

Advanced Maternal Age and Adverse Perinatal Outcome

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OBJECTIVE: The aim of this study was to investigate the influence of maternal age on perinatal and obstetric outcome in women aged 40–44 years and those 45 years or older and to estimate whether adverse outcome was related to intercurrent illness and pregnancy complications.

METHODS: National prospective, population-based, cohort study in women aged 40–44 years and those 45 years or older and in a control group of women aged 20–29 years who delivered during the period 1987–2001. Adjusted odds ratios (OR) were calculated after adjustments for significant malformations, maternal pre-existing diseases, and smoking. Main outcome measures were perinatal mortality, intrauterine fetal death, neonatal death, preterm birth, and preeclampsia.

RESULTS: During the 15-year period, there were 1,566,313 deliveries (876,361 women were 20–29 years of age, 31,662 were 40–44 years, and 1,205 were \geq 45 years). Perinatal mortality was 1.4%, 1.0%, and 0.5% in women 45 years or older, 40–44, and 20–29 years, respectively. Adjusted OR for perinatal mortality was 2.4 (95% confidence interval [CI] 1.5–4.0) in women aged 45 years or older, compared with 1.7 (95% CI 1.5–1.9) in women 40–44 years. Adjusted OR for intrauterine fetal death was 3.8 (95% CI 2.2–6.4) in women aged 45 years or older, compared with 2.1 (95% CI 1.8–2.4) in women 40–44 years. Preterm birth, gestational diabetes, and preeclampsia were more common among women 40–44 years of age and those 45 years or older. Perinatal mortality was increased in women with intercurrent illness or pregnancy complications compared with women without these conditions, but there was no evidence that these factors became more important with increasing age.

CONCLUSION: Perinatal mortality, intrauterine fetal death, and neonatal death increased with age. There was also an increase in intercurrent illnesses and pregnancy complications with increasing age, but this did not entirely explain the observed increase in perinatal mortality with age. (Obstet Gynecol 2004;104:727–33. © 2004 by The American College of Obstetricians and Gynecologists.)

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During the last 3 decades, there has been an increasing trend among women in the industrialized world to delay childbearing. In Sweden, the mean maternal age at the birth of the first child increased between 1974 and 2001 from 24.4 to 28.5 years.¹ The corresponding mean maternal age increased from 21.4 to 24.9 years in the United States and from 25.6 to 28.0 years in Japan between 1970 and 2000.²

The proportion of women delivering in their 40s has also increased, especially during the last decade. In Sweden, the numbers of women giving birth between 40 and 44 years of age and at age 45 or older increased from 5.0 to 10.3 and from 0.2 to 0.5 live births per 1,000 women, respectively, from the early 1980s to 2001.³ In England and Wales, the number of women giving birth between 40 and 44 years and at 45 years or older increased from 5.1 to 8.4 and 0.3 to 0.5 live births per 1,000 women, respectively, between 1991 and 2001.⁴ In the United States, the number of women giving birth between 40 and 44 years and at 45 years or older increased from 3.8 to 7.4 and 0.2 to 0.4 live births per 1,000 women, respectively, between 1981 and 1999.⁵

It is a well-established fact that fecundity decreases and the risk for miscarriage increases with age.⁶ However, the enormous advances in reproductive medicine have compensated, to some extent, for this natural decrease in fecundity, and nowadays even postmenopausal women have become pregnant through oocyte donation.⁷ The influence of advanced maternal age and delayed childbearing on perinatal outcome have previously been studied, but most studies have evaluated outcome in women aged 35 years or older.⁶ It has been shown that pregnant women aged 35 years or older experience an increased risk of intrauterine fetal death, pregnancy-induced hypertension, gestational diabetes, and delivery by cesarean.⁶

Most studies that have dealt with advanced maternal age are hospital-based; there are very few population-based studies.^{8,9} Two hospital-based studies have investigated women aged 45 years or older.^{10,11} The aim of this national population-based study was to 1) investigate the influence of maternal age on perinatal and



obstetric outcome in women aged 40–44 years and those 45 years or older and 2) explore whether the increased risk of perinatal mortality could be explained by the increased occurrence of intercurrent illnesses and pregnancy complications among older women.

MATERIALS AND METHODS

The Swedish Medical Birth Register, managed by the National Board of Health and Welfare, contains data on more than 99% of all births in Sweden.¹² Information is collected prospectively by the staff responsible for the care of the patient and includes demographic data, reproductive history, and complications during pregnancy, delivery, and the neonatal period. Copies of the standardized individual antenatal, obstetric, and pediatric records are forwarded to the Birth Registry, where the information is automatically entered into a database and stored. All births and deaths are validated every year through individual record linkage to the Swedish Register of the total population, using the mothers' and infants' unique national registration numbers, which are assigned to each Swedish resident at birth. The register has been validated and quality is controlled on a yearly basis. Maternal complications during pregnancy are considered to be of acceptable quality.¹²

The women included in the study are part of the homogenous, low-risk population typical for Sweden. Severe poverty does not really exist in Sweden, and access to adequate prenatal and obstetrical care is good. More than 80% of women have an intermediate or high level of education, and the prevalence of drug/alcohol abuse is low in comparison with many other countries.

Pre-existing maternal diseases and medical complications in pregnancy and delivery are recorded in the birth registry according to the Swedish version of the International Classification of Diseases, 9th Revision (ICD-9) 1987–1996. From 1997, the Swedish version of the International Classification of Diseases, 10th Revision (ICD-10) was used. Smoking and marriage/cohabitation status were also recorded at the first antenatal visit and categorized as either nonsmoking (ie, non-daily smoking) or smoking and either marriage/cohabitation or not. *Intercurrent illness* was defined as the presence of a prepregnancy history of existing hypertensive disease, diabetes, bronchial asthma, disseminated lupus erythematosus, or inflammatory bowel disease, and these were recorded at the first antenatal visit. *Complication during pregnancy* was defined as a history of gestational diabetes, pregnancy-induced hypertension, or preeclampsia during the pregnancy.

Pregnancy outcomes, such as stillbirth, birth weight, gestational age at delivery, and infant gender, are recorded in the delivery or pediatric records. Validation of the Birth Register has concluded that data on birth weight, gestational age, and stillbirth are correctly recorded.¹² The Birth Register includes information on all live births, as well as stillbirths, occurring at 28 completed gestational weeks or later. Information necessary to determine maternal mortality was obtained from the national Causes of Death Register. The study was approved by the Ethics Committee, Faculty of Medicine, University of Göteborg, and by the governing board of the Swedish Medical Birth Register.

From 1987 to 2001, there were 1,566,313 recorded births. All deliveries in women aged 40–44 ($n = 31,662$) years and 45 years or older ($n = 1,205$) and in a control

Table 1. Demographic Characteristics and Medical History Grouped According to Maternal Age

	Group A: 20–29 y (n = 876,361)	Group B: 40–44 y (n = 31,662)	Group C: ≥ 45 y (n = 1,205)	Significance of difference between A, B, C ($P < .05$)
Married or cohabiting	776,542/816,720 (95.1)	26,247/28,761 (91.3)	975/1,088 (89.6)	A-B, A-C, B-C
Smoking during pregnancy	171,245 (20.8)	5,710 (18.0)	170 (15.6)	A-C, B-C
Primiparous	446,735 (51.0)	5,418 (17.1)	183 (15.2)	A-B, A-C
Hypertensive disease	2,027 (0.23)	296 (0.93)	17 (1.41)	A-B, A-C, B-C
Diabetes mellitus	2,653 (0.36)	180 (0.57)	4 (0.33)	NS
Renal disease	3,119 (0.36)	182 (0.57)	6 (0.50)	NS
Disseminated lupus erythematosus	542 (0.06)	37 (0.12)	3 (0.25)	A-C, B-C
Bronchial asthma	27,204 (3.10)	908 (2.87)	40 (3.32)	NS
Ulcerative colitis	2,274 (0.26)	118 (0.37)	9 (0.75)	A-C, B-C
One or more of the intercurrent diseases above	36,808 (4.20)	1,628 (5.14)	74 (6.14)	A-C, B-C
Multiple pregnancy	18,921 (2.16)	904 (2.86)	40 (3.32)	A-B, A-C
Significant malformation	15,269 (1.74)	803 (2.54)	34 (2.82)	A-B, A-C

NS, not significant.

Data are expressed as n (%).



Table 2. Selected Antepartum Complications Grouped According to Maternal Age

	20–29 y (n = 876,361)	40–44 y (n = 31,662)	≥ 45 y (n = 1,205)
Gestational diabetes	2,496 (0.28)	307 (0.97)	16 (1.33)
OR (95% CI)	1	3.43 (3.04–3.86)	4.71 (2.87–7.73)
Pregnancy-induced hypertension	4,811 (0.55)	564 (1.78)	41 (3.40)
OR (95% CI)	1	3.29 (3.01–3.59)	6.38 (4.67–8.72)
Mild preeclampsia	18,473 (2.11)	393 (1.24)	8 (0.66)
OR (95% CI)	1	0.58 (0.53–0.64)	0.31 (0.15–0.62)
Severe preeclampsia	7,074 (0.81)	356 (1.12)	18 (1.49)
OR (95% CI)	1	1.40 (1.26–1.56)	1.86 (1.17–2.97)
Placenta previa	1,402 (0.16)	232 (0.73)	2 (0.17)
OR (95% CI)	1	4.61 (4.01–5.30)	1.04 (0.26–4.16)

OR, odds ratio; CI, confidence interval.

Data are expressed as n (%) and OR (95% CI).

group of all women aged 20–29 years (n = 876,361) were included in this study.

Gestational age was calculated by using information from date of birth and estimated date of delivery as determined in early pregnancy. This is usually based on a second-trimester ultrasound scan performed at no later than 18 completed weeks of gestation, which was offered to all pregnant women in Sweden during the study period. More than 95% of pregnant women avail themselves of this opportunity.¹³

Small for gestational age (SGA) was defined as a birth weight below 2 standard deviations from the mean weight corrected for gestational age and gender.¹⁴ *Large for gestational age* (LGA) was defined as a birth weight more than 2 standard deviations from the mean weight corrected for gestational age and gender.¹⁴

Perinatal mortality was defined as stillbirth or death during days 0–6. *Neonatal death* was defined as born alive and death during days 0–28. *Perinatal death* was defined as stillbirth or neonatal death. *Stillbirth* was defined as a dead fetus (both antepartum and intrapartum) born at 28 completed gestational weeks or later (information on weeks 22–27 is not available in the Registry according to Swedish legislation). All mortality and death data were expressed as deaths per 1,000 deliveries.

Dichotomous data were tested for significance with the Fisher exact test, and adjustments (multiplication by 3) of the *P* values due to multiple comparisons were performed by the Bonferroni method (Table 1). Logistic regression was used to analyze selected antepartum complications (diabetes mellitus, hypertensive disease, mild and severe preeclampsia, and placenta previa) (Table 2), as well as intrapartum variables (mode of delivery, induction of labor, and sphincter tears of the third and fourth degree) (Table 3) and perinatal mortality according to the presence or absence of intercurrent illness and/or pregnancy complications (Table 4), in comparing the different age groups. Using multiple logistic regression analysis, perinatal outcomes were adjusted for nulliparity, married/cohabitating, significant malformations, smoking, maternal disease, and multiple pregnancy (Tables 5 and 6).

Odds ratios (OR) were calculated, with women 20–29 years of age as the reference group, with 95% confidence intervals (CI). Statistical software (SAS 8.12; SAS Institute Inc, Cary, NC) was used for the analysis.

RESULTS

The proportion of women giving birth between ages 40 and 44 years and at 45 years or older has increased

Table 3. Peripartum Information and Maternal Age

	20–29 y (n = 876,361)	40–44 y (n = 31,662)	≥ 45 y (n = 1,205)
Normal delivery	728,274 (83.10)	22,556 (71.24)	785 (65.15)
OR (95% CI)	1	0.50 (0.49–0.51)	0.38 (0.34–0.43)
Induction of labor	49,856 (5.69)	3,044 (9.61)	156 (12.95)
OR (95% CI)	1	1.75 (1.68–1.84)	2.47 (2.08–2.92)
Operative vaginal delivery	59,163 (6.75)	1,741 (5.50)	57 (4.73)
OR (95% CI)	1	0.80 (0.76–0.84)	0.69 (0.53–0.90)
Cesarean delivery	90,599 (9.92)	7,425 (23.45)	365 (30.29)
OR (95% CI)	1	2.66 (2.58–2.73)	3.77 (3.33–4.26)
Anal sphincter tears (third and fourth degree)	16,822 (1.92)	796 (2.51)	42 (3.49)
OR (95% CI)	1	1.32 (1.23–1.42)	1.85 (1.36–2.51)

OR, odds ratio; CI, confidence interval.

Data are expressed as n (%) and OR (95% CI).



Table 4. Perinatal Mortality According to Presence or Absence of Intercurrent Illness and/or Pregnancy Complications

	20–29 y	40–44 y	≥ 45 y
Intercurrent illness	222/35,155 (0.63)	16/1,530 (1.05)	0/71
OR (95% CI)	1	1.66 (1.00–2.77)	
Pregnancy complication	217/30,481 (0.71)	15/1,363 (1.10)	0/73
OR (95% CI)	1	1.55 (0.92–2.63)	
Intercurrent illness or pregnancy complication	453/67,289 (0.67)	33/2,991 (1.10)	0/147
OR (95% CI)	1	1.65 (1.15–2.35)	
No intercurrent illness or pregnancy complication	4,260/809,072 (0.53)	269/28,671 (0.94)	17/1,058 (1.61)
OR (95% CI)	1	1.79 (1.58–2.05)	3.09 (1.91–4.99)

OR, odds ratio; CI, confidence interval.

Data are expressed as n (%) and OR (95% CI).

during the study period (Fig. 1, A and B). During the study period (1987–2001), the number of women giving birth between ages 40 and 44 years increased from 6 to 10 live births per 1,000 women. The corresponding

increase for women aged 45 years or older was from 0.2 to 0.3 live births per 1,000 women.

Demographic characteristics and medical history, grouped according to maternal age, are shown in Table 1.

Table 5. Perinatal Outcome According to Maternal Age, Adjusted for Nulliparity, Married/Cohabitation, Significant Malformations, Smoking, Maternal Disease, and Multiple Pregnancy

	20–29 y (n = 876,361)	40–44 y (n = 31,662)	≥ 45 y (n = 1,205)
Perinatal mortality	4,713 (0.54)	302 (0.95)	17 (1.41)
AOR (95% CI)	1	1.67 (1.48–1.88)	2.45 (1.51–3.98)
Perinatal death (including death within first 28 days)	5,246 (0.60)	343 (1.08)	20 (1.66)
AOR (95% CI)	1	1.68 (1.50–1.89)	2.57 (1.64–4.04)
Intrauterine fetal death	2,785 (0.32)	203 (0.64)	14 (1.16)
AOR (95% CI)	1	2.07 (1.79–2.40)	3.76 (2.22–6.40)
Neonatal death (including death within days 0–28)	2,461 (0.29)	140 (0.44)	6 (0.50)
AOR (95% CI)	1	1.29 (1.08–1.54)	1.42 (0.62–3.23)

AOR, adjusted odds ratio; CI, confidence interval.

Data are expressed as n (%) and AOR (95% CI).

Table 6. Peripartum Information According to Maternal Age, Adjusted for Nulliparity, Married/Cohabitation, Significant Malformations, Smoking, Maternal Disease, and Multiple Pregnancy

	20–29 y (n = 876,361)	40–44 y (n = 31,662)	≥ 45 y (n = 1,205)
Preterm birth < 37 wk	54,309 (6.20)	2,762 (8.72)	113 (9.38)
AOR (95% CI)	1	1.54 (1.47–1.60)	1.63 (1.32–2.00)
Preterm birth < 34 wk	15,931 (1.80)	915 (2.89)	33 (3.53)
AOR (95% CI)	1	1.57 (1.46–1.69)	1.88 (1.36–2.59)
Preterm birth < 32 wk	8,953 (1.01)	569 (1.80)	27 (2.24)
AOR (95% CI)	1	1.65 (1.51–1.80)	1.94 (1.30–2.88)
Small for gestational age	21,874 (2.56)	1,151 (3.77)	58 (5.03)
AOR (95% CI)	1	1.94 (1.80–2.09)	2.67 (2.04–3.49)
Large for gestational age	26,033 (2.97)	1,506 (4.76)	63 (5.23)
AOR (95% CI)	1	1.63 (1.55–1.72)	1.80 (1.40–2.32)
Mild preeclampsia	18,473 (2.11)	393 (1.24)	8 (0.66)
AOR (95% CI)	1	0.59 (0.53–0.65)	0.31 (0.15–0.62)
Severe preeclampsia	7,074 (0.81)	356 (1.12)	18 (1.49)
AOR (95% CI)	1	1.29 (1.16–1.44)	1.64 (1.03–2.62)
Preeclampsia	25,547 (2.92)	749 (2.37)	26 (2.16)
AOR (95% CI)	1	1.27 (1.18–1.37)	1.16 (0.78–1.71)
Placenta previa	1,402 (0.16)	232 (0.73)	2 (0.17)
AOR (95% CI)	1	4.10 (3.55–4.73)	0.92 (0.23–3.38)

AOR, adjusted odds ratio; CI, confidence interval.

Data are expressed as n (%) and AOR (95% CI).



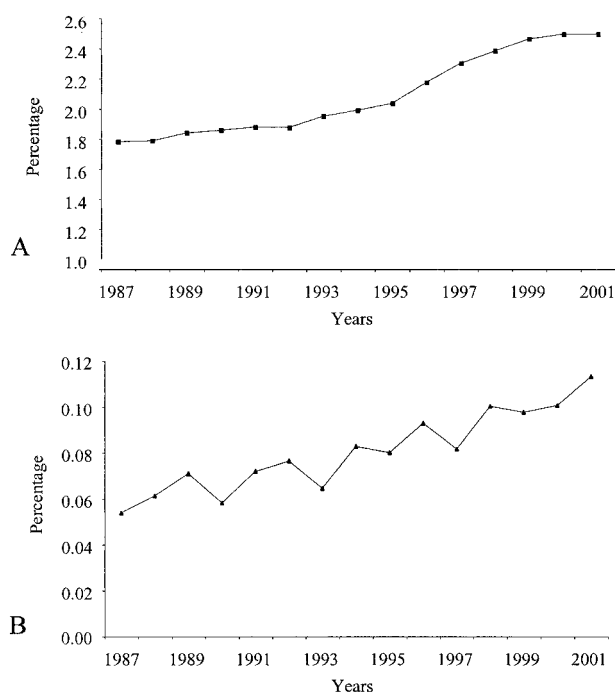


Fig. 1. Percentages of women giving birth during the period 1987–2001 who were aged 40–44 years (A) and 45 years or older (B).

Jacobsson. Maternal Age and Pregnancy Outcome. Obstet Gynecol 2004.

Fewer women in the age groups 40–44 years and 45 years or older smoked and lived with the child's father than women in the age group 20–29 years. The older women had more pre-existing diagnoses of hypertension, disseminated lupus erythematosus, and ulcerative colitis, but not diabetes mellitus or renal disease.

The risk of developing gestational diabetes, pregnancy-induced hypertension, severe preeclampsia, or placenta previa increased with increasing maternal age, but there was a decreased risk of mild preeclampsia (Tables 2 and 6). The number of uncomplicated deliveries was lower in older women (Table 3). Both induction of labor and cesarean delivery were increased, but not operative vaginal delivery (not corrected for multiparity). In women aged 45 years or older, 1 of every 3 women was delivered by cesarean. The risk of experiencing an anal sphincter tear increased with increasing age.

Adjusted ORs were calculated regarding perinatal outcome. Perinatal mortality, perinatal death (including death within the first 28 days of life), and intrauterine fetal death all increased with increasing maternal age. Neonatal death (defined as death within 28 days) was also increased in women aged 40–44 years (Table 5). The absolute risk of an intrauterine fetal death or the death of the live-born child within the first 27 days of life

was 1.1% in women aged 40 years or older and 1.7% in women 45 years or older. Adjusted ORs were also calculated for other important perinatal outcome measures: preterm birth, SGA, LGA, and preeclampsia (mild and severe), and these outcomes were all found to be associated with increased maternal age (Table 6).

Perinatal mortality was increased in women with intercurrent illness or pregnancy complications compared with women not experiencing these conditions, in both women aged 20–29 years and 40–44 years (Table 4). However, there was no evidence that intercurrent illness or pregnancy complications become more important risk factors for perinatal death with increasing age (20–29 years: OR 1.28, 95% CI 1.16–1.41; 40–44 years: OR 1.17, 95% CI 0.82–1.69). Similar results were obtained for intrauterine fetal death and perinatal death in women grouped in the corresponding manner.

During the course of this study, which stretched over 15 years, there were 21 maternal deaths in the age groups studied. Maternal mortality, grouped according to age group, was calculated (age group 20–29 years: 12/876,361, which is equivalent to 1.4/100,000 deliveries; age group 40–44 years: 7/31,662, which is equivalent to 22.1/100,000 deliveries; age group \geq 45 years: 2/1,205, which is equivalent to 166.0/100,000 deliveries). Maternal mortality was compared between groups: age group 40–44 years versus age group 20–29 years OR 16.2 (95% CI 6.38–41.2); age group 45 years or older versus age group 20–29 years OR 121 (95% CI 27–542).

DISCUSSION

This study has demonstrated an increase in perinatal mortality, perinatal death, intrauterine fetal death, and neonatal death in relation to maternal age in childbearing women from the last part of their fertile period, ie, 40–44 years of age and 45 years or older. In addition, there was also an increase in the preterm birth rate and the prevalence of SGA, LGA, and preeclampsia with advancing maternal age, and again, the highest prevalences were seen in women 45 years of age or older. Our data suggest that the increased occurrence of perinatal mortality, perinatal death, and intrauterine fetal death in older women could not be explained by the increased frequency of intercurrent illness or pregnancy complications observed in these women. One can, however, have possible reservations regarding the validity of this conclusion, if pregnancy complications had been underreported, but on the other hand, we see no reason why underreporting should differ between the various age groups.

Being pregnant and giving birth at the age of forty or more years was relatively common until the middle of the 20th century.¹⁴ Women often had their first child



early and their last child late during the reproductive period.¹⁴ The major difference during the last 3 decades is that women are more often using the latter part of their reproductive period to have all their children,¹ and this trend of postponing childbearing has not yet shown any tendency to decrease.¹ Several studies have investigated perinatal outcome in women aged 40 years or older,^{9,15-21} and 2 of the studies have presented population-based data.^{8,9} The study by Cnattingius et al⁸ was population-based and demonstrated a higher prevalence of late fetal death but was unable to demonstrate a higher prevalence of early neonatal death in women who delivered at the age of 40–52 years, compared with 35- to 39-year-old women. In their study the number of women aged 40 years or older was limited (n = 1,069), and it was not possible to compare women aged 40–44 years with those 45 years or older. Thus, it was not possible to demonstrate an increase in perinatal mortality, perinatal death, intrauterine fetal death, and neonatal death with increasing age in women aged 40 years or older as was demonstrated in the present study. In the study by Gilbert et al,⁹ increased infant and neonatal death could only be demonstrated in multiparous women 40 years of age or older compared with the younger control group, and again no distinction was made between women aged 40–44 years and those who were 45 years of age or older.

There are only 2 earlier studies published regarding perinatal outcome in childbearing women aged 45 years or older; both studies are hospital-based and the size of the studies was insufficient to study perinatal mortality.^{10,11} Dildy et al¹⁰ presented 79 cases from their hospital and also performed a review of the literature between 1948 and 1996 of studies presenting data from women aged 45 years or older. Also, Dulitzki et al¹¹ have presented a hospital-based, case-control study with 109 women. The size and comprehensiveness of our present study provided us the opportunity to study the important perinatal outcome variables.

The present study was based on a large national population-based cohort where 31,662 women aged 40–44 years and 1,205 women aged 45 years or older were included in the analyses. It was also possible, because of the design of the Swedish Medical Birth Register, to adjust for important pre-existing maternal conditions, nulliparity, significant malformations, multiple pregnancies, smoking, and cohabitation. The ability to link the Swedish Medical Birth Register to other relevant national population registers enhanced the quality control of the data available for the important mortality figures. Being able to adjust for parity and important potential confounding factors enhanced our ability to investigate the specific influence of age on perinatal

outcome. No attempt was made to adjust for the use of in vitro fertilization techniques or oocyte donation because the validity of this information contained in the antenatal records alone has been considered to be of poorer quality.²² During the study period, oocyte donation was not legally available in Sweden, but it is possible that there may be a few cases in our material because some women may have undergone oocyte donation treatment abroad and were subsequently delivered in Sweden. Another possible limitation of this study is that it covers a 15-year time period, and treatment policies have changed during the course of the study.

We conclude that there is an increase in perinatal and neonatal death with increasing age, as well as an increase in pregnancy complications, eg, preterm delivery, SGA, LGA, gestational diabetes, pregnancy-induced hypertension, severe preeclampsia, and anal sphincter tears. However, although maternal and fetal outcome is compromised, pregnancies in women aged 40–44 years and 45 years or older still may be considered to be relatively safe because the occurrence of perinatal death is rare. An important observation in this study is that the increased risk of bad perinatal outcome is not due to the increased occurrence of maternal pre-existing disease or pregnancy complications in the older women. Our findings are of importance for gynecologists and obstetricians, as well as the general public, when providing information to the increasing numbers of presumptive parents where the woman is aged 40 years or older. However, from the clinician's perspective, there is no simple measure that could be applied to prevent the poor outcome.

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