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INCREASED MATERNAL AGE AND THE RISK OF FETAL DEATH

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Abstract Background. Although the fetal death rate has declined over the past 30 years among women of all ages, it is unknown whether particular characteristics of the mother, such as age, still affect the risk of fetal death. We undertook a study to determine whether older age, having a first child (nulliparity), or other characteristics of the mother are risk factors for fetal death.

Methods. We used data from the McGill Obstetrical Neonatal Database to evaluate risk factors for fetal death among all deliveries at the Royal Victoria Hospital in Montreal (n=94,346) from 1961 through 1993. Data were available for two time periods (1961 through 1974 and 1978 through 1993); data for 1975 through 1977 have not been entered into the data base and were therefore not included. Using logistic regression, we estimated the effect of specific maternal characteristics and complications of pregnancy on the risk of fetal death.

Results. The fetal death rate decreased significantly from 11.5 per 1000 total births (including live births and

stillbirths) in the 1960s to 3.2 per 1000 in 1990 through 1993 ($P<0.001$). Between these periods, the average maternal age at delivery increased from 27 to 30 years ($P<0.001$), and the frequency of the diagnosis of diabetes and hypertension during pregnancy increased fivefold ($P<0.001$). Nevertheless, after we controlled for these and other maternal characteristics, women 35 years of age or older continued to have a significantly higher rate of fetal death than their younger counterparts (odds ratio for women 35 to 39 years of age as compared with women <30 years of age, 1.9; 95 percent confidence interval, 1.3 to 2.7; for those 40 or older, 2.4; 95 percent confidence interval, 1.3 to 4.5).

Conclusions. Changes in maternal health and obstetrical practice have resulted in a 70 percent decline in the rate of fetal death among pregnant women of all ages since the 1960s. Advancing maternal age, however, continues to be a risk factor for fetal death. (N Engl J Med 1995;333:953-7.)

AS women pursue educational and career goals, they are more likely to delay childbearing. In the United States from 1976 to 1986, the rate of first births among women 40 years of age or older has doubled,¹ but the effect of advanced maternal age or of birth order (parity) on fetal outcomes is not clear. Some studies have found no increase in the risk of fetal death or perinatal infant mortality for older as compared with younger pregnant women, but these studies lacked statistical power and focused on women in relatively high socioeconomic groups.²⁻⁷ In contrast, several larger studies have reported an increase in the fetal death rate among older women.⁸⁻¹⁴ None of these studies have examined the absolute and relative risks of fetal death in relation to advanced maternal age over time, taking into account changes in obstetrical practice and the contributions of birth order and maternal risk factors.

In this study, we determined the rate of fetal death

over a 30-year period in a population large enough to allow us to examine temporal changes in maternal characteristics that contribute to the occurrence of fetal death. We also investigated whether older maternal age and having a first child (nulliparity) persist as risk factors after control for potential confounding by medical conditions known to increase the risk of fetal death.

METHODS

Patients

The McGill Obstetrical Neonatal Database contains information on all infants (n=94,346), weighing 500 g or more, born alive or stillborn from January 1961 through April 1993 at the Royal Victoria Hospital, a tertiary care teaching hospital in Montreal. Births from 1975 to 1977 have not yet been entered into the computerized data base, so these births were not available for analysis. In addition, 332 births were excluded from the analysis because of missing information. None of these incomplete records included a case of fetal death.

Women with high-risk pregnancies who were transferred from other hospitals were excluded in order to minimize referral bias and to ensure that the study group would reflect a standard obstetrical population over time. The population was predominantly white and from all socioeconomic strata. Most women had access to obstetrical care throughout their pregnancies; 93.6 percent of women in the period from 1961 through 1974 and 97.6 percent of those in the period from 1978 through 1993 had four or more obstetrical visits.

The data base was designed and maintained by one of us for the entire period, and the definition of birth remained constant. There were 450 computerized internal-consistency checks for each birth rec-

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ord. Each inconsistency identified was reviewed and corrected by one of us. The fetal death rate was calculated as the number of fetal deaths per 1000 total births (including live births and stillbirths). Congenital malformations that resulted in a perinatal death were included in the analysis. Perinatal mortality was defined as the sum of fetal and neonatal deaths before hospital discharge. All cases of fetal death ($n=688$) were reviewed by a committee, and autopsies were performed in 97 percent of the cases.

Statistical Analysis

We calculated odds ratios and their 95 percent confidence intervals, using a low-risk reference group (women less than 30 years of age who were having their second or third child) to evaluate the effect of advancing maternal age, parity, and other maternal characteristics on the risk of fetal death.¹⁵ We chose this reference group to represent a base-line level of risk, so that we could estimate the effect of advancing age (30 through 34, 35 through 39, and ≥ 40 years), as well as the risks posed by nulliparity and high parity (pregnancy with a fourth or subsequent child). The reference group also included pregnant women less than 19 years of age because, in this obstetrical population, these women did not have a higher risk of fetal death than those 20 to 29 years old (data not shown).

To control for potential confounders, the logistic-regression model included the year of the delivery, the mother's marital status, history of previous abortion (of a fetus weighing less than 500 g, whether spontaneous or induced), history of previous fetal death (at a fetal weight ≥ 500 g), multiple gestation, and presence of diabetes, hypertension, placenta previa, and placental abruption.¹⁶

Women were classified as diabetic if they had a history of preexisting diabetes or gestational diabetes mellitus during the pregnancy (i.e., at least two abnormal values on glucose-tolerance tests). Diabetes was further categorized according to the requirement for insulin therapy. Women who had a diagnosis of preexisting hypertension or pregnancy-induced hypertension were classified as hypertensive. Women with antepartum hemorrhage, without evidence of placenta previa, fetal hemorrhage, or uterine rupture, were classified as having placental abruption. During the second half of the study period, ultrasound was used increasingly to evaluate antepartum bleeding.

Of the women who delivered at the Royal Victoria Hospital, 26 percent delivered more than one infant during the 30 years, and each delivery is recorded in the data base. Since the risk of fetal death did not differ significantly between women with one delivery and women with two or more deliveries, each birth was considered an independent observation.

We examined temporal changes in the risk of fetal death by analyzing the data for two periods: 1961 through 1974 and 1978 through 1993. Within each period the year of delivery was used to control for changes over time in the risk of fetal death that could not be explained by changes in maternal age, parity, or other known risk factors. The rate of perinatal mortality was also calculated for each decade.

RESULTS

Perinatal Mortality and Maternal Characteristics, 1961 through 1993

The perinatal mortality rate (the rate of death before hospital discharge per 1000 total births) declined from 25.2 in the 1960s to 6.6 in 1990 through 1993 ($P<0.001$), with parallel declines in both the fetal and the neonatal death rates (Table 1). There was an increase in the average maternal age at delivery from 27 years in the 1960s to 30 years from 1990 through 1993 ($P<0.001$) and a 66 percent decline in the number of multiparous women with four or more children ($P<0.001$) (Table 2). The percentage of pregnant women 40 years of age or older was 2.5 percent in the 1960s, and these women were three times more likely to be having their last pregnancy, rather than their first, than women of the same age in the past two decades.

Table 1. Total Births and Fetal, Neonatal, and Perinatal Mortality from the 1960s through the 1990s.*

VARIABLE	1960s	1970s	1980s	1990-1993
Total births	28,844	17,499	35,338	12,665
Fetal deaths				
Total no.	331	142	174	41
No./1000 total births	11.5	8.1	4.9	3.2
Neonatal deaths				
Total no.	396	159	198	43
No./1000 live births	13.9	9.2	5.6	3.4
Perinatal mortality (per 1000 total births)	25.2	17.2	10.5	6.6

*Total births include both live births and stillbirths. Data collection for the 1960s began in 1961. Information on births from 1975 through 1977 is not available and is therefore not included. Excluded are two births for which the date of delivery was not entered into the data base.

From the 1970s to the 1990s, the proportion of women giving birth who were 40 or older more than doubled ($P<0.001$). In addition, pregnant women in recent decades were more likely to be nulliparous than in the 1960s and 1970s ($P<0.001$), were less likely to be married ($P<0.001$), and had previously had abortions more often ($P<0.001$). They were also more likely to have hypertension ($P<0.001$) or diabetes ($P<0.001$) diagnosed during their pregnancies (Table 2).

We calculated the crude fetal death rate in each decade among women 35 years of age or older and compared it with the rate among younger women (Table 3). In the 1960s, the odds ratio for fetal death among women 35 or older, as compared with their younger counterparts, was 1.5 (95 percent confidence interval, 1.1 to 2.1); in 1990 through 1993 it was 2.2 (95 percent confidence interval, 1.1 to 4.4). Women under the age of 30 had the lowest rate of fetal death; the rate increased with advancing maternal age, with women 40 or older having twice the fetal death rate of women younger than 30. The fetal death rate for women of all ages in 1978 through 1993 was approximately half that in the earlier period (Fig. 1).

We examined the effect of parity on the incidence of fetal death among women 35 years of age or older by comparing changes in the fetal death rates for the periods 1961 through 1974 and 1978 through 1993 (Fig. 2). Both nulliparous (i.e., those having a first child) women and women with high parity were at increased risk for fetal death in the earlier period. In the more recent period, nulliparous older women were no longer at increased risk as compared with older women having a second or third child (odds ratio, 1.2; 95 percent confidence interval, 0.6 to 2.2).

Predictors of Fetal Death, 1961 through 1993

We found that older women had a higher prevalence of conditions that could increase the risk of fetal death. During both study periods women who were 35 or older had a statistically significant increase in the frequency of multiple gestation, hypertension, diabetes mellitus, placenta previa, placental abruption, previous abortion, and previous fetal death. Since the rates of age-associated maternal risk factors were consistent with those in previous reports,^{7,8} the data are not shown. However,

Table 2. Maternal Characteristics According to the Decade in Which the Delivery Occurred.*

CHARACTERISTIC	1960s	1970s	1980s	1990-1993
Mean maternal age (yr)	27.1	27.0	28.9	30.0
	<i>percent</i>			
Age 35-39 yr	9.5	7.0	11.6	14.6
Age ≥40 yr	2.5	1.3	1.9	3.0
First child	36.8	46.0	46.0	47.6
Fourth or subsequent child	16.9	6.7	4.4	5.7
Married	92.0	94.2	87.3	81.7
Hypertension	0.8	1.5	4.3	4.2
Diabetes mellitus				
Treated with diet	0.3	0.2	1.2	2.4
Treated with insulin	0.6	1.2	0.9	2.2
Previous abortion†	19.9	19.1	28.0	33.2
Multiple gestation	2.1	2.2	2.1	2.6
Placental abruption	1.9	1.3	1.5	3.4
Placenta previa	0.5	0.4	0.3	0.5

*Data collection for the 1960s began in 1961. Information on births for 1975 through 1977 is not available and is therefore not included.

†Previous abortion refers to any termination of pregnancy in which the fetus weighed less than 500 g (spontaneous, induced, or of unknown type).

because each of these maternal characteristics could introduce confounding, they were included in the logistic-regression model.

During 1961 through 1974, advancing maternal age did not appear to increase the risk of fetal death over that among women 30 or younger until women reached 40 years of age (odds ratio, 1.8; 95 percent confidence interval, 1.1 to 3.1) (Table 4). However, parity was an important independent predictor of fetal death among all women. Both women having their first child (odds ratio, 1.9; 95 percent confidence interval, 1.5 to 2.4) and women with high parity (odds ratio, 1.7; 95 percent confidence interval, 1.3 to 2.3) were at increased risk for fetal death.

During 1978 through 1993, advancing maternal age was a stronger predictor of fetal death. Women who were 35 to 39 years old had a nearly twofold increase in the risk of fetal death as compared with women under 30 (odds ratio, 1.9; 95 percent confidence interval, 1.3 to 2.7), and women 40 or older had 2.4 times the risk (95 percent confidence interval, 1.3 to 4.5). In the more recent period, having a first child was no longer a significant predictor of fetal death (odds ratio, 1.2; 95 percent confidence interval, 0.9 to 1.6), but women with

high parity, regardless of age, had an odds ratio of 1.8 for fetal death as compared with women having a second or third child (95 percent confidence interval, 1.2 to 2.9). In both the early and the more recent periods, previous abortion was not a significant risk factor for fetal death. When abortions were subclassified as induced, spontaneous, or of unknown type, no subgroup was found to be at an increased risk for subsequent fetal death. In the early period, women who had a previous fetal death had a significantly increased risk of a second fetal death (odds ratio, 3.1; 95 percent confidence interval, 2.0 to 4.8), but in the more recent period such women were no longer at increased risk for fetal death.

Women with multiple gestation were at increased risk for fetal death in both periods. The increasing number of triplet or higher-order gestations in 1978 through 1993 accounts for the significant increase in risk associated with multiple gestation in this period (odds ratio, 3.4; 95 percent confidence interval, 2.1 to 5.2). Pregnancies complicated by diabetes that required insulin treatment were more likely than pregnancies in women without diabetes to result in a fetal death in the early period (odds ratio, 3.5; 95 percent confidence interval, 1.9 to 6.8); diabetes was not an independent predictor of fetal death in the more recent period. Diabetes that could be adequately treated by diet was not a significant risk factor for fetal death in either period. The frequency of placenta previa did not change significantly over the study period, nor did the relative risk of fetal death in patients with placenta previa. In 1978 through 1993, however, there was an increase in both the frequency of placental abruption (Table 2) and the associated risk of fetal death (Table 4).

DISCUSSION

In a large, unselected obstetrical population in Canada, the fetal death rate has declined markedly — by more than 70 percent — during the past three decades. This reduction could not have been due to a reclassification or a shift of fetal deaths to neonatal deaths, since the neonatal death rate declined even more than the fetal death rate. Changes both in obstetrical practice and in the population of pregnant women are likely to be responsible for this decline. Advances in obstetrical practice appear to be responsible for some of the decline in the fetal death rate through the prevention of specific

Table 3. Total Births, Fetal Deaths, and Crude Fetal Death Rates, According to Decade and Maternal Age.*

VARIABLE	1960s		1970s		1980s		1990-1993	
	<35	≥35	<35	≥35	<35	≥35	<35	≥35
No. of total births	25,369	3465	16,042	1453	30,529	4797	10,436	2227
No. of fetal deaths	274	57	124	18	135	39	28	13
Fetal deaths/1000 total births	10.8	16.5	7.7	12.4	4.4	8.1	2.7	5.8
Odds ratio (95% CI)	1.0 (—)	1.5 (1.1-2.1)	1.0 (—)	1.6 (0.9-2.7)	1.0 (—)	1.9 (1.3-2.7)	1.0 (—)	2.2 (1.1-4.4)

*Data collection for the 1960s began in 1961. Information on births for the years 1975 through 1977 is not available and is therefore not included. Excluded are 28 births for which either the mother's age or the date of delivery was not entered into the data base. CI denotes confidence interval. The reference group for each time period is the women under 35 years of age.

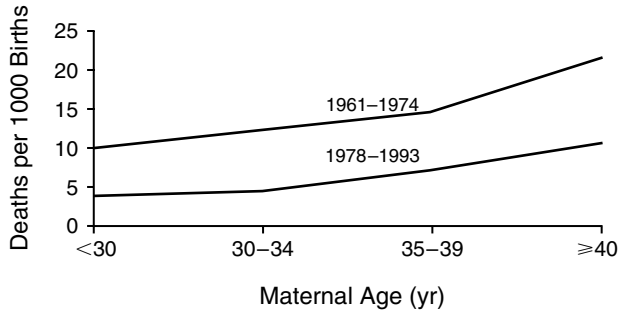


Figure 1. Fetal Deaths per 1000 Total Births, According to Maternal Age and Study Period.

causes of fetal death; such advances include the administration of Rh immune globulin, improved prenatal diagnosis of lethal anomalies, antepartum surveillance for intrauterine growth retardation, and intrapartum surveillance and the resulting reduction in intrapartum asphyxia.^{17,18}

The absolute rate of fetal death has declined significantly for women of all age and parity groups; nevertheless, older women remain at higher risk for fetal death, even after one controls for common diseases associated with older age, such as diabetes and hypertension, and complications of pregnancy such as abruption, which are also associated with increasing maternal age. In our data base, the relative risk of fetal death among women 35 years of age or older, as compared with that among younger women, has actually increased since the 1960s; this increase in risk can largely be attributed to a relatively greater drop in the rate of fetal death among younger women. We did not find that women who were 35 or older had an increased rate of fetal death due to lethal congenital anomalies, as compared with that among younger women. Currently, older women are screened for congenital anomalies by ultrasound examination and amniocentesis. Women who elected to terminate an affected pregnancy did not appear in our data base unless the fetus weighed 500 g or more. Why advanced maternal age is an independent risk factor for fetal death remains unexplained. One possible explanation is the failure of the uterine vasculature in older women to adapt sufficiently to the increased hemodynamic demands of pregnancy.⁸

The principal findings of this study contrast with

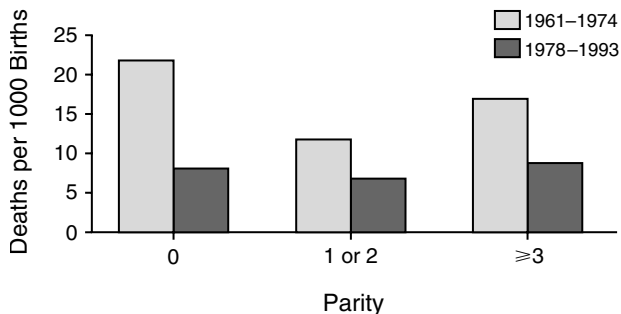


Figure 2. Fetal Deaths per 1000 Total Births among Women 35 Years of Age or Older, According to Parity and Study Period.

those of several previous reports. Berkowitz et al.² reported that in a private obstetrical population of 3917 women (799 of whom were 35 or older) delayed child-bearing posed little, if any, increased risk of adverse perinatal outcome. However, in order to show a doubling of the risk of perinatal mortality, the authors would have needed to double the number of women in their study. Similarly, a case-control study of pregnancy outcomes in a suburban population of nulliparous women 35 or older found that the perinatal mortality rate was not increased by advanced maternal age.⁵ In that study, older women had a 60 percent higher incidence of fetal and neonatal death, but this increase did not reach statistical significance. The authors did state, however, that their study group was too small (1054 women from 25 to 29 years old and 890 women 35 or older) to detect an increase of less than threefold in the risk of perinatal death among older women.

Unlike advanced maternal age, having a first child was no longer an independent risk factor for fetal death in our study, although the data shown in Figure 2 and Table 4 indicate that in the 1960s and early 1970s it clearly was such a risk factor. Forman et al.⁹ reported similar results in Sweden for 1976 to 1980. The factors responsible for fetal mortality among nulliparous women at that time may since have been modified by improved access to medical care and changes in standards of obstetrical practice.

Because of the size of our data base and the length of time it covered, we were able to track temporal changes in other maternal risk factors in addition to age and parity. The diagnoses of diabetes mellitus and hypertension are now made almost four times as often as they were in the 1960s and 1970s. In recent years, the frequency of screening for diabetes has increased, so that in most pregnant women with gestational diabetes the disease is now detected. Since the criteria for the diagnosis remained constant throughout the study period, it is likely that, thanks to more aggressive antepartum screening and treatment, both the absolute and the relative risks of fetal death due to maternal diabetes fell to the point that diabetes was no longer a significant independent risk factor for fetal death in 1978 through 1993.

We found that the prevalence of hypertension had increased, while the absolute risk of fetal death due to hypertension declined. The increasing number of older women giving birth in recent years may contribute to the increased prevalence of hypertension, but this factor alone cannot account for the marked increase. The increasing prevalence of hypertension is likely to be due to a lowering of the threshold for the diagnosis. Despite this potential problem with the classification, when age and parity are accounted for, hypertension remains a significant risk factor for fetal death. A history of abortion, either spontaneous or induced, had no substantial effect on the rate of fetal death at any time in the study period, a finding also noted by others.^{9,19}

The reason for the recent increase in the frequency of placental abruption is unclear. Although the change could be due to a reduction in obstetricians' threshold for classifying active bleeding as placental abruption,

Table 4. Odds Ratios for Fetal Death According to Maternal Variables and Time Period.*

VARIABLE	1961-1974	1978-1993
Total births	39,666	54,680
	<i>odds ratio (95% confidence interval)</i>	
Age <30 yr, parity 1-2	1.0 (—)	1.0 (—)
Age 30-34 yr	1.2 (0.9-1.6)	1.3 (0.9-1.7)
Age 35-39 yr	1.2 (0.9-1.7)	1.9 (1.3-2.7)
Age ≥40 yr	1.8 (1.1-3.1)	2.4 (1.3-4.5)
Pregnant with first child	1.9 (1.5-2.4)	1.2 (0.9-1.6)
Pregnant with fourth or subsequent child	1.7 (1.3-2.3)	1.8 (1.1-2.9)
Previous abortion	1.2 (0.9-1.5)	1.1 (0.8-1.4)
Married	0.7 (0.5-0.9)	0.7 (0.5-0.97)
Diabetes mellitus		
Treated with diet	2.1 (0.6-6.8)	1.2 (0.4-3.2)
Treated with insulin	3.5 (1.9-6.8)	1.7 (0.7-3.9)
Hypertension	2.9 (1.6-5.5)	1.8 (1.2-2.8)
Previous stillbirth	3.1 (2.0-4.8)	1.4 (0.6-3.6)
Multiple gestation	1.5 (1.0-2.6)	3.4 (2.1-5.2)
Placental abruption	10.8 (8.1-14.5)	18.7 (13.4-26.0)
Placenta previa	4.3 (2.0-9.3)	3.6 (1.1-11.5)

*Odds ratios have been adjusted for the date of delivery with a period-appropriate reference group (women less than 30 years of age having their second or third child, with no medical risk factors).

it could also represent a real increase, since the incidence of fetal death associated with placental abruption has also increased. One contributing factor could be the greater frequency of cocaine-induced placental abruption. Recent reports have estimated the frequency of cocaine use at 1 to 17 percent.^{20,21} The women in our study were not routinely screened for cocaine use; therefore, any contribution of this factor remains speculative.

We were unable to evaluate the independent effects of smoking, previous infertility, or social and economic factors. Being married did confer protection against fetal death throughout the 30-year period, presumably because more pregnancies among married women would have been planned and because marriage may have been associated with a more favorable socioeconomic status.

In conclusion, in a general obstetrical population in Canada, there has been a 70 percent decline in the risk of fetal death since the 1960s in all maternal age groups. Maternal characteristics that were important predic-

tors of fetal death 20 years ago, including diabetes, previous fetal death, and having a first child, are no longer independent risk factors. Even when we controlled for recognized coexisting conditions that contribute to fetal death, women 35 years of age or older continued to have a risk of fetal death that was twice as high as that among their younger counterparts.

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