Paternal age and adverse birth outcomes: teenager or 40+, who is at risk?

Xi-Kuan Chen1,2,3, Shi Wu Wen1,2,4,7, Daniel Krewski3,4,5, Nathalie Fleming6, Qiuying Yang1,2 and Mark C. Walker1,2,4

1OMNI Research Group, Department of Obstetrics and Gynecology, University of Ottawa, 501 Smyth Rd, Box 241, Ottawa, Ontario, Canada K1H 8L6; 2OMNI Research Group, Clinical Epidemiology Program, Ottawa Health Research Institute, University of Ottawa, Ottawa, Ontario, Canada; 3McLaughlin Center for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, Ottawa, Ontario, Canada; 4Faculty of Medicine, Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ontario, Canada; 5Risk Sciences International, Ottawa, Ontario, Canada; 6Pediatric Adolescent Gynecology, Children’s Hospital of East Ontario, University of Ottawa, Ontario, Canada

7Correspondence address. E-mail: swwen@ohri.ca

BACKGROUND: Most previous studies on the effect of paternal age have focused on the association of advanced paternal age with congenital anomalies. The objective of this study was to determine whether paternal age is associated with the risk of adverse birth outcomes, independent of maternal confounders. METHODS: We carried out a retrospective cohort study of 2,614,966 live singletons born to married, nulliparous women aged 20–29 years between 1995 and 2000 in the USA. Multiple logistic regressions were applied to estimate the independent effect of paternal age on adverse birth outcomes. RESULTS: Compared with infants born to fathers aged 20–29 years, infants fathered by teenagers (<20 years old) had an increased risk of preterm birth [odds ratio (OR) = 1.15, 95% confidence interval (CI): 1.10, 1.20], low birth weight (OR = 1.13, 95% CI: 1.08, 1.19), small-for-gestational-age births (OR = 1.17, 95% CI: 1.13, 1.22), low Apgar score (OR = 1.13, 95% CI: 1.01, 1.27), neonatal mortality (OR = 1.22, 95% CI: 1.01, 1.49) and post-neonatal mortality (OR = 1.41, 95% CI: 1.09, 1.82). Advanced paternal age (≥40 years) was not associated with the risk of adverse birth outcomes. CONCLUSIONS: Teenage fathers carry an increased risk of adverse birth outcomes that is independent of maternal confounders, whereas advanced paternal age is not an independent risk factor for adverse birth outcomes.

Keywords: paternal age; preterm birth; low birth weight; small for gestational age birth; infant mortality

Introduction

Mounting evidence indicates that maternal age has a significant effect on the risk of adverse birth outcomes. On one hand, advanced paternal age is associated with an increased risk of fetal death (Raymond et al., 1994; Fretts and Usher, 1997), preterm delivery (Astolfi and Zonta, 1999) and low birth weight (Nahum and Stanislaw, 2002). On the other hand, teenage pregnancies are at increased risk for low Apgar score (Chen et al., 2007), preterm delivery (Fraser et al., 1995; Gortzak-Uzan et al., 2001; Gilbert et al., 2004; Chen et al., 2007), low birth weight (Gortzak-Uzan et al., 2001; Gilbert et al., 2004; Chen et al., 2007), small-for-gestational-age births (Fraser et al., 1995; Gortzak-Uzan et al., 2001; Chen et al., 2007) and neonatal mortality (Gilbert et al., 2004; Chen et al., 2007). In contrast to the attention devoted to the influence of maternal age on adverse birth outcomes, several factors have hindered the study of paternal age. The first is the large amount of attention that has traditionally been paid to maternal influences on fetal growth, which are considered to be of more importance than paternal influences. Second, the biological father is unknown in some cases, precluding the investigation of paternal effects. In the USA, paternal age was missing from vital statistics records for 39% of unmarried women, but only 0.4% of married women (Basso and Wilcox, 2006), suggesting that lack of information on paternal characteristics may be more prevalent among unmarried women. Third, from an epidemiological standpoint, it is more convenient to study the effects of maternal factors on birth outcomes. Pregnant women generally make frequent prenatal care visits to their physician or hospital, thereby facilitating the collection of information on maternal characteristics that may affect birth outcomes. Although paternal information is not routinely collected in most perinatal health studies, there are a growing number of epidemiological studies focusing on the effect of paternal age on pregnancy and birth outcomes. The possibility of such paternal effects has some biologic
plausibility, since the placenta is largely dependent on the expression of genes of paternal origins (Miozzo and Simoni, 2002), and potentially harmful mutations in genes involved in placentation may be more frequent among immature men and older men (Schwartz et al., 1983; Slama et al., 2005), leading to adverse birth outcomes.

Most previous studies of the association between paternal age and pregnancy and birth outcomes have focused on the effect of advanced paternal age on congenital anomalies. The effects of younger paternal age were not well studied. Our previous study indicated that advanced paternal age was associated with a higher risk of heart defects, tracheoesophageal fistula, Esophageal atresia, Down’s syndrome and other chromosomal anomalies, whereas younger paternal age was related to an increased risk of spina bifida, meningocoele, microcephalus, omphalocele and gastroschisis (Yang et al., 2006). Recent studies have shown that advanced paternal age is associated with fetal death (Andersen et al., 2004), miscarriage (de la Rochebrodanch and Thonneau, 2002), spontaneous abortion (Slama et al., 2005) and pre-eclampsia (Harlap et al., 2002) during pregnancy, and dyslexia (Jayasekara and Street, 1978), acute lymphatic leukemia (Dockerty et al., 2001) and schizophrenia (Miozzo et al., 2001) among offspring. The observed associations between paternal age and some adverse birth outcomes are somewhat inconsistent. Some studies found that advanced paternal age was not associated with an increased risk of preterm birth (Olshansky et al., 1995; Abel et al., 2002; Tough et al., 2003; Basso and Wilcox, 2006), low birth weight (Parker and Schoendorf, 1992; Olshansky et al., 1995; Abel et al., 2002; Nahum and Stanislaw, 2003; Tough et al., 2003) and small-for-gestational-age birth (Olshansky et al., 1995; Abel et al., 2002), whereas other studies have found advanced paternal age to be linked to preterm birth (Zhu et al., 2005; Astolfi et al., 2006), low birth weight (Reichman and Teitler, 2006) and low Apgar score (Sun et al., 2006).

Materials and Methods

Study population

The data used in this study were derived from the 1995–2000 linked birth/infant death database of the USA, which was based on live births and infant deaths up to 1 year of age registered in the 50 states and the District of Columbia. The data were coded according to uniform specifications, have gone through statistical quality checks and have been carefully edited by the National Center for Health Statistics (NCHS) (Centers for Disease Control and Prevention/National Center for Health Statistics, 2000). An estimated 99% of all births occurring in the USA are registered in this data set. The electronic birth and death registration files were automatically checked for completeness, individual item code validity, and unacceptable inconsistencies between data items by computer programs developed by the NCHS. NCHS staff reviewed the data files on an ongoing basis to detect problems in overall data quality such as inadequate reporting of specific items, failure to follow NCHS coding rules and system and software errors. Missing records and other problems detected by NCHS were returned to registration area and corrected (Centers for Disease Control and Prevention/National Center for Health Statistics, 2000).

Our study was restricted to live singletons born to married, nulliparous women 20–29 years of age. Those subjects with missing data on paternal age, race, maternal education, prenatal care status, gestational age and birth weight were excluded from the present study.

Definition of exposure and outcomes

Paternal age was defined as the age of father in completed years at the time of delivery. Paternal age was categorized into seven groups: <20, 20–29, 30–34, 35–39, 40–44, 45–49 and ≥50 years of age. Since fathers 20–29 years of age have the lowest risk of adverse birth outcomes (Astolfi et al., 2006), they were selected as the reference group for all analysis reported here.

The NCHS calculated gestational age as the time interval between the date of last normal menstrual periods (LMP) and the date of delivery. When the LMP date was missing, a clinical estimate of gestational age was made by the NCHS (~5% of records) (Taffel et al., 1982). The 5 min Apgar score was not included in birth certificates in California (1995–2000) and Texas (1995–2000); subjects from California and Texas were therefore not included in analyses of the Apgar score.

Adverse birth outcomes considered in this study included very preterm delivery (live infant delivered at less than 32 weeks’ gestation), preterm delivery (live infant delivered at less than 37 weeks’ gestation), very low birth weight (live infant weighing less than 1500 g at birth), low birth weight (live infant weighing less than 2500 g at birth), small-for-gestational-age birth [live infants with birth weights below the 10th percentile for gestational age and sex (David, 1983)], very low Apgar score at 5 min (<4), low Apgar score at 5 min (<7), fetal distress, neonatal death (death of a live birth within 28 days) and post-neonatal death (death of a live birth between 28–364 days of age).

Covariates

Data available in this linked data set included demographic characteristics of the parents, obstetric history, antenatal high-risk conditions, maternal lifestyle factors such as smoking and alcohol consumption, time of initiation of prenatal care, total number of prenatal visits, labor and delivery complications, gestational age, birth weight, Apgar score at 5 min, neonatal/infant diseases and vital status. In this study, prenatal care was categorized as adequate plus, adequate, intermediate or inadequate according to the Adequacy of Prenatal Care Utilization (APNCU) Index developed by Kotelchuck (1994), which was generated based on the month of initiation of prenatal care, the number of prenatal visits and gestational age at delivery. Data on maternal tobacco use were not collected in California (1995–2000), Indiana (1995–1998), South Dakota (1995–1999) and New York State (except New York City, 1995–1998). California (1995–2000) and South Dakota (1995–1999) did not report alcohol use on their birth certificates. Subjects with no available information on maternal tobacco use and maternal alcohol use were included in a separate category in this study.
Statistical analysis

Descriptive statistics calculated in this study included the distribution of paternal race, maternal age, race, educational level, tobacco and alcohol use during pregnancy, adequacy of prenatal care and infant sex, stratified by paternal age. Rates of adverse birth outcomes were calculated for each paternal age group. The adjusted ORs along with their 95% CIs associated with paternal age groups, with reference to 20–29 years old, were derived through unconditional multiple logistic regressions with adjustment for potential confounding variables for each paternal age group, using fathers 20–29 years of age as the reference category. In order to control for the dominant role of birth defects, the effects of paternal age on adverse birth outcomes were further evaluated in infants without birth defects after excluding subjects from New Mexico, since birth defects were not included in New Mexico (1995–2000) birth certificate data set. ORs were adjusted for paternal race (white, black and other than white and black, with white as the reference group), maternal age (20–24 and 25–29 years of age, with 20–24 years of age as the reference), race (white, black and other than white and black, with white as the reference), educational level (≤12, 13–15 and ≥16 years, with 13–15 years as the reference), smoking and alcohol drinking during pregnancy (no, yes and not reported, with no as the reference), adequacy of prenatal care (adequate plus, adequate, intermediate and inadequate, with adequate as the reference) and infant sex (male and female, with male as the reference). All data were analysed using Statistical Analysis System, Version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

There were 23,654,785 births in the 1995–2000 linked birth and infant death data set. Among them, 2,757,263 singleton infants were born to married, nulliparous women 20–29 years of age. Subjects with no available information on maternal education (30,546), initiating time of prenatal care (52,867), number of visits of prenatal care (73,345), gestational age at delivery (20,310) or birth weight (773) were excluded. Finally, 15,191 (0.58%) subjects were excluded because of missing information on paternal age or race, leaving 2,614,966 subjects for analysis (some subjects were missing two or more items and were counted twice).

Compared with children born to fathers 20 and 29 years of age, offspring born to teenage fathers were more likely to be of both white paternal and maternal race, and to be born to younger mothers with a lower maternal education level and higher maternal smoking during pregnancy; these children also had a greater prevalence of inadequate prenatal care. The infants born to a father with advanced age were more likely to have had an older mother, to be of both black paternal and maternal race, and higher maternal drinking during pregnancy (Table I).

The rates of very preterm births, preterm births, very low birth weight, low birth weight, small-for-gestational-age births, very low Apgar score, low Apgar score, neonatal mortality and post-neonatal mortality among children born to teenage fathers, when compared with fathers 20–29 years of age (Table III). Advanced paternal age was not associated with an increased risk of adverse birth outcomes. Restricting the analysis to subjects without birth defects yielded similar results (Table IV).

Discussion

Our large population-based study indicated that teenage fathers have an increased risk of adverse birth outcomes (preterm birth, low birth weight, small-for-gestational-age births, low Apgar score and infant mortality) independent of other risk factors, whereas advanced paternal age is not an independent risk factor for adverse birth outcomes.

Age of procreation depends on both fecundity and family planning (Basso and Wilcox, 2006). Some couples have children at an advanced age because they were not able to conceive at a younger age. Because subfecundity might be associated with the risk of adverse birth outcomes (Basso and Baird, 2003), we restricted our study to women 20–29 years of age who have the lowest incidence of subfecundity (Astolfi et al., 2006), thereby minimizing the potential confounding of maternal fecundity. Because parity and multiple births are important risk factors for adverse birth outcomes, we restricted our study to singleton infants born to nulliparous women. Our previous studies have found that missing paternal information was associated with an increased risk of adverse birth outcomes (Tan et al., 2004). Because missing information on paternal age was much more prevalent in unmarried women than in married women (Basso and Wilcox, 2006), we restricted our analyses to married women.

Our study found that advanced paternal age was not associated with an increased risk of adverse birth outcomes, which is consistent with most previous studies in the USA (Parker and Schoendorf, 1992; Olshan et al., 1995; Abel et al., 2002; Nahum and Stanislaw, 2003; Basso and Wilcox, 2006) and Canada (Tough et al., 2003). However, some other studies have reported an association between advanced paternal age and preterm birth (Zhu et al., 2005; Astolfi et al., 2006), low birth weight (Reichman and Teitler, 2006) and low Apgar score (Sun et al., 2006). Reichman and Teitler (2006) found that advanced paternal age (≥35 years) was associated with an increased risk of low birth weight. In that study, births to unmarried women were over-sampled and only 78% of the fathers were interviewed (Reichman and Teitler, 2006), which might lead to selection bias. Maternal age was grouped into three broad categories (<20, 20–34 and >34 years of age) (Reichman and Teitler, 2006), raising the possibility of residual confounding by maternal age. Two Danish studies have reported that advanced paternal age was associated with an increased risk of very preterm birth (Zhu et al., 2005) and low Apgar score (Sun et al., 2006). In Sun et al.’s study (2006), the risk of 1 min Apgar score <4 was elevated among children born to fathers 45–49 years of age relative to children born to fathers 20–29 years of age; significant associations were not found in other age groups. In Zhu et al.’s study (2005), a significant increase in the rate of
preterm births was reported for fathers 40–44 years of age, compared with fathers 20–24 years of age. When the analysis was restricted to infants without malformations, no significant association was found between advanced paternal age and very preterm births (Zhu et al., 2005); this finding suggests that in that study population, the higher risk of very preterm birth...
associated with advanced paternal age might be attributable to the increased risk of congenital anomalies. In an Italian study, a significant association between paternal age and very preterm birth was only found for fathers 45–49 years of age, compared with fathers 25–29 years of age (Astolfi et al., 2006). Several important covariates were not taken into account in these studies, including paternal and maternal race, multiple births, smoking and alcohol drinking during pregnancy, adequacy of prenatal care and prenatal care status.

The association between younger paternal age and adverse birth outcomes is less well documented. Abel et al. (2002) found that younger paternal age (<20 years old) was associated with a higher risk of preterm birth and low birth weight, compared with 20–25 year old paternal age group. Olshan et al. (1995) found that younger paternal age was associated with an increased risk of preterm birth. In both studies, a significant association between advanced paternal age and adverse birth outcomes was not found (Olshan et al., 1995; Abel et al., 2002), consistent with the findings of the present study.

An important strength of this study is the large variation in paternal age and the limited age range of the mothers. This study was specifically designed to assess the effects of paternal age among those women who were at the lowest risk of adverse birth outcomes. Chance and confounding are unlikely to explain the results observed in our study, because of the large sample size and tight control for important covariates.

Our study is subject to a number of inherent limitations. Gestational age was estimated based on self-reported LMP, which is presumably subject to some degree of measurement error. Information on the socio-economic status and lifestyle factors of the fathers, which might be important confounding variables in the observed association, was unavailable in the present study. Although ~5% subjects were excluded because of missing information on observed outcomes or important covariates, missing values were more likely to randomly occur in different paternal age groups and less likely to be caused by selection bias. Because of the lack of detailed clinical information in the study population, extrapolation of

### Table III. Odds ratios for adverse birth outcome in singleton infants born to fathers in different age groups with married, nulliparous mothers 20–29 years of age.

<table>
<thead>
<tr>
<th>Birth outcomes</th>
<th>Paternal age (years)</th>
<th>&lt;20</th>
<th>20–29</th>
<th>30–34</th>
<th>35–39</th>
<th>40–44</th>
<th>45–49</th>
<th>≥50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of live births</td>
<td>28 257</td>
<td>1 791 815</td>
<td>595 881</td>
<td>148 709</td>
<td>36 397</td>
<td>9 581</td>
<td>4 326</td>
<td></td>
</tr>
<tr>
<td>Odds ratio and 95% confidence intervals</td>
<td>1.19(1.07, 1.32)</td>
<td>1.00(0.93, 1.09)</td>
<td>1.03(0.98, 1.09)</td>
<td>1.06(0.96, 1.17)</td>
<td>0.93(0.76, 1.14)</td>
<td>0.84(0.61, 1.15)</td>
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<tr>
<td>With adjustment for paternal race, maternal age, race, educational level, smoking and alcohol drinking during pregnancy, adequacy of prenatal care and infant sex.</td>
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</table>

### Table IV. Odds ratios for adverse birth outcome in singleton infants without birth defects born to fathers in different age groups and married, nulliparous mothers 20–29 years of age.

<table>
<thead>
<tr>
<th>Birth outcomes</th>
<th>Paternal age (years)</th>
<th>&lt;20</th>
<th>20–29</th>
<th>30–34</th>
<th>35–39</th>
<th>40–44</th>
<th>45–49</th>
<th>≥50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of live births</td>
<td>27 130</td>
<td>1 727 036</td>
<td>574 086</td>
<td>143 189</td>
<td>35 011</td>
<td>9 489</td>
<td>4 157</td>
<td></td>
</tr>
<tr>
<td>Odds ratio and 95% confidence intervals</td>
<td>1.18(1.06, 1.31)</td>
<td>1.00(0.92, 1.09)</td>
<td>1.03(0.97, 1.09)</td>
<td>1.05(0.94, 1.16)</td>
<td>0.91(0.74, 1.13)</td>
<td>0.79(0.56, 1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With adjustment for paternal race, maternal age, race, educational level, smoking and alcohol drinking during pregnancy, adequacy of prenatal care and infant sex.</td>
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</table>
the present findings to clinical practice should be done with caution. Nonetheless, these findings may give some insights into paternal influences on adverse birth outcomes.

The mechanisms by which being a teenage father may contribute to an increased risk of adverse birth outcomes are not clear. We speculate that there may be several possible explanations as to why being a teenage father is associated with an increased risk of adverse birth outcomes. First, a previous study demonstrated lower sperm count, semen volume, total number of spermatozoa and percentage of motile forms of sperm in the younger age group (up to 25 years of age) than in the adult group (over 25 years of age). The immature sperm might be associated with an increased risk of adverse birth outcomes, possibly as a result of abnormal placentation. Second, young fathers are more likely to come from economically disadvantaged families and to have lower educational attainment (Kiernan, 2007). Socio-economic factors such as educational and occupation are known to be associated with a number of health outcomes (Bray et al., 2006). People from less affluent background are less likely to utilize prenatal care services (D’Ascoli et al., 1997), which is associated with an increased risk of adverse birth outcomes. Third, it is possible that the social environment, including the dynamics of the parent’s relationships, may contribute to adverse birth outcomes. For example, domestic violence or lack of financial or emotional support in younger paternal age group could affect mothers’ physical, emotional and reproductive health. Finally, lifestyle factors suspected of playing a role in the occurrence of adverse birth outcomes such as illicit drug use, smoking and alcohol drinking are more prevalent in teenage fathers. Previous studies have found associations between paternal smoking and alcohol use and adverse reproductive outcomes (Little and Sing, 1986; Vine, 1996).

It is biologically plausible that paternal age might play a role in the risk of adverse birth outcomes associated with abnormal placentation (Basso and Wilcox, 2006). Our population-based retrospective cohort study indicated that being a teenage father was an independent risk factor for adverse birth outcomes, whereas advanced paternal age was not. The paternal influence of younger fathers on adverse birth outcomes clearly warrants further investigation, and may lead to a deeper understanding of the etiology of such outcomes.

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References


de la Rochebrochard E, Thonneau P. Paternal age and maternal age are risk factors for miscarriage; results of a multicentre European study. Hum Reprod 2002;17:1649–1656.


Kotelchuck M. An evaluation of the Kessner Adequacy of Prenatal Care Index and a proposed Adequacy of Prenatal Care Utilization Index. Am J Public Health 1994;84:1414–1420.


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