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Paternal age and twinning in the Jerusalem Perinatal Study

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Abstract

Objective—To investigate whether incidence of twin deliveries is related to father's age, independently of mother's age, and whether it differs for same-sex or opposite-sex twin sets.

Study Design—In a program of research on effects of paternal age, this study used data from a prospective cohort of 92,408 offspring born in Jerusalem from 1964-1976. Of the 91,253 deliveries in the Jerusalem Perinatal Study, 1,115 were twin deliveries. The data were analyzed with General Estimate Equations to inform unconditional logistic regression.

Results—After controlling for maternal age, Odds Ratios (OR) and 95% Confidence Intervals (95% CI) associated with father's ages 25-34 and 35+ were 1.3 (1.1, 1.7) and 1.5 (1.2, 2.1) respectively, compared with fathers <25 years old. The effect of maternal age was partly explained by paternal age. The ORs for opposite-sex twin sets and male-male twin sets increased slightly with paternal age, while the OR for same-sex and female-female twin decreased.

Conclusion—Studies of twins are used to estimate effects of genes and environment in a variety of diseases. Our findings highlight the need to consider paternal as well as maternal age when analyzing data on twins to explore etiology of diseases.

Keywords

twins; paternal age; maternal age; opposite-sex twin sets; same-sex twin sets

Introduction

Twin deliveries make up 3% of all deliveries in the United States¹. Their incidence increases with increasing maternal age, reaching a maximum at approximately age 37, and decreasing thereafter^{2,3}. It is not known whether multi-fetal deliveries are also related to age of the father. There is a growing recognition that paternal ageing can affect reproductive outcomes, being implicated in miscarriage⁴, preeclampsia⁵ and suboptimal outcomes in offspring including autism, schizophrenia, cancer, and Alzheimer's disease⁶⁻¹¹. Older fathers produce sperm with

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Condensation: Older men may be more likely to father twins, independently of maternal age, and may father more male sets and more opposite-sex sets of twins.

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more genetic errors than younger fathers, and abnormal methylation of paternally imprinted genes is also hypothesized to contribute to the effect of increasing paternal age on offspring ¹²⁻¹⁴. One previous population study has suggested that paternal age might play a role in multiple birth rates ¹⁵, while a study of monozygotic twinning in Sweden found no paternal age effect ¹⁶.

Data on twins have been used extensively to estimate heritability of disease; however, such estimates might be questionable if the disease was one that was affected by paternal age and if twinning were also found to be associated with paternal age. In addition, multiple gestations are at greater risk for complications and the offspring are at increased risk for significant morbidity and mortality, risks that are associated with maternal age. As men and women delay childbearing in many industrialized societies, it is important to understand whether advancing paternal age increases the risk of twin births independently of maternal age and other factors.

Methods

Data source

We used data from the Jerusalem Perinatal Study, a population-based prospective cohort derived from all 92,408 births in 1964-76 to mothers resident in Western (Israeli) Jerusalem. Core information from the notification of birth was supplemented with data abstracted from medical records in obstetric departments, ante-partum and post-partum interviews with mothers and surveillance of pediatric inpatient departments. The methods and characteristics of the population have been described in previous publications ¹⁷⁻¹⁹, as have the characteristics of fathers of different ages ⁷. Use of the data for this study was approved by the institutional review boards at Hebrew University - Hadassah Medical Center, Jerusalem, and Columbia University Medical Center, New York, and was exempted from the requirement for informed consent.

Data analysis

SAS 9.1 (SAS Institute Inc, Cary, North Carolina) was used to analyze the data. After comparing demographic and other characteristics of singleton and multiple deliveries using cross tabulations, we developed unconditional logistic regression models, testing for effects of paternal age and other variables on a binary outcome of twin versus singleton delivery. To account for the correlation of siblings within families, we computed General Estimating Equations for the logistic regressions. Results are presented as odds ratios (OR) with 95% confidence intervals (CI). Binary variables and sets of categories were coded 0 (if absent) or 1 (if present). Paternal and maternal ages were tested first in five year categories and then as continuous variables treated as years deviation from their means. These methods of describing mother's and father's ages allowed us to account for the correlation of mother's and father's ages. Paternal age was best described in three categories, (<25, 25-34, 35+) and maternal age in six categories (<20, 20-24, 25-29, 30-34, 35-39, 40 +). Using an adaptation of the variance inflation factor for logistic regression ²⁰, we confirmed that there was no effect of collinearity in our modeling of parental ages. Other variables tested were three categories of social class (based on father's occupation), four categories of birthplace of father (Israel, other West Asia, North Africa, and Europe, including the U.S.A. and other developed countries) and of mother (same categories as father), secular trend (by year), and three categories of birth order and of parity (1-2, 3-4 or 5+). Offspring with unknown father's age (N=1432) were excluded from the analyses of effects of paternal age. Two tenths of one percent of offspring had unknown maternal ages (N=153), and were assigned to the mean maternal age for the population (27.7). Unknowns for categorical variables (all less than 1%) were assigned to the reference groups. A priori, our strategy for building the models included any variable that was related both to paternal age and to the incidence of twin births ($p < .05$), whose addition to the model altered,

by at least 10%, the crude effect of paternal age on the OR for twin birth. Apart from maternal age no variables met these criteria. We tested for interactions by comparing the -2log likelihoods in models with and without interaction terms; none however, were significant modifiers of the effects of paternal age. The same methods were used to calculate the contribution of paternal age to maternal age's effects on twinning, and the Odds Ratios for paternal age effect on delivery of opposite-sex, same-sex, male-male and female-female twin sets.

Results

There were 91,253 deliveries (92,408 offspring) in the Jerusalem Perinatal Study; with 1,115 sets of twins, 22 of triplets and one of quintuplets. Table 1 shows the numbers and percents of multifetal deliveries, by year. The frequency of twins was constant during 1964-68 but it dipped significantly in 1970 ($p < .02$). Not shown in the table, 1970 was also notable for an excess of stillbirths among singletons, although stillbirth rates declined progressively over time. Table 1 shows that higher order multiple births increased in the 1970s, compared with the 1960s and twinning rates increased in 1974-76. These increases affected opposite-sex sets, while the incidence of same-sex sets did not change over time (data not shown).

Table 2 shows the frequency of twin deliveries associated with demographic and social variables, both as crude odds ratios (OR) and those adjusted for maternal age, the only covariate meeting criteria for inclusion in the final regression models. After adjustment for maternal age, neither parity, nor mother's country of birth or religion, nor social status had any significant relation to twin deliveries. Not shown in the table, these variables were also unrelated to delivery of subsets of twins, i.e. those of same versus opposite sex, male or female twins. On the other hand, table 2 shows a significant increase in twins in 1975-76 compared to the earlier years of the cohort; this was due mainly to opposite sex sets (OR= 1.5, 1.2-1.7) while same-sexed sets changed less (1.2, .98-1.3). However, secular trend did not confound the relationship of paternal age to the risk of twin delivery, and so was not included in the final modeling.

Table 3 shows the distribution of multifetal deliveries over categories of maternal age. Stillborn fetuses weighing less than 1000 gm did not require a notification of birth, so that in some of the twin sets the data for the co-twin was not available and therefore concordance of sexes was unknown. Multiple deliveries increased with maternal age until age 35-39, then decreased in the oldest age category.

Table 4 shows the relationships of paternal and maternal ages to twinning, based on deliveries with known father's age; this was missing in 1.6%, i.e. for 17 twin deliveries and 1,398 singletons. Fathers with unknown age showed a 2.3 % rate of multiple delivery as compared to 1.3% overall. Table 4 shows a significant trend in the effects of paternal age; before adjustment for age of mother the frequency of twins for fathers aged 35+ was double that for fathers aged <25. Adjustment for maternal age attenuated this relationship but did not abolish it; the risk of twin delivery still increased significantly in older fathers.

Table 4 also indicates that part of the maternal age effect on twinning is attributable to confounding by father's age. In our analysis, the correlation of maternal and paternal age was accounted for by modeling each with use of multiple categories. Adjustment for father's age attenuated the effects of maternal age and the odds ratios for twinning in mothers aged 25-29 and 30-34 even lose statistical significance, compared with the reference group of mothers aged 20-24.

Table 5 records effects of paternal age on subsets of twins, adjusted for mother's age. It shows some differences in effects of paternal age according to the different types of twins. While older fathers may have a slight excess of deliveries of opposite-sex twin sets, [OR=1.4, 95%

Confidence Interval (CI) (.80, 2.4) and 1.6, 95% CI(.80, 3.0) for fathers aged 25-34 and 35+ respectively, compared to fathers <25], and a slight decrease in same-sex twin deliveries [OR=.70 95% CI(.41, 1.3) and OR=.64 95% CI(.33, 1.2) for fathers aged 25-34 and 35+ respectively, compared to fathers <25] these are not significant. There is, however, a significant decrease in female-female twin sets with advancing paternal age; compared to fathers <25, fathers age 25-34 have and OR=.66, 95% CI (.41, 1.1) and fathers 35+ have an OR=.46, 95% CI (.26, .83) for female-female twin sets.

Adjustment for year of birth had no significant effects on these estimates because no variables of secular trend met our criteria for inclusion in the models, as they altered the ORs for paternal age by less than 10%. Similarly, further adjustment for the other variables shown in table 2 did not alter the ORs estimated for paternal age.

Discussion

These results show an association of increasing paternal age with an increase in incidence of twin deliveries, independent of maternal age. This association was not explained by changes in twinning rates by year of birth, nor was it confounded by ethnic group, birth order or social class.

While many studies have shown that older mothers deliver more twins than younger ones, only one previous population-based study, to our knowledge, has considered paternal age effects on the rate of twin births. Tough et al ¹⁵ investigated low birth weight, preterm birth and multiple births in Alberta, Canada, and showed that among women aged 25-29 years old, multiple birth rates increased with increasing paternal age ¹⁵. A disadvantage of the study was that paternal age was missing in 8.5% of births, so that a non-random distribution of the missing data could potentially have biased the results; the authors concluded that further population based research was needed to confirm their findings ¹⁵.

Our results also suggest that older men father more opposite-sex twin sets and male-male twin sets, but less same-sex and female-female sets. However, comparisons between these types of sets might be due to chance. Therefore, these latter suggestions should be regarded as “hypothesis generating”, and require confirmation from other populations.

The significant decrease in same-sex and female-female twin sets in older fathers was unexpected. The causes of monozygotic twinning are unknown; some speculate that this type of twinning results from a spontaneous genetic mutation ^{2, 21}. There are more chromosome breaks and acentric fragments in the sperm of older men, as well as an increase in de novo gene mutations ^{12, 22}. We hypothesized that paternal age effects, if found, would have a stronger relation to same-sex twins. Our results did not bear this out, but instead were consistent with a Swedish study on monozygotic twinning ¹⁶. Perhaps some paternal factor that increases with age facilitates survival of twin sets in the presence of a male in the set, or there may be an additional confounding factor not identified in our analysis.

Strengths of the data from the Jerusalem Perinatal Study derive from its size and its being population-based. There is very little missing data; almost all mothers were married and the population's religious conservatism makes it more likely that the legal fathers were the biological fathers. We found that although the rates of twin births did change over time, as in other populations ^{21, 23}, adjustment for such changes did not change the estimated effects of paternal age; other social and demographic variables did not contribute to the frequency of twinning. The change in incidence or twinning over time was likely due to increasing use of ovulation induction as occurred in other countries where rises in twin and triplet births have been observed ^{21, 23}. As in our data, these increases were due to an increase in opposite-sex twin sets. Our cohort does not contain data on parental smoking, maternal BMI or ovulation

induction for all offspring. Some of the potential confounding from ovulation induction, however, might be accounted for by consideration of secular trend in our analyses, since use of clomiphene and pergonal increased over the years of the cohort. In addition, while women with higher BMI are more likely to deliver twins²⁴, there is no reason to suspect that older men tend to father children with heavier women after accounting for women's age.

Scientists study data on twins to investigate causal pathways for disease, and our findings illustrate the need to consider paternal as well as maternal age in these analyses. If data on twins are used to investigate a disease whose risk increases with increasing paternal age, then neglecting to adjust for paternal age might lead to spuriously inflated estimates of the contribution of other risk factors to burden of disease. As people delay childbearing in industrialized societies, it is also valuable to understand whether older men father more twins.

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Table 1
Numbers of deliveries and percent twins and other multiple deliveries, by year of birth

Year	Total deliveries	Twin deliveries	%	Other multiple deliveries	%
1964	5,663	66	1.2	-	-
1965	6,003	73	1.2	1	.02
1966	5,930	73	1.2	-	-
1967	5,838	68	1.2	-	-
1968	6,253	77	1.2	-	-
1969	6,604	83	1.3	2	.03
1970	6,967	59	.85	1	.01
1971	7,432	95	1.3	3	.04
1972	7,247	74	1.0	6	.08
1973	7,867	96	1.2	1	.01
1974	8,212	107	1.3	2	.02
1975	8,502	119	1.4	6	.06
1976	8,735	125	1.4	2	.02
Total	91,253	1115	1.2	23	.02

Table 2
Numbers of deliveries, percent twin deliveries, Odds Ratios (ORs) for twin deliveries adjusted for maternal age, and 95% confidence intervals (CI), for selected characteristics

Characteristic	Deliveries	Twin deliveries	%	Adjusted OR	95% CI
Year of birth					
1964-74	74,016	871	1.2	1	Ref
1975-76	17,237	244	1.4	1.2	1.1, 1.4
Mother's country of birth					
Israel	12,283	155	1.3	1	Ref
Other Western Asia	26,622	324	1.2	.93	.79, 1.1
Northern Africa	20,572	256	1.2	.95	.81, 1.1
Europe etc. *	29,660	352	1.2	.93	.73, 1.1
Other	2116	28	1.3	1.1	.70, 1.7
Mother's religion					
Jewish	89,228	1088	1.2	1	Ref
Muslim and Druze	1,796	23	1.3	1.0	.68, 1.6
Christian	228	4	1.8	1.1	.34, 3.4
Unknown	1	0	0	---	---
Birth Order					
1-2	48,896	530	1.1	1	Ref
3-4	24,492	324	1.3	1.0	.86, 1.2
5+	17,865	261	1.5	1.0	.85, 1.2
unknown	202	2	.99	---	---
Social Class					
Low	32,450	405	1.3	1	Ref
Medium	29,945	342	1.1	.93	.81, 1.1
High	28,858	368	1.3	1.0	.90, 1.2

Table 3
Number of total and twin deliveries, percent twin deliveries, and types of twin deliveries, by maternal age

Total deliveries	<20	20-24	25-29	Maternal age		40+	Unknown	Total
				30-34	35-39			
Twin sets, N	3,586	27,754	29,180	18,187	9,547	2,847	152	91,253
Of these,	18	278	372	261	159	26	1	1,115
Opposite-sex sets	.50	1.0	1.3	1.4	1.7	.91	.66	1.2
Male-Male sets	4	73	108	84	64	8	0	341
Female-Female sets	9	94	138	91	50	9	0	391
Unmatched Twins	4	107	121	84	44	9	1	370
	1	4	5	2	1	0	0	13

Table 4
Odds ratios (OR), 95% confidence intervals (CI) and p values for effects of parents' ages on twinning, both unadjusted, and adjusted for the other parent

	Unadjusted		P	Adjusted for other parent's age		P
	OR	95% CI		OR	95% CI	
Paternal age						
<25	1	Ref	---	1	Ref	---
25-34	1.6	(1.3, 2.0)	<.0001	1.3	(1.1, 1.7)	.02
35+	2.0	(1.6, 2.5)	<.0001	1.5	(1.2, 2.1)	.004
Maternal age						
<20	.45	(.27, .78)	<.004	.49	(.29, .83)	.009
20-24	1	Ref	---	1	Ref	---
25-29	1.3	(1.1, 1.5)	.001	1.2	(.99, 1.4)	.06
30-34	1.4	(1.2, 1.7)	<.0001	1.2	(1.0, 1.5)	.05
35-39	1.7	(1.4, 2.1)	<.0001	1.4	(1.1, 1.8)	.01
40+	.95	(.64, 1.4)	.77	.76	(.50, 1.2)	.20

Table 5
Numbers of total deliveries (N), twin deliveries (n), odds ratios (OR) and 95% confidence intervals (CI) by subsets of twins and paternal age, adjusted for maternal age

Paternal age	<25	25-34	35+
Total deliveries	13,477	51,270	26,506
Twin deliveries	110	611	394
	.80	1.2	1.5
	1	1.3	1.5
	Ref	(1.1, 1.7)	(1.2, 2.1)
	95% CI		
	P	.02	.004
Opposite-sex twin sets	N	178	139
	OR	1.4	1.6
	95% CI	(.80, 2.4)	(.80, 3.0)
	P	.20	.20
Same-sex twin sets	N	426	252
	OR	.70	.64
	95% CI	(.41, 1.3)	(.33, 1.2)
	P	.24	.17
Female twin sets	N	47	111
	OR	.66	.46
	95% CI	(.41, 1.1)	(.26, .83)
	P	.09	.01
Male twin sets	N	36	141
	OR	1.2	1.5
	95% CI	(.71, 1.9)	(.81, 2.7)
	P	.50	.20
Unmatched Twins	3	7	3