The effect of father's age in fertile, subfertile, and assisted reproductive technology pregnancies: A population based cohort study

Judy E. Stern · Barbara Luke · Mark D. Hornstein ·
Howard Cabral · Daksha Gopal · Hafsatou Diop ·
Milton Kotelchuck

Received: 16 May 2014 / Accepted: 26 August 2014 / Published online: 6 September 2014
© Springer Science+Business Media New York 2014

Abstract

Purpose To compare ages of mothers and of fathers at delivery in couples who are fertile, subfertile, and subfertile treated with assisted reproductive technology (ART) and to characterize birth outcomes in the ART population according to paternal age.

Methods Live birth deliveries in Massachusetts between July, 2004 and December, 2008 were identified from vital records and categorized by maternal fertility status and treatment as

Capsule At delivery, maternal and paternal ages were older in subfertile and ART treated women than in fertile women; outcome did not differ by paternal age.

Presented at the 69th annual meeting, American Society for Reproductive Medicine, Boston, Massachusetts, October 12–17, 2013

J. E. Stern (✉)
Department of Obstetrics & Gynecology, Geisel School of Medicine
at Dartmouth, Lebanon, NH, USA
e-mail: judy.e.stern@dartmouth.edu

B. Luke
Department of Obstetrics, Gynecology and Reproductive Biology,
Michigan State University, East Lansing, MI, USA

M. D. Hornstein
Department of Obstetrics and Gynecology Brigham & Women's
Hospital, Harvard Medical School, Boston, MA, USA

H. Cabral
Department of Biostatistics, Boston University School of Public
Health, Boston, MA, USA

D. Gopal
Boston University School of Public Health, Boston, MA, USA

H. Diop
Massachusetts Department of Public Health, Boston, MA, USA

M. Kotelchuck
MassGeneral Hospital for Children, Harvard Medical School,
Boston, MA, USA

ART, subfertile or fertile. The ART births were linked to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) database to obtain cycle-specific treatment data. Parental ages were obtained from birth certificates. Age of mothers and fathers were compared using ANOVA for continuous measures and χ^2 for categories. Risks of prematurity (<37 weeks), low birthweight (<2,500 g), and low birthweight z-score (small for gestational age, SGA) were modeled using logistic regression by categories of paternal age as adjusted odds ratios and 95 % CI.

Results The study population included 9,092 ART, 6,238 subfertile, and 318,816 fertile deliveries. Paternal ages in the ART and subfertile groups were similar and differed significantly from those of the fertile group. Maternal age in the ART and subfertile groups averaged 5–6 years older than their fertile counterparts and fathers averaged 4–5 years older with twice as many being older than 37. The risks for prematurity, low birthweight and SGA did not increase with increasing paternal age.

Conclusions Fathers in ART- treated and subfertile couples are older than in their fertile counterparts. Older paternal age was not associated with increased risk for prematurity, low birthweight, or SGA.

Keywords Paternal age · Maternal age · Subfertility · ART · IVF · Preterm delivery · Birthweight

Introduction

Research on infertility and assisted reproductive technology (ART) has often neglected the biologic contribution of the male partner. While many studies have evaluated the effects of maternal characteristics, female diagnoses, and treatment modalities on ART success and the subsequent health risks in the offspring, there has been substantially less published about the risks posed by the age of the male partner. Neither the Society

for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) database nor the National ART Surveillance System (NASS) currently collects information on any characteristics of the male partner other than race. In our recent paper on intracytoplasmic sperm injection (ICSI) and male-factor outcomes from the SART CORS database [1], the analysis was limited by the lack of data on male age, body mass index, diagnostic category of male factor (e.g. hormonal, mechanical, iatrogenic), and semen analysis parameters.

It has long been known that the average age of women undergoing ART is older than their counterparts with spontaneous conceptions. According to the CDC summary for 2009, the average age of women undergoing cycles of ART in the U.S. was 36 years including 61 % over 35 years of age and 11 % over 40 years of age (<http://www.cdc.gov/art/ART2009/section1.htm>). This compares with the national average for all U.S. mothers at first birth of 25.4 years in 2010 [2]. Increased maternal age has been associated with adverse outcomes including pregnancy complications, reduced gestational age, and lowered birthweight [3, 4], as well as with birth defects [5, 6] and autism [7].

Less is known about the role of paternal age in pregnancy outcome and child health. A paternal age >40 may contribute to increased miscarriage rates, particularly when the woman is also of advanced age [8] but studies differ on the effect of paternal age on ART success rates [9, 10]. In addition, rates of birth defects and autism may also be increased with advanced paternal age [11–15]. Guidelines on advanced age and fertility treatment released in 2011 by the Society of Obstetricians and Gynaecologists of Canada [6] focused primarily on older age in women, but summarized the known data on advanced age in men in the following statement:

“Advanced paternal age appears to be associated with an increased risk of spontaneous abortion and increased frequency of some autosomal dominant conditions, autism spectrum disorders, and schizophrenia. Men > age 40 and their partners should be counselled about these potential risks when they are seeking pregnancy, although the risks remain small.”

Objectives

The objective of this analysis was to evaluate differences in maternal and paternal age among three groups of deliveries: 1) those conceived with ART, 2) those conceived in a subfertile population without ART, and 3) those conceived in a fertile population. Additionally, we evaluated the effect of increasing paternal age on the risks of prematurity, low birthweight and small-for-gestational age among singleton live births conceived with autologous oocytes and semen. This initial analysis in a series of studies on male age and child health

outcome, represents the first demonstration of the comparative ages of fathers in large ART and subfertile populations compared with that of a fertile population.

Methods

Study design and setting

This retrospective cohort study included all live births and fetal deaths in Massachusetts from July 1, 2004 through December 31, 2008. Deliveries were categorized according to maternal fertility or treatment as ART, subfertile, or fertile.

Participants

ART deliveries from cycles with start dates between January 1, 2004 and December 31, 2008 that had either a Massachusetts patient zip code or for which treatment took place at a Massachusetts clinic were obtained from SART. Data for 9,092 ART cycles resulting in delivery were linked to PELL birth or fetal death certificates using mother's first and last name, mother's date of birth, father's name, race of both parents, date of delivery, and number of babies born per delivery. Linked files were later identified by use of a linkage ID from which identifiers were removed. Methods for linkage have been described previously [16]. The linkage rate was 89.7 % overall and 95.0 % for deliveries in which both zip code and clinic were located in MA. The linkage yielded deliveries identified for this study as ART deliveries.

We identified a subfertile group as previously described [17]. Briefly, all Massachusetts deliveries were reviewed for the answer to two questions on the Massachusetts birth certificate about use of fertility drugs and assisted reproduction. Those who answered “yes” to these questions and had not been identified in the SART CORS linkage were included as subfertile. In addition, any woman who at delivery, or previous to delivery, had been hospitalized with a discharge code of female infertility (ICD diagnosis code 628.0, Infertility-Anovulation, 628.2, Infertility-Tubal Origin, 628.3, Infertility-Uterine Origin, 628.8, Female Infertility of other specified origin, 628.9, Female Infertility of unspecified origin or CPT procedural code V230, Pregnancy With Diagnosis of Infertility) was also included as part of the subfertile group if they were not in the SART CORS linkage ($N=6,238$). Deliveries not in either the subfertile or ART groups were listed as fertile ($N=318,822$).

For calculations of outcomes by age, we included only singleton live births to women <40 delivered at ≥ 20 weeks gestation and having >350 g birthweight and no missing covariate data. Within the ART group, deliveries included only those using fresh, autologous oocytes and sperm.

Variables

Parental factors

Parental ages at delivery were obtained from the birth certificates in PELL. Parental age was evaluated as both a continuous and categorical variable (≤ 30 , 31–34, 35–37, 38–40, 41–42, and ≥ 43) in the univariate analyses, and as ≤ 34 , 35–40, 41–45, and ≥ 46 for fathers and ≤ 34 and 35–40 for mothers in the multivariate analyses, with both parents ≤ 34 as the reference group. Parental race/ethnicity was also obtained from the birth certificate, and categorized as white, black, Asian, Hispanic, and other. Parental education was also obtained from the birth certificate and categorized as $\leq$ high school or GED (General Education Development diploma), some college or Associate degree, or Bachelor degree or graduate school. Preexisting maternal medical diagnoses were identified in PELL from either the birth certificate or the hospital discharge delivery record (ICD-9 codes of 648.0 or 250 for diabetes mellitus; 401, 402, 403, 404, or 405 for chronic hypertension). ART treatment parameters of diagnoses (male factor, endometriosis, ovulation disorders, tubal factors, uterine factors, other factors, and unexplained); oocyte and semen sources (autologous or donor); use of ICSI and embryo state (fresh or thawed) were obtained from the SART CORS database.

Length of gestation and prematurity

Length of gestation was calculated by using the birth certificate delivery date minus date of last menstrual period corrected for clinical estimate at early ultrasound. Deliveries prior to 37 weeks gestation were classified as premature and those that were 37 weeks or greater were classified as term.

Low birthweight and small-for-gestation birthweight

Birthweight on each live born infant was obtained from the birth certificate. Birthweights at each gestational age are normally distributed. A z-score (or standard deviation score) is the deviation of the value for an individual from the mean value of the reference population divided by the standard deviation for the reference population [18]. Birthweight z-scores were calculated to evaluate adequacy of weight-for-age using population-based standards, as recommended by Land [19] and modeled as continuous and categorical variables. We generated gender-, race/ethnicity-, and gestation-specific birthweight means and standard deviations using Massachusetts data for all live births from 1998–2008. Infants with z-scores of ≤ 1.28 (below the 10th percentile for gestation) were classified as small-for-gestational age (SGA).

Birthweights that were less than 2,500 g were classified as low birthweight.

Data sources

The pregnancy to early life longitudinal (PELL) data system

The PELL system functions within the Massachusetts Department of Public Health and links vital records from birth and fetal death certificates, hospital discharges, and program data from child health and development programs.

The society for assisted reproductive technology clinic outcome reporting system (SART CORS)

SART CORS data are collected by SART under the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102–493) and reported to the Centers for Disease Control and Prevention (CDC). SART CORS includes patient demographic data, cycle specific treatment data and outcome data for all cycles of ART in the U.S. performed at SART member clinics.

Massachusetts outcome study of assisted reproductive technology (MOSART)

The Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) project links data from the SART CORS with the PELL data system to evaluate pregnancy and child health outcomes on a population basis. A Memorandum of Understanding was executed between SART and the three entities that participate in the PELL project, Boston University, the Massachusetts Department of Public Health, and the Centers for Disease Control and Prevention. Human subjects approval was obtained from all entities and participating Universities. The study had the approval of the SART Research Committee.

Statistical methods

Maternal and paternal age comparisons were performed using chi-square for categorical data and analysis-of-variance for continuous data. The effect of paternal age on adverse pregnancy outcomes (prematurity, low birthweight, small-for-gestation birthweight) in singleton live births limited to mothers ages 40 and younger and within the ART group conceived using fresh, autologous oocytes and semen, was modeled using multivariate logistic regression adjusting for covariates, and additionally stratifying by maternal age using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA). Statistical significance was considered with p values less than 0.05 in the univariate analyses, and when the 95 %

confidence intervals did not include 1 in the multivariate analyses.

Results

The study population included 9,092 ART, 6,238 subfertile, and 318,816 fertile deliveries. The age distributions of the study population in the three groups are shown in Table 1. Mothers in the ART and subfertile groups were significantly older compared to mothers in fertile group. The percentage of mothers over 37 years of age was 34.3 % in the ART group, 26.6 % in the subfertile group and 8.5 % in the fertile population. The pattern for fathers was similar. Fathers were generally older in the ART and subfertile groups. Fathers older than 37 years of age accounted for 46.2 % of ART births, 41.0 % of subfertile births, and 20.5 % of births to fertile couples. The percentage of fathers over the age of 50 for each group was 3.6 % ART, 1.9 % subfertile, and 1.0 % fertile.

Table 2 gives a description of differences in parental ages by group. In all cases, the proportion of deliveries where fathers were older than mothers was greater than the proportion of situations in which mothers were older than fathers. Interestingly, however, the comparative ages of mothers and fathers was more likely to be within ± 4 years in the ART and subfertile groups than in the fertile population ($P < 0.0001$).

Table 3 describes the use of ICSI and donor sperm in ART pregnancies by the diagnosis of male factor and paternal age. The proportion of couples with no male factor who used ICSI or donor sperm were 21.1 % and 2.0 % respectively. The overall proportion of couples with male factor who used these options was 73.3 % ICSI and 3.0 % donor sperm. Increasing paternal age resulted in a small increase in use of these options when there was no male factor (from 19.2 % to 28.9 %) but minimal change in use for male factor cases (from 79.0 % to 75.9 %). No information on presence of male factor infertility or use of donor sperm was available for the subfertile and fertile groups; by definition these groups did not use ICSI.

Table 4 presents AORs and 95 % CIs for prematurity, birthweight, and SGA in ART singleton deliveries stratified by mother's age according to age of the male partner in live birth deliveries using fresh, autologous oocytes and sperm. There was a small increase in prematurity as a result of increased female age, however, compared to men ≤ 30 years of age, there were no significant differences in any parameter as a function of paternal age

Discussion

In this study we characterized the age of parents in three large fertility groups of patients who had delivered babies: couples

Table 1 Maternal and parental ages at delivery by fertility group

	ART	Subfertile	Fertile	P Value ³
Across Groups				
Mothers (N) ¹	(9,091)	(6,238)	(318,816)	
Age (years, mean, SD)	35.7 (4.6)	34.7 (4.5)	29.3 (6.1)	<0.0001
% ≤ 30	12.8	16.9	54.6	
31–34	27.5	30.0	24.1	
35–37	25.4	26.5	12.9	<0.0001
38–40	19.8	17.7	6.2	
41–42	7.6	5.7	1.6	
≥ 43	6.9	3.2	0.7	
Fathers (N) ²	(8,945)	(6,090)	(290,152)	
Age (years, mean, SD)	37.7 (5.7)	36.7 (5.5)	32.3 (6.7)	<0.0001
% ≤ 30	7.5	10.5	38.5	
31–34	22.2	24.1	25.1	
35–37	24.1	24.4	16.0	<0.0001
38–40	19.5	19.5	10.1	
41–42	9.0	8.1	4.1	
≥ 43	17.7	13.4	6.3	

¹ Missing maternal ages in the vital records: there was 1 missing value in the ART group and 6 missing values in the fertile group

² Missing paternal ages in the vital records: there were 147 missing values in the ART group, 148 missing values in the subfertile group and 28,670 missing values in the fertile group

³ Mean ages are compared across study groups (fertile, subfertile without ART, ART) via one-way analysis-of-variance (ANOVA). Percentages in age categories are compared across study groups using chi-square tests

Table 2 Difference in mother's and father's age at time of delivery¹

Difference in age ²	Art n (%)	Subfertile n (%)	Fertile n (%)
–10 years or more	61 (0.7)	23 (0.4)	1,314 (0.5)
–5 to –9 years	348 (3.9)	208 (3.4)	8,599 (3.0)
–4 to +4 years ³	6,537 (73.1)	4,532 (74.4)	207,169 (71.4)
+5 to +9 years	1,471 (16.4)	996 (16.4)	51,963 (17.9)
+10 years or more	528 (5.9)	331 (5.4)	21,105 (7.3)
Total	8,945 (100)	6,090 (100)	290,150 (100)

¹ Missing values for maternal or paternal age: there were 147 missing values in the ART group, there are 148 missing values in the subfertile group and 28,672 missing ages in the fertile group

² + means that fathers are older than mothers; – means that fathers are younger than mothers

³ The comparative ages of mothers and fathers was more likely to be within ± 4 years in the ART and subfertile groups than in the fertile population ($P < 0.0001$)

who had undergone ART, those classified as subfertile but who did not have ART, and parents for whom the woman had no indications of subfertility. The results clearly demonstrate that both mothers and fathers in the ART and subfertile groups were older than those in the fertile group. The risks for prematurity, low birthweight and SGA did not change with increasing paternal age.

Male infertility makes up nearly 40 % of all indications for infertility [20]. In the 2012 ART data listed on the SART website (www.sart.org), male infertility was the sole diagnosis in 17 % of cycles while male plus female factors was reported in an additional 17 % of cycles. The contribution of paternal characteristics to both ART success and ART outcome is incompletely understood. Even when male factor (as expressed by compromised sperm parameters) is not present, there is a possibility that paternal age or other

paternal characteristics can have adverse effects on childhood health.

Age of the father has been implicated in reducing the rates of ART fertilization, implantation, pregnancy, and live birth [10, 21, 22] although these results are not found consistently [9]. Other studies have linked paternal age to increased miscarriage rates [8], as well as birth defects and autism [11–15, 21, 23]. Yang et al. [12] reviewed literature on birth defects as a function of paternal age and found a weak but consistent association. Unfortunately, the national SART CORS and NASS datasets lack information on the male partner. Our previous study using the SART CORS data revealed small differences in live birth rates in cycles with male factor infertility and the use of ICSI [1], however, whether these differences were associated with characteristics of the father could not be determined.

There have been reports that paternal age leads to impaired sperm parameters including reduced volume, concentration, sperm motility, and possibly normal morphology [24–26]. Other sperm parameters of more concern for child health may also be affected. Schmid et al. [27] demonstrated a correlation of male age and DNA damage and Wyrobek et al. [28] suggested that increasing male age could increase gene mutations. DNA damage could be associated directly with morphological parameters, as suggested by Silva et al. [29]. Paternal age has also been associated with methylation defects in sperm [30], the implications of which have yet to be elaborated. Telomere length, which is linked to age-associated diseases, may shorten more rapidly in males than females [23]. These studies support the possibility that increasing male age could lead to more frequent abnormalities in pregnancies and offspring.

The data in this study demonstrate that although ICSI was used for the majority of ART deliveries with male factor, its

Table 3 The use of ICSI and donor sperm in ART singleton and twin pregnancies by diagnosis of male factor and father's age

	No Male Factor		Yes Male Factor	
	ICSI ¹ (%)	Donor Sperm ¹ (%)	ICSI ² (%)	Donor Sperm ² (%)
Overall (%)	21.1	2.0	75.3	3.0
Father's Age (years)				
≤30	19.2	2.3	79.0	1.2
31–34	19.4	0.8	75.0	2.3
35–37	20.2	1.6	74.5	3.2
38–40	17.7	2.2	74.6	3.0
41–45	24.7	3.4	75.1	3.9
≥45	28.9	3.0	75.9	4.8
χ^2 p value	<0.0001	0.001	0.77	0.19

¹ Percent of cases with no male factor for which use of ICSI or sperm source are known

² Percent of cases with male factor for which use of ICSI or sperm source are known

Table 4 Singleton live births by maternal fertility group and parental ages*

Mother's Fertility Age Group		Prematurity				Low Birthweight				Small-for-Gestation				
		Father's Age				Father's Age				Father's Age				
35-40	ART	(N)	≤34 (1,234)	35-40 (713)	41-45 (120)	≥46 (43)	≤34 (1,234)	35-40 (713)	41-45 (120)	≥46 (43)	≤34 (1,234)	35-40 (713)	41-45 (120)	≥46 (43)
	%		10.0	10.8	9.2	14.0	7.7	8.6	8.3	9.3	10.1	8.4	10.8	14.0
	OR (95 % CI)	1.00	1.09 (0.81, 1.48)	0.91 (0.48, 1.74)	1.47 (0.61, 3.54)	1.00	(Reference)	1.12 (0.80, 1.57)	1.09 (0.55, 2.15)	1.23 (0.43, 3.51)	1.00	0.82 (0.60, 1.14)	1.09 (0.59, 1.99)	1.45 (0.60, 3.51)
	AOR (95%CI)	1.00	1.07 (0.79, 1.45)	0.89 (0.46, 1.71)	1.44 (0.59, 3.51)	1.00	(Reference)	1.11 (0.79, 1.56)	1.11 (0.56, 2.20)	1.22 (0.42, 3.52)	1.00	0.82 (0.59, 1.14)	1.17 (0.64, 2.15)	1.55 (0.64, 3.78)
	Subfertile	(N)	(1,506)	(816)	(137)	(38)	(1,506)	(816)	(137)	(38)	(1,506)	(816)	(137)	(38)
	%	6.9	7.7	6.6	10.5	5.3	5.5	5.5	9.5	13.2	5.9	7.0	8.8	7.9
	OR (95 % CI)	1.00	1.13 (0.81, 1.56)	0.95 (0.47, 1.92)	1.59 (0.55, 4.55)	1.00	(Reference)	1.04 (0.71, 1.51)	1.87 (1.01, 3.45)	2.70 (1.03, 7.11)	1.00	1.20 (0.85, 1.69)	1.53 (0.81, 2.87)	1.36 (0.41, 4.52)
	AOR (95%CI)	1.00	1.16 (0.84, 1.62)	0.96 (0.47, 1.96)	1.54 (0.53, 4.47)	1.00	(Reference)	1.07 (0.73, 1.57)	1.92 (1.03, 3.57)	2.53 (0.95, 6.75)	1.00	1.19 (0.84, 1.68)	1.52 (0.81, 2.87)	1.49 (0.45, 4.98)
	Fertile	(N)	(164,353)	(39,719)	(7,713)	(2,820)	(164,353)	(39,719)	(7,713)	(2,820)	(164,353)	(39,719)	(7,713)	(2,820)
	%	6.0	5.7	6.4	7.4	5.1	4.6	4.6	5.2	6.3	8.3	7.1	7.5	7.2
OR (95 % CI)	1.00	0.94 (0.90, 0.99)	1.07 (0.97, 1.17)	1.24 (1.08, 1.43)	1.00	(Reference)	0.91 (0.87, 0.96)	1.02 (0.92, 1.13)	1.26 (1.08, 1.46)	1.00	0.85 (0.82, 0.89)	0.90 (0.83, 0.98)	0.87 (0.75, 1.00)	
AOR (95%CI)	1.00	0.97 (0.93, 1.02)	1.02 (0.93, 1.12)	1.15 (0.99, 1.33)	1.00	(Reference)	0.96 (0.91, 1.01)	0.97 (0.87, 1.07)	1.12 (0.96, 1.30)	1.00	0.89 (0.85, 0.93)	0.92 (0.85, 1.01)	0.89 (0.77, 1.03)	
ART	(N)	(273)	(1,419)	(508)	(189)	(273)	(1,419)	(508)	(189)	(273)	(1,419)	(508)	(189)	
	%	9.5	9.6	11.6	7.9	7.3	7.6	10.6	9.5	7.0	8.9	8.9	10.6	
	OR (95 % CI)	0.95 (0.61, 1.48)	0.96 (0.74, 1.24)	1.19 (0.85, 1.65)	0.78 (0.45, 1.36)	0.95 (0.57, 1.56)	0.99 (0.74, 1.32)	1.43 (1.00, 2.03)	1.26 (0.74, 2.14)	0.67 (0.41, 1.11)	0.87 (0.67, 1.13)	0.87 (0.61, 1.24)	1.06 (0.64, 1.75)	
	AOR (95%CI)	0.94 (0.60, 1.47)	0.96 (0.74, 1.24)	1.16 (0.83, 1.62)	0.74 (0.42, 1.31)	0.94 (0.57, 1.56)	0.99 (0.74, 1.33)	1.41 (0.99, 2.01)	1.24 (0.72, 2.12)	0.68 (0.41, 1.12)	0.86 (0.66, 1.11)	0.83 (0.57, 1.19)	1.08 (0.74, 1.79)	
Subfertile	(N)	(317)	(1,470)	(506)	(168)	(317)	(1,470)	(506)	(168)	(317)	(1,470)	(506)	(168)	
	%	8.2	8.3	10.9	13.1	6.0	5.7	5.5	8.3	6.3	6.3	5.7	7.7	
	OR (95 % CI)	1.20 (0.77, 1.89)	1.22 (0.93, 1.60)	1.64 (1.17, 2.32)	2.03 (1.24, 3.32)	1.14 (0.68, 1.90)	1.08 (0.79, 1.48)	1.04 (0.67, 1.63)	1.62 (0.90, 2.93)	1.07 (0.65, 1.77)	1.08 (0.80, 1.45)	0.97 (0.63, 1.49)	1.34 (0.73, 2.45)	
	AOR (95%CI)	1.21 (0.77, 1.91)	1.32 (1.00, 1.75)	1.74 (1.23, 2.47)	2.12 (1.29, 3.49)	1.17 (0.70, 1.98)	1.19 (0.86, 1.64)	1.10 (0.70, 1.73)	1.67 (0.92, 3.05)	1.11 (0.67, 1.83)	1.10 (0.81, 1.49)	0.97 (0.63, 1.50)	1.42 (0.77, 2.62)	
Fertile	(N)	(10,451)	(31,901)	(10,659)	(3,731)	(10,451)	(31,901)	(10,659)	(3,731)	(10,451)	(31,901)	(10,659)	(3,731)	
	%	6.8	5.8	6.6	7.3	5.4	4.2	5.3	5.8	6.7	6.2	6.7	8.0	
	OR (95 % CI)	1.13 (1.05, 1.23)	0.97 (0.92, 1.02)	1.11 (1.03, 1.20)	1.23 (1.08, 1.39)	1.07 (0.98, 1.16)	0.82 (0.77, 0.87)	1.04 (0.95, 1.14)	1.15 (1.00, 1.32)	0.79 (0.73, 0.86)	0.74 (0.70, 0.77)	0.79 (0.73, 0.86)	0.96 (0.86, 1.09)	
	AOR (95%CI)	1.17 (1.08, 1.27)	1.05 (0.99, 1.10)	1.12 (1.04, 1.22)	1.14 (1.01, 1.30)	1.17 (1.07, 1.28)	0.96 (0.91, 1.02)	1.12 (1.02, 1.22)	1.09 (0.95, 1.26)	0.84 (0.78, 0.91)	0.80 (0.76, 0.84)	0.85 (0.78, 0.91)	1.02 (0.90, 1.15)	

*Models adjusted for mothers' race/ethnicity, education, and ages; maternal pre-pregnancy diabetes mellitus and chronic hypertension. All models limited to women ages 40 and younger and cases containing no missing values for any adjusted parameter. ART group models limited to pregnancies conceived with fresh, autologous oocytes and semen

use did not increase with advancing age (Table 3). For cycles not identified as male factor, the percentage that used ICSI increased slightly with paternal age, however, we cannot rule out that this difference resulted more from the associated female age than the age of the male. A similar pattern was seen with use of donor sperm when there was no male factor although the overall percentage of deliveries resulting from donor sperm was low. One cautionary note when evaluating these data is that the definition of male factor within SART CORS is very general. SART defines male factor as “abnormal semen parameters or function” but gives no specifics of count, motility, morphology or other characteristics to consistently apply this definition. Similarly, we have incomplete information on the reason that ICSI is used for particular cases. These limitations suggest we use caution in interpretation of these data.

Maternal age is well known to influence birth outcomes with advancing maternal age leading to a greater prevalence of compromised outcomes [6] and a small increase in prematurity was seen with increased maternal age in this study (Table 4). We saw no significant differences in prematurity, birthweight, or SGA according to paternal age. These factors, however, may not be the optimal parameters to study to see a paternal age effect. In future studies we plan to look further at perinatal and birth outcomes based on paternal age and whether ICSI was used and sperm was collected by ejaculation, retrograde collection, aspiration or biopsy. We are waiting to link additional cycles of data from several more years before pursuing these analyses in order to increase statistical power. With increased power, we will also be able to look at whether paternal age has an influence on birth defects and other rare events.

This study has several limitations. It is possible that linkage of ART births with women in Massachusetts missed some women, although, with our high overall linkage rate it is likely that this number is small [16]. The definition of the subfertile group was a conservative one and we are likely to be missing some deliveries to couples with infertility issues. For example, our definition of subfertility depends in part on hospital discharges containing a woman’s diagnosis of infertility even though we are aware that many infertile couples have the majority of treatment in outpatient facilities. This limitation has been fully discussed previously [17]. Infertile couples whose only diagnosis was male factor infertility may have been captured by the checkbox for fertility treatment on the birth certificate, but were not captured in the subfertile group defined by diagnosis codes since only codes for hospital discharges of women were included. ART deliveries did have a category for male factor infertility. The above limitations would result in an underestimation of the subfertile population which, if anything, would mean that the age of fathers estimated for the fertile population was higher than it actually is.

Also, these data are from a single state, Massachusetts, and may not apply to all locations. Finally, we acknowledge that perinatal outcomes are influenced by other factors not available in these analyses including maternal BMI, gestational weight gain, occupational and home factors and nutritional status (anemia, vitamin D status, supplement use). In contrast to the limitations, the major strength of the study is in the large number of patients in each of the three fertility groups providing significant statistical power.

In conclusion, paternal age was found to be significantly older among infertile parents in both an ART treated and a diagnosed subfertile population, than in the general population but this increased age did not significantly affect birth outcomes in any fertility group. Our future studies will include paternal age in evaluating perinatal and child development outcomes in these populations. We hypothesize that the increased age of fathers in the infertile population may add to other factors such as maternal age and diagnosis to affect child health. Although this linkage study has important potential to clarify these issues, we strongly encourage those collecting national data to include more complete information on male parameters.

Acknowledgements The authors would like to thank additional MOSART team members for analytic and programming contributions: Eugene Declercq, PhD, Marlene Anderka, PhD, Bruce Cohen, PhD, Dmitry Kissin, PhD, Candice Belanoff, ScD, Daksha Gopal, Lan Hoang, Donna Richard, Katrina Plummer.

SART thanks all of its members for providing clinical information to the SART CORS database for use by patients and researchers. Without the efforts of SART members, this research would not have been possible.

This work was supported by R01HD064595 and R01HD067270. The views expressed in this article are those of the authors and do not necessarily represent the official view of the National Institutes of Health.

References

1. Nangia AK, Luke B, Smith JF, Mak W, Stern JE, Group SW. National study of factors influencing assisted reproductive technology outcomes with male factor infertility. *Fertil Steril*. 2011;96:609–14.
2. Martin JA, Hamilton BE, Ventura S.J., Osterman M., JK, Wilson E.C., Mathews T. Births: Final Data for 2010. National Vital Statistics Reports 2012;61:1–72.
3. Johnson J, Tough S. Society of O, Gynaecologists of C Delayed child-bearing. *J Obstet Gynaecol Can*. 2012;34:80–93.
4. Luke B, Brown MB. Elevated risks of pregnancy complications and adverse outcomes with increasing maternal age. *Hum Reprod*. 2007;22:1264–72.
5. Reefhuis J, Honein MA. Maternal age and non-chromosomal birth defects, Atlanta–1968–2000: teenager or thirty-something, who is at risk? *Birth Defects. Res Part A Clin Mol Teratol*. 2004;70:572–9.
6. Committee REaI, Liu K, Case A. Advanced Reproductive Age and Fertility: Clinical Practice Guideline. *Journal of Obstetrics & Gynaecology Canada: JOGC* 2011;269:1165–1175.
7. Sandin S, Hultman CM, Kolvezon A, Gross R, MacCabe JH, Reichenberg A. Advancing maternal age is associated with

- increasing risk for autism: a review and meta-analysis. *J Am Acad Child Adolesc Psychiatry* 2012;51:477–486.e1.
8. De La Rochebrochard E, Thonneau P. Paternal age: are the risks of infecundity and miscarriage higher when the man is aged 40 years or over? *Rev Epidemiol Sante Publique* 2005;53 Spec No 2:2S47-55.
 9. Bellver J, Garrido N, Remohi J, Pellicer A, Meseguer M. Influence of paternal age on assisted reproduction outcome. *Reprod Biomed Online*. 2008;17:595–604.
 10. Dain L, Auslander R, Dirnfeld M. The effect of paternal age on assisted reproduction outcome. *Fertil Steril*. 2011;95:1–8.
 11. Reichenberg A, Gross R, Weiser M, Bresnahan M, Silverman J, Harlap S, et al. Advancing paternal age and autism. *Arch Gen Psychiatry*. 2006;63:1026–32.
 12. Yang Q, Wen SW, Leader A, Chen XK, Lipson J, Walker M. Paternal age and birth defects: how strong is the association? *Hum Reprod*. 2007;22:696–701.
 13. Green RF, Devine O, Crider KS, Olney RS, Archer N, Olshan AF, et al. Association of paternal age and risk for major congenital anomalies from the National Birth Defects Prevention Study, 1997 to 2004. *Ann Epidemiol*. 2010;20:241–9.
 14. Grewal J, Carmichael SL, Yang W, Shaw GM. Paternal age and congenital malformations in offspring in California, 1989–2002. *Maternal & Child Health Journal*. 2012;16:385–92.
 15. Fonseka KGL, Griffin DK. Is there a paternal age effect for aneuploidy? *Cytogenetic & Genome Research*. 2011;133:280–91.
 16. Kotelchuck M, Hoang L, Stern JE, Diop H, Belanoff C, Declercq E. The MOSART database: Linking the SART CORS clinical database to the population-based Massachusetts PELL reproductive public health data system. *Maternal and Child Health Journal* 2014;In Press.
 17. Declercq E, Belanoff C, Diop H, Gopal D, Hornstein MD, Kotelchuck M, et al. Identifying women with indicators of subfertility in a statewide population database: Operationalizing the missing link in ART research. *Fertility & Sterility* 2014;101:463–471.
 18. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediatr*. 2003;3:6.
 19. Land JA. How should we report on perinatal outcome? *Hum Reprod*. 2006;21:2638–9.
 20. Practice Committee of American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: a committee opinion. *Fertil Steril* 2012;98:294–301.
 21. Belloc S, Hazout A, Zini A, Merviel P, Cabry R, Chahine H, et al. How to overcome male infertility after 40: Influence of paternal age on fertility. *Maturitas*. 2014;78:22–9.
 22. Humm KC, Sakkas D. Role of increased male age in IVF and egg donation: is sperm DNA fragmentation responsible? *Fertil Steril*. 2013;99:30–6.
 23. Wiener-Megnazi Z, Auslander R, Dirnfeld M. Advanced paternal age and reproductive outcome. *Asian J Androl*. 2012;14:69–76.
 24. Kidd SA, Eskenazi B, Wyrobek AJ. Effects of male age on semen quality and fertility: a review of the literature. *Fertil Steril*. 2001;75: 237–48.
 25. Eskenazi B, Wyrobek AJ, Slotter E, Kidd SA, Moore L, Young S, et al. The association of age and semen quality in healthy men. *Hum Reprod*. 2003;18:447–54.
 26. Nie ZY, Wu HF, Zhang N, Guo LN, Zhao SY, Zhen XL, et al. Influence of male age on the outcome of conventional IVF-ET. *Zhonghua Nan Ke Xue*. 2012;18:248–52.
 27. Schmid TE, Eskenazi B, Baumgartner A, Marchetti F, Young S, Weldon R, et al. The effects of male age on sperm DNA damage in healthy non-smokers. *Hum Reprod*. 2007;22:180–7.
 28. Wyrobek AJ, Eskenazi B, Young S, Arnheim N, Tiemann-Boege I, Jabs EW, et al. Advancing age has differential effects on DNA damage, chromatin integrity, gene mutations, and aneuploidies in sperm. *Proc Natl Acad Sci U S A*. 2006;103:9601–6.
 29. Silva LFI, Oliveira JBA, Petersen CG, Mauri AL, Massaro FC, Cavagna M, et al. The effects of male age on sperm analysis by motile sperm organelle morphology examination (MSOME). *Reprod Biol Endocrinol*. 2012;10:19.
 30. Jenkins TG, Aston KI, Cairns BR, Carrell DT. Paternal aging and associated intraindividual alterations of global sperm 5-methylcytosine and 5-hydroxymethylcytosine levels. *Fertility & Sterility*. 2013;100:945–51.