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Original article

Advanced maternal age and pregnancy outcomes: a multicountry assessment

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Objective To assess the association between advanced maternal age (AMA) and adverse pregnancy outcomes.

Design Secondary analysis of the facility-based, cross-sectional data of the WHO Multicountry Survey on Maternal and Newborn Health.

Settings A total of 359 health facilities in 29 countries in Africa, Asia, Latin America, and the Middle East.

Sample A total of 308 149 singleton pregnant women admitted to the participating health facilities.

Methods We estimated the prevalence of pregnant women with advanced age (35 years or older). We calculated adjusted odds ratios of individual severe maternal and perinatal outcomes in these women, compared with women aged 20–34 years, using a multilevel, multivariate logistic regression model, accounting for clustering effects within countries and health facilities. The confounding factors included facility and individual characteristics, as well as country (classified by maternal mortality ratio level).

Main outcome measures Severe maternal adverse outcomes, including maternal near miss (MNM), maternal death (MD), and severe maternal outcome (SMO), and perinatal outcomes, including preterm birth (<37 weeks of gestation), stillbirths, early neonatal mortality, perinatal mortality, low birthweight (<2500 g), and neonatal intensive care unit (NICU) admission.

Results The prevalence of pregnant women with AMA was 12.3% (37 787/308 149). Advanced maternal age significantly increased the risk of maternal adverse outcomes, including MNM, MD, and SMO, as well as the risk of stillbirths and perinatal mortalities.

Conclusions Advanced maternal age predisposes women to adverse pregnancy outcomes. The findings of this study would facilitate antenatal counselling and management of women in this age category.

Keywords Advanced maternal age, maternal death, maternal near miss, perinatal outcomes, pregnancy outcomes, severe maternal outcomes.

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Introduction

Advanced maternal age (AMA) is generally defined as pregnancy in women aged 35 years or older. As maternal age increases, fertility declines and the rate of spontaneous abortion increases.[1] Women over 35 years of age represent a significant proportion of pregnancies in higher-income countries: a historical cohort of 6619 singleton pregnancies between 2004 and 2007 from Norway found a 33.4% prevalence of AMA.[2] A recent report from Taiwan indicated that the proportion of women with AMA at delivery increased from 11.4 to 19.1%.[3] A large, population-based cohort study in the UK showed an 18.2% prevalence of maternal ages of 35 years or older.[4] There is a clear trend in higher-income countries towards delaying childbirth to later reproductive years.[5,6] Lower-income countries differ

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significantly in the sociodemographic characteristics of expectant mothers and the availability of obstetric care services; however, AMA still represents a significant – and growing – fraction of pregnant women in these countries.[7]

Studies of pregnancies in older women from higher-income countries have shown higher inherent risks for a number of maternal and perinatal morbidities. A population-based cohort study in Australia, demonstrated that women with AMA were more likely to have pre-existing medical conditions, obstetric complications, and adverse labour and birth outcomes.[8] A retrospective cohort study in Taiwan between July 1990 and December 2003, involving 39 763 women who delivered after 24 weeks of gestation, found that women aged 35–39 years had a significantly increased risk for operative vaginal and caesarean deliveries, whereas women aged 40 years and older were at increased risk for preterm delivery.[3] The risk of trisomy 21 and chromosomal abnormalities also increases with increasing maternal age.[1] A population-based cohort study consisting of 215 344 births in the UK found that women aged 40+ years at delivery had a significantly increased risk of stillbirth, preterm and very preterm birth, macrosomia, extremely large for gestational age, and caesarean delivery.[4] Advanced maternal age was also found to be associated with an increased risk of fetal death from intrapartum asphyxia at term.[9] There are sparse data on pregnancy outcomes of older women in lower-income countries. Furthermore, it is difficult to extrapolate the literature from developed higher-income to lower-income countries, where ecological differences, decreased access to antenatal care and delivery services, and dramatically higher rates of maternal and perinatal morbidity and mortality complicate comparisons.

In 2009, the WHO developed a standard definition for maternal near miss (MNM) based on markers of organ dysfunction.[10] There have been no reports evaluating severe maternal outcome (SMO), maternal death (MD), and MNM in women of AMA, probably because of the extremely low incidence of these outcomes in higher-income countries.

This report aims to evaluate the association between AMA and severe maternal and perinatal outcomes using the 2010–2011 WHO Multicountry Survey on Maternal and Newborn Health (WHOMCS) data set of over 314 000 deliveries from 29 countries.

Methods

Study design and setting

The design of the WHOMCS is described in detail elsewhere.[11,12] In brief, this is a multicentre, cross-sectional study aimed to determine the prevalence of MNM cases in a worldwide network of health facilities. It was approved by the World Health Organization Ethical Review Committee and implemented in a random sample of 359 health facilities in 29 countries from Africa, Asia, Latin America, and the Middle East. Because of the financial and practical constraints, we did not conduct the survey in developed countries, except Japan, which volunteered to participate. A stratified, multistage cluster sampling strategy was used to select countries, provinces, and health facilities. The study population included women giving birth, all MNM cases, regardless of the gestational age and delivery status, and all maternal deaths during the study period between 1 May 2010 and 31 December 2011.

Data collection took place at two levels: at the individual level and at the facility level. At the individual level, data related to the pregnancy outcomes, severe complications, and their management, for the women included in the study, and for their respective newborns, were extracted from the medical records of the participating facilities by trained data collectors. The data were completed in the pre-established form at hospital discharge, transfer, or death. There was no contact between data collectors and the women included in the study; however, data clarification was occasionally sought from facility staff. At the facility level, data characteristics of each health facility, including infrastructure, obstetric and intensive care services, and their ability to identify and manage severe complications, were collected through a specific survey among the professionals responsible for the participating facilities. Data were collected for 2 months if the health facility had 6000 deliveries or more per year, and for 3 months if the health facility had less than 6000 deliveries per year. If the anticipated sample size for a country was anticipated to be less than 3000 women, the data collection period was 4 months in all facilities. Online data entries were performed in each country, either at the health facility or at a central level, depending on the logistics and available infrastructure, in the web-based data management system developed by the Centro Rosarino de Estudios Perinatales (CREP), Rosario, Argentina. Data quality control was undertaken by having data managers from CREP and Thailand monitor data validity and consistency during data collection and online entries.

Study population

In this analysis, the population included all women aged at least 20 years who gave birth to singleton babies, either live births or stillbirths, at the participating facilities. The women were classified into four maternal age categories: 20–34, 35–39, 40–44, and 45 years of age or older. Women aged less than 20 years were excluded from this analysis. A study on the association between teenage pregnancy (<20 years) and adverse pregnancy outcomes will be published in a separate paper.

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Variables and definitions

We defined AMA as women aged 35 years or older. Pregnancy adverse outcomes were classified into maternal and perinatal outcomes. For maternal outcomes, we studied severe maternal outcomes, including MNM, MD, and SMO. In accordance with the WHO MNM approach, we defined MNM as a woman who nearly died but survived a complication that occurred during pregnancy, childbirth, or within 42 days of termination of pregnancy. MD was the death of a woman while pregnant or within 42 days of termination of pregnancy. SMO was defined as women having had a maternal death or a MNM up to 7 days after giving birth or having an abortion, irrespective of gestational age or delivery status.[11]

For perinatal outcomes, we studied preterm birth, stillbirth, early neonatal mortality, perinatal mortality, low birthweight (<2500 g), and neonatal intensive care unit (NICU) admission. We defined preterm birth as any birth before 37 weeks of gestation. Stillbirth was any death of a fetus after 22 weeks of gestation or weighing ≥500 g. Early neonatal mortality was the death of a liveborn baby within the first 7 days of life.

Potential confounding factors were taken from both facility and individual characteristics. The potential facility confounding factors included the availability of a blood bank, an adult intensive care unit (AICU) for adverse maternal outcomes, and an NICU for adverse perinatal outcomes. The potential individual confounding factors included maternal demographic and labour characteristics, i.e. marital status, maternal education (years of school attendance), and parity. Labour characteristics included onset of labour, fetal presentation, and mode of delivery. Countries were stratified by the level of maternal mortality ratio (MMR),[11] and counted as a confounding factor at the country level.

Statistical analysis

For this analysis, women aged 20–34 years represented the reference group. Frequencies were used to describe country groups, baseline maternal characteristics, and prevalence of pregnancy outcomes in relation to the maternal age groups. The association between each AMA group and each adverse outcome was analysed using a multilevel, multivariate logistic regression model by the procedure GLIMMIX in SAS 9.1 (SAS Institute Inc, Cary, NC), USA. This procedure was intended to account for clustering effects within countries and health facilities. The analysis was also adjusted for the potential confounding factors, including maternal and health facility characteristics and country groups. For this analysis maternal school attendance was classified according to the United Nations Educational, Scientific and Cultural Organization (UNESCO) international standard classification of education. This classification allocates individuals to one of five categories that correspond to the level of education expected after a given number of years of education: no education (0 years); primary (1–6 years); lower secondary (7–9 years); upper secondary (10–12 years); post-secondary/tertiary (>12 years). The risks of maternal and perinatal outcomes associated with each AMA group were presented by adjusted odds ratios (aORs), with corresponding 95% confidence intervals (95% CIs). Statistical analysis was performed using SAS 9.1.

Results

During the study period there were 308 149 women with singleton deliveries, after excluding women who did not deliver vaginally or by caesarean section, such as laparotomy for ectopic pregnancy, etc. (360 women), and women with missing maternal age (79), in the WHOMCS. A total of 276 291 women (89.6% from 308 149) were 20 years or older. In this report, the overall prevalence of AMA (pregnant women aged 35 years and over) was 12.3%. The highest prevalence of 9.5% was seen in women aged 35–39 years, and only 0.5% was seen in women aged 45 years or older (Figure 1). The prevalence of AMA varied greatly among the participating countries, from 2.8% in Nepal to 31.1% in Japan (Figure 2).

Maternal and neonatal characteristics were quite similar among the four maternal age groups: 20–34, 35–39, 40–44, and 45 years of age or older. However, more than 40% of the women aged 20–34, 35–39, and 40–44 years were from countries with a moderate MMR. Interestingly, 68.5% of the women aged 45 years or older were from countries with very high MMR. Single marital status was more common (14.9%) in the very advanced age group, with women aged 45 years or older, whereas less than 10% was seen in the other age groups. Less education was observed with increasing maternal age. Caesarean section rates were 28, 36, 37, and 23% in women aged 20–34, 35–39, 40–44, and 45 years or older, respectively (Table 1).

Prevalence of severe adverse pregnancy outcomes

The prevalence of MNM, MD, and SMO increased with maternal age, as shown in Table 2. The SMO ratio varied from 5/1000 live births in women aged 20–34 years up to 20/1000 live births in women aged 45 years or older. For perinatal outcomes, an increasing trend was observed in the prevalence of fetal and perinatal mortalities. The rates of stillbirths and perinatal mortalities per 1000 total births were 19 and 27 in women aged 20–34 years, and up to 43 and 53 in women aged 45 years or older, respectively. The prevalence of preterm births, early neonatal mortality, low birthweight, NICU admission, and Apgar score <7 at 5 minutes were also increased in women with AMA.

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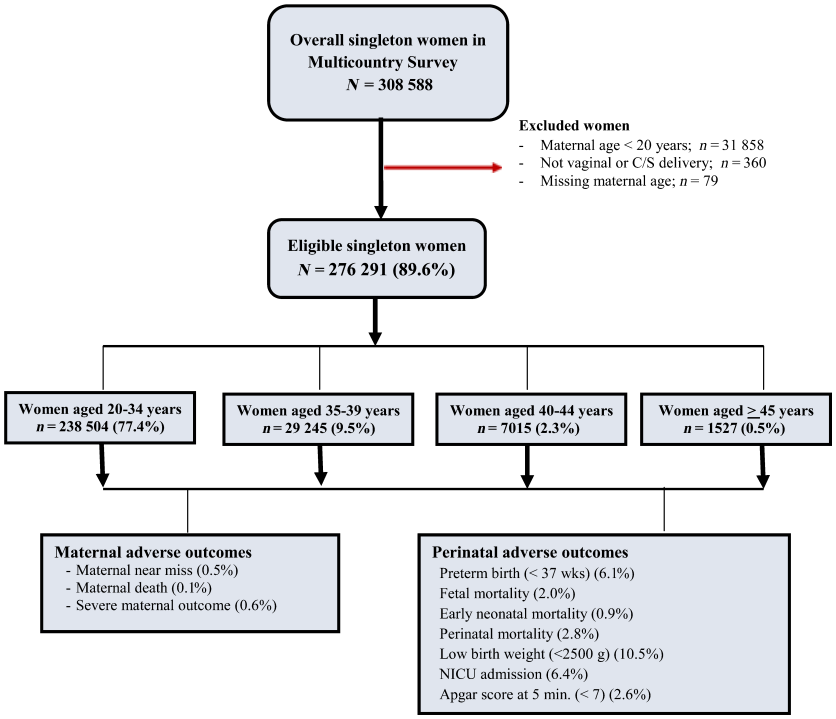

Figure 1. Study flow chart.

Association between advanced maternal age and maternal severe adverse outcomes

The aORs of the association between maternal age and maternal severe adverse outcomes (MNM, MD, and SMO) are presented in Table 3. Increased aORs of the three severe adverse outcomes were significantly associated with AMA in women in age groups of 35 years or older, when compared with women aged 20–34 years. However, the increasing trends of MNM, MD, and SMO with AMA were not significant. The 95% CIs for aORs overlapped among AMA groups.

Association of advanced maternal age and perinatal adverse outcomes

The aORs of the association between maternal age and perinatal adverse outcomes are also shown in Table 3. The risk of stillbirths and perinatal mortalities significantly increased with increasing AMA; however, the increased trends of these outcomes were not significant, as the 95% CIs for aORs overlapped among AMA groups. Preterm birth, early neonatal mortality, low birthweight, NICU admission, and Apgar score <7 at 5 minutes were significantly associated with some AMA groups when compared with women aged 20–34 years. There was no evidence to support the association between high AMA (45 years of age or older) and preterm birth, early neonatal mortality, low birthweight, and NICU admission compared with women aged 20–34 years.

Discussion

Main findings

The overall prevalence of AMA in this large multicountry analysis was 12.3%, ranging from 2.8% in Nepal to 31.1% in Japan. Advanced maternal age was found to be significantly associated with severe maternal adverse outcomes, including MNM, MD, and SMO. It was also found to be significantly associated with fetal and perinatal mortalities. Excluding the data from Japan did not change the results of these associations.

Strengths and limitations

To our knowledge, this analysis is the first report to describe the significant risk of AMA on MNM, MD, and SMO. The WHOMCS was conducted in 359 health facilities from 29 countries in Africa, Asia, Latin America, and the Middle East, and involved 276 291 pregnant women. All of these countries except Japan are developing countries, where there were no previous reports addressing these associations. We used pre-tested, standardised data collection forms by trained data collectors and methodology from the previous WHO global survey; however, our analysis did not have information on some variables known to be associated with fetal and neonatal mortality, including smoking, obesity, diabetes, syphilis, and difficult labour. As we used medical records as our

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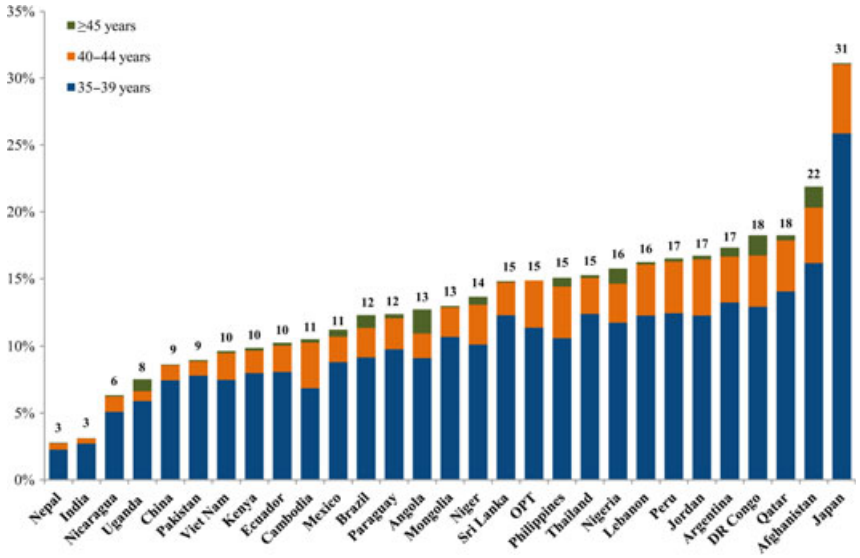

Figure 2. Prevalence of women with advanced maternal age by country.

Table 1. Maternal and neonatal characteristics in relation to maternal age

Characteristics	Maternal age (years)				
	Total 276 291	20–34 238 504	35–39 29 245	40–44 7015	≥45 1527
Country groups					
Low MMR	7273 (2.6)	5476 (2.3)	1452 (5.0)	327 (4.7)	18 (1.2)
Moderate MMR	118 385 (42.9)	100951 (42.3)	13669 (46.7)	3364 (48.0)	401 (26.3)
High MMR	63 671 (23.0)	59736 (25.1)	3211 (11.0)	663 (9.5)	61 (4.0)
Very high MMR	86 962 (31.5)	72341 (30.3)	10913 (37.3)	2661 (37.9)	1047 (68.6)
Marital status					
Married/cohabiting	251 555 (92.1)	216712 (91.9)	27239 (94.0)	6510 (93.2)	1094 (85.1)
Single	21 625 (7.9)	19228 (8.2)	1733 (6.0)	472 (6.8)	192 (14.9)
Maternal school attendance, in years					
0	43 074 (15.6)	35 202 (14.8)	5791 (19.8)	1636 (23.3)	445 (29.1)
1–6 (primary)	33 982 (12.3)	28 965 (12.1)	3771 (12.9)	1029 (14.7)	217 (14.2)
7–9 (lower secondary)	47 876 (17.3)	43 013 (18.0)	3812 (13.0)	890 (12.7)	161 (10.5)
10–12 (upper secondary)	79 645 (28.8)	71 066 (29.8)	6808 (23.3)	1573 (22.4)	198 (13.0)
>12 (tertiary)	71 714 (26.0)	60 258 (25.3)	9063 (31.0)	1887 (26.9)	506 (33.1)
Parity					
Primiparous	86 838 (31.4)	83 220 (34.9)	2773 (9.5)	574 (8.2)	271 (17.8)
Multiparous	189 452 (68.6)	155 284 (65.1)	26 472 (90.5)	6441 (91.8)	1255 (82.2)
Onset of labour					
Spontaneous	211 871 (76.8)	184 792 (77.6)	20 888 (71.5)	4965 (70.9)	1226 (80.3)
Induced	29 094 (10.6)	25 649 (10.8)	2708 (9.3)	615 (8.8)	122 (8.0)
No labour	34 903 (12.7)	27 693 (11.6)	5604 (19.2)	1428 (20.4)	178 (11.7)
Mode of delivery					
Vaginal delivery	196 194 (71.0)	171 805 (72.0)	18 804 (64.3)	4406 (62.8)	1179 (77.2)
Caesarean section	80 097 (29.0)	66 699 (28.0)	10 441 (35.7)	2609 (37.2)	348 (22.8)
Fetal presentation					
Non-cephalic	12 114 (4.4)	9970 (4.2)	1606 (5.5)	462 (6.6)	76 (5.0)
Cephalic	263 627 (95.6)	228 095 (95.8)	27 556 (94.5)	6534 (93.4)	1442 (95.0)

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Table 2. Prevalence of adverse pregnancy outcomes in relation to maternal age

Outcomes	Maternal age (years)				
	Total	20–34	35–39	40–44	≥45
Maternal	276 291	238 504	29 245	7015	1527
MNM**	1372 (5)	1007 (4)	243 (9)	98 (14)	24 (16)
MD**	270 (1)	207 (1)	43 (2)	15 (2)	5 (3)
SMO**	1642 (6)	1214 (5)	286 (10)	113 (17)	29 (20)
Neonatal; total births	276 291	238 504	29 245	7015	1527
Live births	270 744	234 057	28 445	6780	1462
Preterm birth (<37 weeks)*	16 966 (61)	14 352 (60)	1964 (67)	548 (78)	102 (67)
Stillbirths*	5547 (20)	4447 (19)	800 (27)	235 (34)	65 (43)
Early neonatal mortality**	2297 (9)	1962 (8)	249 (9)	71 (11)	15 (10)
Perinatal mortality*	7776 (28)	6357 (27)	1036 (35)	303 (43)	80 (53)
Low birthweight (<2500 g)**	28 543 (105)	24 985 (107)	2649 (93)	774 (114)	135 (92)
NICU admission**	17 247 (64)	14 498 (62)	2044 (72)	633 (93)	72 (49)
Apgar score <7 at 5 minutes**	6896 (26)	5887 (25)	721 (25)	214 (32)	74 (51)

*Per 1000 total births.
**Per 1000 live births.

primary data source, missing data or errors in these records could have affected data quality; however, we have tried our best to minimize this bias as much as possible by intensively training our data collectors before the study. Clinical staff were available for data collectors to consult, as necessary.

Interpretation (findings in light of other evidence)

The prevalence of AMA in this analysis varied greatly across countries. Previous reports on the prevalence of AMA varied from 33.4% in Norway to 11.4% in Taiwan;[2,3] however, we have demonstrated that even in lower-income countries AMA accounts for a significant proportion of all deliveries.

Advanced maternal age has been previously shown to increase the risk of gestational diabetes, antepartum haemorrhage, and placenta praevia.[13] The prevalence of pre-existing hypertension, placenta praevia, suspected intrauterine growth restriction, and gestational diabetes also appear to increase with maternal age.[8] AMA also independently increases the risk of operative vaginal and caesarean deliveries.[3,14–16] Studies of AMA have largely not explored SMO, however, probably because of the size of the sample needed for such a study in a high-income setting, where SMO is infrequent. Our analyses therefore focused on evaluating the associations between AMA and MNM, MD, and SMO that have not been evaluated before, especially in developed or developing countries.

This report indicates that AMA (all age groups) significantly increased the risk of fetal and perinatal mortalities. Previous reports indicated that women with AMA had an increased risk of fetal death.[3,4] Women with AMA also had significantly increased risks of antepartum and intrapartum stillbirth.[17] Lisonkova et al., using the causal fetus-at-risk model, showed that mothers of AMA had a consistently increased risk of perinatal death at all gestational ages.[18] Other reports also showed that women with AMA had a significantly increased risk of perinatal death.[3,19] Our studies showed that women with AMA had a significantly increased risk of preterm birth, early neonatal mortality, low birthweight, NICU admission, and Apgar score <7 at 5 minutes, although not across all AMA groups. Previous studies have reported the association between AMA and preterm labour.[3,4,13,19] AMA was found to be significantly associated with low birthweight.[13,19]

The findings clearly show a significantly increased risk of severe adverse maternal outcomes with AMA, whereas just a slightly increased risk of adverse perinatal outcomes was demonstrated. The explanation is that the prevalence of perinatal outcomes was only slightly higher among AMA groups than those of the reference group (20–34 years). In addition, the prevalence of low birthweight and NICU admission in women with very advanced age (45 years of age or older) was even lower than those of the reference group.

The public health focus generally tends to be on adolescents or younger women in terms of risks associated with pregnancy. Although a much greater focus on contraceptive availability and reproductive health education for adolescents is indeed warranted, women over 35 years of age represent a larger, and growing, population group that also

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Table 3. Association between maternal age and adverse pregnancy outcomes

Outcomes	Maternal age (years) aOR* (95% CI)		
	35–39	40–44	≥45
Maternal**			
MNM	1.5 (1.3, 1.8)	2.2 (1.7, 2.8)	3.5 (2.2, 5.5)
MD	1.7 (1.2, 2.6)	2.6 (1.4, 4.7)	4.3 (1.5, 12.1)
SMO	1.6 (1.4, 1.8)	2.3 (1.8, 2.8)	3.7 (2.4, 5.6)
Neonatal***			
Preterm birth (<37 weeks)	1.2 (1.1, 1.2)	1.4 (1.2, 1.5)	1.3 (0.9, 1.6)
Stillbirths	1.5 (1.4, 1.7)	1.8 (1.5, 2.1)	2.1 (1.5, 2.8)
Early neonatal mortality	1.2 (1.0, 1.4)	1.4 (1.1, 1.8)	1.4 (0.7, 2.7)
Perinatal mortality	1.4 (1.3, 1.5)	1.7 (1.5, 1.9)	1.9 (1.5, 2.6)
Low birth weight (<2500 g)	1.1 (1.0, 1.1)	1.4 (1.3, 1.5)	1.2 (0.9, 1.5)
NICU admission****	1.2 (1.1, 1.2)	1.6 (1.4, 1.7)	1.1 (0.8, 1.5)
Apgar score <7 at 5 minutes	1.0 (0.9, 1.1)	1.4 (1.2, 1.6)	1.6 (1.2, 2.3)

*Reference group: 20–34 years.
**Models were adjusted for country groups by MMR levels, blood bank, adult intensive care unit, marital status, maternal school attendance (in years), parity, onset of labour, fetal presentation, and mode of delivery. The country and facility levels were also adjusted as random effects.
***Models were adjusted for country groups by MMR levels, blood bank, neonatal intensive care unit, marital status, maternal school attendance (in years), parity, onset of labour, fetal presentation, and mode of delivery. The country and facility levels were also adjusted as random effects.
****Models were adjusted for country groups by MMR levels, marital status, maternal school attendance (in years), parity, onset of labour, fetal presentation, and mode of delivery. The country and facility levels were also adjusted as random effects.

has inherently higher risks of severe adverse outcomes compared with women aged 20–34 years.

Conclusion

Advanced maternal age significantly increases the risk of MNM, MD, and SMO. It also significantly increases the risk of preterm birth, fetal mortality, early neonatal mortality, perinatal mortality, low birthweight, NICU admission, and birth asphyxia. International and national maternal health policies should focus more on AMA pregnancies. More research is needed to find appropriate and timely interventions to reduce the impact of AMA on pregnancy outcomes.

Disclosure of interests

We declare that we have no conflicts of interest to disclose.

Contribution to authorship

PL, ML, RM, TG, JV, JPS, and MG conceptualised the research question. PL and ML drafted the analysis plan. ML and NI analysed the data. PL and ML drafted the article. All authors critically reviewed and approved the final version of the article.

Details of ethics approval

The HRP Specialist Panel on Epidemiological Research reviewed and approved the study protocol for technical content. This study was approved by the World Health Organization Ethical Review Committee and the relevant ethical clearance mechanisms in all countries (protocol ID A65661; 27 October 2009).

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