An exploration of secondary sex ratios among women diagnosed with anxiety disorders

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BACKGROUND: Theory suggests that natural selection conserved reactivity in part because highly reactive women spontaneously abort less fit conceptuses, particularly small males. Other literature argues that high reactivity manifests clinically as anxiety disorders. If true, births to women diagnosed with anxiety disorders should exhibit a low secondary sex ratio (i.e. ratio of male to female births). We explored whether births to women diagnosed with anxiety disorders exhibit a lower sex ratio than births to women diagnosed with other psychiatric disorders, or to women without mental health diagnoses.

METHODS: We performed a case–control comparison of the secondary sex ratios among groups of women categorized by mental health diagnosis using birth records linked to data from California County Mental Health system records. We compared sex ratios among 5994 deliveries to mothers diagnosed with anxiety disorders, 23 443 deliveries to mothers diagnosed with other psychiatric disorders and 1 099 198 ‘comparison’ births.

RESULTS: Although comparison births exhibited a higher sex ratio than births to women diagnosed with anxiety disorders or with other diagnoses, differences were not statistically significant. Births to African American women diagnosed with anxiety disorders, however, exhibited sex ratios significantly lower than comparison births among African Americans (OR = 0.89, P = 0.038) or births to African American women with other mental health diagnoses (OR = 0.88, P = 0.042).

CONCLUSIONS: We found that infants born to African American women diagnosed with anxiety disorders exhibited a significantly lower secondary sex ratio than reference groups. We urge confirmatory tests of our findings and discuss implications of the reactivity/anxiety hypothesis for psychiatry, obstetrics and public health.

Key words: reactivity / anxiety disorders / sex ratio / stress / selection in utero

Introduction

The fact that more than half of human conceptions spontaneously abort (Wilcox et al., 1988; Boklage, 1990) implies that gestation provides as much an opportunity for selection as for maturation. Indeed, the literature includes no claims that live births represent the conceived population. Animal and human research, on the contrary, supports the argument that natural selection has conserved mechanisms by which females spontaneously abort conceptuses and fetuses least likely to yield grandchildren (Trivers and Willard, 1973; Stearns, 1987; Wells, 2000). Males supposedly predominate among these abortuses because, if born, they would more likely die before reproductive age than would a female, despite receiving greater maternal investment (Wells, 2000).

Selection against males in utero supposedly increases in a threatening environment because their chances of survival decrease more than those of females in the face of emergent hazards (Wells, 2000; James, 2009). Consistent with this supposition, the ratio of male to female live births (i.e. secondary sex ratio) reportedly drops in populations subjected to exogenous stressors (Catalano, 2003; Catalano and Bruckner, 2005; Catalano et al., 2006; James, 2009). Whereas controversy remains over the biological mechanisms that connect the environment to spontaneous miscarriage, many explanations focus on hormonal changes associated with the maternal stress response (James, 2006, 2009).
Research suggests that human populations include highly reactive persons who exhibit autonomic, immune and neuroendocrine responses at relatively low levels of provocation, and have a stronger response than others to stimuli that provoke responses in most individuals (Matthews, 1986; Suomi, 1997; Cacioppo et al., 1998; Boyce and Ellis, 2005). Natural selection presumably conserved high reactivity because responding at low levels of threat increased fitness by increasing chances of survival through childhood (Kajantie et al., 2003; Jones et al., 2006; Entringer et al., 2009) and reproductive age in the dangerous environments presumed common during much of human evolution (Boyce and Ellis, 2005; Stevens et al., 2009). The literature argues that high reactivity can present clinically as anxiety (Mick and Telch, 1998; Kagan et al., 1999; Gladstone et al., 2005; Boyce et al., 2006). Individuals with anxiety disorders appear highly reactive to threats and mount greater autonomic and neuroendocrine responses to stressors when compared with controls (Roth, 2005; Cornwell et al., 2006). Neuroimaging studies support these findings, reporting an association between anxiety and regulation of fear circuits in the brain (Liberzon et al., 1999; Liberzon and Martis, 2006).

Anxiety during pregnancy increases the risk of spontaneous miscarriage and preterm delivery in humans (Mulder et al., 2002). Reports of hypothalamic–pituitary–adrenal (HPA) axis hyperactivity in rats bred for high anxiety (Landgraf et al., 1999), and increased HPA activity during pregnancy among high anxiety rats (Neumann et al., 1998), suggest that HPA axis activity may mediate the hypothesized connection between anxiety and gestational outcomes in rodents.

If highly reactive women are more likely to present with anxiety symptoms than other women, and if the biological markers of high reactivity in women include low secondary sex ratios, then women diagnosed with anxiety disorders should exhibit relatively low secondary sex ratios. In this study, we explore whether births to women diagnosed with anxiety disorders exhibit a lower sex ratio than births to women diagnosed with other disorders or to women without mental health diagnoses.

Materials and Methods

Data and variables
With approval of Institutional Review Boards of the State of CA, USA and University of California, we linked information from two large population-based California datasets. We acquired birth records from the State of California for the period 1998–2002 (California Department of Health Services, 2004). These records include more than 99% of California deliveries (~525 000 per year) and include parents’ demographics, mother’s insurance status and characteristics of the birth (California Department of Health Services, 2004). The California Department of Public Health, Vital Statistics Division, uses various quality control measures to validate birth records. The National Center for Health Statistics, the federal agency that compiles birth statistics from all states within the USA, independently evaluates selected certificate information by reviewing a sample of birth and death records to identify random errors. Error rates typically fall within 1–2% (Resources, Prevention, & Division of Vital Statistics, 2003).

Experts separate from our research team used probabilistic linkage methods (Fellegi and Sunter, 1969) to link the birth records with data describing services received by clients of county mental health systems between 1998 and 2002. Counties provide community- and hospital-based mental health services to adults and children with mental illness, who may pay for services through the California public health insurance program for poor families or on a sliding-scale fee basis.

We could not determine if women diagnosed with psychiatric disorders during our test period had previous episodes of disorder. Nor could we know when the symptoms of disorder in the diagnosed episode first appeared. Much evidence suggests that individuals experiencing psychiatric disorders frequently delay seeking treatment for several years, especially if symptoms appear early in life (Wang et al., 2005). Barriers to treatment also can impede receipt of timely care. Diagnosis, therefore, often occurs much later than actual symptoms. Given these circumstances, and the exploratory nature of our study, we decided to characterize all women who both gave birth and received mental health services between 1998 and 2002 as mothers with diagnosed psychiatric disorders, regardless of the timing of the services.

We excluded multiple births from our study because the theoretical and empirical literature suggests that selection among multiples in utero may differ from that among singletons (Catalano et al., 2009). We also excluded births with unknown/indeterminate sex. We then divided the remaining births into three groups. First, we classified 5994 deliveries to mothers diagnosed with anxiety disorders comprising: anxiety state (unspecified), panic disorder without agoraphobia; generalized anxiety disorder; obsessive-compulsive disorder; agoraphobia with panic disorder; agoraphobia without mention of panic attacks; social phobia; other isolated or specific phobias; acute stress disorder; or posttraumatic stress disorder as births to women diagnosed with anxiety disorders.

Second, we classified 23 443 deliveries to mothers diagnosed with psychiatric disorders not listed above as births to women with other disorders. Third, we created a comparison group including 1 099 198 births to women not diagnosed in county mental health systems and whose deliveries were (i) paid for by public insurance, or (ii) were not covered by any insurance (including births categorized as ‘no insurance, N/A or medically unattended’, ‘self-pay’, ‘no charge’, ‘other nongovernment programs’, ‘medically indigent’ or ‘unknown’). Clients of county mental health systems typically fall into these insurance categories (Swartz et al., 1998; Snowden et al., 2002; see Table I), although some may have access to private health insurance for physical health conditions, including pregnancy and delivery.

Our explorations used the adjusted odds of a male birth as the dependent variable. We adjusted the odds in our three groups for mother’s age, race and education. We scored age as a continuous variable and grouped maternal race into five categories including non-Hispanic white, Hispanic, non-Hispanic African American, Asian and Other. We grouped maternal education into less than high school (i.e. <12 years of education), high school graduate (i.e. 12 years of education), some college (i.e. 13–15 years) and college degree or higher (i.e. 16 or more years).

Maternal substance abuse can cause fetal defects that, in turn, can lead to spontaneous miscarriage (Andres and Larrabee, 1996; Nayak and Murthy, 2008). The mental health system data noted women for whom substance use affected diagnosis or treatment. We scored all women diagnosed with mental health problems as either having used substances or having an unknown substance use status during contact with the mental health system, and included the variable as a covariate in the comparisons described below.

Statistical analyses
We used logistic regression, performed with SAS version 9.1 (SAS Institute, Cary, NC, USA), to make three comparisons. First, we compared the secondary sex ratio among births to women diagnosed with anxiety disorders to the ratio among comparison births. Second, we compared the secondary
Results

Table I shows the demographic characteristics for each of our three birth groups. Table II shows the unadjusted secondary sex ratios among the groups.

Table III shows the results of the first set of logistic regressions. Although comparison births exhibited a higher adjusted sex ratio than births to women diagnosed with anxiety disorders or with other diagnoses, the differences were not statistically significant. In both these estimations, births to Hispanic and non-Hispanic African American mothers had lower sex ratios than births to non-Hispanic whites, whereas those to Asian mothers had the highest sex ratio. Women with less than a high school education and those who had completed high school only delivered birth cohorts with significantly lower sex ratios than did women with 4 years of college or more. The estimations involving only clients of county mental health systems yielded no statistically significant predictors of male births.

We then repeated the three separate regressions for each of the four race/ethnicity groups. As shown in Table IV, births to African American women diagnosed with anxiety disorder exhibited sex ratios significantly lower than either comparison births (OR = 0.89, P = 0.038) or births to women with other psychiatric diagnoses (OR = 0.88, P = 0.042). None of the covariates significantly affected sex ratios among births to African American mothers.

None of the other race/ethnicity groups yielded significant differences between births to women diagnosed with anxiety disorder and the reference groups. Among non-Hispanic whites, no significant predictors emerged in any of the three regressions. Among Hispanics, maternal age significantly predicted the sex ratio in the regression including births to women diagnosed with other disorders and comparison births (OR = 0.99, P = 0.049). In the model comparing births to women diagnosed with anxiety disorders to comparison births, Asians with less than a high school education delivered infants with a lower sex ratio than their counterparts with 4 years of college or more (OR = 0.94, P = 0.020).

As the last step in our exploration, we determined whether the interaction of births to women diagnosed with anxiety disorders and African American maternal race/ethnicity significantly predicted the sex ratio in two of our original regresions: that estimated for births to women diagnosed with anxiety disorders and comparison births, as well as that estimated for births to women diagnosed with anxiety disorders and births to women diagnosed with other psychiatric disorders. We entered the interaction term into each of the two
regressions and, as suggested in the epidemiologic literature (Selvin, 1996), relaxed the significance level to $\alpha = 0.20$ for interaction terms. The interaction was significant in both estimations. The coefficient for the interaction term was $0.11 \ (P = 0.11)$ when comparing the sex ratio among infants of African American women diagnosed with anxiety to that among infants of comparison African American mothers, and $-0.13 \ (P = 0.087)$ when comparing the sex ratio of births to African American women diagnosed with anxiety to those among African American women with other diagnoses.

**Discussion**

Our exploration suggests that among African Americans, women diagnosed with anxiety disorder in county mental health systems deliver fewer male infants than women diagnosed with other psychiatric disorders and women not in contact with those systems. Offspring of African American women diagnosed with anxiety disorder in these systems exhibited a sex ratio of 0.92, the lowest sex ratio observed among all the analyzed groups (Table II). To place this in context, an analysis of sex ratio trends in the USA between 1970 and 2002 reported that births to African American mothers exhibited the lowest sex ratio, 1.03, of any demographic group (Mathews and Hamilton, 2005). That value corresponds exactly to the sex ratio we observed among our African American comparison births. As our estimations show, a sex ratio of 1.03 is significantly higher than the 0.92 ratio observed among births to African American mothers diagnosed with anxiety disorder.

Several limitations of our data should be noted. Women in our population with anxiety disorders may have either sought care...
outside the county mental health system or sought no care. We would have misclassified these women as not having any anxiety disorder. This misclassification may have biased our estimates toward the null.

Our diagnostic data came from the public mental health system and 83% of mothers receiving services in that system had either public or no insurance to pay for their deliveries, suggesting that they were predominantly of low income. We therefore restricted the comparison group to births to women with public health insurance or no insurance. It is possible that insurance status acts as a proxy for other socioeconomic factors that could influence either anxiety or the sex ratio. We consider, however, that our inclusion of educational status in the regression models reduces bias arising from the potentially unequal distribution of socioeconomic status among the three groups.

Potentially important covariates may be missing from our dataset. Literature suggests, for example, that smoking may be associated with lower sex ratios (Fukuda et al., 2002). Whether African American women diagnosed with anxiety disorders are more likely to smoke than their African American counterparts not diagnosed in the mental health system remains a question we cannot answer with our data, but such a finding has not been previously reported. Our finding of a lower sex ratio among African American women diagnosed with anxiety disorder than among African American women diagnosed with other disorders suggests that smoking did not bias our findings.

We can offer only post hoc explanations for why the association appeared strongest among African Americans. The most intuitive of these include that African American women probably experience, on average, more frequent—or possibly more virulent—stressful stimuli, and enjoy fewer coping assets, than other women (Hatch and Dohrenwend, 2007). The physiologic toll of this stress has already been demonstrated in studies of ‘allostatic load’ (an indicator of physiologic dysregulation across multiple systems), in which African American women of child bearing age have higher loads than white women (Geronimus et al., 2006). The most reactive among African American women, those who also exhibit clinically significant anxiety, may therefore suffer more episodes of physiologic reactivity (and the effects of the biological mediators involved) than similarly anxious women in less stressed populations.

Although African Americans demonstrate lower prevalence of most anxiety disorders compared with other racial groups, symptom severity and functional impairment among those with diagnosed disorder is significantly higher compared with whites (Himle et al., 2009). It is possible that this increased severity of anxiety disorders among African Americans drives our results. We, however, cannot test whether symptom severity induced the lower sex ratio observed among infants of African American women diagnosed with anxiety disorder, and know of no literature describing such an effect.

Another line of post hoc speculation suggests that selection in utero may not just ‘cull’ less fit males, it may also ‘preserve’ reactive females. It makes evolutionary sense for a system to conserve any adaptation that enabled females in dangerous environments to increase the likelihood that their daughters would yield grandchildren. Furthermore, mechanisms that either select for, or induce, reactivity (Wadhwa, 2005) in daughters further this end. Thus, natural selection in utero or in very early life may have increased the prevalence of high reactivity among women in stressed populations more than among those in benign environments. The question of how many generations would have to pass for selection in utero to yield a significant difference in the prevalence of high reactivity between populations subject to more and less dangerous environments is beyond the scope of this paper, and should be left to evolutionary theorists. As noted above, however, at least half of all pregnancies end without live births. Selecting only 50% or fewer of the candidates for birth would, at least intuitively, allow for much variation in reactivity among births cohorts born in differing environments.

The theory of selection in utero motivated our study, but our findings do not rule out other mechanisms. James’ (2000, 2006) argument, for example, that the levels of androgens at the time of conception affects the primary sex ratio and, in turn, the secondary sex ratio, suggests at least one other mechanism that could have contributed to our findings. This additional mechanism requires that African Americans...

### Table IV Logistic regression results for comparisons of diagnostic groups among African Americans.

<table>
<thead>
<tr>
<th>Group Coded 1</th>
<th>Births to women diagnosed with anxiety disorders (coded 1) versus Births to comparison group (coded 0)</th>
<th>Births to women diagnosed with other disorders (coded 1) versus Births to comparison group (coded 0)</th>
<th>Births to women diagnosed with anxiety disorders (coded 1) versus Births to women diagnosed with other disorders (coded 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Group Coded 1</td>
<td>0.89 (0.79, 0.99)</td>
<td>0.88 (0.78, 1.00)</td>
<td>0.88 (0.78, 1.00)</td>
</tr>
<tr>
<td>Mother’s age</td>
<td>1.00 (0.99, 1.00)</td>
<td>1.00 (0.99, 1.00)</td>
<td>1.00 (1.00, 1.01)</td>
</tr>
<tr>
<td>Mother’s education&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.00 (0.99, 1.00)</td>
<td>1.00 (0.99, 1.00)</td>
<td>1.00 (1.00, 1.01)</td>
</tr>
<tr>
<td>Less than high school</td>
<td>0.98 (0.91, 1.05)</td>
<td>0.97 (0.90, 1.05)</td>
<td>0.97 (0.90, 1.05)</td>
</tr>
<tr>
<td>High school graduate</td>
<td>0.96 (0.90, 1.03)</td>
<td>0.95 (0.89, 1.02)</td>
<td>0.95 (0.89, 1.02)</td>
</tr>
<tr>
<td>Some college</td>
<td>1.00 (0.93, 1.07)</td>
<td>0.99 (0.92, 1.07)</td>
<td>0.99 (0.92, 1.07)</td>
</tr>
<tr>
<td>Substance abuse&lt;sup&gt;b&lt;/sup&gt;</td>
<td>n/a</td>
<td>n/a</td>
<td>1.00 (0.83, 1.20)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reference level = Four years of college or more.

<sup>b</sup>Reference level = Substance abuse status no/unknown; variable excluded for models including comparison group due to lack of data.
American women diagnosed with anxiety have different androgen profiles than other women including African Americans diagnosed with psychiatric disorders other than anxiety. Although Potischman et al. (2005) reported higher androgen levels among pregnant African Americans compared with both Hispanic and whites, Spencer et al. (2007) finds lower androgen levels in eumenorheic African American women compared with white women. Furthermore, we know of no tests of these differences in women diagnosed with psychiatric disorders.

James’ androgen hypothesis represents one of several suggesting that the secondary sex ratio varies not only with selection in utero but also with sex bias in the formation of zygotes. Much controversy remains regarding the determinants of the sex ratio at conception (Boklage, 2005), but we acknowledge that these could have contributed to our findings. We also note, however, that the literature includes tests intended to determine whether the low secondary sex ratios reported after population stressors result from selection in utero or from mechanisms that reduce the primary sex ratio (Catalano et al., 2005, 2010). These tests use monthly data and assume that low sex ratios should appear 2–4 months after population stressors if selection in utero were at work, but 8–10 months later if low primary sex ratios were the cause. These prior results support selection in utero.

Tests based on monthly data suggest further research that could estimate the relative contribution of selection in utero and low primary sex ratios to our findings. Using time series, researchers could empirically test whether sex ratios among African American women treated for anxiety fall 2–4 or 8–10 months after an event known to predict low secondary sex ratios in the population. If sex ratios in this group fall 2–4 months after a stressful event, this would suggest that low primary sex ratios may contribute to the findings presented here. Research (Catalano et al., 2006) reported in this journal suggests, for example, that the events of 11 September 2001 might serve as a population stressor in such tests.

We hope the findings reported here will motivate confirmatory tests of the reactivity/anxiety hypothesis and further discussion of its implications for psychiatry, obstetrics and public health. The psychiatric literature has begun exploring the clinical implications of the hypothesis (Mick and Telch, 1998; Gladstone et al., 2005), but to our knowledge, the obstetric and public health literature has not. Although we do not judge ourselves qualified to probe the implications for obstetric practice, a case record of anxiety disorders among African Americans should trigger attention to fetal loss in prenatal care. Our findings also suggest that public health programs aimed at increasing prenatal care might focus on mothers in treatment for anxiety, and that these women may benefit from interventions aimed at reducing provocation of anxiety during pregnancy (for example, relaxation techniques or generous employer maternity benefits).

Conclusion

We found that infants born to African American women diagnosed with anxiety disorders exhibited a significantly lower secondary sex ratio than infants born to African American women either diagnosed with other psychiatric disorders or without diagnosed disorder. The difference exceeds that expected at the conventional level of chance and survives controlling for the principal predictors of sex-biased births. The difference, however, does not appear in Hispanic, Asian or non-Hispanic white women. Although our results offer only limited support for a connection between anxiety and low secondary sex ratios, a potential physiologic maker of reactivity, they offer an explanation for low sex ratios often observed among African Americans.

We hope that other researchers will pursue more confirmatory research in larger samples than ours. If more controlled work with larger samples confirms an association between clinically significant anxiety and low sex ratios, the finding would not only contribute to what we know of how natural selection affects contemporary human populations, but may also influence clinical and lay understanding of a common psychiatric disorder. Such an association would imply that some, perhaps much, of anxiety among women in contemporary populations results not from aberrant development, learning or culture, but rather from the ubiquitous and essential process of natural selection.

Authors’ roles

All authors participated in study design, execution, analysis, manuscript drafting and critical discussion.

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