous		
	AMA ( <i>n</i> = 616)	Non-AMA ( <i>n</i> = 2,213)	<i>p</i>	AMA ( <i>n</i> = 1,597)	Non-AMA ( <i>n</i> = 2,193)	<i>p</i>
Mean age (years) <sup>a</sup>	37.3 ± 2.3	29.4 ± 3.4		37.6 ± 2.4	31.0 ± 2.7	
Chronic hypertension, % (no.)	0.8 (5)	0.5 (1)	0.357	0.6 (10)	0.4 (8)	0.248
Heart disease, % (no.)	1.5 (9)	2.1 (47)	0.296	2.3 (37)	1.3 (29)	0.021
Diabetes mellitus, % (no.)	1.9 (12)	1.4 (32)	0.373	1.4 (21)	1.3 (29)	0.984
Chronic renal disease, % (no.)	0.6 (4)	0.6 (14)	0.963	0.8 (13)	0.4 (8)	0.066
Epilepsy, % (no.)	0.6 (4)	0.9 (21)	0.482	0.7 (11)	0.5 (12)	0.579

<sup>a</sup> Data presented as mean ± standard deviation

disease, and epilepsy. However, women of AMA had a higher rate of pregestational heart disease than non-AMA among multiparous women. Obstetric complications after stratification according to parity in the univariate analysis are presented in Table 2. Among the nulliparous women, AMA women had significantly increased incidences of caesarean section before labour, caesarean section in labour, and forceps/vacuum delivery compared to non-AMA women. A similar association was observed in AMA compared with non-AMA among multiparous women. Also, there was a significantly higher frequency of postpartum haemorrhage in AMA compared with the non-AMA group among multiparous women, which was not the case among nulliparous women. However, there were no differences between the two age groups with regard to other obstetric complications, including pre-eclampsia, gestational diabetes, antepartum haemorrhage, breech

presentation, placental abruption and pre-term delivery, irrespective of parity. The perinatal outcomes after stratification according to parity in the univariate analysis are presented in Table 3. Among nulliparous women, AMA had a significantly higher incidence of abnormal CTG compared to the non-AMA group. In the multiparous group, however, no such difference was observed between the two age groups. There were no differences between the two age groups for other perinatal outcomes, including birth weight, intrauterine foetal death and Apgar score <7 at 5 min, irrespective of parity.

To determine the independent role of AMA on the various obstetric and perinatal outcomes, multiple logistic regression analysis was performed for variables which were significantly different between the two age groups in the univariate analysis (Table 4). Among nulliparous women, AMA was associated with higher rates of caesarean

**Table 2** Obstetrical complications of gestations

	Nulliparous			Multiparous		
	AMA ( <i>n</i> = 616)	Non-AMA ( <i>n</i> = 2,213)	<i>p</i>	AMA ( <i>n</i> = 1,597)	Non-AMA ( <i>n</i> = 2,193)	<i>p</i>
Gestational age (day) <sup>a</sup>	277 ± 20	275 ± 20	0.965	275 ± 18	276 ± 17	0.228
Preterm delivery, % (no.)	10.4 (64)	11.5 (254)	0.45	9.0 (143)	8.1 (178)	0.36
Pre-eclampsia, % (no.)	7.3 (45)	6.7 (148)	0.591	3.9 (62)	3.5 (77)	0.548
Antepartum haemorrhage, % (no.)	1.8 (11)	1.9 (43)	0.801	1.3 (21)	1.2 (26)	0.722
Gestational diabetes, % (no.)	1.1 (7)	1.4 (31)	0.614	2.5 (40)	2.0 (43)	0.259
Breech presentation, % (no.)	6.7 (41)	5.2 (115)	0.161	3.4 (55)	2.9 (64)	0.36
Placental abruption, % (no.)	1.0 (6)	1.1 (25)	0.743	0.3 (5)	0.7 (15)	0.12
Delivery methods, % (no.) <sup>b</sup>			<0.005			<0.005
Caesarean before labour	18.0 (111)	10.3 (229)		19.3 (309)	14.4 (316)	
Caesarean in labour	15.1 (93)	12.4 (274)		6.4 (102)	5.5 (121)	
Forceps/vacuum delivery	20.8 (128)	16.4 (362)		5.3 (84)	4.2 (92)	
Postpartum haemorrhage, % (no.)	18.5 (114)	15.5 (343)	0.073	14.7 (234)	11.7 (257)	0.008

<sup>a</sup> Data presented as mean ± standard deviation

<sup>b</sup> Delivery methods including caesarean before labour, caesarean in labour, forceps/vacuum delivery and normal vaginal delivery were compared with each other by the Chi-square test

**Table 3** Perinatal outcomes of gestations

	Nulliparous			Multiparous		
	AMA ( <i>n</i> = 616)	Non-AMA ( <i>n</i> = 2,213)	<i>p</i>	AMA ( <i>n</i> = 1,597)	Non-AMA ( <i>n</i> = 2,193)	<i>p</i>
Births weight (g) <sup>a</sup>	3,368 ± 687	3,347 ± 681	0.887	3,528 ± 668	3,542 ± 651	0.653
Low birth weight <2,500 g, % (no.)	8.3 (51)	8.6 (191)	0.78	5.6 (89)	5.3 (117)	0.751
Stillbirth, % (no.)	0.5 (3)	0.5 (10)	0.909	0.5 (8)	0.5 (11)	0.998
Abnormal CTG, % (no.)	22.6 (139)	16 (354)	<0.005	7.2 (115)	6.0 (132)	0.146
Apgar score <7 at 5 min, % (no.) <sup>b</sup>	5.4 (33)	4.9 (109)	0.663	2.8 (62)	2.5 (40)	0.54

CTG cardiotocography

<sup>a</sup> Data presented as mean ± standard deviation

<sup>b</sup> 4 nulliparous and 10 multiparous delivered before they were admitted to the hospital, Apgar score at 5 min were not available for these newborn babies

**Table 4** Multiple logistic regression analysis of obstetric and perinatal outcomes

	ORs	95% CI	<i>p</i>
Nulliparous (AMA) <sup>a</sup>			
Caesarean before labour	2.26	1.74–2.94	<0.005
Caesarean in labour	1.44	1.07–1.93	0.016
Forceps/vacuum delivery	1.49	1.13–1.96	0.004
Abnormal CTG	1.28	0.98–1.67	0.068
Multiparous (AMA) <sup>a</sup>			
Caesarean before labour	1.42	1.19–1.69	<0.005
Caesarean in labour	1.22	0.92–1.61	0.168
Forceps/vacuum delivery	1.35	0.99–1.83	0.058
Postpartum haemorrhage	1.20	0.99–1.46	0.068
Heart disease	1.56	0.95–2.57	0.077

ORs Odds ratio, 95% CI 95% confidence interval

<sup>a</sup> The reference category is <35 years

sections both before labour and in labour, as well as with more instrumental vaginal deliveries. AMA was not seen as an independent risk factor for a higher incidence of abnormal CTG in this group. However, among multiparous women, AMA was only associated with more caesarean sections before labour. AMA was not seen to have any independent effect on the incidence of caesarean sections in labour, instrumental vaginal delivery, postpartum haemorrhage and pregestational heart disease.

Among multiparous women, 44% (275/625) of caesarean sections before labour were performed because of the patient's request, while the corresponding proportion was 36.5% (124/340) among nulliparous women. There was no significant difference between AMA and non-AMA either among multiparous (43 vs. 44.9%, *p* = 0.633) or among nulliparous women (38.7 vs. 35.4%, *p* = 0.545).

In addition, we classified all patients into three age groups (<35 years, between 35–39 years and ≥40 years). Compared with the group less than 35 years, similar

associations were observed in the other two age groups among nulliparous and multiparous women, except for a significantly higher incidence of stillbirth among multiparous women in the group ≥40 years (1.5%, 5/323) compared to the other two groups, 35–39 years (0.2%, 3/1,274) and <35 years (0.5%, 11/2,193) in univariate analysis (*p* = 0.012). This remained a significant association in multiple logistic regression analysis (ORs 3.53 with 95% CI 1.21–10.27).

## Discussion

In the present study, the prevalence of AMA was 33.4%, which is higher than the nation wide 19.1% in 2008 (*The Medical Birth registry of Norway*, <http://www.fhi.no>). The percentage of nulliparous AMA was 21.8% in the present study. Data stratified for age and parity are not available from our catchment area. Besides, our centre has more higher risk women than the parturient population in general in Norway. We, therefore, do not know how representative our sample is compared to the population from which they were retrieved.

There was no significant difference between the two age groups in the incidence of pre-eclampsia, gestational diabetes, antepartum haemorrhage, breech presentation, placental abruption and pre-term delivery, irrespective of parity. These findings differ somewhat from those of several previous studies [4–6, 10], which reported a higher incidence of adverse obstetric complications in AMA. There are, however, a number of studies which could not confirm that AMA has a significant association with adverse obstetric outcomes [9–11] and which suggested that, if these women do not have hypertension or diabetes, the course and outcome of pregnancy would be comparable to that in gravidas of younger age. Consequently, age alone may not explain adverse obstetric outcomes. Associated

risk factors, such as hypertension and diabetes are seen more frequently in the older gravida and may account for these observations. Indeed, Taddei et al. [13] suggested that, advancing age is associated with endothelial dysfunction in both normotensive subjects and essential hypertensive patients, an alteration caused by a progressive impairment of the nitric oxide pathway and production of oxidative stress. A dysfunctioning endothelium due to reduced nitric oxide availability and increased production of oxidative stress is considered an early indicator of atherothrombotic damage and of cardiovascular events. Seoud et al. [4] studied 319 women, aged 40 years or older with a singleton delivery and concluded that, multiparous women of at least 40 years of age have a higher antepartum complication rate, including intrauterine foetal death, compared to younger women. They suggested that, medical complications are more important than age in relation to the development of obstetrical complications. Looking at the two age groups in the present study, a higher incidence of pregestational heart disease in multiparous AMA women was not independently associated with AMA in multiple logistic regression analysis. Nor was there any significant difference in the incidence of other pregestational maternal chronic diseases, including chronic hypertension, diabetes mellitus and chronic renal disease. This may partly explain why AMA had no significant effect on most adverse obstetric outcomes in the present study. Two large studies [14, 15] have shown that advanced maternal age is an independent predictor of stillbirth, especially for those women of at least 40 years old. Indeed, when we classified patients into three age groups, we observed a higher incidence of stillbirth in multiparous women of at least 40 years of age compared to women younger than 35 years old.

In the present study, a significant relationship was observed between advancing maternal age and an increased likelihood of a caesarean section irrespective of parity, which is consistent with previous studies [11, 16–19]. In a large retrospective cohort study of 16,427 singleton pregnancies, Chan et al. [7] compared obstetric outcome in women aged 40 years or older versus women younger than 40 years. Caesarean delivery and pre-term birth were independently associated with older age irrespective of parity. Multiple causes in each woman may contribute to the indications for caesarean delivery. Main et al. [20] found more caesarean deliveries due to failure to progress with AMA. Importantly, they noted that, there was not a sudden increase in these outcomes at the age of 35, but rather a steady change beginning at the age of 25, a pattern suggesting a gradual decrease in myometrial function with increasing age. Besides, in singleton AMA gestations, an increased rate of caesarean sections for foetal distress has been demonstrated. It has never been determined whether it is the obstetrician's and/or the patient's preference that contributes to the higher

rate of caesarean births in older pregnant women by considering them to be at high risk or their pregnancies to be more precious. However, while previous studies have compared the effect of AMA on caesarean sections in general, the present study also investigated caesarean sections before and in labour. We found that AMA had a significantly increased incidence of caesarean sections before labour compared to that of the non-AMA group, irrespective of parity. However, the increase of incidence of caesarean sections in labour was only found among nulliparous AMA women and not among multiparous AMA women. Most caesarean sections before labour are elective caesarean sections. In our study, a large number of these caesarean sections (44%) were performed because of the patient's request and without definite medical indications. However, there was no significant difference in the percentage of patient-requested caesarean sections between the two age groups, irrespective of parity. So the preferences of obstetricians and patients may arguably contribute to the higher rate of caesarean section in general in our department (23.8% at our institution vs. 15.4% in 2004 on the national basis in Norway), although it probably does not explain why AMA shows a significantly higher rate of caesarean sections before labour than in younger patients.

There was no significant difference in perinatal outcomes between the two age groups irrespective of parity, while previous studies have shown contradicting results [8, 11, 21–23]. Salem et al. [24] in a most recent study investigated the perinatal outcomes in elderly nulliparous women and showed a significant linear association between advanced maternal age and adverse perinatal outcome (intrauterine growth restriction, low birth weight, congenital malformations and perinatal mortality). However, after controlling for gestational age, intrauterine growth restriction and malformations, advanced maternal age was not found to be an independent risk factor for perinatal mortality. It is important to point out that in the present study, the population is quite different from that in Salem's study as there were no significant differences between the two age groups for maternal chronic diseases and obstetric complications, irrespective of parity. In Salem's study, however, significantly more cases with chronic hypertension, mild and severe pre-eclampsia and gestational diabetes were found in older women. Pregestational chronic maternal disease and obstetric complications per se may have an effect on perinatal outcomes which should be controlled for in multivariate analysis. In a systematic review on maternal age and risk of stillbirth [25], seven of 16 hospital-based cohort studies showed no statistically significant increase in the risk of stillbirth with older maternal age. However, most of the seven studies were performed in academic hospitals or medical centres where older women with higher socioeconomic status may seek

obstetric care, especially, when delivering their first baby. In contrast, younger women with low socioeconomic status typically receive routine obstetric care. The better financial situation of older women, resulting in less physical stress and a better health, can be a possible explanation for the comparable perinatal outcomes between the two age groups. In the present study, there was no significant difference in the percentage of Apgar score <7 at 5 min in both groups among nulliparous women, although 23.6% of the cases had abnormal CTG in the AMA group compared with 16.3% in the non-AMA group. This may be partly explained by the fact that obstetricians might have a lower threshold to perform a caesarean section in labour or an instrumental vaginal delivery in AMA patients with a “precious pregnancy”. This might have been a contributing factor to the higher incidence of caesarean sections in labour and instrumental vaginal delivery among nulliparous AMA women.

A retrospective study, such as our study, has several limitations. First, as suggested above, it has the attendant limitations of a hospital-based study with a possible risk of selection. Second, it failed to adjust for all confounding/intermediate variables, which may affect the obstetric outcomes in AMA, but are not commonly collected in the administrative database, such as pregestational body mass index, socioeconomic status, educational level, marital status, smoking practices and alcohol exposure. Third, we could not provide information on the gestations conceived by IVF in the study, which could be associated with increased adverse obstetric outcome as reported before from our institution [26]. With the socioeconomic changes worldwide, populations in the developed countries are paying more and more attention to lifestyle and health. The 35 years threshold as “Elderly primigravidae” may no longer be applicable for modern healthy women. In the absence of pre-existing medical disorders, pregnancy even at 45–50 years of age seems to be safe [27].

## Conclusions

Operative delivery is increased with AMA, which includes both caesarean and instrumental vaginal delivery among nulliparous women, but only caesarean sections before labour among multiparous women. AMA had no significant effect on other adverse obstetric and perinatal outcomes irrespective of parity.

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**Conflict of interest statement** None.

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