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Sex ratio variations among the offspring of women with diabetes in pregnancy

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Abstract

Aims—It has long been hypothesized that natural selection would favour a reproductive strategy biased towards females under adverse circumstances in order to maximize the number of surviving grandchildren. An excess of daughters in women with Type 1 diabetes and a greater likelihood of gestational diabetes in women carrying male fetuses have also been reported. This study aims to compare the sex ratio across categories of maternal glycaemia.

Methods—Among 288 009 mother–infant pairs delivering at Kaiser Permanente Northern California in 1996–2008, sex ratios were calculated for the following categories: pregravid diabetes, gestational diabetes, mild pregnancy hyperglycaemia (defined as an abnormal screening but normal diagnostic test for gestational diabetes) and normoglycaemia. Odds ratios for delivering a male were estimated with logistic regression; normoglycaemic pregnancies comprised the reference.

Results—Women with pregravid diabetes delivered the fewest males (ratio male/female = 1.01), followed by women with normoglycaemic pregnancies and those with an abnormal screening only (both sex ratios = 1.05); women with gestational diabetes delivered the most males (sex ratio = 1.07). Odds ratio estimates suggested the same pattern, but none attained statistical significance.

Conclusions—The crude sex ratios in this cohort suggest a possible gradient by category of maternal glycaemia. Women with gestational diabetes, a condition characterized by excessive fuel substrates, appear to deliver more males. Women with pregravid diabetes delivered the fewest males, possibly reflecting the unfavourable state of chronic disease.

Keywords

diabetes; gestational diabetes; sex ratio

Introduction

In populations of European ancestry, 106 male newborn infants per 100 females are typically observed [1,2], yet in populations of African ancestry, the ratio is typically 103 male newborn infants per 100 females [2]. Otherwise, there is very little fluctuation in the sex ratio across populations, except under extraordinary circumstances. Trivers & Willard [3] hypothesized that the sex ratio would be altered in difficult times, with natural selection

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favouring a reproductive strategy biased towards females under adverse circumstances to maximize the number of surviving grandchildren. Males have lower future reproductive success than their female counterparts, largely because they are less likely to reach reproductive age [4].

As a potential mechanism for the Trivers & Willard hypothesis, Catalano *et al.* [5,6] provide empirical evidence for a maternal screening mechanism that ranks gestations by the expected yield of grandchildren and a corresponding rank threshold below which a woman would spontaneously terminate the pregnancy. In contrast, James [7] hypothesizes that abnormal hormonal profiles in either parent at the time of conception is the cause of sex ratio perturbances. Mammalian (excluding human) sex ratio studies demonstrate that excess maternal glucose levels *in utero* favour the development of male blastocysts during early cell division [8]. *In vitro* exposure of bovine blastocysts to glucose-containing medium also results in significantly fewer female embryos able to progress to more advanced stages of development [9,10]. These findings suggest that, in the absence of chronic disease, an abundance of nutritional substrates may result in more male embryos.

Previously, an excess of female births was reported among women with Type 1 diabetes [11]. One study has since considered the association between the sex of the fetus and gestational diabetes mellitus [12], defined as glucose intolerance with onset or first recognition during pregnancy [13], and found that women carrying male fetuses were more likely to have gestational diabetes.

To better understand the relationship between maternal diabetes and sex of the fetus, we compared the sex ratio at birth across several glycaemic categories: women with pregravid diabetes, laboratory-confirmed gestational diabetes, laboratory confirmed mild pregnancy hyperglycaemia, and normoglycaemic pregnancies.

Patients and methods

This study utilized the Gestational Diabetes and Pregnancy Glucose Tolerance Registry [14] and the Diabetes Registry [15] of Kaiser Permanente Northern California, a large group-practice, prepaid health plan that provides comprehensive medical services to approximately 3.2 million members residing in a 14-county region. Approximately 30% of the population that resides in the area served by the Kaiser Permanente Northern California is enrolled in the health plan, which is representative of the underlying population.

Women with recognized diabetes before the index pregnancy were identified in the Kaiser Permanente Northern California Diabetes Registry [15], which identifies patients from four data sources: primary hospital discharge diagnoses of diabetes mellitus; two or more outpatient visit diagnoses of diabetes; any prescription for a diabetes-related medication; or any record of an abnormal HbA_{1c} test [greater than 50 mmol/mol (6.7%)]. Diabetes type was defined by the inpatient or outpatient diagnosis occurring closest to date of conception (calculated as the delivery date minus gestational age at delivery). Diagnoses of diabetes type were identified according to the International Classification of Disease (ICD-9) codes as follows: Type 1, 250.x1 and 250.x3; Type 2, 250.x0 and 250.x2. Of the 2261 women with recognized diabetes before pregnancy, 88% were thus classified as Type 1 or Type 2.

In addition to women with recognized diabetes before pregnancy, women with gestational diabetes who were subsequently diagnosed with diabetes from 6 weeks to 12 months postpartum were also considered to have pregravid diabetes. These women were identified in the Kaiser Permanente Northern California Diabetes Registry or by the following postpartum laboratory tests: 75-g, 2-h oral glucose tolerance test with fasting value greater than or equal to 7.0 mmol/l or 2-h value greater than or equal to 11.1 mmol/l; stand-alone

fasting value greater than or equal to 7.0 mmol/l; 2-h post-prandial value greater than or equal to 11.1 mmol/l; random value greater than or equal to 11.1 mmol/l; or HbA_{1c} greater than or equal to 48 mmol/mol (6.5%) [16]. Among women diagnosed with gestational diabetes in this cohort (n = 18 285), 44% performed a glucose screening between 6 weeks and 12 months postpartum. Based on the postpartum glucose screening results, there were 271 women who met the criteria for unrecognized pregravid diabetes [17]. Therefore, these women were combined with those who had been diagnosed with diabetes before pregnancy, resulting in a total of 2532 women classified as having pregravid diabetes.

The Kaiser Permanente Northern California (KPNC) Gestational Diabetes and Pregnancy Glucose Tolerance Registry [14] was used to classify the pregnancy glucose tolerance of women without pregravid diabetes. In this setting, among women without diabetes diagnosed before pregnancy, 94% underwent the recommended 50-g, 1-h glucose challenge test to screen for gestational diabetes [18] (hereafter, referred to as the screening test) during a routine prenatal visit. Women with plasma glucose values greater than or equal to 7.8 mmol/l on the screening test went on to receive a diagnostic 100-g, 3-h oral glucose tolerance test (hereafter referred to as the diagnostic test). All plasma glucose measurements were performed using the hexokinase method at the KPNC regional laboratory, which participates in the College of American Pathologists' accreditation and monitoring programme. Gestational diabetes was defined according to the American Diabetes Association plasma glucose thresholds [19] for the diagnostic test, or two or more values meeting or exceeding the following cut points: fasting 5.3 mmol/l; 1 h 10.0 mmol/l; 2 h 8.6 mmol/l; 3 h 7.8 mmol/l.

Another glycaemic category comprised women who had an abnormal screening test (plasma glucose ≥ 7.8 mmol/l) but whose diagnostic test results did not meet the American Diabetes Association [19] criteria for gestational diabetes (hereafter referred to as those with only abnormal screening test results). This group was considered to have mild pregnancy hyperglycaemia. Women in the normoglycaemic category were those who had a normal screening test result during pregnancy.

Newborn sex was obtained by linking the Kaiser Permanente Northern California database with birth certificate data from the State of California (99% successful linkage). Maternal race-ethnicity, age at delivery and educational attainment were also obtained through linkage with the birth certificate database.

To estimate the ratio of males to females at birth in each maternal glycaemic category, we began with all members of the Kaiser Permanente Northern California who delivered liveborn singletons between 1996 and 2008 and were 15–45 years of age at delivery. The cohort was then restricted to the first liveborn singleton delivered to a woman within the study period (n = 313 698); 21 014 women that had not been diagnosed with diabetes before pregnancy and did not perform the screening or the diagnostic tests for gestational diabetes were subsequently excluded. An additional 4675 women who were not screened but performed a diagnostic test and did not meet the diagnostic thresholds for gestational diabetes were also excluded from the final analytical cohort (n = 288 009); however, these 4675 mother–infant pairs were considered further in sensitivity analyses. Additional sensitivity analyses excluded women with recognized, pregravid Type 2 diabetes (n = 1,742). Unlike those diagnosed with diabetes postpartum and those with Type 1 diabetes, women with recognized, pregravid Type 2 diabetes received treatment and had a less chronic form of disease, respectively. Women with recognized, pregravid Type 2 diabetes were thus less likely to experience sex ratio deviations. Data are presented for a final analytical cohort of 288 009 mother–infant pairs (92%).

We first examined the crude sex ratio for each category of maternal glycaemia; a χ^2 test tested the null hypothesis of independence and a Cochran–Armitage test for trend tested the null hypothesis of no linear trend in the proportion of male infants across the following categories: pregravid diabetes, normoglycaemic pregnancies, abnormal screening test only and gestational diabetes. Logistic regression analyses were then used to examine the association between maternal glycaemic category and delivering a liveborn, singleton male compared with a liveborn, singleton female. The odds of delivering a male in women with pregravid diabetes, gestational diabetes and those with an abnormal screening test only were compared with that in women with normoglycaemic pregnancies. Unadjusted estimates, as well as estimates adjusted for maternal race–ethnicity (model 1) [20] and maternal race–ethnicity, education and age (model 2) [21] are presented. Further adjustment for parity [20] did not alter the odds ratio estimates (data not shown). The Hosmer & Lemeshow [22] χ^2 test statistic was used to assess model fit.

Maternal race–ethnicity was categorized as non-Hispanic Caucasian, African American, Asian, Hispanic and Other. Educational attainment was classified as elementary or secondary school only, high school graduate, some college (1–3 years of college), college graduate (4 years of college) or graduate studies (5+ years of college). Maternal age was modelled as a continuous variable.

Modification of the association between maternal glycaemic category and fetal sex by maternal race–ethnicity and age were further explored. Cross-products for these variables and the maternal glycaemic categories were entered into logistic regression models, the results of which offered no evidence for interaction on the multiplicative scale (all *P* values > 0.20). Stratum-specific odds ratios (ORs) were also calculated for each racial–ethnic group, which again revealed no modification of effect.

We used SAS 9.1 (SAS Institute Inc., Cary, NC) for all analyses. This study was approved by the human subjects committees of Kaiser Permanente Northern California (KPNC), the University of California, Berkeley, and the State of California, USA.

Results

The characteristics of the cohort and stratified sex ratios are listed in Table 1. The mean age at delivery was 28.6 years (SD 6.0 years) and over half of the women were primiparous. Forty per cent were non-Hispanic Caucasian, 29% were Hispanic, 22% were Asian and 9% were African American; 12% of the cohort had less than a high school education. The crude sex ratio (male/female) for the entire cohort was 1.05. The sex ratio varied by race–ethnicity: African American women showed the lowest sex ratio (1.02); the next highest were Hispanic women (1.04) followed by non-Hispanic Caucasian women (1.05) and Asian women (1.07). Those reporting Other as their race–ethnicity demonstrated the highest sex ratio (1.10).

The number of women in each category of maternal glycaemia, along with the crude sex ratio for that category, is shown in Table 2. Women with gestational diabetes had the highest sex ratio (1.07), followed by women with abnormal screening values only (1.05) and normoglycaemic pregnancies (1.05). Women with pregravid diabetes, who constituted the smallest category, had the lowest sex ratio (1.01; χ^2 for independence, $P = 0.51$; Cochran–Armitage test for trend across groups, $P = 0.22$). In women with pregravid diabetes, the 1742 women with Type 2 diabetes had a sex ratio of 1.05, the 271 women identified postpartum had a sex ratio of 0.88 and the 245 women with Type 1 diabetes had a sex ratio of 0.87.

The 4675 women who were not screened for gestational diabetes during pregnancy but did perform the diagnostic test were considered further in sensitivity analyses; the sex ratio

estimates remained identical to those presented in Table 2 when these women were included and categorized either as having abnormal screening values only or as normoglycaemic pregnancies.

Results of the logistic regression models are presented in Table 3; the 95% confidence intervals for all estimates included the null value; thus none attained statistical significance. Compared with women with normoglycaemic pregnancies, those with gestational diabetes were more likely to deliver males. Women with abnormal screening values only did not differ from those with normoglycaemic pregnancies. Women with pregravid diabetes were more likely to deliver females than women with normoglycaemic pregnancies. The exclusion of women with recognized, pregravid Type 2 diabetes ($n = 1742$) yielded equivalent results to those presented in Table 3.

A total of 2480 women had no data on race–ethnicity and 5482 had no data on educational attainment; these women were excluded from the adjusted multiple regression models. Unadjusted odds ratios estimates among those with complete data only were identical to those presented in Table 3.

Adjustment for maternal race–ethnicity, education and age did not appreciably alter the odds ratio estimates. For all models, there was no suggestion of lack of fit based on the Hosmer & Lemeshow χ^2 statistic (all $P > 0.75$) [22].

Discussion

Despite the large cohort investigated in this study, the odds of delivering a liveborn male singleton across several categories of maternal glycaemia did not vary significantly, even after adjustment for covariates. However, the crude sex ratios suggest a possible gradient by category of maternal glycaemia: women with pregravid diabetes delivered the fewest males, followed by women with normoglycaemic pregnancies and those with an abnormal screening values only (or mild pregnancy hyperglycaemia); women with a gestational diabetes delivered more males than any other group. Women with abnormal screening values only did not appear to differ from women with normoglycaemic pregnancies. United States national vital statistics [20] confirm the variation by race–ethnicity described in these data: Asian women had the highest sex ratio (most males), the next highest were Non-Hispanic women of Caucasian ancestry, followed by Hispanic women and last were African American women, who exhibited the lowest sex ratio.

The observed sex ratio trend across maternal glycaemic categories supports the original Trivers & Willard hypothesis [3], whereby the spontaneous abortion of those conceptions with the lowest probability of producing grandchildren is believed to contribute to fetal loss. A maternal screening mechanism that ranks gestations based on their expected yield of grandchildren, along with a corresponding rank threshold below which a woman would spontaneously terminate a pregnancy, have been proposed [5,6]. This rank threshold would account for a mother's ability to sustain her offspring through reproductive age and reflect the probability that a given conception would reach reproductive age, thus male conceptions would hold a lower rank than females [4]. Extending this logic further, female twins would be the most desirable, followed by female singletons, male singletons and lastly male twins, in terms of the yield of grandchildren [6].

Pregravid diabetes is characterized by insufficient metabolic regulation owing to either insulin deficiency, as in Type 1 diabetes mellitus, or increased insulin resistance, as in Type 2 diabetes mellitus. The resulting state of pathologic hyperglycaemia is also associated with oxidative and metabolic stress. These unfavourable conditions may lead to a higher rank threshold for fetal loss to maximize reproductive success, thereby resulting in the loss of

male fetuses and a lower overall sex ratio in this group. In these data, women with more severe disease, such as those with Type 1 diabetes recognized before pregnancy and those identified with diabetes postpartum (who would not have received monitoring or treatment for their disease during pregnancy) demonstrated the greatest sex ratio perturbances. Women with Type 2 diabetes identified before pregnancy demonstrated the same sex ratio as normoglycaemic women; these women received monitoring or treatment for their disease, thereby diminishing stress experienced early in pregnancy.

Gestational diabetes, in contrast, is a condition associated with increased metabolic substrates that results in fetal over-nutrition. According to the Trivers & Willard hypothesis [3], women with gestational diabetes should have more males. Compared with women with normoglycaemic pregnancies, those who develop gestational diabetes are more likely to have experienced higher glycaemic levels early in pregnancy because of a predisposition towards insulin resistance before pregnancy [23,24]. The maternal state of abundant fuel, although not high enough to constitute an unfavourable state of overt disease, may signal an increased maternal ability to sustain offspring and thus lower the rank threshold for fetal loss, thereby resulting in more males overall and a higher sex ratio in this group.

Gestational diabetes is diagnosed late in the second or early in the third trimester in women displaying hyperglycaemia despite the increased insulin response to oral glucose that accompanies normal pregnancy [25]. Thus, it cannot be determined whether some pre-pregnancy manifestation of gestational diabetes affects early sex selection *in utero* or, conversely, if the sex of the fetus affects the later development of gestational diabetes. A meta-analysis of mammalian sex ratio studies (excluding human) found that studies examining maternal body condition, weight or food availability assessed or manipulated around the time of conception demonstrated the most consistent and significant support for the Trivers & Willard hypothesis of increased maternal investment in male gestations under favourable conditions [8]. Mammalian reproductive research demonstrates that high concentrations of glucose have detrimental effects on early embryonic development *in vitro* [26,27]; specifically, glucose supplementation of culture media results in the preferential loss of female bovine blastocysts [9,10].

Previous work has similarly reported an association between gestational diabetes and delivering a male. Sheiner *et al.* [12] found that Israeli women carrying males were 10% more likely to have gestational diabetes in a sample of 108 995 mother–infant pairs, with the odds ratio estimate attaining statistical significance. Rjasanowski *et al.* [11] reported more female than male offspring (ratio = 0.45) among children born to a small sample (n = 112) of women with Type 1 diabetes in Germany. The sample of women with Type 1 diabetes in the current study was twice the size (n = 245); in our data, women with pregravid diabetes delivered fewer males than any other glycaemic category, with females in absolute excess among women with Type 1 diabetes and those identified postpartum (ratio male to female < 1.00). It should be noted that members of the Kaiser Permanente Northern California (KPNC) health plan with recognized diabetes before pregnancy receive medical treatment and monitoring of their disease. It is possible that we did not observe sex ratio perturbances in women with Type 1 diabetes as extreme as those reported by Rjasanowski *et al.* [11] because of secular trends of improved treatment for patients with diabetes. Population differences may also play a role, as the Rjasanowski *et al.* [11] study included primarily Caucasians.

Near-universal pregnancy glucose screening and the availability of plasma glucose values for the identification of laboratory-confirmed cases of gestational diabetes and mild pregnancy hyperglycaemia are strengths of the current study. Limitations include the small number of women with pregravid diabetes. In women with pregravid diabetes, suboptimal

glycaemic control before conception increases the risk of miscarriage. Unfortunately, we lacked data on perinatal deaths; we also lacked data on paternal glucose tolerance and diabetes status. Less than half of the women with gestational diabetes were screened for diabetes in the postpartum period, thus some women with pregravid diabetes were likely misclassified as having gestational diabetes, suggesting that the difference in infant sex ratio between women with pregravid diabetes and those with gestational diabetes may be larger than observed.

The findings of this study suggest that sex ratio at birth may vary by category of maternal glycaemia. Our findings also demonstrate the stability of the sex ratio, as only very small differences were observed between categories of maternal glycaemia, as well as between racial–ethnic groups. Although this cohort contained over 250 000 mother–infant pairs, data from even larger cohorts, particularly data on glucose control around the time of conception in women with pregravid diabetes, would address several questions raised by these findings.

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Table 1

Characteristics and corresponding sex ratios (male/female) for women delivering a liveborn singleton at Kaiser Permanente Northern California, 1996–2008

	n (%)	Sex ratio	*P* *
All women	288 009	1.05	
Age (years)			0.85
15–19	22 214 (7.7)	1.03	
20–24	53 876 (18.7)	1.05	
25–29	83 698 (29.1)	1.05	
30–34	77 685 (27.0)	1.05	
35–39	40 580 (14.1)	1.06	
40–45	9956 (3.5)	1.05	
Parity† (*n* = 287 790)			0.87
0	166 756 (57.9)	1.05	
1	71 677 (24.9)	1.04	
2	33 437 (11.6)	1.05	
3+	15 920 (5.5)	1.04	
Education† (*n* = 282 527)			0.27
Elementary or secondary school only	34 785 (12.3)	1.04	
High school graduate	79 188 (28.0)	1.04	
Some college	79 923 (28.3)	1.06	
College graduate	50 985 (18.1)	1.06	
Graduate studies	37 646 (13.3)	1.04	
Race–ethnicity† (*n* = 285 529)			0.05
Non-Hispanic Caucasian	114 838 (40.2)	1.05	
Hispanic	83 009 (29.1)	1.04	
African American	24 256 (8.5)	1.02	
Asian	62 284 (21.8)	1.07	
Other	1142 (0.4)	1.10	
Year of delivery			0.18
1996–1997	51 309 (17.8)	1.04	
1998–1999	47 462 (16.5)	1.03	
2000–2001	42 258 (14.7)	1.05	
2002–2003	43 087 (15.0)	1.05	
2004–2005	40 449 (14.0)	1.04	
2006–2007	42 553 (14.8)	1.07	
2008	20 891 (7.3)	1.06	

* χ^2 test of independence for variable of interest and infant sex.

† *n* differs because of missing values.

Table 2

Sex ratio (male/female) by category of maternal glycaemia for 288 009 women delivering liveborn singletons at Kaiser Permanente Northern California, 1996–2008

Maternal glycaemic category	n	Sex ratio
Pregravid diabetes	2532	1.01
Identified postpartum	271	0.88
Type 1	245	0.87
Type 2	1742	1.05
Normoglycaemic pregnancy	232 106	1.05
Abnormal screening and normal diagnostic test	35 357	1.05
Gestational diabetes	18 014	1.07

Table 3

Odd ratios (ORs) and 95% confidence intervals (CIs) for delivering a male infant among 288 009 women delivering liveborn singletons at Kaiser Permanente Northern California, 1996–2008

	Unadjusted (*n* = 288 009)		Model 1* (*n* = 285 529)		Model 2† (*n* = 282 236)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Maternal glycaemic category						
Pregravid diabetes	0.97	0.90, 1.05	0.97	0.90, 1.05	0.96	0.89, 1.04
Normoglycaemic pregnancy	Ref		Ref		Ref	
Abnormal screening/normal diagnostic test	1.00	0.98, 1.02	1.00	0.98, 1.02	1.00	0.98, 1.02
Gestational diabetes	1.02	0.99, 1.05	1.02	0.99, 1.05	1.02	0.99, 1.05
Race–ethnicity						
African American			0.98	0.95, 1.01	0.98	0.95, 1.01
Hispanic			0.99	0.97, 1.01	0.99	0.97, 1.01
Non-Hispanic Caucasian			Ref		Ref	
Asian			1.02	1.00, 1.04	1.02	1.00, 1.04
Other			1.05	0.93, 1.18	1.06	0.94, 1.19
Educational attainment						
Less than high school					Ref	
High school graduate					1.00	0.98, 1.03
Some college					1.02	0.99, 1.04
College graduate					1.01	0.98, 1.04
Graduate studies					1.00	0.96, 1.03
Age					1.00	1.00, 1.00

*Adjusted for maternal race–ethnicity.

†Adjusted for maternal race–ethnicity, educational attainment, and age.