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ORIGINAL RESEARCH ARTICLE

Risk of adverse pregnancy outcomes of late- and postterm pregnancies in advanced maternal age: A national cohort study

Joep C. Kortekaas[1,2] | Brenda M. Kazemier[2] | Judit K. J. Keulen[2] | Aafke Bruinsma[2] | Ben W. Mol[3] | Frank Vandenbussche[1] | Jeroen Van Dillen[1] | Esteriek De Miranda[2]

[1]Department of Obstetrics & Gynecology, Radboud University Medical Center, Nijmegen, the Netherlands

[2]Department of Obstetrics and Gynecology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

[3]Department of Obstetrics and Gynecology, Monash University, Clayton, VIC, Australia

Correspondence
Joep C. Kortekaas, Department of Obstetrics & Gynecology, Radboud University Medical Center, Nijmegen, the Netherlands.
Email: joep.kortekaas@radboudumc.nl

Abstract

Introduction: There is an increase in women delivering ≥35 years of age. We analyzed the association between advanced maternal age and pregnancy outcomes in late- and postterm pregnancies.

Material and methods: A national cohort study was performed on obstetrical low-risk women using data from the Netherlands Perinatal Registry from 1999 to 2010. We included women ≥18 years of age with a singleton pregnancy at term. Women with a pregnancy complicated by congenital anomalies, hypertensive disorders or diabetes mellitus were excluded. Composite adverse perinatal outcome was defined as stillbirth, neonatal death, meconium aspiration syndrome, 5-minute Apgar score <7, neonatal intensive care unit admittance and sepsis. Composite adverse maternal outcome was defined as maternal death, placental abruption and postpartum hemorrhage of >1000 mL.

Results: We stratified the women into three age groups: 18-34 (n = 1 321 366 [reference]); 35-39 (n = 286 717) and ≥40 (n = 40 909). Composite adverse perinatal outcome occurred in 1.6% in women aged 18-34, 1.7% in women aged 35-39 (relative risk [RR] 1.06, 95% confidence interval [95% CI] 1.03-1.08) and 2.2% in women aged ≥40 (RR 1.38, 95% CI 1.29-1.47), with 5-minute Apgar score <7 as the factor contributing most to the outcome. Composite adverse maternal outcome occurred in 4.6% in women aged 18-34, 5.0% in women aged 35-39 (RR 1.08, 95% CI 1.06-1.10) and 5.2% in women aged ≥40 (RR 1.14, 95% CI 1.09-1.19), with postpartum hemorrhage >1000 mL as the factor contributing most to the outcome. In all age categories, the risk of adverse pregnancy outcomes was higher for nulliparous than for multiparous women. The risk of adverse outcomes increased in both nulliparous and parous women with advancing gestational age. When adjusted for parity, onset of labor and gestational age, advanced maternal age is associated with an increase in both composite adverse perinatal and maternal outcomes.

Abbreviations: AMA, advanced maternal age; CAMO, composite adverse maternal outcomes; CAPO, composite adverse perinatal outcome; CI, confidence interval; OR, odds ratio; RR, relative risk.

Conclusions: The risk of adverse pregnancy outcome increases with advancing maternal age. Women aged ≥40 have an increased risk of adverse perinatal and maternal outcome when pregnancy goes beyond 41 weeks.

KEYWORDS

adverse pregnancy outcome, cesarean, delivery, induction of labor, maternal age, morbidity, mortality, postpartum hemorrhage, stillbirth

1 | INTRODUCTION

Advanced maternal age (AMA) is mostly defined as a pregnancy in women ≥35 or ≥40 years of age during their pregnancy or delivery.[1-6] In the Netherlands, there has been an increase in women ≥35 years giving birth, from 5.6% during the 1970s to 21.4% in 2010, with increasing age at first child from 24.3 years in 1970 to 29.4 years in 2010.[7] In 2010, of all women who delivered in the Netherlands 18.2% were aged 35-39 years, 3.2% 40-44 years and 0.1% >45 years.[8]

AMA is associated with adverse perinatal outcomes such as fetal death and adverse maternal outcomes, eg, emergency operative deliveries.[3-6,9-13] In some countries it is advised in guidelines to induce women with an AMA in order to prevent adverse pregnancy outcomes.[14,15] Women with AMA have an increased risk of a late-term (41 weeks + 0 days to 41 weeks + 6 days) and postterm (≥42 weeks + 0 days) pregnancy.[16] Postterm pregnancy at any age is associated with adverse perinatal and maternal outcome, though the absolute risk of fetal death remains low.[17,18] In the Netherlands and Scandinavian countries, it is being debated whether to induce labor at 41 weeks + 0 days or allow pregnancy to continue until 42 weeks + 0 days in low-risk women.[19-22] However, little is known of the association of maternal age with perinatal and maternal outcomes in each gestational week. To get more insight into possible associations, we analyzed the effects of both maternal age and gestational age on adverse pregnancy outcomes using data from the Dutch Perinatal Registry (Perined) to determine the effects of AMA on adverse perinatal and maternal outcomes in term-, late- and postterm pregnancies.

Suggestion of the team to keep the focus more on AMA:

In our cohort from 1999 to 2010, we found increasing composite adverse perinatal and maternal outcomes in pregnancies between 37 weeks + 0 days to 42 weeks + 6 days in women with advanced maternal age (≥35 years), after adjustment for parity, gestational age and onset of labor.

2 | MATERIAL AND METHODS

2.1 | Database

A national retrospective cohort study was performed according to the STROBE guidelines.[23] Births registered between 1999 and 2010 in Perined were used. Perined contains information on all pregnancies, deliveries, neonatal admissions and resubmissions until 28 days after birth in the Netherlands, with a coverage of 96%.[24] Since this study used anonymous data collected by Perined, no ethical approval was needed under Dutch law and regulations.[25]

2.2 | Inclusion and exclusion

We selected women with a singleton birth, no known fetal congenital anomalies, ≥37 weeks of gestation and a fetus in cephalic position. Women <18 of age, women with both preexisting and pregnancy-induced hypertensive disorder or preexisting or gestational diabetes mellitus were excluded from analysis. Thereby, we created a cohort mimicking a group of women with a relatively high probability of reaching 41 weeks + 0 days of gestation without medical or obstetrical interventions.

In general, pregnancy dating in the Netherlands is performed by first trimester ultrasound or, if ultrasound is not performed, by known last menstruation.[26] Body mass index and smoking were not reliably reported and could therefore not be included in the analyses. The women were stratified into three maternal age categories: 18-34, 35-39 and ≥40 years.[1] We defined age category 18-34 years as the reference group and both the 35-39 and ≥40 years categories as AMA. Within these age groups, women were also stratified by gestational age by week of gestation. We defined pregnancies with a gestational age of 37 weeks + 0 days to 40 weeks+ 6 days as the reference group, 41 weeks + 0 days to 41 weeks + 6 days as late-term and 42 weeks + 0 days to 42 weeks + 6 days as postterm pregnancy.

2.3 | Outcome measures

We studied the incidence of adverse perinatal and adverse maternal outcomes. Composite adverse perinatal outcome (CAPO) consisted of stillbirth, neonatal death (up to 28 days), meconium aspiration syndrome, Apgar score at 5 minutes <7, neonatal intensive care unit admittance for at least 24 hours and sepsis. Composite adverse

maternal outcomes (CAMO) consisted of maternal death, placental abruption and postpartum hemorrhage of >1000 mL. Though a case (woman or neonate) could suffer from more than one adverse event, it was counted as one event in the composite adverse perinatal outcome or composite adverse maternal outcome. Mode of delivery was categorized as (1) spontaneous, (2) operative vaginal delivery due to fetal distress, operative vaginal delivery due to arrest of labor or operative vaginal delivery due to a combination of fetal distress and arrest of labor and (3) cesarean section, either elective cesarean section or emergency cesarean section based on fetal distress, arrest of labor or a combination. We analyzed all modes of delivery separately in each age group.

2.4 | Statistical analyses

All outcomes were stratified for the three maternal age groups. Live birth was used as the denominator to assess the variables neonatal death, meconium aspiration syndrome, Apgar score at 5 minutes <7, neonatal intensive care unit admission and sepsis. In all other variables, "birth" was used as denominator to calculate proportions. Comparisons on percentages of mode of delivery were made by stating the numerator as number of "mode of delivery" and the denominator as "the total number of deliveries". We used age 18-34 as a reference group and compared proportions in age group 35-39 and ≥40 with proportions in the reference group on each variable with Chi-square testing. Relative risks (RR) and 95% confidence intervals (95% CI) are provided. Tests were performed two-sided and, because of multiple testing, $P < .001$ was considered statistically significant.

The association between maternal age and the occurrence of CAPO and CAMO was analyzed with risk ratios, estimated with a generalized linear model with the CAPO/CAMO event as dependent variable, and with age as the covariable (categories 18-34, 35-39 and ≥40), adjusting for parity (categories nulliparous, multiparous), onset of labor (categories spontaneous onset of labor, induction of labor or elective cesarean) and gestational age (categories 37 weeks + 0 days to 40 weeks + 6 days , 41 weeks + 0 days to 41 weeks + 6 days and 42 weeks + 0 days to 42 weeks + 6 days), and used a binomial distribution for the dependent variable and a log link. Data analyses were conducted with SPSS Statistics 23 (IBM Corp.).

2.5 | Ethical approval

No ethical approval was needed under Dutch law and regulations.[25] This study was approved by Perined under approval number 16.16.

3 | RESULTS

In the Perined database, 1 810 372 women had a term singleton birth in cephalic position without known congenital anomalies from 1 January 1999 through 31 December 2010. We excluded 139 958 (7.7%) women with a hypertensive disorder, 14 809 (0.8%) women with diabetes mellitus and 6613 women <18 years of age (0.4%), leaving 1 648 992 births in the total cohort (Figure 1).

Baseline characteristics and mode of delivery are shown in Table 1. Women with AMA were more often multiparous. Mode of delivery is shown in Table 2. Women with AMA had more labor inductions and fewer spontaneous vaginal deliveries in comparison with women without AMA. The rate of cesarean section was 8.8% in women aged 18-34, 12.3% in women aged 35-39 (RR 1.35, 95% CI 1.34-1.36), and 16.3% in women aged ≥40 (RR 1.98, 95% CI 1.93-2.03), mainly due to an increase in elective cesarean section (2.5%, 5.2% and 7.1%, respectively). There was an increase in cesarean section due to fetal distress (1.3%, 1.6% and 2.5% at age 18-34;

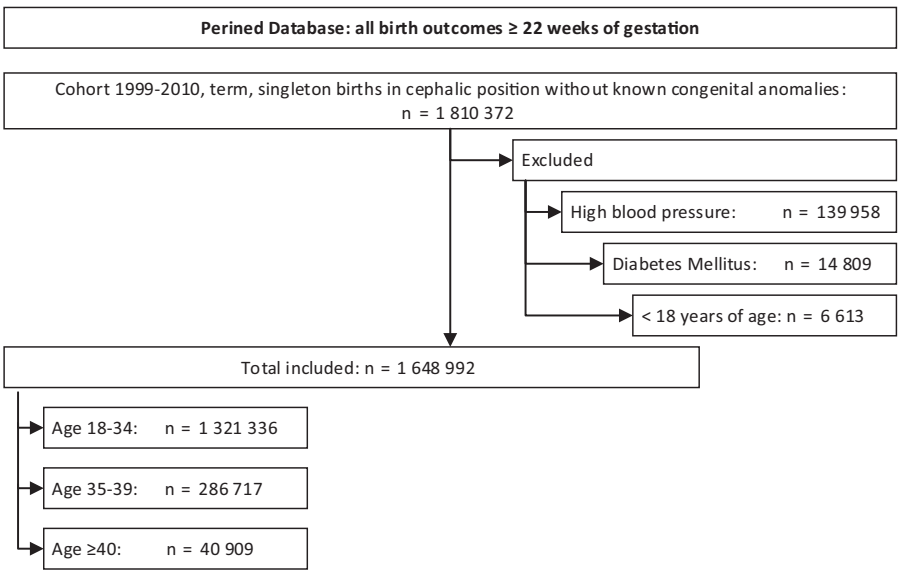

FIGURE 1 Flowchart cohort

TABLE 1 Baseline characteristics

	Cohort characteristics of the different age groups									
	Age									
	18-34 (ref)		35-39				≥40			
	n	(%)	n	(%)			n	(%)		
	1 321 366	80.1	286 717	17.4	RR	95% CI	40 909	2.5%	RR	95% CI
Maternal characteristics										
Nulliparous	632 797	47.9	69 999	24.4	0.42	0.41-0.42[a]	9390	23.0	0.33	0.33-0.34[a]
Low SES	346 327	26.2	57 786	20.2	0.75	0.75-0.76[a]	10 305	25.2	0.95	0.93-0.97[a]
White ethnicity	1 055 459	79.7	241 439	84.2	1.28	1.27-1.29[a]	31 505	77.0	0.85	0.83-0.87[a]
Gestational age at delivery										
37^{+0} -37^{+6} wk	68 095	5.2	14 573	5.1	0.99	0.97-1.00	2383	5.8	1.13	1.09-1.18[a]
38^{+0}-38^{+6} wk	174 002	13.2	40 691	14.2	1.07	1.06-1.08[a]	6435	15.7	1.22	1.19-1.26[a]
39^{+0}-39^{+6} wk	327 518	24.8	71 208	24.8	1.00	0.995-1.01	10 102	24.7	1.00	0.97-1.02
40^{+0}-40^{+6} wk	412 785	31.2	87 165	30.4	0.97	0.96-0.98[a]	11 654	28.5	0.88	0.86-0.90[a]
41^{+0}-41^{+6} wk	269 398	20.4	58 252	20.3	1.00	0.99-1.01	8063	19.7	0.96	0.94-0.98
42^{+0}-42^{+6} wk	69 568	5.3	14 828	5.2	0.99	0.97-0.999	2272	5.6	1.06	1.01-1.10
Onset of labor										
Induction of labor	160 442	12.1	39 335	13.7	1.21	1.11-1.13[a]	6819	16.7	1.43	1.39-1.47[a]
Elective cesarean section	32 730	2.5	14 941	5.2	1.80	1.78-1.82[a]	2902	7.1	2.84	2.74-2.95[a]

[a]$P < .001$.

TABLE 2 Mode of delivery

	Maternal age									
	18-34 (ref)		35-39				≥40			
	n	%	n	%			n	%	RR	
	1 321 366	80.1	286 717	17.4	RR	95% CI	40 909	2.5	RR	95% CI
Mode of delivery[a]										
Spontaneous	1 055 271	79.9	226 451	79.0	0.96	0.95-0.97[#]	30 515	74.6	0.75	0.73-0.76[#]
Operative vaginal delivery	150 232	11.4	25 125	8.8	0.79	0.78-0.79[#]	3707	9.1	0.78	0.76-0.81[#]
Fetal distress	39 464	3.0	7396	2.6	0.88	0.86-0.90[#]	1191	2.9	0.98	0.92-1.03
Arrest of labor	92 212	7.0	14 403	5.0	0.75	0.73-0.76[#]	1994	4.9	0.69	0.66-0.72[#]
Fetal distress and arrest of labor	15 602	1.2	2827	1.0	0.86	0.83-0.89[#]	439	1.1	0.91	0.83-.999
Cesarean section	115 863	8.8	35 141	12.3	1.35	1.34-1.36[#]	6687	16.3	1.98	1.93-2.03[#]
Elective	32 730	2.5	14 941	5.2	1.80	1.78-1.82[#]	2902	7.1	2.84	2.74-2.95[#]
Fetal distress	16 778	1.3	4583	1.6	1.21	1.18-1.24[#]	1034	2.5	1.96	1.84-2.08[#]
Arrest of labor	51 408	3.9	11 412	4.0	1.02	1.00-1.04	1889	4.6	1.19	1.14-1.24[#]
Fetal distress and arrest of labor	9340	0.7	2421	.8	1.16	1.12-1.20[#]	480	1.2	1.64	1.50-1.79[#]
Neonatal characteristics										
Male	674 001	51.0	146 583	51.1	1.00	0.997-1.01	20 731	50.7	0.99	0.97-1.01
Birthweight										
≥4000 g	219 662	16.6	57 370	20.0	1.20	1.19-1.21[#]	7627	18.6	1.14	1.12-1.17[#]
≥4500 g	36 244	2.7	10 600	3.7	1.28	1.26-1.30[#]	1382	3.4	1.23	1.17-1.30[#]

[a]Separate items do not add to total % in mode of delivery, due to missing numbers.

[b]$P < .001$.

35-39 and ≥40, respectively) or arrest of labor (3.9%, 4.0% and 4.6%, respectively).

Adverse perinatal and maternal outcomes are shown in Table 3. Composite adverse perinatal outcome was found in 1.6% of women aged 18-34 years, 1.7% of women aged 35-39 years (RR 1.06, 95% CI 1.03-1.08, *P* < .001) and 2.2% of women aged ≥40 years (RR 1.38, 95% CI 1.29-1.47, *P* < .001). A 5-minute Apgar score <7 was the main contributor to this composite outcome. Composite adverse maternal outcome was found in 4.6% of women aged 18-34, 5.0% of women aged 34-39 (RR 1.08, 95% CI 1.06-1.10, *P* < .001) and 5.2% of women aged ≥40 (RR 1.14, 95% CI 1.09-1.19, *P* < .001). Postpartum hemorrhage was the main contributor to this composite outcome.

Table 4 shows the association of AMA stratified by gestational age, parity and onset of labor with the composite adverse perinatal and maternal outcome in each age category. The incidence of both composite adverse perinatal and maternal outcome increased in women with AMA, irrespective of gestational age, parity or onset of labor, though the absolute risk difference is small and did not always reach statistical significance. Women with a higher gestational age and nulliparous women are more at risk for composite adverse perinatal or maternal outcomes, irrespective of maternal age. Women with a spontaneous onset of labor have a lower risk for composite adverse perinatal or maternal outcome in comparison with all other "onset of labor", except for women ≥40 years having an elective CS. Composite perinatal and maternal outcomes were more strongly associated with gestational age than AMA was. For example, the risk difference between a gestational age of 42 weeks + 0 days to 42 weeks + 6 days and 37 weeks + 0 days to 40 weeks + 6 days on a composite adverse perinatal outcome is 0.9%in women aged 18-34 years, 0.9% in women aged 35-39 years and 0.7% in women aged ≥40 years. These risk differences between gestational ages are slightly larger than the risk differences between the maternal age groups on composite adverse perinatal outcomes. The risk difference between women aged 18-34 and ≥40 is 0.6% in women with a gestational age of 37 weeks + 0 days to 40 weeks + 6 days, 0.8% in women with a gestational age of 41 weeks + 0 days to 41 weeks + 6 days and 0.4% in women with a gestational age of 42 weeks + 0 days to 42 weeks + 6 days. Induction of labor was associated with an increased risk for composite adverse perinatal and maternal outcomes. Induction of labor in comparison with spontaneous onset of labor was more strongly associated with adverse outcomes than AMA was.

AMA is significantly associated with a higher incidence of CAPO (*P* < .001) after adjustment for parity, onset of labor and gestational age. Compared with women aged 18-34 years, risk ratios were 1.53 (95% CI 1.43-1.63) for women ≥40 years and 1.22 (1.18-1.25) for women aged 35-39 years. AMA is also significantly associated with a higher incidence of CAMO (*P* < .001) after adjustment for parity, onset of labor and gestational age. Compared with women aged 18-34 years, risk ratios were 1.21 (95% CI 1.16-1.27) for women ≥40 years and 1.17 (95% CI 1.15-1.19) for women aged 35-39 years.

4 | DISCUSSION

In our cohort, we found an increase of both composite adverse perinatal and maternal outcomes in both advancing maternal age and increasing gestational age. However, the association between gestational age and composite adverse perinatal and maternal outcomes was slightly stronger than the association with AMA. In general, the absolute risk of a serious event remains low and the differences between the different age groups are small.

TABLE 3 Composite adverse perinatal and maternal outcomes

	Maternal age									
	18-34 (ref)		35-39				≥40			
	n	%	n	%	RR	95% CI	n	%	RR	95% CI
Composite adverse perinatal outcome	20 629	1.6	4778	1.7	1.06	1.03-1.08[b]	884	2.2	1.38	1.29-1.47[c]
Stillbirth	2211	.17	619	.22	1.22	1.15-1.32[b]	122	.30	1.74	1.47-2.07[c]
Neonatal death[a]	684	.05	154	.05	1.03	0.70-1.19	22	.05	1.04	0.69-1.57
Meconium aspiration syndrome[a]	1168	.09	291	.10	1.12	1.01-1.24	62	.15	1.69	1.32-2.15[c]
5-min Apgar score <7[a]	12 229	.93	2748	.96	1.03	0.997-1.07	531	1.30	1.40	1.28-1.52[c]
Neonatal intensive care unit[a]	4362	.33	1125	.39	1.15	1.09-1.21[b]	199	.49	1.46	1.27-1.67[c]
Sepsis[a]	6172	.47	1429	.50	1.06	1.01-1.107	252	.62	1.30	1.16-1.48[c]
Composite adverse maternal outcome	60 196	4.6	14 261	5.0	1.08	1.06-1.10[b]	2 123	5.2	1.14	1.09-1.19[c]
Maternal death	38	.003	12	.004	1.35	0.62-2.20	0	.000	Not calculable	
Placental abruption	261	.020	68	.024	1.16	0.94-1.43	14	.034	1.70	1.02-2.63
Postpartum hemorrhage >1000 mL	59 972	4.5	14 204	5.0	1.08	1.06-1.09[b]	2 113	5.2	1.14	1.09-1.19[c]

[a]Live birth.

[b]*P* < .001 between 18-35 and 35-39 y.

[c]*P* < .001 between 18-35 and ≥40 y.

TABLE 4 Association of advanced maternal age with adverse outcome stratified by gestational age, parity and onset of labor

	18-34 y (ref)		35-39 y				≥40 y			
	n	%	n	%	RR	95% CI	n	%	RR	95% CI
Composite adverse perinatal outcome	20 629	1.6	4778	1.7	1.06	1.03-1.08[a]	884	2.2	1.38	1.29-1.47[a]
Gestational age										
37^{+0}-40^{+6} wk	14 234	1.4	3334	1.6	1.06	1.03-1.10[a]	616	2.0	1.38	1.28-1.49[a]
41^{+0}-41^{+6} wk	4828	1.8	1069	1.8	1.02	0.97-1.08	206	2.6	1.42	1.24-1.63[a]
42^{+0}-42^{+6} wk	1567	2.3	375	2.5	1.10	1.01-1.21	62	2.7	1.21	0.94-1.55
Parity										
Nulliparous	12 907	2.0	1980	2.8	1.35	1.29-1.40[a]	335	3.6	1.76	1.58-1.96[a]
Multiparous	7722	1.1	2798	1.3	1.11	1.08-1.15[a]	549	1.7	1.53	1.41-1.66[a]
Onset of labor										
Spontaneous onset of labor	15 424	1.4	3366	1.4	1.05	1.01-1.08	592	1.9	1.37	1.26-1.48[a]
Induction of labor	4581	2.9	1165	3.0	1.03	0.98-1.09	247	3.6	1.26	1.12-1.43[a]
Elective SC	624	2.1	247	1.8	0.91	0.82-1.01	45	1.8	0.85	0.64-1.13
Composite adverse maternal outcome	60 196	4.6	14 261	5.0	1.08	1.06-1.10[a]	2123	5.2	1.14	1.09-1.19[a]
Gestational age										
37^{+0}-40^{+6} wk	40 576	4.1	9886	4.6	1.10	1.08-1.12[a]	1471	4.8	1.17	1.11-1.23[a]
41^{+0}-41^{+6} wk	15 027	5.6	3323	5.7	1.02	0.99-1.05	485	6.0	1.08	0.99-1.18
42^{+0}-42^{+6} wk	4593	6.6	1052	7.1	1.07	1.01-1.13	167	7.4	1.12	0.96-1.31
Parity										
Nulliparous	33 418	5.3	4808	6.9	1.28	1.25-1.32[a]	661	7.0	1.35	1.25-1.46[a]
Multiparous	26 778	3.9	9453	4.4	1.09	1.08-1.11[a]	1462	4.6	1.19	1.13-1.25[a]
Onset of labor										
Spontaneous onset of labor	49 235	4.4	10 952	4.7	1.07	1.05-1.08[a]	1537	4.9	1.12	1.07-1.18[a]
Induction of labor	9629	6.0	2659	6.8	1.11	1.07-1.15[a]	452	6.6	1.11	1.01-1.22
Elective SC	1332	4.5	650	4.9	1.05	0.99-1.12	134	5.3	1.17	0.99-1.38

[a]$P < .001$ between 18-35 and 35-39 y.

[b]$P < .001$ between 18-35 and ≥40 y.

Internationally, there is no predefined reference group of maternal age and no official definition of "advanced maternal age" or an "age interval" between groups which makes a clear comparison with the literature difficult.[1-4,11,27-30] Most studies and guidelines use a reference group ≥18 or ≥20 years of age, or define AMA at ≥35 or ≥40 years and use a 5-year age interval between groups in sub-analyses. To make our study more comparable to the existing literature, we chose to evaluate the risks in women aged 18-34, 35-39 and ≥40 years.

Of all women in our cohort, 19.9% had a maternal age of 35 years or older, which is higher than in the WHO multicountry survey on maternal and newborn health in women from 29 countries in Africa, Asia, Latin America and the Middle East (12.3%)[4] but more comparable to studies in high-income countries.[3,28] Our results are applicable to low-risk women with white ethnicity in high-income countries with similar baseline characteristics. When adding up the risks for late-term and postterm pregnancy, we did not find age ≥40 years to be a risk factor for late-term pregnancy 41 weeks + 0 days. As described in a retrospective cohort study from 1995 to 1999 in 199 162 term women showing an odds ratio (OR) of 1.07 (95% CI 1.02-1.12) for AMA on late-term pregnancy.[16] This difference can be due to a higher rate of induction of labor in women with AMA in our cohort, which decreases the number of women who can reach a higher gestational age or may be due to the fact that we studied a predefined low-risk population.

We showed an increase in risk of cesarean section overall and on all components separately in women with AMA. In two population-based cohorts (in the UK and the USA) containing 214 296 and 78 880 women, respectively, the proportions of cesarean section increased in both elective and overall cesarean section as well in multi- and nulliparous women. We found a much lower absolute

incidence of elective cesarean section, which is possibly due to the absolute lower rate of cesarean section in the Netherlands (around 12.5% in 2000 and 16.8% in 2010).[3,8,31] Despite the lower incidence in our cohort, women ≥40 years of age received an elective cesarean section more often than woman aged 18-35 did, possibly indicating a lower threshold for performing a cesarean section in women with AMA. This observation could also be due to more parous women with a previous cesarean section in the AMA group. Since we did not have access to the complete Perined database but only to our requested frequencies and outcomes, we were not able to find evidence for our speculations. In our cohort, AMA is associated with an increase in emergency cesarean section (defined as fetal distress and/or arrest of labor) in both nulli- and multiparous women, which is in concordance with several other studies.[2,12,32-35] In our cohort, the impact of increasing maternal age on cesarean section as mode of delivery is larger if fetal distress was the indication for cesarean section than if the indication was arrest of labor. In absolute numbers, the incidence of an emergency cesarean due to arrest of labor is higher than cesarean due to fetal distress. Induction of labor in women with AMA showed no significant increase of cesarean section rates in more recent studies.[27,29]

The components of the composite adverse perinatal and maternal outcome are considered to be clinically relevant and reliably entered in the database, though the content of this composite outcome can be discussed. Composite adverse perinatal outcome was significantly more often present in women with AMA, 5-minute Apgar score <7 being the factor which contributed most to this outcome. After approval of our study, the American College of Obstetricians and Gynecologists (ACOG) Committee published an update of their Committee opinion on the use and interpretation of the Apgar score in which a 5-minute Apgar score <4 is considered a nonspecific sign of illness which "may be one of the first indications of encephalopathy". The ACOG recommends using this lower cut-off in outcome studies instead of a 5-minute Apgar score <7.[36] We did not have data on the 5-minute Apgar score <4, though this has most probably led to a decrease in the absolute risk of the composite adverse perinatal outcome. Sepsis is the second factor contributing most to the composite adverse perinatal outcome, although maternal age is not a known risk factor for sepsis. One other study using a population-based cohort in Denmark containing 369 516 women, addressed the composite adverse perinatal outcome by combining chromosomal abnormalities, congenital malformation, miscarriage, stillbirth and birth before 34 weeks of gestation. They found an increase in this composite outcome in women aged 35-39 years (7.0%) and ≥40 years (10.8%) in comparison with women aged 20-34 years (5.5%).[28] In our cohort, stillbirth is seen more often in women with AMA, with an absolute risk between 0.2% and 0.3%, which is comparable to other studies in high-income countries in women with white ethnicity.[3,6,37,38] In a retrospective cohort study in the USA that included 37 504 230 women, there was an increase in rates of stillbirth from age ≥35.[11] In a systematic review and meta-analysis in women aged ≥35 years, an increased risk of stillbirth was seen in comparison with the reference group (OR 1.75, 95% CI 1.62-1.89).[39] Most stillbirths in AMA are explained by congenital abnormalities.[40] Stillbirths in our study, however, should not be attributable to congenital abnormalities, since we excluded all neonates with a congenital anomaly. However, misclassification of congenital anomalies cannot be ruled out.[41] We found no difference in neonatal death, as described by others, possibly due to the low incidence of neonatal death in our cohort.[39]

Composite adverse maternal outcome was seen significantly more in women with AMA, with postpartum hemorrhage >1000 mL as the most contributing factor. Uterine atony accounts for most cases of postpartum hemorrhage.[42] We were not able to differentiate between the multiple etiologies for postpartum hemorrhage in our study based on the Perined data. We found no increase in maternal death, which is a rare outcome in high-income countries, whereas in both low- and high-income countries an increase in maternal death is described with AMA.[4,37] Adverse maternal outcomes such as placental abruption have been studied before and have been associated with AMA.[39,43] In our study, we did not find a relation between AMA and placental abruption, probably due to the low incidence of this outcome.

The Royal College of Obstetricians and Gynaecologists' opinion paper on induction of labor at term in older mothers provides an argument for offering induction of labor at 39-40 weeks of gestation to women ≥40 years of age because of an increased risk of, for example, stillbirth. This practice would reduce both perinatal and maternal adverse outcomes, but they raise awareness of the effect of induction of labor in women of AMA.[44] In addition, the 35/39 trial found that, among nulliparous women aged ≥35 years, induction of labor at 39 weeks of gestation had no significant effect on rate of cesarean section or on other adverse perinatal and maternal outcomes, as compared with expectant management.[29] In our cohort study, we showed that the risks on adverse perinatal or maternal events increase in late- and postterm pregnancies, irrespective of maternal age, although women aged ≥40 carried the highest risk of an adverse outcome. This implies that they probably would benefit from labor induction before 41 weeks + 0 days of gestation. Our findings could be helpful in the process of shared decision-making weighing different management strategies in low-risk women with AMA and/or increasing gestational age.

The Perined database consists of all types of maternal and perinatal characteristics and pregnancy outcomes.[8] We used perinatal and maternal birth outcomes to create a composite adverse perinatal and maternal outcome which represents a clinically relevant adverse outcome. We excluded women with gestational diabetes. Since the prevalence of gestational diabetes in the study period was expected to be 5%, and we excluded 14 809 (.8%) of women with gestational diabetes, we could not rule out the possible influence of women with (unreported) gestational diabetes in our cohort. We could not use data on perinatal high care admission, cephalic hematoma, umbilical cord pH, plexus brachialis lesions, shoulder dystocia

and maternal obstetric anal sphincter injuries because these items are not registered systematically (free entry field) in the database or are known for underreporting. We were also not able to define the indications to induce labor and therefore we could not assess possible associations between induction of labor and composite adverse perinatal outcomes. Risk factors for adverse perinatal and maternal outcome such as smoking and body mass index were not entered in the Perined registration before 2011. Therefore, we were not able to make statements on these risk factors. We used data from a historical cohort from 1999 to 2010 because after 2010 the coding in the Perined registration system changed. Therefore, the newer database could not yet be combined with our data. Data should also be interpreted in the light of changing policy in term and late-term pregnancy in the Netherlands to more frequent induction of labor at 41 weeks + 0 days of gestation.[45-47]

We are aware of the limitations and pitfalls of using national register-based data.[24,41] One of the major pitfalls, besides the historical cohort as mentioned earlier, is the representation of our cohort for the Dutch and high-income countries. These findings may therefore not apply to other maternity care settings. Another limitation could be that we excluded women with high blood pressure and gestational diabetes, both of which occur more often in women with AMA and are associated with adverse outcomes. Therefore, we excluded women who would have been at a higher risk on adverse perinatal outcomes, thereby underestimating the effect of AMA on adverse perinatal outcomes.

The strength of our study is that we could use a large nationwide cohort which still contained data on pregnancies ≥42 weeks + 0 days. Therefore, our study could determine the association of gestational age and maternal age with composite adverse perinatal and maternal outcome.

5 | CONCLUSION

In low-risk women, the risk of adverse pregnancy outcomes increases with advancing maternal age. When adjusted for parity, onset of labor and gestational age, AMA is associated with an increase in both composite adverse perinatal and maternal outcomes. Women aged ≥40 have an increased risk of adverse perinatal and maternal outcomes when pregnancy goes beyond 41 weeks, though the absolute risk of perinatal death is low. Our conclusions can help clinicians to inform women of AMA to guide clinical decision-making.

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CONFLICT OF INTEREST

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ORCID

Joep C. Kortekaas https://orcid.org/0000-0002-5851-3728
Brenda M. Kazemier https://orcid.org/0000-0002-6656-2482
Judit K. J. Keulen https://orcid.org/0000-0003-0694-0637
Aafke Bruinsma https://orcid.org/0000-0001-8902-8795
Ben W. Mol https://orcid.org/0000-0001-8337-550X
Frank Vandenbussche https://orcid.org/0000-0003-2705-8416
Jeroen Van Dillen https://orcid.org/0000-0001-6958-572X
Esteriek De Miranda https://orcid.org/0000-0002-0392-4626

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