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Effect of advanced maternal age on perinatal outcomes in twins: the impact of chorionicity

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ABSTRACT

Purpose: In contrast to singletons, twins born to older mothers have lower rates of perinatal mortality than twins born to younger mothers. We examined whether differences in chorionicity could explain this unexpected maternal age effect.
Methods: We used population-based data on twins born to mothers aged 20–29 (n = 3702) and ≥35 years (n = 1880) in the North of England, UK, 1998–2007. We calculated rate ratios (RR) and 95% confidence intervals (CIs) to estimate the effect of maternal age; adjusted RRs (ARRs) were estimated by the use of generalized estimating equations for Poisson regression controlling for chorionicity and other confounders.
Results: Older mothers had a lower proportion of monochorionic twins (17.6% vs. 24.3%, $P < .01$); lower neonatal (RR, 0.57; 95% CI, 0.34–0.95) and perinatal mortality (RR, 0.74; 95% CI, 0.53–1.04). Adjustment for chorionicity attenuated these associations (ARR, 0.59; 95% CI, 0.35–0.98 and ARR, 0.80; 95% CI, 0.57–1.12, respectively) and after further adjustment for additional factors, both associations became nonsignificant. Older mothers had greater rates of small-for-gestational-age infants (ARR, 1.59; 95% CI, 1.24–2.05), and cesarean delivery (ARR, 1.31; 95% CI, 1.16–1.48).
Conclusions: Perinatal death rates were lower but not statistically different for twins born to older versus younger mothers. This association was attenuated by adjustment for chorionicity.

Introduction

The trend towards delayed childbearing and use of assisted reproduction technologies (ARTs) during the past few decades has led to an increase in the rate of multiple pregnancies in most industrialized countries [1–4]. The temporal increase in twinning has occurred mainly because of the growing use of ovulation-enhancing fertility drugs and other ARTs [5–7]. In the United Kingdom, for example, approximately half of all twins are conceived as a result of fertility treatment [8]. Women with ART-conceived twins have significantly greater average maternal age compared with those who conceive twins spontaneously [9,10]. Assisted conception involving both ovulation (over) stimulation and in vitro fertilization techniques along with advanced maternal age are associated with dizygotic twinning [11].

Dizygotic twins give rise to dichorionic (DC) placentation; monochorionic (MC) placentation among such twins is very rare [12,13]. In contrast, approximately two-thirds of monozygotic twins develop MC placentation, and one-third develop DC placentation [14], with the type of placentation depending on the timing of zygotic division. The rates of perinatal mortality vary significantly by chorionicity and zygosity, with a greater rate of mortality observed among monozygotic MC twins whereas monozygotic DC twins have a similar risk as dizygotic DC twins [15]. Chorionicity is thus the strongest predictor of adverse perinatal outcomes among twins [16,17]. Compared with DC twins, MC twins have a 3.5-fold greater risk of stillbirth and a 50% greater risk of neonatal death [18].

Although older maternal age typically is associated with an increased risk for pregnancy complications and adverse perinatal outcomes among singletons [19,20], older maternal age is observed to have an unexpected favorable effect in twin pregnancy. Several studies have shown lower rates of preterm birth, intrauterine growth restriction, and perinatal death among twins born to older mothers [21–25]. However, the reasons behind this phenomenon remain poorly understood [26,27].

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In this work, we sought to describe the association between maternal age and chorionicity and to examine the effect of chorionicity on the association between maternal age and adverse birth outcomes among twins. We hypothesized that older mothers would have a significantly greater proportion of DC twins and that the confounding effect of chorionicity would partly explain the relatively favorable effect of older maternal age on perinatal mortality and adverse birth outcomes among twins.

Methods

Northern Survey of Twin and Multiple Pregnancy (NorSTAMP)

We used data on twins born between 1998 and 2007 to mothers residing in the North of England, UK, which has a population of approximately 3 million and 31,000 deliveries per year. In NorSTAMP, multiple pregnancies were ascertained from the earliest antenatal ultrasound scan at which a multiple pregnancy was determined (recommended at 10–13 weeks in the UK; National Institute for Health and Clinical Excellence [28]), and then successively at the 20-week routine ultrasound and at delivery. Multiple pregnancy may have also been identified after miscarriage or by the discovery of the remains of a second fetus at the time of an apparently singleton birth. The initial ascertainment was provided on a notification card that included basic identifying information and, where possible, the ultrasound assessment of chorionicity. Birth information was then obtained from a birth registration form at the delivery hospital [29,30]. The average notification rate was found to be 95% (with variations between the maternity units), based on a case ascertainment validation study with the Office for National Statistics data [31].

The records were maintained and held at the Regional Maternity Survey Office and linked to a number of other regional surveys, including the Perinatal Morbidity and Mortality Survey [32] and the Northern Congenital Abnormality Survey [33]. Information on the following maternal characteristics was collected: maternal age, marital status, smoking during pregnancy, and parity. Clinical information included previous stillbirth or neonatal death, previous spontaneous or induced abortions, previous cesarean deliveries, gestational age at the first ultrasound, chorionicity, major congenital anomalies, and the infant's sex. Socioeconomic deprivation was estimated from the index of multiple deprivation (an area-based measure derived from mothers' residential postal code at booking) [34], and analyzed in tertiles of rank, with tertile 1 being most deprived and tertile 3 least deprived. The index of multiple deprivation combines indices such as income, employment, health and disability, education, skills and training, barriers to housing and services, living environment, and crime.

Definitions and statistical analyses

Twin maternities were defined as twin pregnancies with at least one live birth or stillbirth, including pregnancies with one fetal loss before 24 weeks, and twins from these maternities were used as the denominator for calculating stillbirth and perinatal mortality rates. Stillbirth was defined as birth after fetal death at 24 or more completed weeks of gestation (the gestational age criterion for stillbirth registration in England and Wales since 1992). According to this criterion, all fetal deaths identified and delivered before 24 weeks (e.g. vanishing twins, miscarriages) were not included in the numerator for calculation of stillbirth/perinatal mortality rates. Neonatal death was defined as death during the first 28 days after live birth. Perinatal death included both stillbirth and neonatal death (extended/obstetric definition). The final diagnosis of chorionicity for same-sex twin pregnancies was based on placental examination and histology, which is more accurate than the diagnosis based on ultrasound [35]. When placental examination results were not available (13.6% of same-sex twin pregnancies), the first trimester ultrasound diagnosis was used. Placental examination and ultrasound-based diagnosis of chorionicity yielded the same results among 96.4% DC twins and 88.5% MC twins. Overall, chorionicity was unknown for 9.5% of all twin pregnancies. Twins with unknown chorionicity were excluded from the main analyses presented in Tables 1–4. Causes of stillbirth and neonatal death were categorized using a clinicopathological classification [36] based on the Wigglesworth classification [37]. All comparisons we made between twins born to younger women (aged 20–29 years at the time of birth) and twins born to older women (aged 35 years or more).

Poisson regression models and generalized estimating equations were used to calculate rate ratios (RRs) and 95% confidence intervals (95% CIs) with adjustment for intertwin correlation in outcomes. The outcomes examined included very low birth weight (VLBW; <1500 g), small-for-gestational age (SGA), stillbirth, neonatal death, and perinatal death. SGA was defined as birth weight less than the 10th percentile using Scottish birth weight by gestational age and sex standards for twins [38]. Generalized Linear Models (Poisson log-linear model) were used for analyzing preterm birth (<37 weeks, <34 weeks, and <32 weeks' gestation), birth weight discordance and cesarean delivery. Birth weight discordance was defined as a 25% or greater difference in cotwin birth weights. Adjustment was made for the following covariates: maternal index of multiple deprivation (tertiles: most deprived, medium, least deprived), parity (nulliparous vs. multiparous women, based on the total number of previous births), smoking during pregnancy, infant's sex, and major congenital anomalies (yes/no). Major congenital anomalies were defined according to European Surveillance

Table 1
Maternal and fetal/infant characteristics for twins* of older (≥35 years) and younger (20–29 years) mothers, North of England, 1998–2007

Risk factor	Maternal age		
	20–29 years, n (%)	≥35 years, n (%)	*P* value
Maternal characteristics	n = 1676	n = 865	—
Chorionicity			
Monochorionic	408 (24.3)	152 (17.6)	<.01
Dichorionic	1268 (75.7)	713 (82.4)	—
Primiparity	789 (47.1)	312 (36.1)	<.01
Missing	97 (5.8)	60 (6.9)	—
Index of multiple deprivation			
Tertile 1 (most deprived)	703 (41.9)	204 (23.6)	<.01
Tertile 2	599 (35.7)	251 (29.0)	—
Tertile 3 (least deprived)	374 (22.3)	410 (47.4)	—
Smoking during pregnancy	499 (29.8)	155 (17.9)	<.01
Missing	97 (5.8)	50 (5.8)	—
One parent (marital status)	51 (3.0)	12 (1.4)	.01
Missing	56 (3.3)	26 (3.0)	—
Previous stillbirth or neonatal death	25 (1.4)	21 (2.4)	.09
Missing	96 (5.7)	59 (6.8)	—
Previous spontaneous abortions (any)	260 (15.5)	216 (25.0)	<.01
Missing	96 (5.7)	58 (6.7)	—
Previous induced abortions (any)	77 (4.6)	36 (4.2)	.62
Missing	96 (5.7)	58 (6.7)	—
Previous Cesarean delivery	105 (5.7)	100 (10.6)	<.01
Missing	131 (7.1)	72 (7.7)	—
Gestational age at the first ultrasound, weeks			
<13	1056 (64.4)	578 (69.2)	.02
≥19	140 (8.5)	44 (5.2)	<.01
Infant characteristics	N = 3352	N = 1730	—
Male sex	1649 (49.2)	817 (47.2)	.18
Major congenital anomaly (any)	116 (3.5)	81 (4.7)	.03

* Twin pregnancies with known chorionicity (monochorionic and dichorionic) only are included.