Human Reproduction, Vol.36, No.3, pp. 785–793, 2021
Advance Access Publication on December 18, 2020 doi:10.1093/humrep/deaa332

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Association between preconception paternal health and pregnancy loss in the USA: an analysis of US claims data

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Submitted on August 4, 2020; resubmitted on October 24, 2020; editorial decision on November 5, 2020

STUDY QUESTION: Is preconception paternal health associated with pregnancy loss?

SUMMARY ANSWER: Poor preconception paternal health is associated with a higher risk of pregnancy loss as confirmed in sensitivity analyses accounting for maternal age and health.

WHAT IS KNOWN ALREADY: Preconception paternal health can negatively impact perinatal outcomes.

STUDY DESIGN, SIZE, DURATION: Retrospective cohort study of US insurance claims database from 2009 to 2016 covering 958 804 pregnancies.

PARTICIPANTS/MATERIALS, SETTING, METHODS: US insurance claims database including women, men and pregnancies within the USA between 2007 and 2016. Paternal preconception health status (e.g. metabolic syndrome diagnoses (MetS), Charlson comorbidity index (CCI) and individual chronic disease diagnoses) was examined in relation to pregnancy loss (e.g. ectopic pregnancy, miscarriage and stillbirth).

MAIN RESULTS AND THE ROLE OF CHANCE: In all, 958 804 pregnancies were analyzed. The average paternal age was 35.3 years (SD 5.3) and maternal age was 33.1 years (SD 4.4). Twenty-two percent of all pregnancies ended in a loss. After adjusting for maternal factors, the risk of pregnancy loss increased with increasing paternal comorbidity. For example, compared to men with no components of MetS, the risk of pregnancy loss increased for men with one (relative risk (RR) 1.10, 95% CI 1.09–1.12), two (RR 1.15, 95% CI 1.13–1.17) or three or more (RR 1.19, 95% CI 1.14–1.24) components. Specifically, less healthy men had a higher risk of siring a pregnancy ending in spontaneous abortion, stillbirth and ectopic pregnancies. Similar patterns remained with other measures of paternal health (e.g. CCI, chronic diseases, etc.). When stratifying by maternal age as well as maternal health, a similar pattern of increasing pregnancy loss risk for men with 1, 2 or 3+ MetS was observed. A statistically significant but weak association between timing of pregnancy loss and paternal health was found.

LIMITATIONS, REASONS FOR CAUTION: Retrospective study design covering only employer insured individuals may limit generalizability

WIDER IMPLICATIONS OF THE FINDINGS: Optimization of a father's health may improve pregnancy outcomes.

STUDY FUNDING/COMPETING INTERESTS: National Institutes of Health National Center for Advancing Translational Science Clinical and Translational Science Award (UL1 TR001085). M.L.E. is an advisor for Sandstone Diagnostics, Dadi, Hannah and Underdog. No other competing interests were declared.

TRIAL REGISTRATION NUMBER: N/A

Key words: paternal health / pregnancy outcomes / pregnancy loss / preconception / metabolic syndrome

Introduction

A father contributes half of the genome to a child yet relatively little is known about the potential association between preconception paternal health and fetal development as observed by pregnancy outcomes. Due to the well-established impact that maternal health has on the developing fetus as well as on neonatal events, preconception counseling has traditionally focused on the mother (Gluckman *et al.*, 2008). However, recent literature has suggested that paternal preconception health, both lifestyle and medical comorbidity, is associated with pregnancy trajectory (Abbasi, 2017).

Prior reports have explored the association between advanced paternal age and pregnancy outcomes (Khandwala *et al.*, 2018). Andersen *et al.* (2004) studied more than 23 000 pregnancies within the Danish National Birth Cohort and found that pregnancies fathered by men over 45 years old had a significantly higher risk of fetal loss compared with younger fathers. This finding and limitations are similar to that of Rochebrochard and Thonneau (2002) who analyzed an European cohort of pregnancies and found the risk of fetal loss to increase for those fathers more than 40 years old. Within the assisted reproduction literature, the impact of male age on pregnancy outcomes has been heterogeneous though does not appear associated with pregnancy or live birth rates (Sagi-Dain *et al.*, 2015). However, there are limited data examining the potential impact of a father's health on the developing fetus or newborn among natural conceptions. Within the last decade, few studies have examined this relationship, however, paternal diabetes has been identified as a potential risk for fetal growth restriction and lower gestational age at birth (Hillman *et al.*, 2013; Moss and Harris, 2015). Recently, our group demonstrated that men with more comorbidities sired pregnancies with higher odds of preterm birth and low birth weight (LBW) (Kasman *et al.*, 2020).

Approximately 30% of conceptions have a pregnancy trajectory that end prior live birth (Hoyert and Gregory, 2016). Though some pregnancy losses may be explained by embryonic aneuploidy, many pregnancy losses remain unexplained after ruling out chromosomal abnormalities and a thorough investigation of maternal risk factors (Halit *et al.*, 2018). While the cause of pregnancy loss is often uncertain, maternal factors remain the primary suspected etiologic pathway with paternal contributions largely unknown. Indeed, for couples with recurrent miscarriage, the majority of the evaluation focuses on maternal factors (e.g. age, uterine factors, antiphospholipid syndrome and maternal comorbidities). The paternal clinical evaluation includes a karyotype and review of modifiable lifestyle factors but other evaluation is not routinely performed as other paternal factors are not known to influence early pregnancy outcomes (The Practice Committee of the American Society of Reproductive Medicine, 2012; Bender Atik *et al.*, 2018). As paternal health is known to affect semen quality, it is possible that heritable factors, including epigenomic factors, could be passed onto the developing embryo and impact the pregnancy trajectory. Therefore, we sought to further elucidate the potential association between paternal health and pregnancy loss through a retrospective cohort study.

Materials and methods

Study cohort

We utilized the IBM® Marketscan® Research database which provides data on reimbursed healthcare claims regarding inpatient and outpatient encounters covering over 153 million individuals who are privately insured through employment sponsored health insurance, and Medicare encounters as supplemental coverage, within the USA. Claims data were analyzed from years 2007 to 2016. As this dataset contains de-identified patient information, Institutional Review Board approval was not required for the present study. Patients were not involved in the design, conduct or reporting of this study.

We identified all male/female couples linked to the same primary insurance by identifying the primary and spouse (allowing both women and men to be the primary or spouse) under enrollee relations with at least 2 years of continuous enrollment. We limited our analysis to women aged 20–45.

We identified pregnancy outcomes using relevant ICD (International Classification of Diseases, 9th and 10th edition) and CPT (Current Procedure Terminology) and DRG (Diagnosis-Related Group) codes from inpatient and outpatient files of both the mother and newborn. Infants were then linked with their mothers and fathers using family ID. Through member enrollment files, we verified babies' records using the estimated birth dates and enrollment start dates. We included only those pregnancies with both one male and one female parent at birth.

Pregnancy outcomes analyzed in the study included live birth (N = 785 809), stillbirth (N = 9064, ICD-9/10-CM: 6564, V271, Z371, O364), ectopic pregnancy (N = 20 043, DRG: 777, CPT: 59100, 59120, 59121, 59130, 59135, 59136, 59140, 59150, ICD-9-PCS: 6662, 743, ICD-9/10-CM: 633, 7614, O00, P014), spontaneous abortion (N = 143 888, CPT: 59820, 59812, 59830, 59821, ICD-9-PCS: 6951, ICD-9/10-CM: 631, 632, 634, O020, O021, O0281, O0289, O03). For each outcome, to determine adjudicated gestational age, we utilized the appropriate ICD/CPT/DRG code using the methodology of Ailes *et al.* (2016) and Wall-Wieler *et al.* (2020) from inpatient and outpatient files from both the mother and newborn (ICD-9: 644.21, 765.09, 765.19, 765.20-765.28, 72.0-73.6, 73.8, 73.9, 74.x, ICD-10: O60.12X0, O60.13X0, O60.14X0, P07.20-P07.26, P07.3x, DRG: 790, 791, 792, CPT: 59612, 59614, 59620). Trimesters were divided according to the following weeks: first trimester—GA <13, second trimester—GA 13–28, third trimester—≥29.

Parental health

Women and men had to be enrolled in insurance plans associated with the database for at least 1 year prior to the estimated date of

conception. We identified parental comorbidities utilizing diagnosis codes from inpatient and outpatient records occurring in the year prior to conception or earlier to ensure all conditions diagnosed were present prior to conception. The components of a metabolic syndrome diagnosis included hypertension, hyperlipidemia, obesity and diabetes (as per diagnosis codes below). To further determine the health of parents, the most common chronic conditions in the USA were also identified individually for all parents including: hypertension (ICD 9: 401-405, ICD 10: I10-I16), hyperlipidemia (ICD 9:270.2-270.4, ICD 10: E78.4, E78.5, E78.1, E78.2, E78.00), diabetes mellitus (ICD 9: 250, ICD 10: E08-E13), chronic obstructive pulmonary disease (COPD, ICD 9: 490-496, ICD 10: J40-J47), obesity (ICD 9: 278.0, ICD 10: E66.9, E66.01, E66.3, E66.2), cancer (ICD 9: 140-172, 174-209.36, 209.7, 173.00, 173.10, 173.20, 173.30, 173.40, 173.50, 173.60, 173.70, 173.80, 173.90, 173.09, 173.19, 173.29, 173.39, 173.49, 173.59, 173.69, 173.79, 173.89, 173.99, ICD 10: C00-C26, C30-C34, C37-C41, C43, C88, C45-C58, C60-C76, C81-C85, C90-C97,), depression (ICD 9: 311, 296.2, 296.3, 298.0, 300.4, 309.1, ICD 10: F32, F33) and heart disease (ICD9: 410-414, I20-I29, ICD10: I20-I25, ICD10 I30-I52) (Chapel *et al.*, 2017). In addition to these chronic conditions and metabolic syndrome diagnosis components, the Charlson comorbidity index (CCI) was calculated for all patients which includes age, history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular event, dementia, COPD, connective tissue disorder, liver disease, chronic kidney disease, peptic ulcer disease, diabetes mellitus, hemiplegia, cancer components and autoimmune deficiency syndrome (Quan *et al.*, 2011). Despite its development in an inpatient setting to evaluate mortality, it has been used in ambulatory and reproductive settings to predict health outcomes (Sundararajan *et al.*, 2004; Salonia *et al.*, 2009).

Statistical analysis

Descriptive statistics were presented as mean ± SD. Categorical variables were expressed in frequencies with percentages. Spearman's correlation coefficients were used to evaluate correlations between ordinal and continuous variables. The number of fathers with each comorbidity, components of metabolic syndrome and CCI components was compared with each pregnancy outcome as a categorical variable. A parametric trend test using General Linear Model was used for maternal and paternal age, as well as CCIs and Jonckheere–Terpstra trend test was used for all categorical variables.

Generalized estimated equations were used to estimate the risk ratios for binary outcomes to allow for some families to contribute subsequent births. For multinominal outcomes, the proportional odds assumption was tested and the null hypothesis of all predictors being the same across different levels was rejected, and generalized logit model was used. All analyses were adjusted for pregnancy outcome year, region, maternal hypertension, maternal diabetes mellitus, maternal obesity, maternal age, maternal smoking, paternal age and paternal smoking. In order to further assess the relation between paternal health and pregnancy outcomes, analyses were also stratified by maternal age and by maternal health (i.e. defined by metabolic syndrome diagnoses (MetS) components). The risk of pregnancy loss during each trimester was assessed in relation to paternal health. As a sensitivity analysis, we examined other definitions of paternal health (i.e. CCI, individual and total chronic diseases). The primary findings were similar when examining individual types of pregnancy loss with increasing number of paternal chronic diseases (Supplementary Table SI). To evaluate the within family effect, we performed two types of sensitivity analyses. One was selecting the first pregnancy of each family and applying generalized logit regression. Another one was by bootstrapping technique whereby randomly select only one pregnancy from each family for 100 times, apply identical generalized logit regression for each random sample and calculate the aggregated relative risks. We then compared the coefficients from the single-pregnancy sample and averaged coefficients to the analysis results using the whole cohort with similar results. All tests were two-sided and $P < 0.05$ was considered significant. All analyses were done in SAS software version 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

In all, there were a total of 956 804 pregnancies during the analysis period with an average paternal age of 35.3 years (SD 5.3) and maternal age of 33.1 years (SD 4.4) (Table I). A total of 4.6% of men were over the age of 45 years. The average observation period of men prior to conception was 3.9 years (SD 1.6) versus 3.7 years for women (SD 1.5). A total of 23.3% of men had at least one component of the metabolic syndrome prior to conception. In total, there were 785 809 live births and 172 995 pregnancy losses (i.e. ectopic pregnancy, spontaneous abortion or stillbirth). Paternal and maternal age were strongly correlated via Spearman correlation ($r_s = 0.74$) while paternal MetS components and maternal MetS components were not ($r^2 = 0.17$). Maternal MetS components and maternal age ($r^2 = 0.10$) and paternal MetS components and paternal age ($r^2 = 0.20$) were also not correlated.

There was a higher risk of pregnancy loss (i.e. not live birth) with increasing number of paternal components of MetS (relative risk (RR) 1.19, 95% CI 1.14–1.24; Table II). In addition, the highest risk of pregnancy loss among men with more comorbidities was also observed for each individual pregnancy loss type including: stillbirth, spontaneous abortion and ectopic pregnancy. Moreover, as the number of chronic diseases in a man increased so did the risk of pregnancy loss with the highest risk among men with four or more conditions (RR 1.18, 95% CI 1.11–1.26; Supplementary Table SI). Similar results were noted for increasing paternal CCI (Supplementary Table SI).

To delineate the possible interaction of maternal factors on the association between paternal health and pregnancy loss and investigate whether paternal health was simply a proxy for maternal health, outcomes were stratified by components of maternal MetS and maternal age (Tables III and IV). As expected, as woman's age and comorbidity increased, the frequencies of pregnancy losses increased. Across all levels of preconception maternal MetS, increased risk remained between paternal comorbidity and pregnancy loss in a similar 'dose-dependent' fashion. The relationships were also observed when stratifying based on maternal CCI (data not shown). Across each maternal age group (i.e. <30 years, 30–35 years and >5 years), there was a similar increased risk of pregnancy loss comparing the least to most comorbid men (RR 1.20, 95% CI 1.07–1.33, RR 1.18, 95% CI 1.12–1.25, RR 1.17, 95% CI 1.11–1.23, respectively, for MetS components; Table IV). Additionally, when stratified by paternal age across paternal MetS components, a similar trend was noted

Table I Characteristics of the study population stratified by paternal components of the metabolic syndrome (MetS).

		Paternal MetS Components				
		0	1	2	3+	Total
N		740 203	153 272	49 948	15 381	958 804
Paternal age	Mean age (SD)	34.7 ± 5.1	36.8 ± 5.5	38.0 ± 5.9	39.0 ± 6.1	35.3 ± 5.3
Maternal age	Mean age (SD)	32.7 ± 4.3	34.0 ± 4.3	34.6 ± 4.4	35.1 ± 4.5	33.1 ± 4.4
Father observation time before birth*	Mean, years (SD)	3.8 ± 1.5	4.1 ± 1.7	4.3 ± 1.8	4.6 ± 1.8	3.9 ± 1.6
Mother observation time before birth*	Mean, years (SD)	3.6 ± 1.5	3.9 ± 1.6	4.1 ± 1.6	4.3 ± 1.7	3.7 ± 1.5
	>1 year before conception (%)	740 203 (100)	153 272 (100)	49 948 (100)	15 381 (100)	958 804
	Father >2 years before conception (%)	737 662 (99.7)	152 936 (99.8)	49 855 (99.8)	15 357 (99.8)	95 5810
	Mother >2 years before conception (%)	737 436 (99.6)	152 869 (99.7)	49 824 (99.8)	15 359 (99.9)	955 488
Births (%)	Live birth	614 738 (83.1)	121 418 (79.2)	38 351 (76.8)	11 302 (73.5)	785 809
	Ectopic	14 037 (1.9)	3919 (2.6)	1494 (3.0)	593 (3.9)	20 043
	Spontaneous abortion	104 724 (14.2)	26 373 (17.2)	9511 (19.0)	3280 (21.3)	143 888
	Stillbirth	6704 (0.91)	1562 (1.0)	592 (1.2)	206 (1.3)	9064
Year of pregnancy outcome (%)	2009–2010	182 335 (24.6)	32 446 (21.2)	8801 (17.6)	1773 (11.5)	225 355
	2011–2012	239 283 (32.3)	49 005 (32.0)	15 555 (31.1)	4530 (29.5)	308 373
	2013–2014	195 315 (26.4)	43 203 (28.2)	15 042 (30.1)	5016 (32.6)	258 576
	2015–2016	123 270 (16.7)	28 618 (18.7)	10 550 (21.1)	4062 (26.4)	166 500
Region of childbirth (%)	Northeast	133 463 (18.0)	35 439 (23.1)	12 587 (25.2)	4105 (26.7)	185 594
	North Central	191 335 (25.9)	33 846 (22.1)	9999 (20.0)	2997 (19.5)	238 177
	South	244 939 (33.1)	51 551 (33.6)	17 146 (34.3)	5028 (32.7)	318 664
	West	157 238 (21.2)	29 843 (19.5)	9418 (18.9)	3011 (19.6)	199 510
	Unknown	13 228 (1.8)	2593 (1.7)	798 (1.6)	240 (1.6)	16 859

*Average time a man or women prior to the birth of their child had accessible information within the insurance database.

Table II Association of pregnancy loss and paternal metabolic syndrome (MetS).*

	Ectopic		Spontaneous abortion		Stillbirth		Not live birth§	
Paternal MetS components	**N (%)**	**RR (95% CI)**	**N (%)**	**RR (95% CI)**	**N (%)**	**RR (95% CI)**	**N (%)**	**RR (95% CI)**
0	14 037 (1.9)	Ref	104 724 (14.2)	Ref	6704 (0.91)	Ref	125 465 (17.0)	Ref
1	3919 (2.6)	1.22 [1.17–1.26]	26 373 (17.2)	1.11 [1.10–1.13]	1562 (1.0)	1.03 [0.97–1.09]	31 854 (20.8)	1.10 [1.09–1.12]
2	1494 (3.0)	1.31 [1.24–1.38]	9511 (19.0)	1.17 [1.14–1.20]	592 (1.2)	1.12 [1.02–1.22]	11 597 (23.2)	1.15 [1.13–1.17]
3+	593 (3.9)	1.54 [1.41–1.66]	3280 (21.3)	1.24 [1.19–1.29]	206 (1.3)	1.16 [0.992–1.32]	4079 (26.5)	1.19 [1.14–1.24]
P_{Trend}		<0.0001		<0.0001		<0.0001		<0.0001

*Adjusted for outcome year, region, maternal hypertension, diabetes mellitus, obesity, hyperlipidemia, age, smoking, paternal age and smoking. Percentages represent row totals of all pregnancy outcomes and may not add to 100% due to rounding.
§Not live birth = ectopic pregnancy + spontaneous abortion + stillbirth.
RR, relative risk.

Table III Association of pregnancy loss and paternal metabolic syndrome (MetS) stratified by maternal MetS.*

Maternal MetS components	Paternal MetS components	Ectopic		Spontaneous abortion		Stillbirth		Not live birth§	
		N (%)	RR (95% CI)	N (%)	RR (95% CI)	N (%)	RR (95% CI)	N (%)	RR (95% CI)
0	0	11 189 (74.1)	Ref	88 198 (76.5)	Ref	5503 (78.2)	Ref	104 890 (76.4)	Ref
	1	2756 (18.3)	1.28 [1.23–1.34]	19 272 (16.7)	1.13 [1.11–1.14]	1081 (15.4)	1.03 [0.96–1.10]	23 109 (16.8)	1.11 [1.10–1.13]
	2	868 (5.8)	1.37 [1.27–1.46]	6078 (5.3)	1.20 [1.16–1.23]	353 (5.0)	1.14 [1.02–1.10]	7299 (5.3)	1.17 [1.14–1.19]
	3+	290 (1.9)	1.80 [1.59–2.01]	1678 (1.5)	1.30 [1.23–1.36]	98 (1.4)	1.25 [0.998–1.50]	2066 (1.5)	1.27 [1.22–1.32]
	P_{Trend}		<0.0001		<0.0001		<0.0001		<0.0001
1	0	2104 (61.1)	Ref	12 781 (61.4)	Ref	897 (63.3)	Ref	15 782 (61.5)	Ref
	1	802 (23.3)	1.06 [0.97–1.15]	5070 (24.4)	1.08 [1.04–1.12]	326 (23.0)	1.04 [0.91–1.18]	6198 (24.2)	1.06 [1.03–1.09]
	2	388 (11.3)	1.25 [1.11–1.39]	2149 (10.3)	1.12 [1.06–1.18]	145 (10.2)	1.14 [0.94–1.34]	2682 (10.5)	1.10 [1.06–1.14]
	3+	149 (4.3)	1.33 [1.10–1.56]	803 (3.9)	1.16 [1.06–1.25]	50 (3.5)	1.09 [0.77–1.40]	1002 (3.9)	1.13 [1.07–1.20]
	P_{Trend}		0.01		<0.0001		<0.0001		<0.0001
2+	0	744 (49.7)	Ref	3745 (47.7)	Ref	304 (49.8)	Ref	4793 (48.1)	Ref
	1	361 (24.1)	1.04 [0.90–1.17]	2031 (25.8)	1.12 [1.05–1.19]	155 (25.4)	1.06 [0.85–1.26]	2547 (25.6)	1.07 [1.03–1.12]
	2	238 (15.9)	1.12 [0.95–1.29]	1284 (16.3)	1.13 [1.05–1.22]	94 (15.4)	1.03 [0.78–1.27]	1616 (16.2)	1.09 [1.04–1.14]
	3+	154 (10.3)	1.28 [1.05–1.52]	799 (10.2)	1.24 [1.13–1.35]	58 (9.5)	1.10 [0.78–1.42]	1011 (10.1)	1.16 [1.09–1.23]
	P_{Trend}		0.03		<0.0001		<0.0001		<0.0001

*Adjusted for outcome year, region, maternal hypertension, diabetes mellitus, obesity, hyperlipidemia, age, smoking, paternal age and smoking. Percentages represent row totals of all pregnancy outcomes and may not add to 100% due to rounding. Data presented as relative risk with 95% CI.
§Not live birth = ectopic pregnancy + spontaneous abortion + stillbirth.
RR, relative risk.

Table IV Association of pregnancy loss and paternal metabolic syndrome (MetS) stratified by maternal age.*

Maternal age, years	Paternal MetS components	Ectopic		Spontaneous abortion		Stillbirth		Not live birth§	
		N (%)	RR (95% CI)	N (%)	RR (95% CI)	N (%)	RR (95% CI)	N (%)	RR (95% CI)
<30	0	2792 (80.5)	Ref	19 644 (82.3)	Ref	1336 (83.1)	Ref	23 772 (82.1)	Ref
	1	487 (14.0)	1.14 [1.04–1.24]	3061 (12.8)	1.09 [1.06–1.13]	191 (11.9)	0.98 [0.83–1.13]	3739 (12.9)	1.13 [1.10–1.17]
	2	136 (3.9)	1.07 [0.90–1.24]	929 (3.9)	1.18 [1.11–1.24]	64 (4.0)	1.14 [0.85–1.43]	1129 (3.9)	1.22 [1.15–1.30]
	3+	53 (1.5)	1.41 [1.06–1.75]	234 (0.98)	1.08 [0.96–1.20]	16 (1.0)	1.01 [0.51–1.50]	303 (1.1)	1.20 [1.07–1.33]
	P_{Trend}		0.009		<0.0001		<0.0001		<0.0001
30–35	0	6617 (71.5)	Ref	46 216 (75.6)	Ref	3086 (75.4)	Ref	55 919 (75.1)	Ref
	1	1785 (19.3)	1.22 [1.16–1.28]	10 463 (17.1)	1.07 [1.05–1.09]	689 (16.8)	1.02 [0.93–1.10]	12 937 (17.4)	1.11 [1.09–1.13]
	2	625 (6.8)	1.30 [1.20–1.40]	3399 (5.6)	1.10 [1.07–1.14]	238 (5.8)	1.07 [0.93–1.21]	4262 (5.7)	1.16 [1.13–1.20]
	3+	222 (2.4)	1.44 [1.26–1.62]	1021 (1.7)	1.10 [1.04–1.15]	81 (2.0)	1.12 [0.87–1.38]	1324 (1.8)	1.18 [1.12–1.25]
	P_{Trend}		<0.0001		<0.0001		<0.0001		<0.0001
>35	0	4628 (63.2)	Ref	38 864 (66.0)	Ref	2282 (67.9)	Ref	45 774 (65.8)	Ref
	1	1647 (22.5)	1.15 [1.09–1.21]	12 849 (21.8)	1.09 [1.07–1.11]	682 (20.3)	0.989 [0.90–1.07]	15 178 (21.8)	1.09 [1.07–1.11]
	2	733 (10.0)	1.25 [1.16–1.35]	5183 (8.8)	1.10 [1.07–1.13]	290 (8.6)	1.05 [0.92–1.18]	6206 (8.9)	1.11 [1.08–1.14]
	3+	318 (4.3)	1.46 [1.29–1.62]	2025 (3.4)	1.20 [1.14–1.25]	109 (3.2)	1.07 [0.86–1.28]	2452 (3.5)	1.17 [1.11–1.23]
	P_{Trend}		<0.0001		<0.0001		<0.0001		<0.0001

*Adjusted for outcome year, region, maternal hypertension, diabetes mellitus, obesity, hyperlipidemia, smoking, paternal age and smoking. Percentages represent row totals of all pregnancy outcomes and may not add to 100% due to rounding. Data presented as relative risk with 95% CI.
§Not live birth = ectopic pregnancy + spontaneous abortion + stillbirth.
RR, relative risk.

Table V Association of pregnancy loss and paternal metabolic syndrome (MetS) stratified by trimester.*

Paternal MetS components	Live birth	T1	T2	T1 v. LB	T2 v. LB	T1 v. T2
	N (%)	N (%)	N (%)	RR (95% CI)	RR (95% CI)	RR (95% CI)
0	614 738 (83.1)	61 900 (8.4)	63 565 (8.6)	Ref	Ref	Ref
1	121 418 (79.2)	15851 (10.3)	16 003 (10.4)	1.15 [1.13–1.17]	1.10 [1.08–1.13]	1.006 [1.003–1.010]
2	38 351 (76.8)	5978 (12.0)	5619 (11.3)	1.25 [1.22–1.29]	1.13 [1.09–1.16]	1.017 [1.011–1.023]
3+	11 302 (73.5)	2206 (14.3)	1873 (12.2)	1.40 [1.34–1.46]	1.17 [1.11–1.23]	1.029 [1.020–1.038]
P_{Trend}				<0.0001	<0.0001	<0.0001

*Adjusted for outcome year, region, maternal hypertension, diabetes mellitus, obesity, hyperlipidemia, age, smoking, paternal age and smoking. Percentages represent row totals of all pregnancy outcomes and may not add to 100% due to rounding. Data presented as relative risk with 95% CI.
T1, trimester 1; T2, trimester 2; LB, live birth; RR, relative risk..

(Supplementary Table SII). We examined the estimated trimester of pregnancy loss in relation to paternal morbidity and found a small association (Table V).

Furthermore, sensitivity analyses were performed to examine the role of families with multiple pregnancies/pregnancy losses influencing the results. We examined only the first pregnancy outcome per couple and identified similar point estimates for the association between paternal MetS and pregnancy outcomes (Supplementary Table SIII). We then used bootstrapping for those families with multiple outcomes to compare the average coefficients to single outcome parents and found that the point estimates were also similar.

Discussion

To our knowledge, this is the first study to suggest that pregnancies sired by men with increasing numbers of comorbidities are at higher risk of ending in losses (i.e. ectopic pregnancy, spontaneous abortion or stillbirth). When a man had increasing components of metabolic syndrome, increasing CCI or multiple chronic diseases, there was increased risk of ectopic pregnancy, miscarriage and stillbirth. While maternal health remains paramount to pregnancy, paternal health is also associated with pregnancy outcome. Indeed, paternal health contributed significantly with similar point estimates when stratifying for maternal age and health, even among those women considered highest risk (e.g. older and with more comorbidities) implying that the paternal contribution is independent of maternal factors for risk of pregnancy loss.

Paternal influence on pregnancy outcomes is not novel as Wilhem Weinberg described the association of achondroplasia in relation to birth order (and paternal age) around the turn of the century (Crow, 2003). While our study is the first to report the association of pregnancy loss and preconception paternal health, there are previous studies that have examined paternal factors and adverse pregnancy outcomes such as advancing paternal age, abnormal semen parameters/infertility or environmental exposure to toxins prior to conception. Indeed, advanced paternal age is associated with adverse pregnancy/child outcomes. Bergh *et al.* (2019) reviewed the potential effects that an 'older' father may have on the health of the child including birth abnormalities or mental health/genetic disorders (e.g. esophageal atresia, type 1 diabetes, cerebral palsy, autism spectrum disorder trisomy 21). Notably, Khandwala *et al.* (2018) examined all US births over the past decade and reported that older fathers (e.g. >45 years of age) had higher odds of having children that suffered adverse perinatal outcomes such as premature birth and LBW, even after controlling for maternal factors. Interestingly, we have found that poor paternal health transcends the age effect and adverse pregnancy outcomes were observed across all unhealthy paternal age groups. The reason for this observation is unknown, however, the negative impact of poor health on spermatogenesis is likely multifactorial and thus may have a stronger impact than age.

While the paternal age effect has been well established in relation to some pregnancy outcomes, the literature on other paternal factors (e.g. exposures, obesity, tobacco) is limited. Paternal obesity has been examined in regard to childhood outcomes, however, it is only within the assisted reproductive technology literature that increased paternal BMI has been shown to decrease live birth rates (Bakos *et al.*, 2011; Umul *et al.*, 2015; Oldereid *et al.*, 2018; Campbell and Mcpherson, 2019). Several studies have suggested that paternal exposures prior to conception, such as decreased folate levels, smoking and alcohol consumption, may impair the pregnancy leading to an increased risk of either restricted growth or spontaneous miscarriage (Windham, *et al.*, 1992; Wang et al., 2018; Hoek *et al.*, 2019).

The underlying etiologies for an association between paternal health and pregnancy loss are unknown, however, epigenetic changes in sperm have been shown to be a potential mechanism by which fathers influence their offspring (Abbasi, 2017; Ibrahim and Hotaling, 2018). It is possible that alterations within the chromatin structure of sperm caused by paternal comorbidities may lead to systemic defects during embryogenesis and development *in utero* that could result in an outcome such as miscarriage or stillbirth. Indeed, paternal obesity, diet and smoking can affect sperm epigenetic profiles (Schagdarsurengin and Steger, 2016; Craig, *et al.*, 2017; Jenkins *et al.*, 2017; Marcho *et al.*, 2020). Additionally, chromatin methylation patterns in sperm may play a role as Alu methylation status within sperm used for ART has been associated with the odds of live birth (Castellano-Castillo *et al.*, 2019; El Hajj *et al.*, 2011). Abnormal sperm DNA fragmentation has also been shown to increase the risk of recurrent spontaneous abortions (Khadem *et al.*, 2014; Yuan et al., 2019). However, how these changes would lead to a higher risk of ectopic pregnancy versus stillbirth or spontaneous abortion, as we observed, is unclear. It is conceivable that there may be a larger impact on abnormal placentation leading to a higher risk of ectopic pregnancies. Alternatively, as ectopic pregnancies often require

medical intervention, coding may be more precise for this compared to other pregnancy loss explaining different measures of association. Finally, paternal factors could influence placental changes that may directly impact the developing fetus. Paternal age has been shown to increase placental weight which may then lead to changes in fetal birth weight or premature birth (Eskild *et al.*, 2009; Shehata *et al.*, 2011; Haavaldsen *et al.*, 2013; Strøm-Roum *et al.* 2013). While epigenetics may play a role in poor pregnancy outcomes mediated through changes in sperm, it is also possible that paternal comorbidity may simply be a marker for poor health/lifestyle of the couple. However, we identified a low correlation between paternal and maternal health. In addition, adjustment for and stratification by maternal health did not meaningfully influence the point estimates suggesting an independent association.

A few additional limitations warrant mention. As with any large administrative database, there is the potential for lack of granular detail though we did utilize several different definitions of comorbidity including MetS, CCI and chronic diseases. Additionally, as analysis of diagnoses within a claims database relies upon accurate coding by providers, errors may occur leading to misclassification. As we used established codes to estimate gestational ages of pregnancy losses, inaccuracies may also influence our results. In addition, pregnancy outcomes which did not result in a medical claim (e.g. early miscarriage) would not be captured. However, our observed frequencies of miscarriage (14.4%), stillbirth (0.91%) and ectopic pregnancy (2%) are similar to US population estimates of up to 22%, 1% and 1–2%, respectively (Avalos *et al.*, 2012; Shapiro-Mendoza *et al.*, 2016; Jatlaoui *et al.*, 2018; Mann *et al.*, 2020). Slight differences compared to the general US population likely reflect the fact that our study examined employer-based insured parents and pregnancy outcomes can be impacted by a number of factors, including sociodemographic and healthcare utilization rates. Indeed, as the current cohort includes only privately insured and employed individuals our findings may not be generalizable to other populations within the USA or elsewhere (e.g. those uninsured or unemployed). Finally, several important factors (e.g. sociodemographic status, race, substance abuse) were not available or incompletely captured in the database which may affect our results. While we did utilize codes for tobacco smoking, such coding may incompletely capture the exposure. The direction that such potential confounding influences might take is unknown.

The present study suggests an important association between preconception paternal health and pregnancy loss, whereby worsening paternal health is associated with a higher risk of pregnancy loss. While maternal health is important for preconception care, paternal health is emerging as an important factor for healthy pregnancies and could be integrated into prenatal counseling. Future studies are required to confirm these findings across different populations as well as explore the underlying mechanisms and potential interventions.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article were provided by IBM® Marketscan® under licence/by permission to the Stanford Center for Population Health Sciences Data Core. Data therefore cannot be shared freely and only under a similar agreement with the third party.

Authors' roles

Dr. M.L.E. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: A.M.K. and M.L.E.. Acquistion, analysis and data interpretation: A.M.K., M.L.E., C.A.Z. and S.L. Drafting of the manuscript: A.M.K., M.L.E.; D.K.S. and G.M.S. Critical revision of the manuscript for important intellectual content: A.M.K., M.L.E., C.A.Z., S.L., D.K.S., G.M.S. and Y.L. Statistical analysis: C.A.Z., S.L. and Y.L. Obtaining funding: none. Administrative, technical or material support: M.L.E. Supervision: M.L.E.

Funding

Data access for this project was provided by the Stanford Center for Population Health Sciences Data Core. The PHS Data Core and the Biostatistics, Epidemiology and Research Design Resource (Y.L.) are supported by a National Institutes of Health National Center for Advancing Translational Science Clinical and Translational Science Award (UL1 TR001085) and internal Stanford funding. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Conflict of interest

All authors have completed the Unified Competing Interest form (available on request from the corresponding author). M.L.E. is an advisor for Sandstone Diagnostics, Dadi, Hannah and Underdog. No other competing interests were declared. No support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, no other relationships or activities that could appear to have influenced the submitted work.

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