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Original Article

Advanced maternal age and adverse pregnancy outcomes: A cohort study

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ABSTRACT

Objectives: To assess the association between advanced maternal age and adverse perinatal outcomes in single pregnancies.

Materials and methods: A cohort study was conducted using data from 27,455 singleton births attended at our hospital between 2007 and 2018. Three maternal age groups were established, and perinatal outcomes were compared between-groups (<35 years (n = 19,429; 70.7%), 35–40 years (n = 7189; 26.2%), and >40 years (n = 846; 3.1%). The data were compared using chi-square analysis and the results were adjusted using a logistic regression model. Decision trees were designed to examine the fetal mortality and caesarean section variables. We used the SPSS 23 statistical software program for the statistical analysis.

Results: The mean age of the women was 31.21 years. No differences were found associated with age for neonatal acidosis, an Apgar score <7 at 5 min after birth, threatened preterm labour, preterm rupture of membranes, or high-grade perineal tear. The analyses found statistically significant increases in the rates of hypertensive disorders, diabetes mellitus, induction of labour, and caesarean section, after 35 years of age. The risks of fetal death, neonatal admission, small for gestational age, placenta previa, instrument delivery, maternal ICU admission, and postpartum haemorrhage were greater after 40 years of age.

Conclusions: The results of our study indicated that women >35 years of age had worse perinatal outcomes, compared with younger women. This finding was more evident in patients >40 years of age, which highlighted the greater risk of fetal death and serious maternal complications in this group.

Introduction

Mean maternal age has increased in the last decades in many high-income countries. In 1978 in Spain, the mean life expectancy at birth for women was 76 years and the mean age at pregnancy was 26 years. By 2017, life expectancy increased to 85.7 years at birth, and the mean age at pregnancy was 32 years. Similar trends have occurred in Europe [1–3].

Advanced maternal age (AMA) is commonly defined as childbearing in a woman >35 years of age [4]. Cultural, social, and economic changes, and reproductive technologies such as egg donation, contribute to the increasing incidence of pregnancies in women who are older than the usual biological reproductive age. For that reason, some studies use >40 years as the definition of AMA [5,6].

Studies have examined associations between AMA and adverse perinatal outcomes, including stillbirth, pre-eclampsia, gestational hypertension, gestational diabetes mellitus (DM), preterm birth, delivery of a small for gestational age (SGA) neonate, and elective or emergency caesarean section. These studies have found contradictory results [6–8].

The aim of our study was to assess associations between AMA and adverse perinatal outcomes in our population.

Materials and Methods

A total of 27,455 singleton and consecutive pregnancies attended at the Hospital Clinico Lozano Blesa in Zaragoza from 2007 to 2018 were included in this cohort study. The only exclusion

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criterion was multiple gestation. The data were collected from the hospital maternity database. The women were categorised into three age groups: <35 years, 35–40 years and >40 years.

This study was authorized by the Research Committee and the Director of the Hospital Clínico Universitario Lozano Blesa.

The variables included to analyse perinatal outcomes were fetal death, neonatal admission, umbilical artery pH, Apgar score at 5 min after birth, preterm delivery, threatened preterm labour (TPL), SGA, hypertensive disorders, DM, placenta previa, premature rupture of membranes (PRM), labour induction, caesarean section, instrument delivery, high grade perineal tear, maternal intensive care unit (ICU) admission, and postpartum haemorrhage (HPP).

Fetal death was defined as death of a fetus of at least 22 weeks gestation or 500 g birth-weight if the gestation time was unknown. Intrapartum death was also included. Neonatal admission included all newborns admitted to the ICU for any reason, according to the criteria of the pediatricians at the hospital. We defined a low umbilical cord artery pH as <7.10 and a low Apgar score at 5 min after birth as <7. Preterm delivery included those with an onset of labour occurring before 37 completed weeks of pregnancy. TPL was defined as progression of cervical dilatation and ripening caused by regular uterine contractions occurring before 37 weeks of pregnancy. All patients with these criteria admitted or in follow-up for that reason were included in the study, even if preterm delivery did not occur. SGA was defined as a birthweight below the 10th percentile [9], adjusted by sex and gestational age. Hypertensive disorders were diagnosed clinically by the obstetricians, according to guidelines [10]. The study group included patients who had a diagnosis of chronic hypertension, pregnancy-induced hypertension, preeclampsia, or HELLP syndrome, or some combination of these conditions. DM was diagnosed using a pathological oral glucose tolerance test; the DM group included non-insulin users and insulin users. The variable also included previous DM. PRM included membrane rupture that occurred before 35 weeks of pregnancy. Placenta previa (included occlusive and marginal) was confirmed using ultrasound at 32–35 weeks of pregnancy. Induction of labour grouped all pregnancies in which it was necessary to finalise pregnancy before the start of spontaneous delivery, based on the decision of a physician, regardless of the cause and number of weeks of gestation. All cases (elective and emergency) of caesarean section were included in the analysis. Forceps and vacuum deliveries performed for any cause were grouped in the variable instrument delivery. High grade perineal tear included the third and fourth grades, and was identified by the physician who attended the birth. Maternal ICU admission included women transferred to that unit for any reason. HPP included patients who had greater than normal blood loss after delivery, which required the use of additional pharmacological measures.

For the statistical analysis, the test for the normal distribution for the maternal age variable was calculated using the Kolmogorov–Smirnov test. The chi-square test was used to compare quantitative data. The associations between AMA and adverse outcomes were analysed using logistic regression models. The models were adjusted for previous births, previous miscarriages, and previous caesarean sections. Odds ratios and their 95% confidence intervals were calculated for the main outcome measures. A predictive model for the occurrence of fetal mortality and caesarean delivery was constructed using a decision-tree analysis algorithm (IBM SPSS Statistics v. 23.0, IBM, Armonk, NY, USA). The decision tree was developed using the Classification and Regression Trees CHAID method (Quick, Unbiased and Efficient Statistical Tree algorithm), which generates binary decision trees with the P-value set at 0.05 (Bonferroni-adjusted for multiple comparisons). Cut-off values were selected automatically for the parameters maternal age (years), previous abortions, births, or caesarean sections, hypertensive disorders, gestational diabetes, TPL, PRM, SGA, placenta previa, and preterm delivery. The caesarean section tree included the variable “induction of labour.”

Results

A flow chart of study group selection is presented in Fig. 1.

The women were categorised into three age groups: <35 years (n = 19,420; 70.7%), 35–40 years (n = 7189; 26.2%), and >40 years (n = 846; 3.1%).

The Kolmogorov–Smirnov test indicated that the data for maternal age did not meet the requirements for a normal distribution [Fig. 2]. The boxplot did not have the required bell shape and was diverted to the left. This result indicated that most of the pregnancies occurred at younger ages in this population. Thirty-three years was the most frequent maternal age in the study population, and the numbers of pregnancies decreased above that age.

In this sample population of 27,455 pregnancies, the mean maternal age was 31,21 years (median, 32 years; mode, 33 years). The range in maternal age was 13–53 years. A total of 19,420 (70,7%) of the women were <35 years of age, 7189 (26,2%) were 35–40 years, and 846 (3,1%) were >40 years of age.

The results for perinatal outcomes according to maternal age group are presented in Table 1; the analysis found statistically significant differences ($p < 0.05$). There was a progressive increase in complications in every age group (<35, 35–40, >40 years) for the variables hypertensive disorders (1,8%, 2,2%, and 4,8%, respectively), DM (3,7%, 6,5%, and 9,7%, respectively), induction of labour (25,2%, 28,4%, and 34,3%, respectively), and caesarean section (18,2%, 24,1%, and 29,3%, respectively).

The results for the odds ratios for the risk of pregnancy complications according to maternal age, after adjustment for obstetric history, are presented in Table 2. The analysis revealed that from the age of 35 years, there were progressive increases in the odds of developing hypertensive disorders (OR 1,37; CI95%: 1,10–1,70), DM (OR 1,84; CI95%: 1,60–2,13), induction of labour (OR 1,36; CI95%: 1,26–1,47), and caesarean section (OR 1,58; CI95%: 1,45–1,72). The highest odds for those variables were found in women >40 years of age.

The greatest risks of fetal death (OR 2,45; CI95%: 1,15–5,21), neonatal admission (OR 1,50; CI95%: 1,14–1,98), SGA (OR 1,51; CI95%: 1,17–1,94), placenta previa (OR 4,08; CI95%: 2,00–8,30), instrument delivery (OR 1,58; CI95%: 1,21–2,07), HPP (OR 1,85; CI95%: 1,08–3,17), and maternal ICU admission (OR 2,70; CI95%: 1,22–5,99) were found in the group of women who had a maternal age >40 years. No significant risk was found in women 35–40 years for these variables.

The statistical analysis did not find significant differences according to maternal age for the variables umbilical artery pH < 7.10, Apgar score <7 at 5 min, TPL, PRM, or high-grade perineal tear [Tables 1 and 2].

The decision tree analysis revealed that preterm delivery was the factor most likely to predict fetal death. Mortality occurred in 5% of preterm and in 0,2% of term deliveries. For term deliveries, fetal weight was the factor most likely to predict mortality (0,5% of mortality in term SGA versus 0,1% in term no SGA, $p < 0,001$). In those cases, at term and with normal weight, an AMA >35 years was the factor most likely to affect the risk of fetal mortality. Fetal mortality occurred in 0.3% of cases for women >35 years and 0,1% of cases in women <35 years ($p < 0.001$) [Fig. 3].

The results for the decision tree analysis indicated that the strongest predictor of having a caesarean delivery was having a previous caesarean delivery. Caesarean section was performed in 52.7% of women with previous caesarean section and 16.3% of women with no previous caesarean delivery ($p < 0,001$). The next

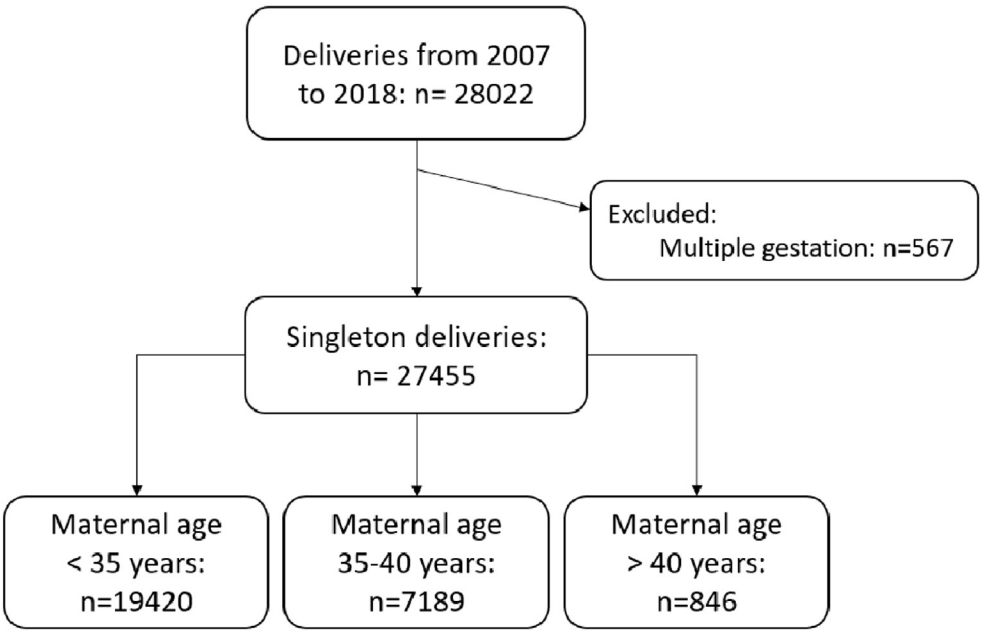

Fig. 1. Flow chart of study group selection.

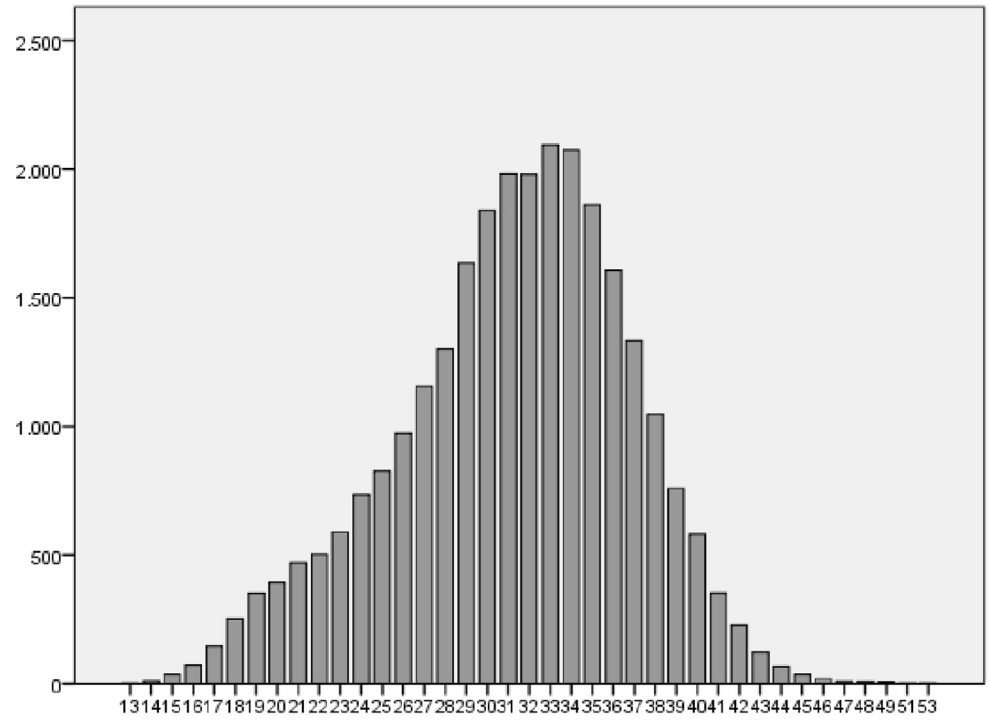

Fig. 2. Maternal age boxplot.

strongest predictor was a history of previous vaginal delivery. Among the women who had a previous caesarean delivery and no previous vaginal deliveries, maternal age was the factor most likely to predict having another caesarean section (54% had caesarean sections in women <35 years versus 64% in women >35 years, $p < 0.001$) [Fig. 4].

Table 1
Perinatal outcome according to maternal age group.

	<35 years n = 19,420 (70,7%)	35–40 years n = 7189 (26,2%)	>40 years n = 846 (3,1%)	p (x^2)
Fetal death	84 (0,4%)	41 (0,6%)	9 (1,1%)	0,018
Neonatal admission	1291 (9,2%)	541 (9,5%)	96 (14%)	0,001
Ph AU≤7,10	479 (3,4%)	185 (3,2%)	23 (3,3%)	0,837
Apgar min5 <7	142 (0,7%)	63 (0,9%)	9 (1,1%)	0,317
Preterm delivery	1253 (6,5%)	490 (6,8%)	77 (9,1%)	0,008
TPL	216 (1,1%)	88 (1,2%)	4 (0,5%)	0,142
SGA	1869 (9,6%)	668 (9,3%)	102 (12,1%)	0,036
Hypertensive disorders	345 (1,8%)	156 (2,2%)	35 (4,8%)	0,001
DM	711 (3,7%)	469 (6,5%)	82 (9,7%)	0,001
PRM	38 (0,2%)	15 (0,2%)	3 (0,4%)	0,602
Placenta previa	58 (0,3%)	38 (0,5%)	12 (1,4%)	0,001
Labor induction	4620 (25,2%)	1933 (28,4%)	273 (34,3%)	0,001
Caesarean section	3526 (18,2%)	1726 (24,1%)	246 (29,3%)	0,001
Instrumental delivery	2216 (11,4%)	710 (9,9%)	97 (11,7%)	0,002
High grade perineal tear	366 (1,9%)	166 (1,6%)	10 (1,2%)	0,133
PPH	265 (1,4%)	105 (1,5%)	23 (2,7%)	0,005
Maternal admission in ICU	79 (0,4%)	42 (0,6%)	11 (1,3%)	0,001

DM: Diabetes mellitus.
Ph AU: pH of umbilical cord artery.
PPH: Post partum haemorrhage.
PRM: Preterm rupture of membranes.
SGA: Small for gestational age.
TPL: Threatened preterm labor.

Table 2
Adjusted Odds Ratio (CI95%) of perinatal outcomes according to maternal age groups.

	35–40 years	>40 years
Fetal death	1,26 (0,82–1,93)	2,45 (1,15–5,21)
Neonatal admission	1,06 (0,93–1,20)	1,50 (1,14–1,98)
Hypertensive disorders	1,37 (1,10–1,70)	2,66 (1,77–3,99)
SGA	1,06 (0,95–1,19)	1,51 (1,17–1,94)
DM	1,84 (1,60–2,13)	3,09 (2,34–4,08)
Placenta previa	1,50 (0,94–2,50)	4,08 (2,00–8,30)
Labor induction	1,36 (1,26–1,47)	1,78 (1,48–2,14)
Caesarean section	1,58 (1,45–1,72)	2,05 (1,66–2,52)
Instrumental delivery	1,08 (0,96–1,21)	1,58 (1,21–2,07)
PPH	1,13 (0,87–1,49)	1, 85 (1,08–3,17)
Maternal admission ICU	1,29 (0,82–2,02)	2,70 (1,22–5,99)

DM: Diabetes mellitus.
PPH: Postpartum haemorrhage.
SGA: Small for gestational age.
[a] Explanation: Table 2 shows the adjusted odds ratio (IC95%) of perinatal outcomes according to maternal age groups: 35–40 years and >40 years. Odds ratio have been calculated by the comparison of these groups with the group of lower risk (<35 years). Maternal age below 35 years old is not included in the table because the aim of the study is to prove the adverse perinatal outcome in advanced maternal age, which is commonly defined as childbearing in a woman over 35 years of age [4].

Discussion

Age is an inherent risk factor for developing metabolic and cardiovascular diseases. Populations are experiencing important changes in lifestyle, such as increasing trends toward obesity and a sedentary lifestyle. These changes increase the risks of developing these complications [11]. Changes in social and economic circumstances and developments in assisted reproductive technology have resulted in delays in childbearing. Taken together, these factors contribute to increase the risks of pathologies during gestation that are not dependent on pregnancy. Consequently, adverse perinatal outcomes occur more frequently in older patients [12].

Many studies have found associations between AMA and higher risks of adverse maternal and neonatal outcomes. However, some of the studies have found results that are not consistent in terms of the specific outcomes adversely affected by maternal age and the strengths of the associations [4,7,12]. These discrepancies in results are partly due to the way that AMA is defined. After we performed the analysis in our population, we concluded that not all complications appeared at 35 years and older. Therefore, it is not as important to determine a definition of AMA as it is to consider which pathologies increase in each age range.

Similar to other studies in this area, in our study AMA was characterised by an increased incidence of pregnancy complications such as gestational diabetes and hypertensive disorders [4,7]. The risk was proportional to maternal age and increased after 35 years. Our results indicated that women must be informed of the importance of being screened for gestational DM and of blood pressure control, especially women who are >35 years.

Our findings are consistent with the many studies that found that the risk of fetal death and prematurity increases during the AMA years [4,14]. In our population, we found there was a trend in premature births in the group of older women. In contrast, some studies have found higher risks of preterm birth in groups of younger women. This difference could be explained by sample heterogeneity and variations in sociodemographic or clinical risk factors across different studies [4].

The decision tree analysis found that AMA was a predictive factor for fetal death, prematurity and SGA were the only stronger predictors. This risk increased from the age of 40 years. The absolute rates of perinatal death remain low, at generally <10 per thousand births in high income countries. Taken together, these results suggest that with careful prenatal care, most women in this age group will achieve a live birth [7].

The analysis found significant differences in SGA (<10th neonatal centile, adjusted by sex and gestational age) associated with maternal age. These results are consistent with those of other studies finding that women of AMA are at greater risk for having low birth weight newborns [2,7,13]. However, the results of other studies indicate that a teenage pregnancy is associated with an additional risk for SGA. The optimal maternal age to minimise the risk of this adverse outcome appears to be 26–30 years [15].

Consistent with the results of other studies, we also found incremental but highly significant increases in the rates of both elective and emergency Caesarean deliveries in the group of women >35 years of age [16–18]. The decision tree revealed that AMA was the strongest factor to predict caesarean section in

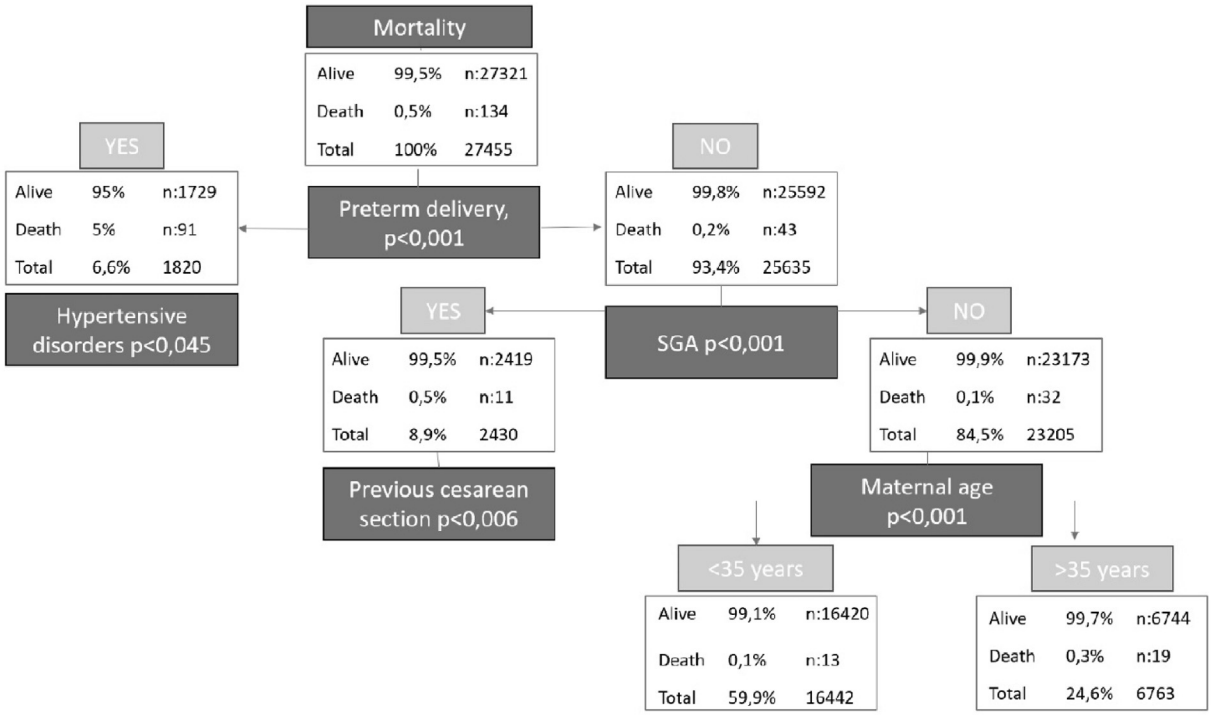

Fig. 3. Decision tree model for Fetal Mortality.

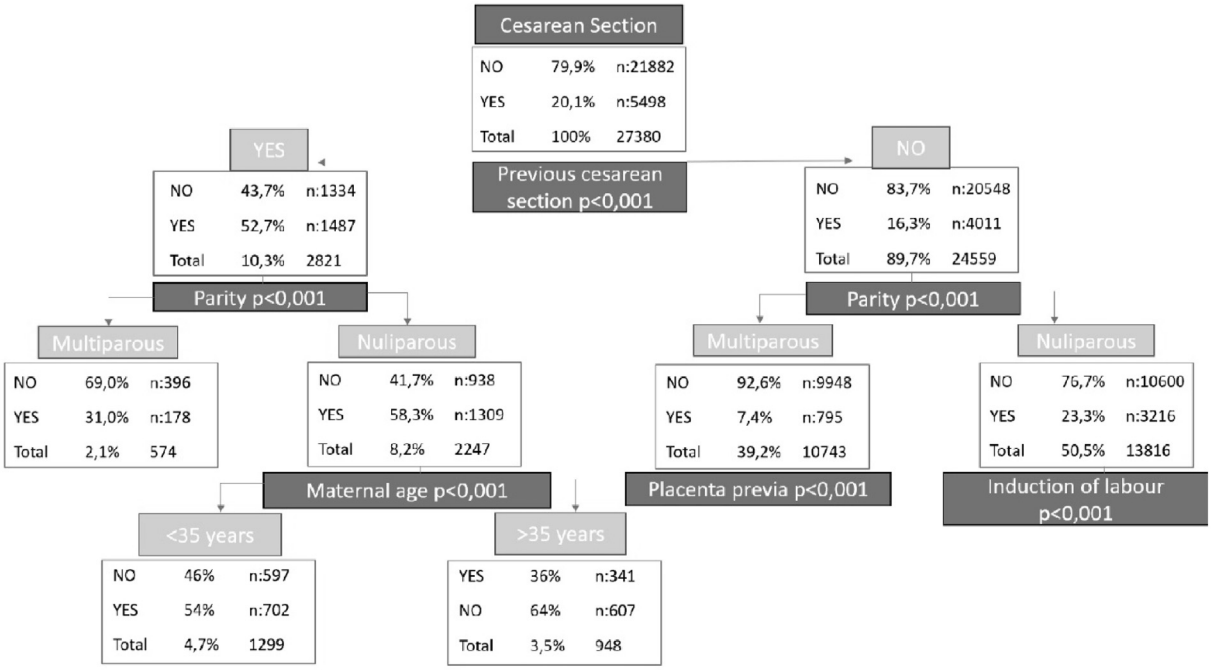

Fig. 4. Decision tree model for Cesarean Section.

women with a previous caesarean section and no previous vaginal deliveries. Some studies found that a delay in the onset of the first stage of labour is associated with maternal age [18], especially in primiparous women, and that oxytocin should be administered during the dilatation period. These findings can be used to inform choice of delivery methods. Other study findings suggest that labour progress slowly in women with AMA and fetal malposition, which is more frequent in primigravid nulliparous women with AMA [17,18]. Other hypotheses for an increased need for caesarean section among women with AMA include atherosclerotic changes in the uterine arteries, lower contraction potential, and decreased oxytocin receptor levels [19].

A greater incidence of instrument delivery was found in the younger women in our population. A possible reason for this finding is that we are part of a teaching medical centre. The increase in the rate of caesarean section in the older women would

coincide with a decrease in the use of instrument delivery in this group.

The analysis revealed statistical differences in PPH and maternal admission in ICU according to maternal age; the differences were greater in the >40 years age group. Despite the fact that it is largely a preventable and most often a treatable condition, PPH is the number one cause of maternal death worldwide [20]. PPH has shown an increase unrelated to the temporal trends in the known risk factors, such as AMA [20]. Although severe maternal morbidity is uncommon, older women with higher rates of DM hypertensive disorder, and caesarean section experience increased risks of severe morbidity and higher rates of ICU admission during pregnancy [21]. For that reason, our results are similar to the results of other studies [21].

Depending on maternal age, all these results have consequences for pregnant women and for obstetricians. As the trend in AMA continues, obstetricians should work to provide rigorous surveillance, improved clinical counselling, and optimised antenatal care services. This study also revealed some encouraging findings. Maternal and perinatal outcomes were favourable for most of the women and newborns.

The principal strength of this study was the sample size of the population, which included >27,000 patients. Many outcomes were included and were adjusted for potential confounders in different age ranges. The limitation of this study was that we had no information about maternal weight, nationality, or use of assisted reproductive technologies.

Conclusion

This study found that the risk of hypertensive disorders, DM, induced delivery, and caesarean section increased exponentially with maternal age in pregnant women >35 years. However, the risks of fetal death, neonatal admission, SGA, placenta previa, instrument delivery, maternal ICU admission, and HPP were increased after 40 years of age. Maternal age did not seem to affect the odds of neonatal acidosis or Apgar score at 5 min.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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